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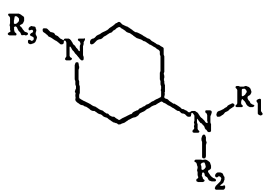
(54) Title: 4-AMINOPIPERIDINE DERIVATIVES AND THEIR USE AS MEDICINE

(54) Titre: DERIVES DE 4-AMINOPIPERIDINE ET LEUR UTILISATION EN TANT QUE MEDICAMENT



(I)

(57) Abstract: The invention concerns novel 4-aminopiperidine derivatives of formula (I) wherein: R_1, R_2 and R_3 represent various variable groups, their preparation methods by parallel synthesis processes in liquid and solid phase. Said products have good affinity with certain sub-types of somatostatin receptors, and they are particularly useful for treating pathological conditions or diseases wherein one (or several) somatostatin receptor(s) is/are involved.

(57) Abrégé: La présente demande a pour objet de nouveaux dérivés de 4-aminopipéridines de formule (I) dans laquelle R_1, R_2 et R_3 représentent divers groupes variables, leurs procédés de préparation par des méthodes de synthèse en parallèle en phase liquide et solide. Ces produits ayant une bonne affinité avec certains sous-types de récepteurs de la somatostatine, ils sont particulièrement intéressants pour traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s).

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Derivatives of 4-aminopiperidine and their use as a medicament

A subject of the present application is new derivatives of 4-aminopiperidines and their preparation processes by synthetic methods in parallel in liquid and solid phase. These products having a good affinity with certain sub-types of somatostatin receptors, they are particularly useful for treating the pathological states or diseases in which one (or more) somatostatin receptors are involved.

Somatostatin (SST) is a cyclic tetradecapeptide which was isolated for the first time from the hypothalamus as a substance which inhibits the growth hormone (Brazeau P. et al., *Science* 1973, **179**, 77-79). It also operates as a neurotransmitter in the brain (Reisine T. et al., *Neuroscience* 1995, 67, 777-790; Reisine T. et al., *Endocrinology* 1995, **16**, 427-442). Molecular cloning has allowed it to be shown that the bioactivity of somatostatin depends directly on a family of five receptors linked to the membrane.

The heterogeneity of the biological functions of somatostatin has led to studies which try to identify the structure-activity relationships of peptide analogues on somatostatin receptors, which has led to the discovery of 5 sub-types of receptors (Yamada et al., *Proc. Natl. Acad. Sci. U.S.A*, **89**, 251-255, 1992; Raynor, K. et al, *Mol. Pharmacol.*, **44**, 385-392, 1993). The functional roles of these receptors are currently being actively studied. The affinities with different sub-types of somatostatin receptors have been associated with the treatment of the following disorders/diseases. Activation of sub-types 2 and 5 has been associated with suppression of the growth hormone (GH) and more particularly with that of adenomas secreting GH (acromegalia) and those secreting hormone TSH. Activation of sub-type 2 but not sub-type 5 has been associated with the treatment of adenomas secreting prolactin. Other indications associated with the activation of sub-types of somatostatin receptors are the recurrence of stenosis, inhibition of the secretion of insulin and/or of glucagon and in particular diabetes mellitus, hyperlipidemia, insensitivity to insulin, Syndrome X, angiopathy, proliferative retinopathy, dawn phenomenon and nephropathy; inhibition of the secretion of gastric acid and in particular peptic ulcers, enterocutaneous and pancreaticocutaneous fistulae, irritable colon syndrome, dumping syndrome, aqueous diarrhea syndrome, diarrhea associated with AIDS, diarrhea induced by chemotherapy, acute or chronic pancreatitis and secretory gastrointestinal tumors; the treatment of cancer such as hepatomas; the inhibition of angiogenesis, the treatment of inflammatory disorders

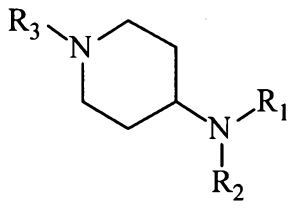
such as arthritis; chronic rejection of allografts; angioplasty; the prevention of bleeding of grafted vessels and gastrointestinal bleeding. The agonists of somatostatin can also be used to reduce the weight of a patient.

Among the pathological disorders associated with somatostatin (Moreau J.P. et al., Life Sciences 1987, **40**, 419; Harris A.G. et al., *The European Journal of Medicine*, **1993**, 2, 97-105), there can be mentioned for example: acromegalia, hypophyseal adenomas, Cushing's disease, gonadotrophinomas and prolactinomas, catabolic side-effects of glucocorticoids, insulin dependent diabetes, diabetic retinopathy, diabetic nephropathy, hyperthyroidism, gigantism, endocrine gastroenteropancreatic tumors including carcinoid syndrome, VIPoma, insulinoma, nesidioblastoma, hyperinsulinemia, glucagonoma, gastrinoma and Zollinger-Ellison's syndrome, GRFoma as well as acute bleeding of the esophageal varices, gastroesophageal reflux, gastroduodenal reflux, pancreatitis, enterocutaneous and pancreatic fistulae but also diarrheas, refractory diarrheas of acquired immunodeficiency syndrome, chronic secretary diarrhea, diarrhea associated with irritable bowel syndrome, disorders linked with gastrin releasing peptide, secondary pathologies with intestinal grafts, portal hypertension as well as hemorrhages of the varices in patients with cirrhosis, gastro-intestinal hemorrhage, hemorrhage of the gastroduodenal ulcer, Crohn's disease, systemic scleroses, dumping syndrome, small intestine syndrome, hypotension, scleroderma and medullar thyroid carcinoma, illnesses linked with cell hyperproliferation such as cancers and more particularly breast cancer, prostate cancer, thyroid cancer as well as pancreatic cancer and colorectal cancer, fibroses and more particularly fibrosis of the kidney, fibrosis of the liver, fibrosis of the lung, fibrosis of the skin, also fibrosis of the central nervous system as well as that of the nose and fibrosis induced by chemotherapy, and other therapeutic fields such as, for example, cephaleas including cephalea associated with hypophyseal tumors, pain, panic attacks, chemotherapy, cicatrization of wounds, renal insufficiency resulting from delayed development, obesity and delayed development linked with obesity, delayed uterine development, dysplasia of the skeleton, Noonan's syndrome, sleep apnea syndrome, Graves' disease, polycystic disease of the ovaries, pancreatic pseudocysts and ascites, leukemia, meningioma, cancerous cachexia, inhibition of H pylori, psoriasis, as well as Alzheimer's disease. Osteoporosis can also be mentioned.

The Applicants found that the compounds of general formula described hereafter have an affinity and a selectivity for the somatostatin receptors. As somatostatin and its peptide analogues often have a poor bioavailability by oral route and a low selectivity (Robinson, C., *Drugs of the Future*, 1994, **19**, 992; Reubi, J.C. et al.,

TIPS, 1995, **16**, 110), said compounds, non-peptide agonists or antagonists of somatostatin, can be advantageously used to treat pathological states or illnesses as presented above and in which one (or more) somatostatin receptors are involved. Preferably, said compounds can be used for the treatment of acromegalia, hypophyseal adenomas or endocrine gastroenteropancreatic tumors including carcinoid syndrome.

Therefore a subject of the present invention is the compounds of general formula



I

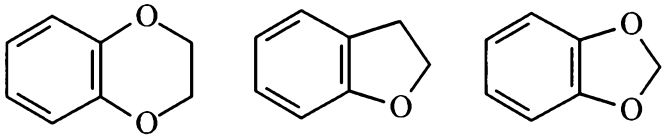
in racemic, enantiomeric form or all combinations of these forms, in which:

R_1 represents a linear or branched $(C_1\text{-}C_{16})$alkyl, alkenyl, alkynyl, $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $-(CH_2)_m\text{-}Z_{12}$ radical in which

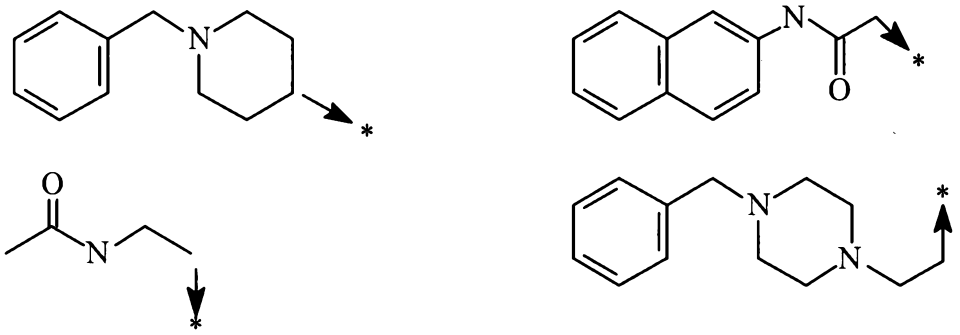
Z_{11} represents a $(C_1\text{-}C_6)$alkyl or aryl optionally substituted,

Z_{12} represents cyano, cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, optionally substituted $(C_3\text{-}C_7)$ heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl,

or Z_{12} represents a radical of formula

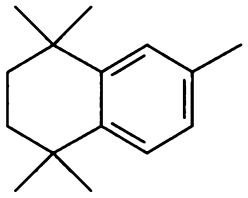


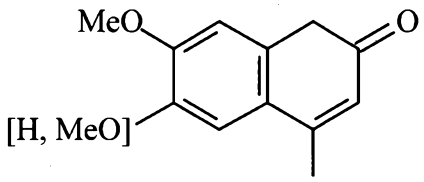
or R_1 represents a radical of formula



R_2 represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3;

R_3 represents the hydrogen atom, an optionally substituted alkyl, alkenyl, alkynyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl radical, or a radical of formula $-C(Y)-NHX_1$, $-(CH_2)_n-C(O)X_2$, SO_2X_3 or



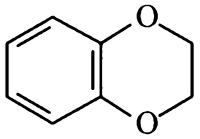


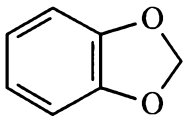
X_1 represents a linear or branched (C_1-C_{15})alkyl, alkenyl, alkynyl, $-(CH_2)_m-Y-Z_{21}$ or $-(CH_2)_pZ_{22}$ radical in which

Z_{21} represents a (C_1-C_6)alkyl

Z_{22} represents cyclohexenyl, indanyl, *bis*-phenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl or heteroaryl optionally substituted,

or Z_{22} represents a radical of formula



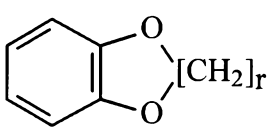


X_2 represents a linear or branched (C_1-C_{10})alkyl radical, an alkenyl radical optionally substituted by a phenyl radical (the phenyl radical being itself optionally substituted), an alkynyl radical, or a radical of formula $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ or $-(CH_2)_p-U-Z_{24}$ in which

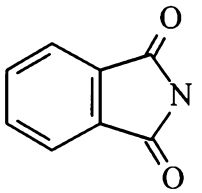
Z_{23} represents a (C_1-C_6)alkyl or aryl optionally substituted;

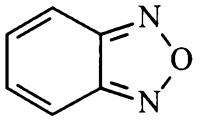
Z_{24} represents alkyl, cyclohexenyl, *bis*-phenyl, (C_3-C_7)cycloalkyl optionally substituted, (C_3-C_7)heterocycloalkyl, cyano, amino, mono or di-alkylamino, or aryl or heteroaryl optionally substituted,

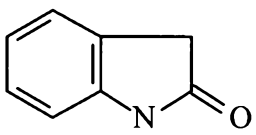
or Z_{24} represents a radical of formula

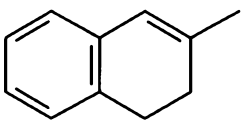


r = 1,2 or 3

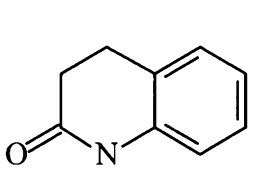
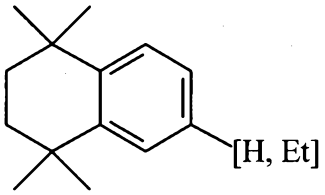


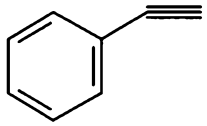
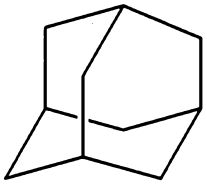






or X_2 represents a radical represented below:

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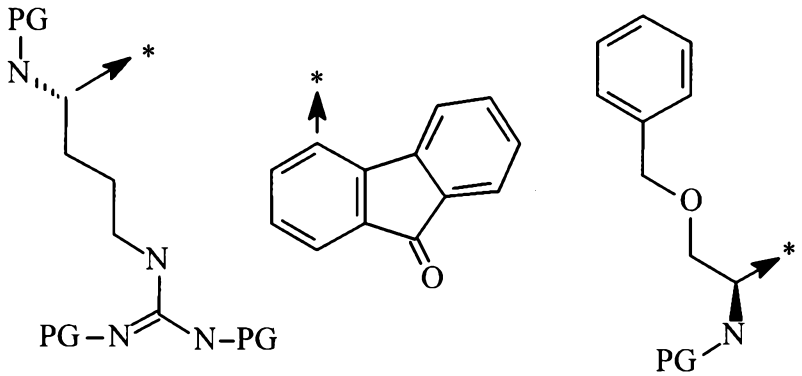
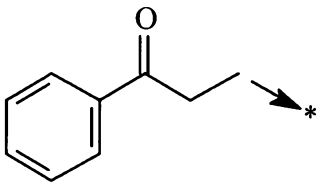
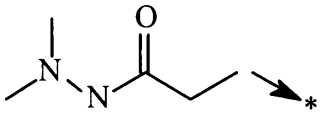
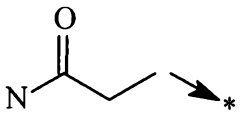
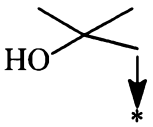
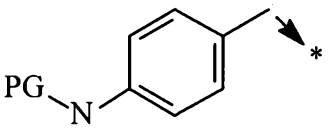
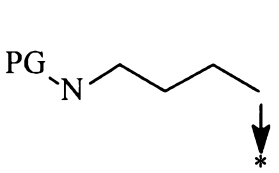
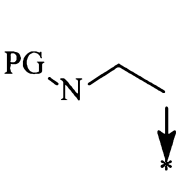
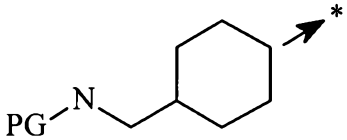




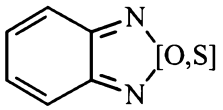




where the protective group (PG) represents H or *tert*-butyloxycarbonyl;

X_3 represents a linear or branched (C_1-C_{10})alkyl radical, an alkenyl radical optionally substituted by a phenyl radical (the phenyl radical being itself optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ in which

Z_{25} represents aryl or heteroaryl optionally substituted,

or X_3 represents a radical of formula



optionally substituted by one or more halo radicals

identical or different;

Y represents an oxygen or sulphur atom;

W represents an oxygen, sulphur or SO_2 atom;

U represents a covalent bond or the oxygen atom;

n is an integer from 0 to 4;

m is an integer from 1 to 6;

p is an integer from 0 to 6;

q is an integer from 0 to 2,

or their addition salts with pharmaceutically acceptable mineral or organic acids, except for the compounds of general formula I in which R_1 represents the alkyl, alkenyl or benzyl radical, R_2 represents optionally substituted benzyloxy and R_3 represents aralkyl.

A more particular subject of the invention is the products of general formula I as defined above, characterized in that

i) the substituent or substituents which can be carried by the aryl radicals represented by Z_{11} and Z_{12} and heteroaryl represented by Z_{12} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phenyl, phenoxy, aminosulphonyl radicals;

ii) the substituent or substituents which can be carried by the heterocycloalkyl radical represented by Z_{12} are chosen independently from the oxy and alkyl radicals;

iii) the substituent or substituents which can be carried by the aryl and heteroaryl radicals represented by Z_{22} are chosen independently from the fluoro, chloro, bromo,

iodo, alkyl, alkenyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, aminosulphonyl, piperidinosulphonyl, mono- or di-alkylamino, -C(O)-O-alkyl, -C(O)-alkyl, or phenyl, phenoxy, phenylthio, benzyloxy radicals, the phenyl radical being able to be substituted;

iv) the substituent or substituents which can be carried by the aryl radicals represented by Z_{23} and Z_{24}, cycloalkyl and heteroaryl represented by Z_{24} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, $OCHF_2$, SCF_3, nitro, cyano, azido, hydroxy, -C(O)O-alkyl, -O-C(O)-alkyl, -NH-C(O)-alkyl, alkylsulphonyl, mono- or di-alkylamino, amino, aminoalkyl, pyrrolyl, pyrrolydinyl or the phenyl, phenoxy, phenylthio, benzyl, benzyloxy radicals the aryl radical of which is optionally substituted by one or more alkyl, CF_3 or halo radicals;

v) the substituent or substituents which can be carried by the aryl and heteroaryl radicals represented by Z_{25} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, nitro, cyano, -NH-C(O)-alkyl, alkylsulphonyl, amino, mono- and di-alkylamino, phenyl, pyridino radicals;

vi) the substituent which can be carried by the alkyl radical represented by R_3 is the cyano radical.

vii) the substituent or substituents which can be carried by the aralkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, nitro, cyano, -C(O)O-alkyl, alkylsulphonyl, thiadiazolyl radicals, or the phenyl and phenoxy radicals the phenyl radical of which is optionally substituted by one or more halo radicals.

viii) the substituent or substituents which can be carried by the heteroarylalkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo or nitro radicals.

In the definitions indicated above, the expression halo represents the fluoro, chloro, bromo or iodo radical, preferably chloro, fluoro or bromo. The expression alkyl (when it is not specified otherwise), preferably represents a linear or branched alkyl radical having 1 to 6 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl, pentyl or amyl, isopentyl, neopentyl, hexyl or isohexyl radicals. Among the alkyl radicals containing 1 to 15 carbon atoms, there can be mentioned the alkyls as defined above but also the heptyl, octyl, nonyl, decyl, dodecyl, tridecyl or pentadecyl radicals.

By alkenyl, when it is not specified otherwise, is understood a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one unsaturation (double bond), such as for example vinyl, allyl, propenyl, butenyl or pentenyl. By alkynyl, when it is not specified otherwise, is understood a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one double unsaturation (triple bond) such as for example an ethynyl, propargyl, butynyl or pentynyl radical.

The term cycloalkyl designates a monocyclic carbon system comprising 3 to 7 carbon atoms, and preferably the cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl rings. The expression heterocycloalkyl designates a saturated cycloalkyl containing 2 to 7 carbon atoms and at least one heteroatom. This radical can contain several identical or different heteroatoms. Preferably, the heteroatoms are chosen from oxygen, sulphur or nitrogen. As examples of a heterocycloalkyl, there can be mentioned the pyrrolidine, pyrrolidinone, imidazolidine, pyrrazolidine, isothiazolidine, thiazolidine, isoxazolidine, piperidine, piperazine or morpholine ring.

The alkoxy radicals can correspond to the alkyl radicals indicated above such as for example the methoxy, ethoxy, propyloxy or isopropyloxy radicals but also linear, secondary or tertiary butoxy, pentyloxy. The term lower alkylthio preferably designates the radicals in which the alkyl radical is as defined above such as for example methylthio, ethylthio. The term alkylsulphonyl preferably designates the radicals in which the alkyl radical is as defined above.

The expression aryl represents an aromatic radical, constituted by a condensed ring or rings, such as for example the phenyl or naphthyl radical. The expression heteroaryl designates an aromatic radical, constituted by a condensed ring or rings, with at least one ring containing one or more identical or different heteroatoms chosen from sulphur, nitrogen or oxygen. As an example of a heteroaryl radical, there can be mentioned the thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, oxazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, quinoxalinyl, benzothienyl, benzofuryl, indolyl, benzoxadiazoyl radicals.

The terms mono- and di-alkylamino preferably designate the radicals in which the alkyl radicals are as defined above, such as for example methylamino, ethylamino, dimethylamino, diethylamino or (methyl)(ethyl)amino.

The symbol -> * corresponds to the attachment point of the radical. When the attachment site is not specified on the radical, this signifies that the attachment is

carried out on one of the sites which are available to this radical for such an attachment.

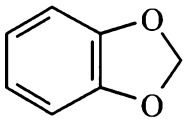
A more particular subject of the present invention is the compounds of general formula I as defined above in which:

R_1 represents a linear or branched $(C_1\text{-}C_6)$alkyl radical, the $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $-(CH_2)_m\text{-}Z_{12}$ radical in which

Z_{11} represents a $(C_1\text{-}C_6)$alkyl,

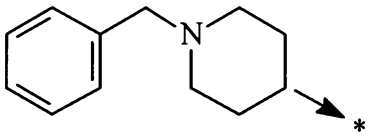
Z_{12} represents *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl optionally substituted, or aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy radicals,

or Z_{12} represents



Y represents the oxygen atom,

or R_1 represents a radical of formula

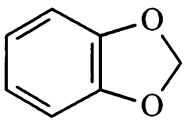


R_2 represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{15})$alkyl radical, or $-(CH_2)_pZ_{22}$ in which

Z_{22} represents cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl or heteroaryl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, –C(O)-O-alkyl, -C(O)-alkyl, or phenyl radicals,

or Z_{22} represents a radical of formula



X_2 represents a linear or branched $(C_1\text{-}C_{10})$alkyl , alkynyl, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $-(CH_2)_p\text{-}U\text{-}Z_{24}$ radical in which

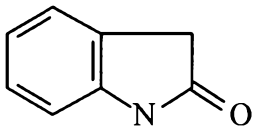
W represents SO_2,

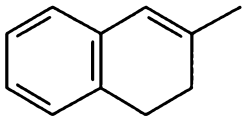
U represents a covalent bond,

Z_{23} represents an aryl radical;

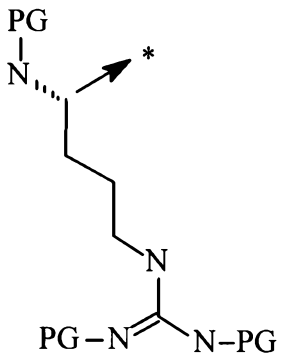
Z_{24} represents cyclohexenyl, *bis*-phenyl, (C_3-C_7)cycloalkyl optionally substituted by an aminoalkyl, or aryl or heteroaryl radical optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, -CF_3, -OCF_3, SCF_3, hydroxy, -O-C(O)-alkyl, mono- or di-alkylamino, amino

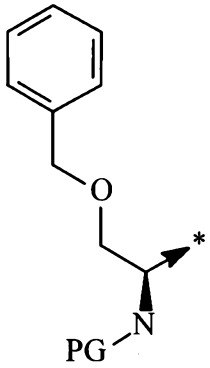
or Z_{24} represents a radical of formula





or X_2 represents





X_3 represents a–$(CH_2)_pZ_{25}$ radical in which Z_{25} represents an aryl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3,

R_3 represents the hydrogen atom, an alkyl, alkenyl, heteroarylalkyl radical optionally substituted or a radical of formula –C(Y)-NHX_1, -C(O)X_2 or SO_2X_3 in which

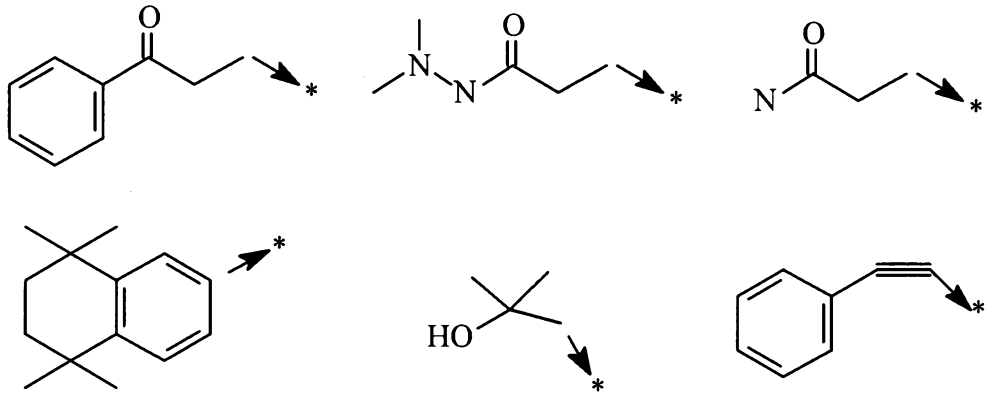
X_1 represents a–$(CH_2)_pZ_{22}$ radical in which

Z_{22} represents an aryl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals;

X_2 represents the vinyl radical substituted by a phenyl, the phenyl radical being itself optionally substituted by one or more halo, or –$(CH_2)_p$-U-Z_{24} radicals in which

Z_{24} represents alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, *bis*-phenyl, amino, mono or di-alkylamino, or aryl or heteroaryl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, hydroxy, CF_3, nitro, amino, mono- and di-alkylamino, pyrrolyl,

or X_2 represents a radical of formula



X_3 represents a linear or branched (C_1-C_{10})alkyl radical, the vinyl radical substituted by a radical (the phenyl radical being itself optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ in which

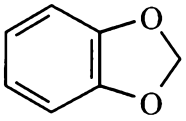
Z_{25} represents aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals.

Preferentially, R_1 represents a linear or branched (C_1-C_6)alkyl radical, the $-(CH_2)_m$-Y-Z_{11} or $-(CH_2)_m$-Z_{12} radical in which

Z_{11} represents a (C_1-C_6)alkyl,

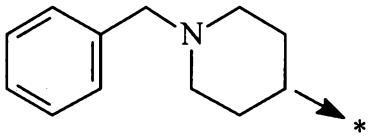
Z_{12} represents naphthyl, morpholino, *bis*-phenyl, pyrrolidinyl substituted by the oxy radical, or the phenyl, piperazinyl, pyridinyl and indolyl radicals which are optionally substituted by one or more substituents chosen independently from the bromo, fluoro, chloro, alkyl, alkoxy, $-CF_3$, $-OCF_3$ radicals;

or Z_{12} represents



Y represents the oxygen atom,

or R_1 represents a radical of formula given below:

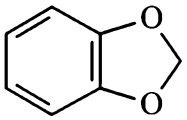


Preferentially, R_2 represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{10})$alkyl, or $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents cyclohexyl, cyclohexenyl, *bis*-phenyl, morpholino, piperidino, mono- or di-alkylamino, -C(O)-O-alkyl, or phenyl, naphthyl or furyl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, –C(O)-O-alkyl, -C(O)-alkyl or phenyl radicals,

or Z_{22} represents a radical of formula



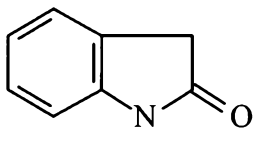
X_2 represents an alkyl, alkynyl, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $-(CH_2)_pZ_{24}$ radical in which

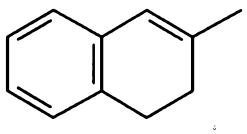
W represents SO_2;

Z_{23} represents the phenyl radical;

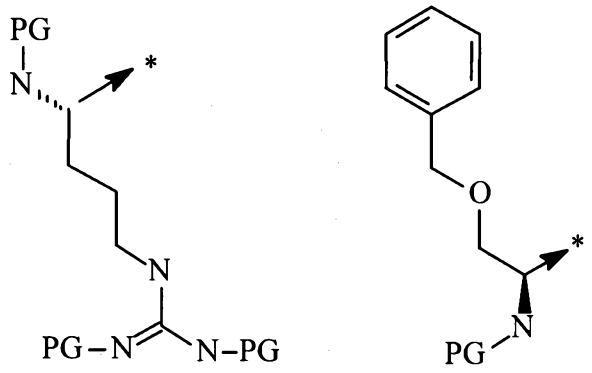
Z_{24} represents cyclohexenyl, *bis*-phenyl, cyclohexyl optionally substituted by an aminoalkyl, or phenyl, naphthyl, benzothienyl, thienyl or indolyl radical optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyl, -NH-C(O)-alkyl, mono- or di-alkylamino, amino, or

Z_{24} represents a radical of formula





or X_2 represents



X_3 represents a $-(CH_2)_pZ_{25}$ radical in which Z_{25} represents the phenyl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3 ,

Preferentially, R_3 represents the hydrogen atom, an alkyl, alkenyl or furyl-methyl radical substituted by one or more nitro radicals, or a radical of formula $-C(Y)-NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

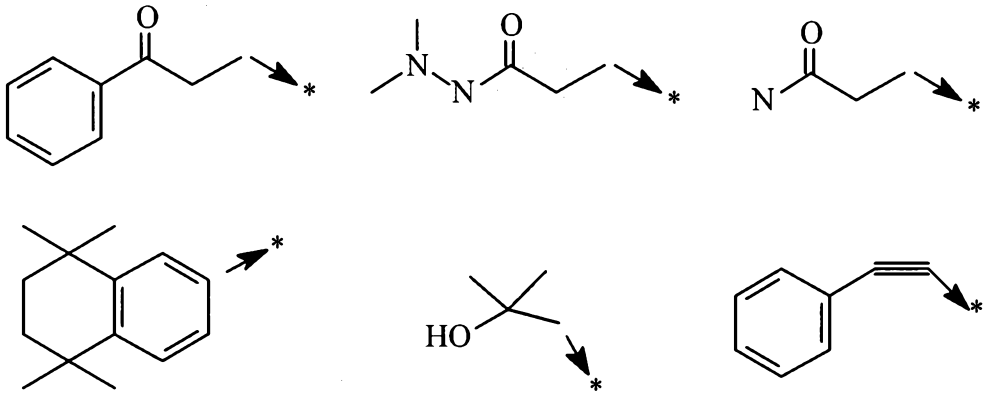
X_1 represents a $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents the phenyl or naphthyl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals,

X_2 represents the vinyl radical substituted by a phenyl radical itself optionally substituted by one or more halo, or $-(CH_2)_p-U-Z_{24}$ radicals in which

Z_{24} represents alkyl, cyclohexyl, tetrahydrofuryl, *bis*-phenyl, amino, mono or di-alkylamino, or phenyl, indolyl, thienyl, pyridinyl, benzothienyl and furyl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, amino, mono- and di-alkylamino, nitro, hydroxy, pyrrolyl

or X_2 represents a radical of formula



X_3 represents a linear or branched (C_1-C_{10})alkyl radical, the vinyl radical substituted by a phenyl, CF_3, or $-(CH_2)_pZ_{25}$ radical in which

Z_{25} represents a phenyl, naphthyl, thienyl, pyrazolyl or thiazolyl radical optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals;

Very preferentially, R_1 represents the $-(CH_2)_mZ_{12}$ radical in which m = 2 and Z_{12} represents *bis*-phenyl or the radical indolyl substituted by one or more substituents chosen independently from the alkyl and alkoxy radicals.

Very preferentially, R_2 represents the radicals of formula $-C(Y)NHX_1$ and $-C(O)X_2$ in which

Y represents S;

X_1 represents a phenyl radical optionally substituted by one or more azido radicals,

X_2 represents $-(CH_2)_pZ_{24}$ in which

p is equal to 1, 2 or 3,

Z_{24} represents cyclohexyl, or phenyl or benzothienyl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo or $-CF_3$.

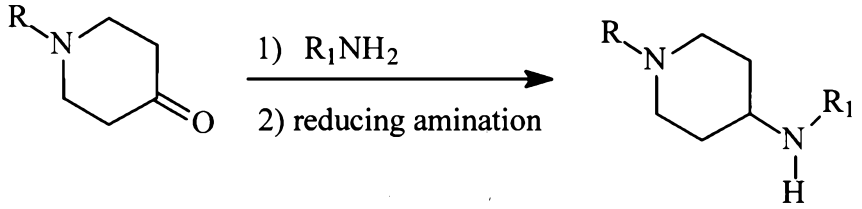
Very preferentially, R_3 represents the hydrogen atom or the methyl radical.

The compounds according to the invention can be prepared in solid or liquid phase.

A) <u>Syntheses in liquid phase *via* the N-substituted piperidone</u>

A1) Reducing amination

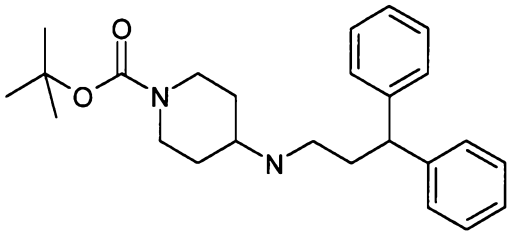
It is carried out according to the following stage:



in which R represents methyl or Boc and R_1 has the meaning indicated above.

The general procedure is as follows: the reducing amination (Abdel-Magid, A.F.; Maryanoff, C.A.; Carson, K.G. *Tetrahedron Lett.* **1990**, *31*, 5595-5598; Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D., *J. Org. Chem.* **1996**, *61*, 3849-3862) of the N-substituted piperidone is carried out in anhydrous chlorinated solvents such as dichloroethane in the presence of a primary amine (1.1 to 1.5 eq.), a reducing agent such as sodium triacetoxyborohydride (1.1 to 1.5 eq.) and acetic acid (10 % by mass relative to the N-substituted piperidone). The reaction mixture is stirred for 1 to 4 hours at ambient temperature. In certain cases, a solution of soda (0.1 M) is added and the mixture is stirred for 20 to 90 minutes. If not, the reaction mixture is washed with a saturated solution of sodium bicarbonate, with sodium chloride, dried over magnesium sulphate, filtered and concentrated. The desired product is purified by flash chromatography on silica gel.

<u>Preparation 1</u>: *tert*-butyl 4-[(3,3-diphenylpropyl)amino]-1-piperidine carboxylate ($C_{25}H_{34}N_2O_2$, M = 394.56)

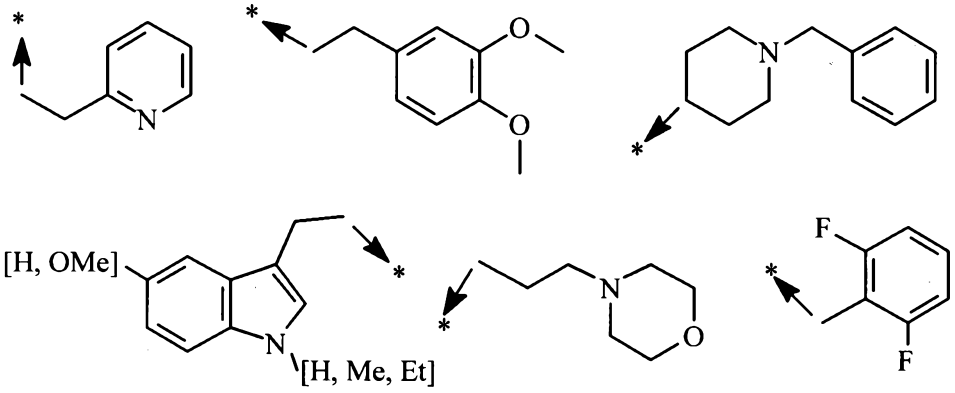


3,3-diphenylpropylamine (5.8 g, 27.5 mmol), sodium triacetoxyborohydride (6.36 g, 30 mmol) and 0.5 ml of acetic acid are added to 5 g (25 mmol) of N-Boc-piperidone in 100 ml of dry dichloroethane. The turbid yellow solution is stirred at ambient temperature for 1 hour. 50 ml of a soda solution (0.1 M) is then added and the mixture is stirred for 30 minutes. The organic phase is washed with a saturated

solution of sodium bicarbonate, with sodium chloride, dried over magnesium sulphate, filtered and concentrated in order to produce 10 g of a yellow solid. This solid is purified by flash chromatography on silica gel eluting with a heptane/ethyl acetate mixture (4/1, 3 /1, 2/1 then 1/1) then with pure ethyl acetate. The fractions are concentrated under vacuum in order to produce 5.6 g (yield = 57 %) of a pale yellow solid.

NMR ^{1}H (CD_3OD, 400 MHz) δ: 7.27 (m, 8H); 7.16 (m, 2H); 4 (dd, J = 6.4 and 14Hz, 3H); 2.73 (m, 2H); 2.55 (m, 3H); 2.26 (q, J = 7.6Hz, 2H); 1.78 (d, J = 12Hz, 2H); 1.45 (s, 9H); 1.15 (qd, J = 4.4 and 12.8Hz, 2H). MS/LC: m/z = 395.2 (M+H).

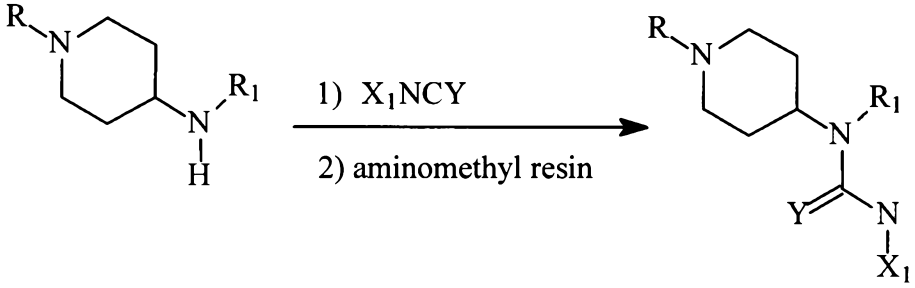
A series of 4-aminosubstituted-1-piperidine was prepared according to this procedure with the following other R_1 groups:



A2) Functionalization of piperidines

A2a) Syntheses of ureas and thioureas

The syntheses of ureas and thioureas are implemented according to the procedure described in the literature (Kaldor, S.W.; Siegel, M.G.; Fritz, J.E.; Dressman, B.A.; Hahn, P.J. *Tetrahedron Lett.* **1996**, *37*, 7193-7196; Kaldor, S.W.; Fritz, J.E.; Tang, J.; McKinney, E.R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041-3044; Booth, R.J.; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886; Flynn, D.L.; Crich, J.Z.; Devraj, R.V.; Hockerman, S.L.; Parlow, J.J.; South, M.S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874-4881) according to the following diagram:

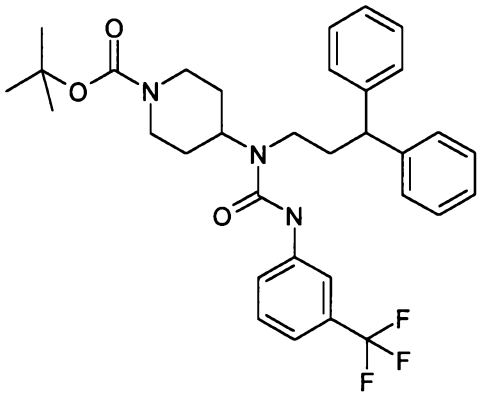


in which R represents methyl or Boc and X_1 and Y have the meaning indicated above. It should be noted that in the case where R represents Boc, the product thus obtained is a final product corresponding to formula I according to the invention but can also be used as a synthesis intermediate.

The general procedure is as follows: the isocyanate or the isothiocyanate (1.1 to 1.5 eq.) is added to the 4-aminosubstituted-1-piperidine in aprotic solvents such as dichloromethane, tetrahydrofuran or dimethylformamide and the mixture is stirred for 45 minutes to 18 hours at ambient temperature. The aminomethyl resin (Novabiochem, 1.33 mmol/g, 0.2 to 1 eq.) is added and the mixture is stirred for 45 minutes to 18 hours. In certain cases, basic ion exchange resin such as IRA-68 (Gayo, L.M.; Suto, M.J. *Tetrahedron Lett.* **1997**, *38*, 513-516) can be added. The resins are filtered and the filtrate is concentrated. Other purifications on silica gel or basic alumina cartridges (500 mg, Interchim) can optionally be carried out.

Example A2a: *tert*-butyl-4-((3,3-diphenylpropyl) {[3-(trifluoro methyl) anilino] carbonyl}amino)-1-piperidine carboxylate

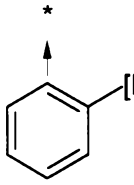
($C_{33}H_{38}F_3N_3O_3$, M = 581.68)



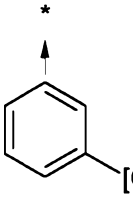
246 mg (1.32 mmol) of 3-(trifluoromethyl)phenyl isocyanate is added to a solution of *tert*-butyl 4-[(3,3-diphenylpropyl)amino]-1-piperidine carboxylate (470 mg, 1.2 mmol) in 5 ml of dichloromethane. The solution is agitated for 45 minutes, and the aminomethyl resin (180 mg, 0.36 mmol) is added and the reaction medium is again placed on an orbital shaker for 45 minutes. The resin is filtered and washed with dichloromethane. The filtrate is concentrated *in vacuo* in order to produce 610 mg (yield = 87 %) of a white foam.

NMR ^{1}H (CD_3OD, 400 MHz) δ: 7.71 (s, 1H); 7.57 (d, 1H); 7.43 (t, 1H); 7.26 (m, 10H); 7.15 (m, 1H); 4.1 (m, 3H); 3.97 (dd, J = 7.6 and 10Hz, 1H); 3.17 (m, 2H); 2.75 (m, 2H); 2.35 (m, 2H); 1.65 (d, J = 12Hz, 2H); 1.46 (s, 9H, *t*butyl group); 1.39 (dd, J = 2.4 and 10.8Hz, 2H); 1.29 (s, 1H). MS/LC: m/z = 582 (M+H).

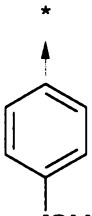
For the R_1 groups as illustrated in point A1 above, the X_1 groups which can be envisaged for the synthesis of ureas (Y = O) according to the above procedure, are the following:



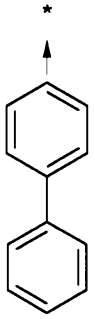
[H, Br, F, Cl, OMe, SMe, OEt, CF_3, Me, Et, nPr, iPr, tBu, Ph, NO_2, CN]

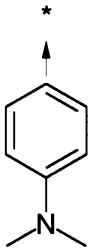


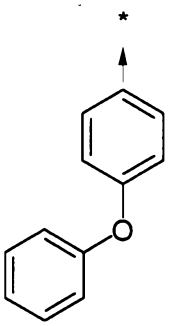
[OMe, COMe, CF_3, Br, F, Cl, Me, Et, NO_2, CN, SMe]

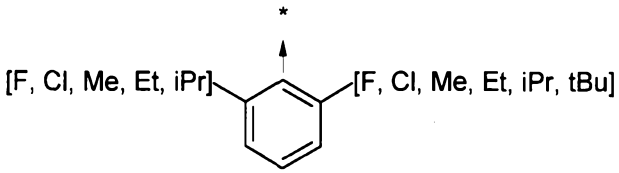


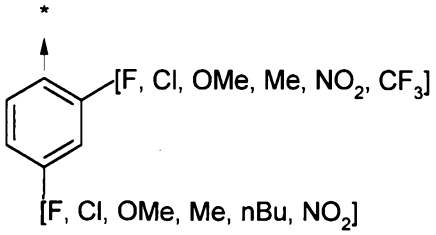
[SMe, CO_2Et, OCF_3, OnBu, Br, F, Cl, OMe, CF_3, Me, NO_2, OEt, Et, iPr, nBu, CN]

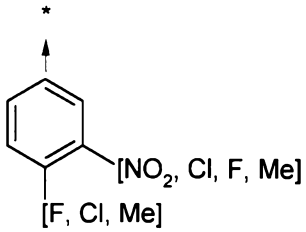


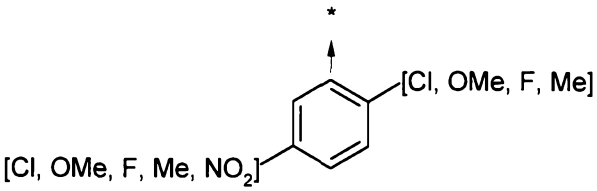


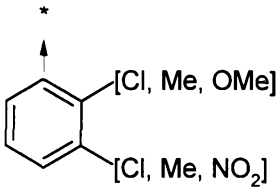


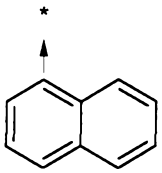

*
[F, Cl, Me, Et, iPr]
[F, Cl, Me, Et, iPr, tBu]


*
[F, Cl, OMe, Me, NO2, CF3]
[F, Cl, OMe, Me, nBu, NO2]


*
[NO2, Cl, F, Me]
[F, Cl, Me]


*
[Cl, OMe, F, Me]
[Cl, OMe, F, Me, NO2]


*
[Cl, Me, OMe]
[Cl, Me, NO2]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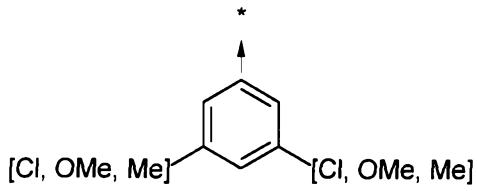
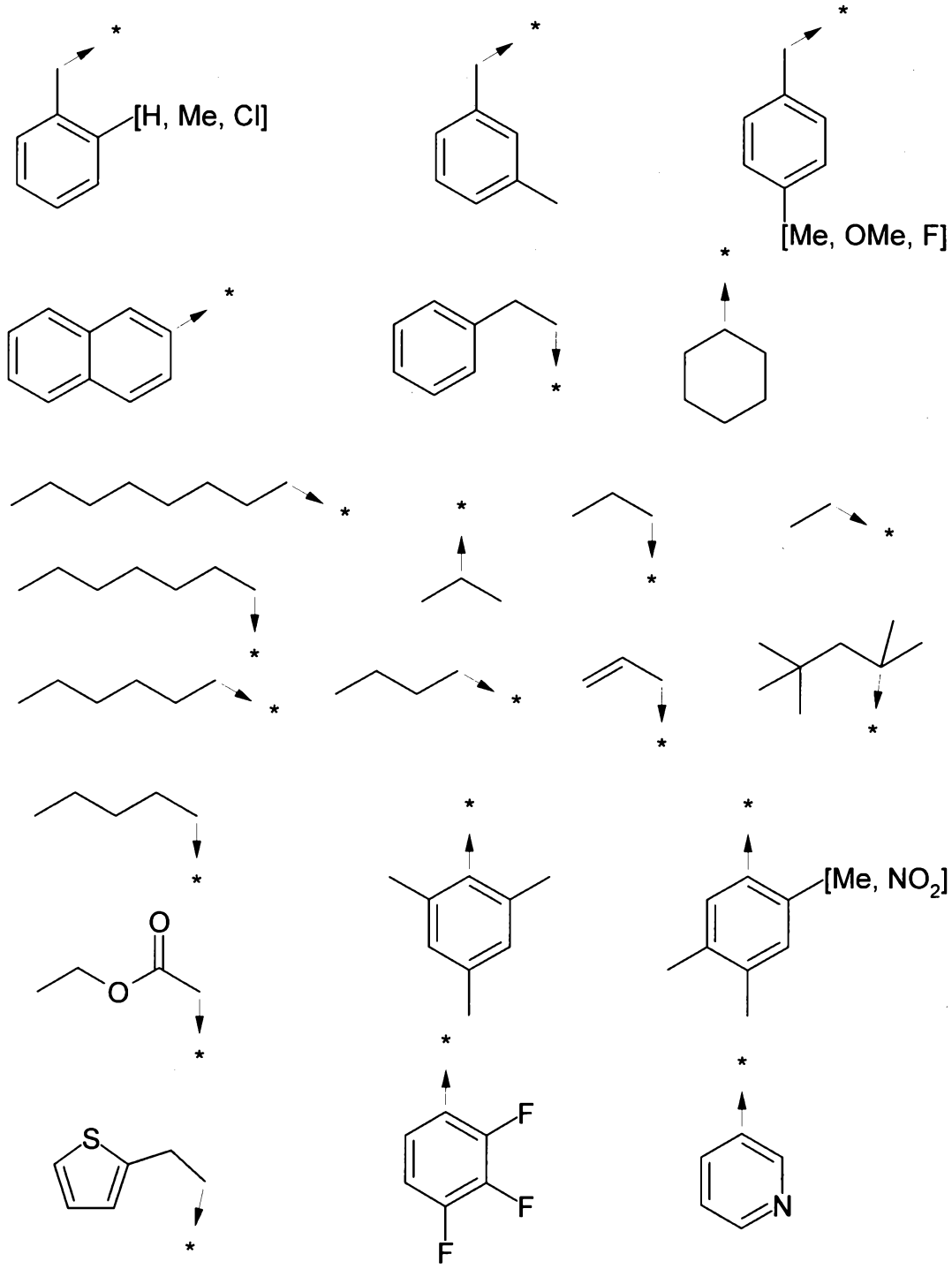
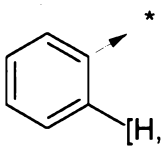
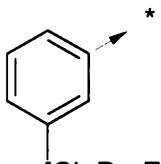

*
[Cl, OMe, Me]
[Cl, OMe, Me]


[H, Me, Cl]
[Me, OMe, F]
O
O
S
F
F
F
N
[Me, NO2]

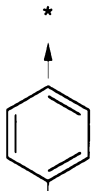
For the R_1 groups as illustrated in point A1 above, the X_1 groups which can be envisaged for the synthesis of thioureas (Y = S) according to the above procedure, are the following:



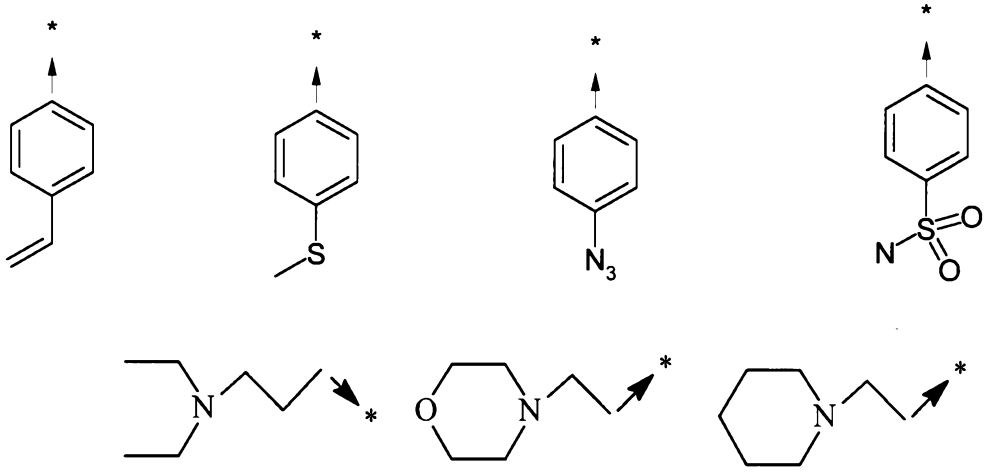
[H, Cl, Br, F, I, OMe, SMe, OEt, CF_3, OCF_3, NO_2, CN, Me, Et, iPr, Ph]

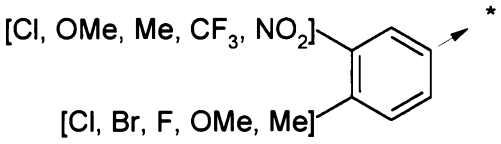


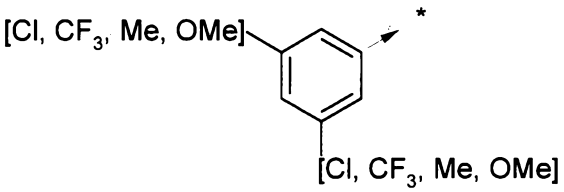
[Cl, Br, F, I, OMe, SMe, CF_3, OCF_3, NO_2, CN, Me, Et, iPr, OCH_2Ph]

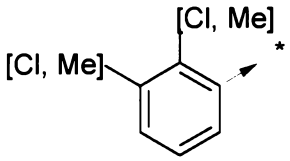


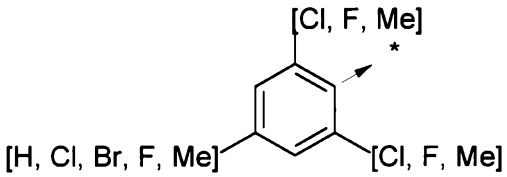
[Cl, Br, F, I, OMe, OEt, CF_3, OCF_3, NO_2, CN, Me, Et, iPr, nBu, tBu, NMe_2, NEt_2]

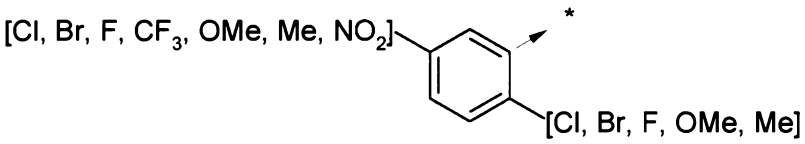


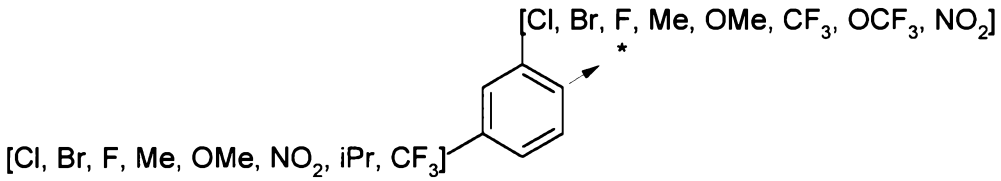

[Cl, OMe, Me, CF3, NO2]
[Cl, Br, F, OMe, Me]
*

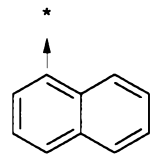

[Cl, CF3, Me, OMe]
[Cl, CF3, Me, OMe]
*

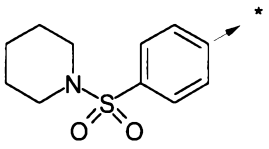

[Cl, Me]
[Cl, Me]
*

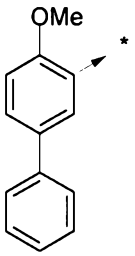

[Cl, F, Me]
*
[H, Cl, Br, F, Me]
[Cl, F, Me]

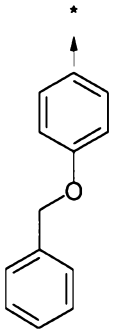

[Cl, Br, F, CF3, OMe, Me, NO2]
*
[Cl, Br, F, OMe, Me]

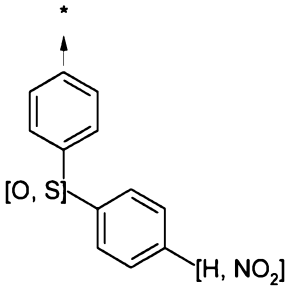

[Cl, Br, F, Me, OMe, CF3, OCF3, NO2]
*
[Cl, Br, F, Me, OMe, NO2, iPr, CF3]

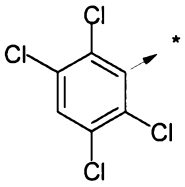


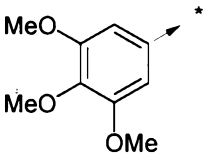

N
S
O
O

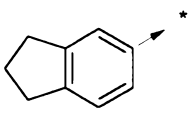

OMe

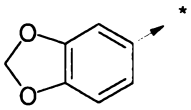

O

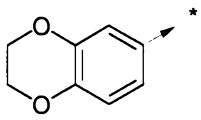

[O, S]
[H, NO2]

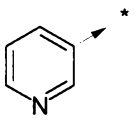

Cl
Cl
Cl
Cl

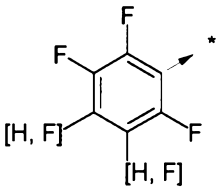

MeO
MeO
OMe

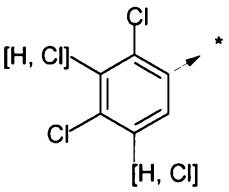


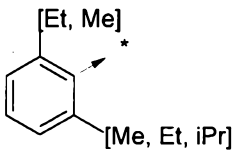

O
O

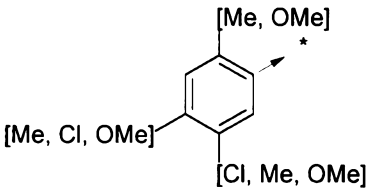

O
O

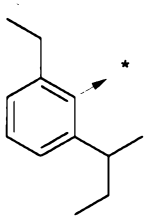

N

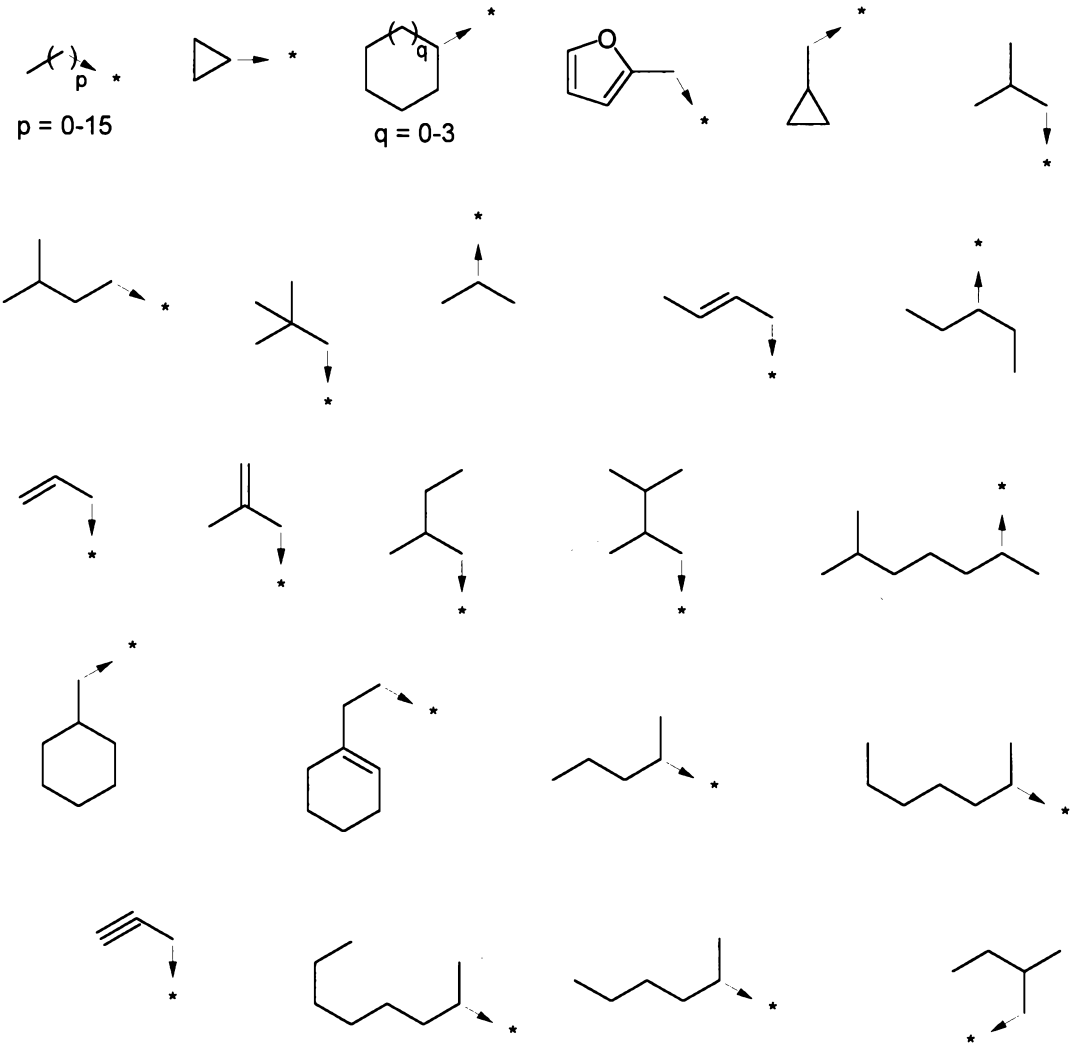

F
F
[H, F]
F
[H, F]

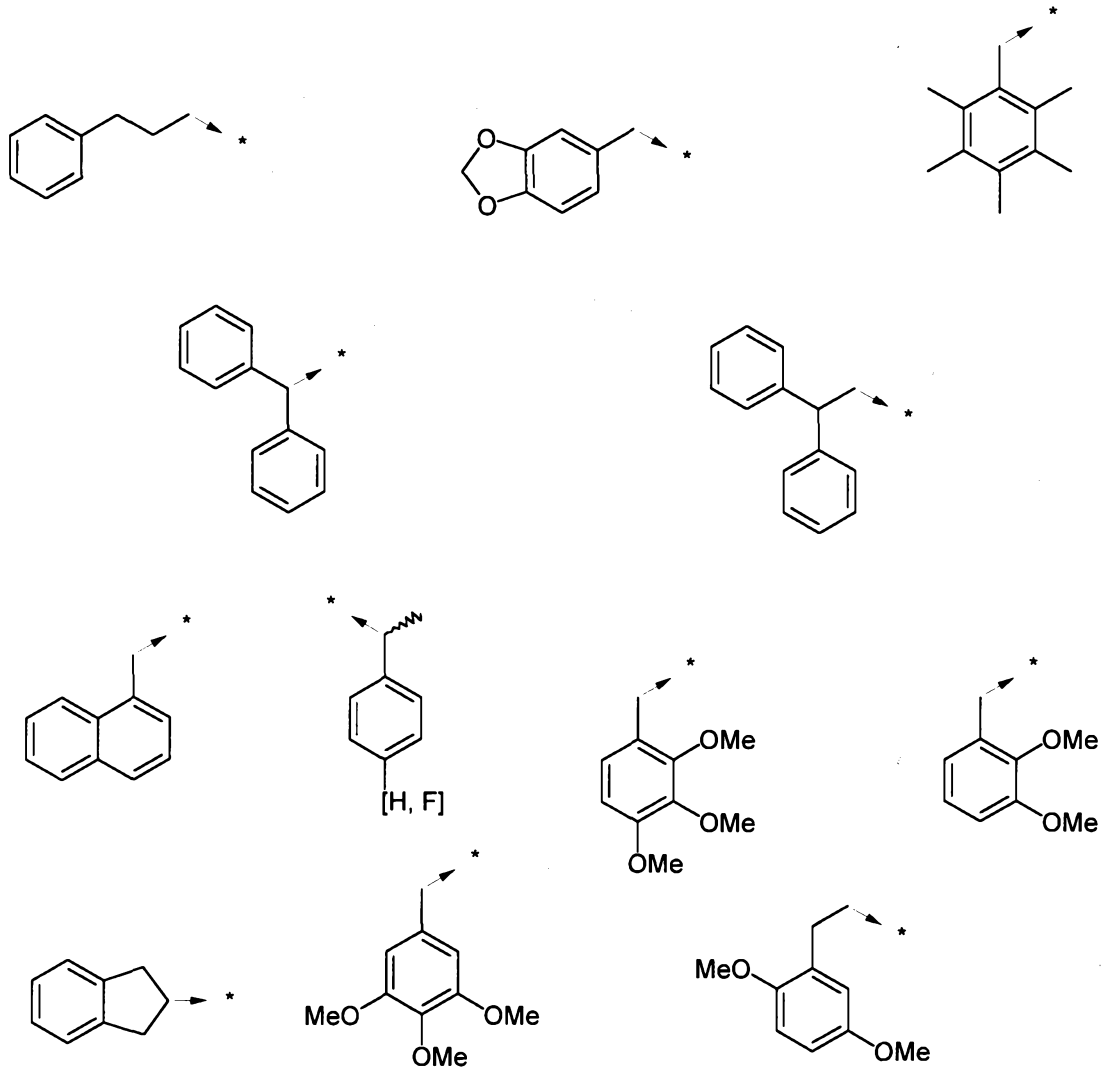

Cl
[H, Cl]
Cl
[H, Cl]


[Et, Me]
[Me, Et, iPr]


[Me, OMe]
[Me, Cl, OMe]
[Cl, Me, OMe]

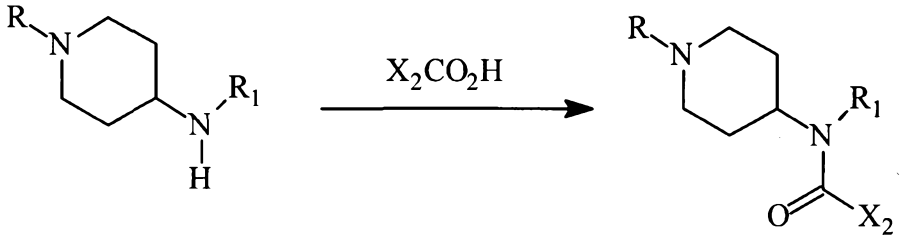



p = 0-15
q = 0-3
O
[H, Cl, OMe, F, Me]
O
MeO
MeO
[Cl, F, OMe, Me]
[Cl, OMe]
[Cl, OMe, Me]
[F, Cl, OMe, Me]
Cl
Cl
[H, Cl, Me]



A2b) Synthesis of amides from carboxylic acids

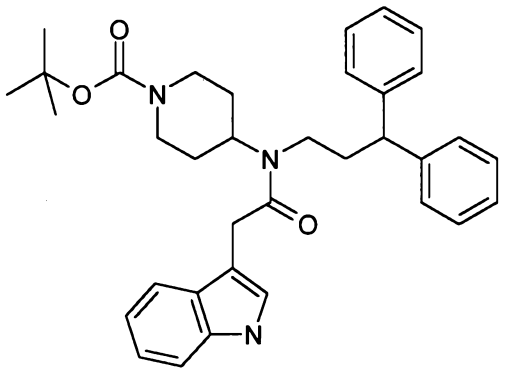
The syntheses of amides from carboxylic acids are implemented according to the following reaction diagram:



in which R represents methyl or Boc and X_2 has the meaning indicated above. It should be noted that in the case where R represents Boc, the product thus obtained is a final product corresponding to formula I according to the invention but can also be used as a synthesis intermediate.

The general procedure is as follows: carboxylic acid (1.1 to 2.5 eq.) dissolved in an anhydrous aprotic solvent such as dichloromethane, dimethylformamide or tetrahydrofuran is activated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide bonded on resin (P-EDC, Novabiochem, 2.33 mmol/g, 1.3 to 3 eq.) (Desai, M.C.; Stephens Stramiello, L.M. *Tetrahedron Lett.* **1993**, *34*, 7685-7688). This mixture is stirred for 5 to 30 minutes at ambient temperature. 4-aminosubstituted-1-piperidine dissolved beforehand in an anhydrous aprotic solvent such as dichloromethane, dimethylformamide or tetrahydrofuran is then added and the reaction mixture is stirred at ambient temperature for 1 to 18 hours. In certain cases, basic ion exchange resin (IRA-68, SAX) is added and the mixture is again stirred at ambient temperature for 1 to 18 hours. The resins are filtered on frit or on a basic ion exchange resin cartridge (IRA-68, SAX) or on an alumina cartridge (500 mg, Interchim).

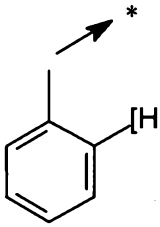
Example A2b: *tert*-butyl 4-{(3,4-dimethoxyphenethyl)[2-(1H-indol-3-yl)acetyl] amino}-1-piperidine carboxylate ($C_{35}H_{41}N_3O_3$, M = 551.74)



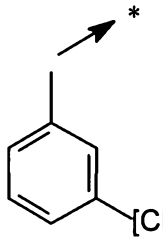
512 mg (1.12 mmol, 1.4 eq.) of P-EDC resin is preswollen in dichloromethane. 2-(1*H*-indol-3-yl)acetic acid (153 mg, 0.875 mmol, 1.1 eq.) is added and the mixture is stirred for 10 minutes. *Tert*-butyl 4-[(3,3-diphenylpropyl)amino]-1-piperidine carboxylate (292 mg, 0.8 mmol) in tetrahydrofuran is added and the reaction medium is stirred overnight. 2 spatulas of basic ion exchange resin IRA-68 are added and the reaction medium is again stirred overnight. The resins are filtered and the filtrate is concentrated under vacuum in order to produce 250 mg (yield = 86 %) of a pale yellow foam.

NMR ^{1}H (CD_3OD, 400 MHz) δ: 7.63 (d, J = 8Hz, 1H); 7.44 (d, J = 8Hz, 1H); 7.36 (d, J = 8Hz, 1H); 7.26 (d, J = 8Hz, 1H); 7.2 (m, 6H); 7.13 (m, 3H); 7.1 (m, 2H); 6.68 (s, 1H); 4-3.75 (m, 4H); 3.65 (s, 1H); 3.2 (m, 1H); 3 (m, 1H); 2.75 (m, 1H); 2.26 (m, 3H); 1.6 (m, 2H); 1.44 (s, 9H); 1.13 (m, 2H). MS/LC: m/z = 552.4 (M+H).

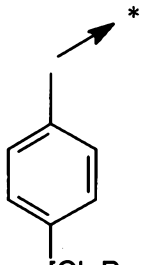
A series of amides was synthesized according to this procedure. The X_2 radicals which can be envisaged are the following:



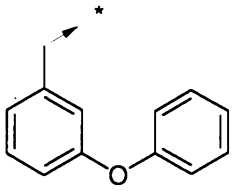
[H, Cl, Br, F, I, OMe, OEt, NO_2, CF_3, OH, Me, OCF_3, SCF_3, $OCHF_2$]

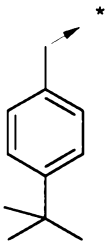


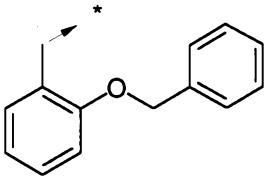
[Cl, Br, F, I, OMe, OEt, NO_2, Me, OH, CF_3, OCF_3, SCF_3, $OCHF_2$]

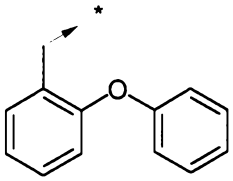


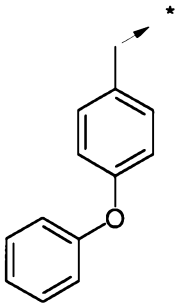
[Cl, Br, F, I, OMe, OEt, OnBu, NO_2, CF_3, Me, OH, NMe_2, Ph, iPr, OCF_3, SCF_3]

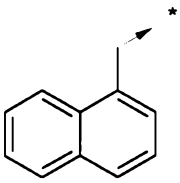


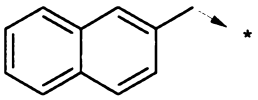


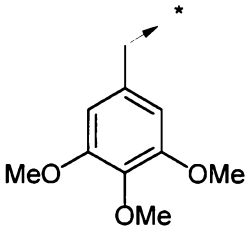


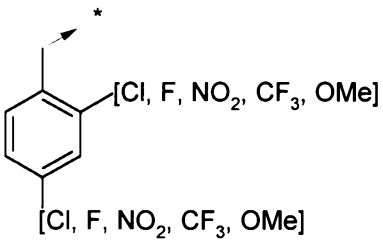


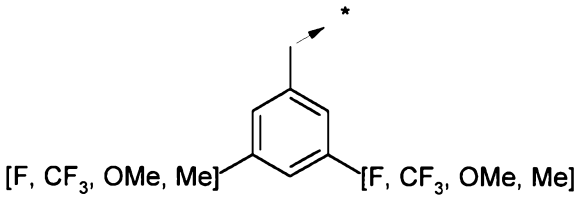


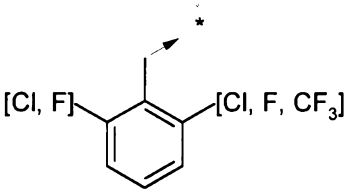





MeO
OMe
OMe


[Cl, F, NO2, CF3, OMe]
[Cl, F, NO2, CF3, OMe]


[F, CF3, OMe, Me]
[F, CF3, OMe, Me]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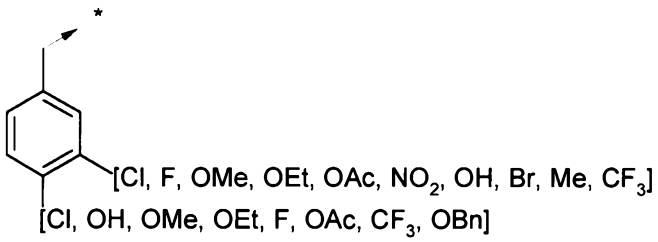
[Cl, F, CF3]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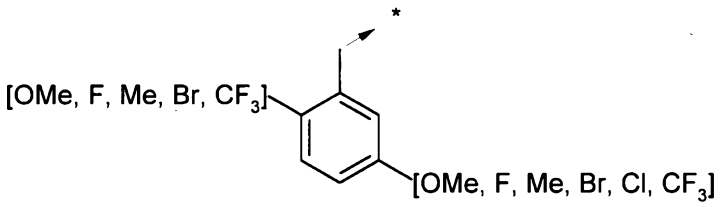
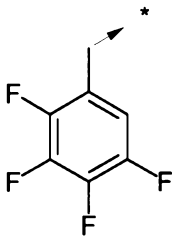
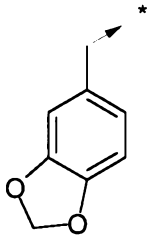
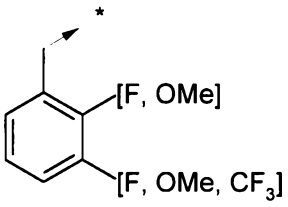
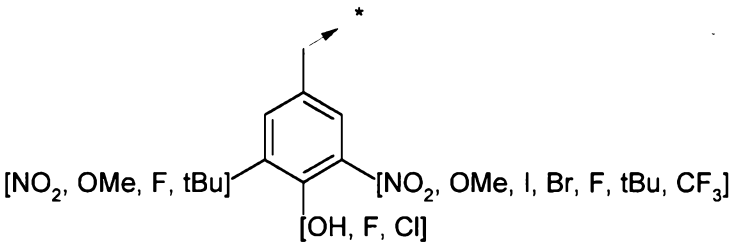
[Cl, OH, OMe, OEt, F, OAc, CF3, OBn]


[OMe, F, Me, Br, CF_3]
[OMe, F, Me, Br, Cl, CF_3]


F
F
F
F


O
O


[F, OMe]
[F, OMe, CF_3]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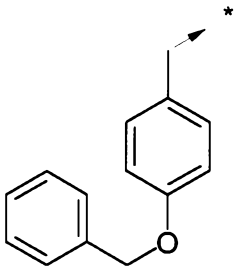
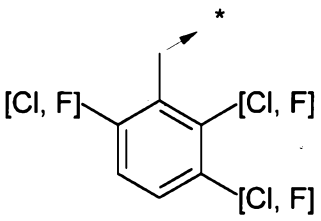
[NO_2, OMe, I, Br, F, tBu, CF_3]
[OH, F, Cl]

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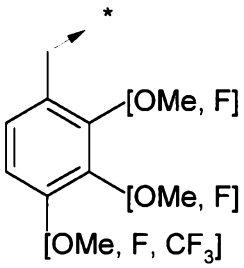
[Cl, F]
[Cl, F]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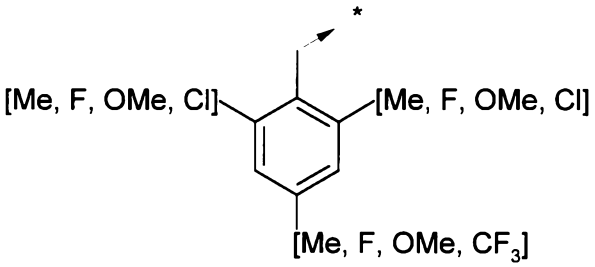
[OMe, F]
[OMe, F, CF3]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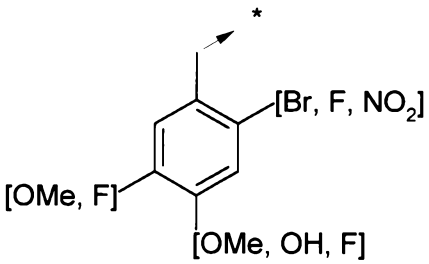
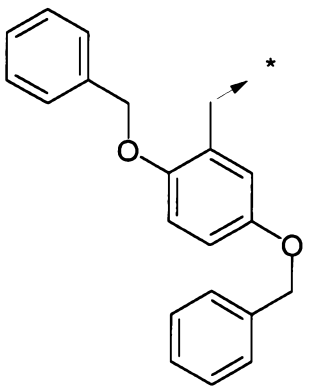
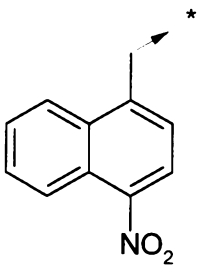
[Me, F, OMe, Cl]
[Me, F, OMe, CF3]


[Br, F, NO2]
[OMe, F]
[OMe, OH, F]

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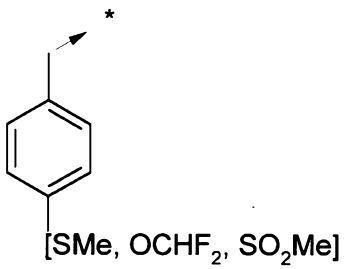
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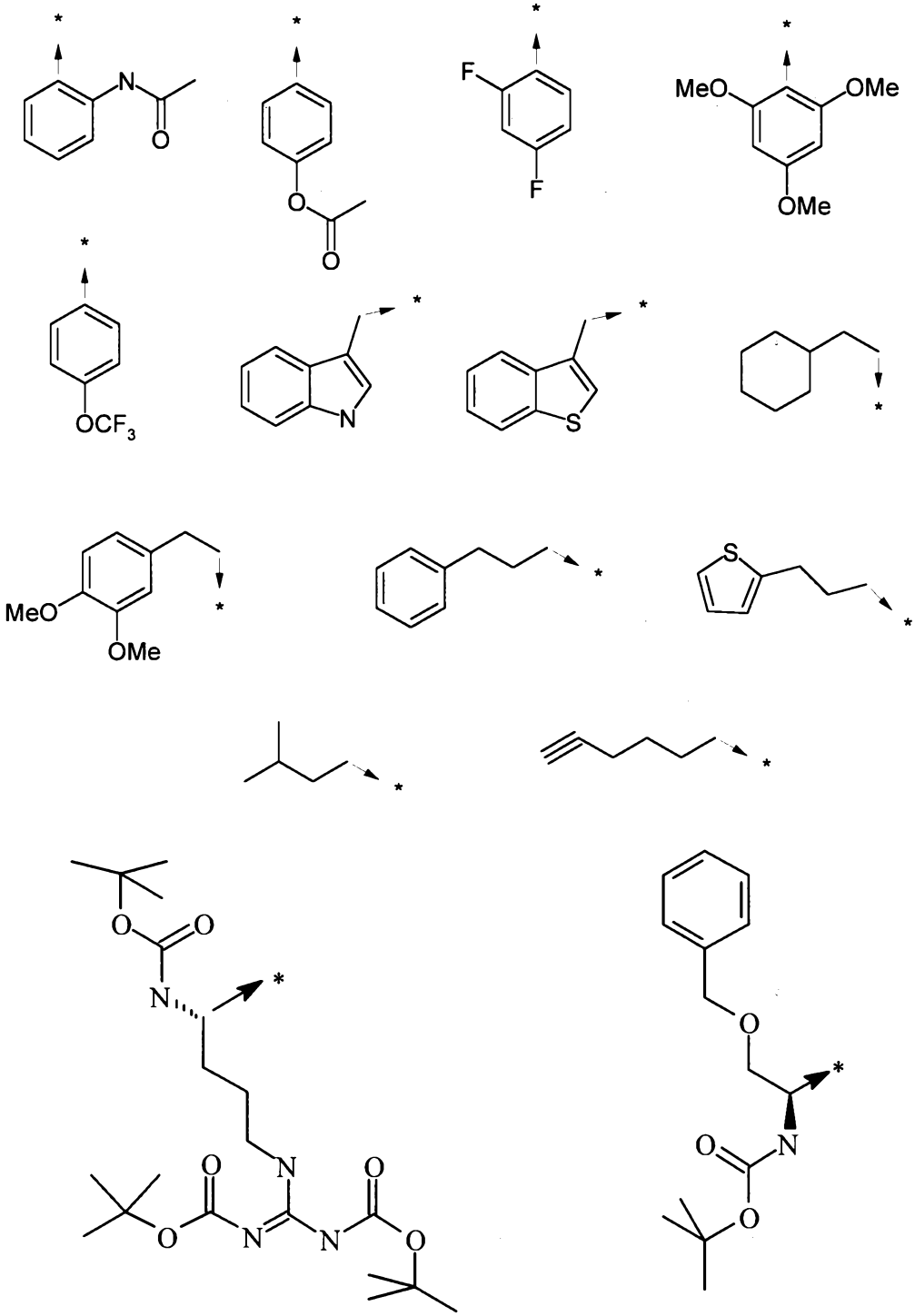
N
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F
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MeO
OMe
OMe
OCF3
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S
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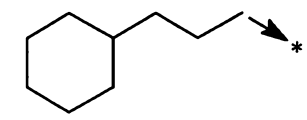

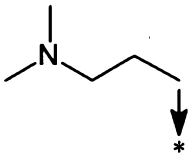

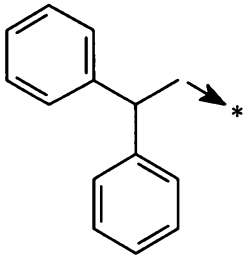

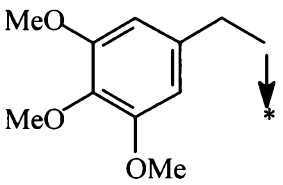
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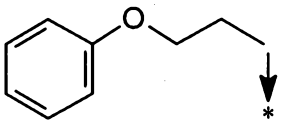
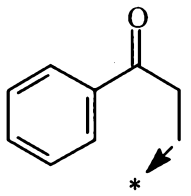
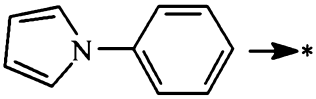
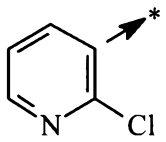
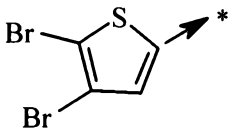
MeO
OMe

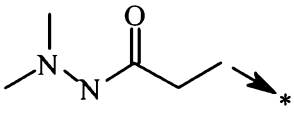


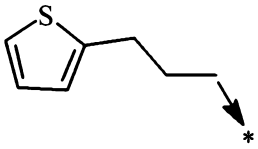


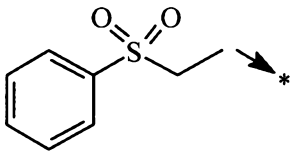


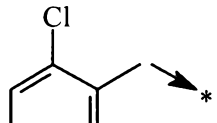


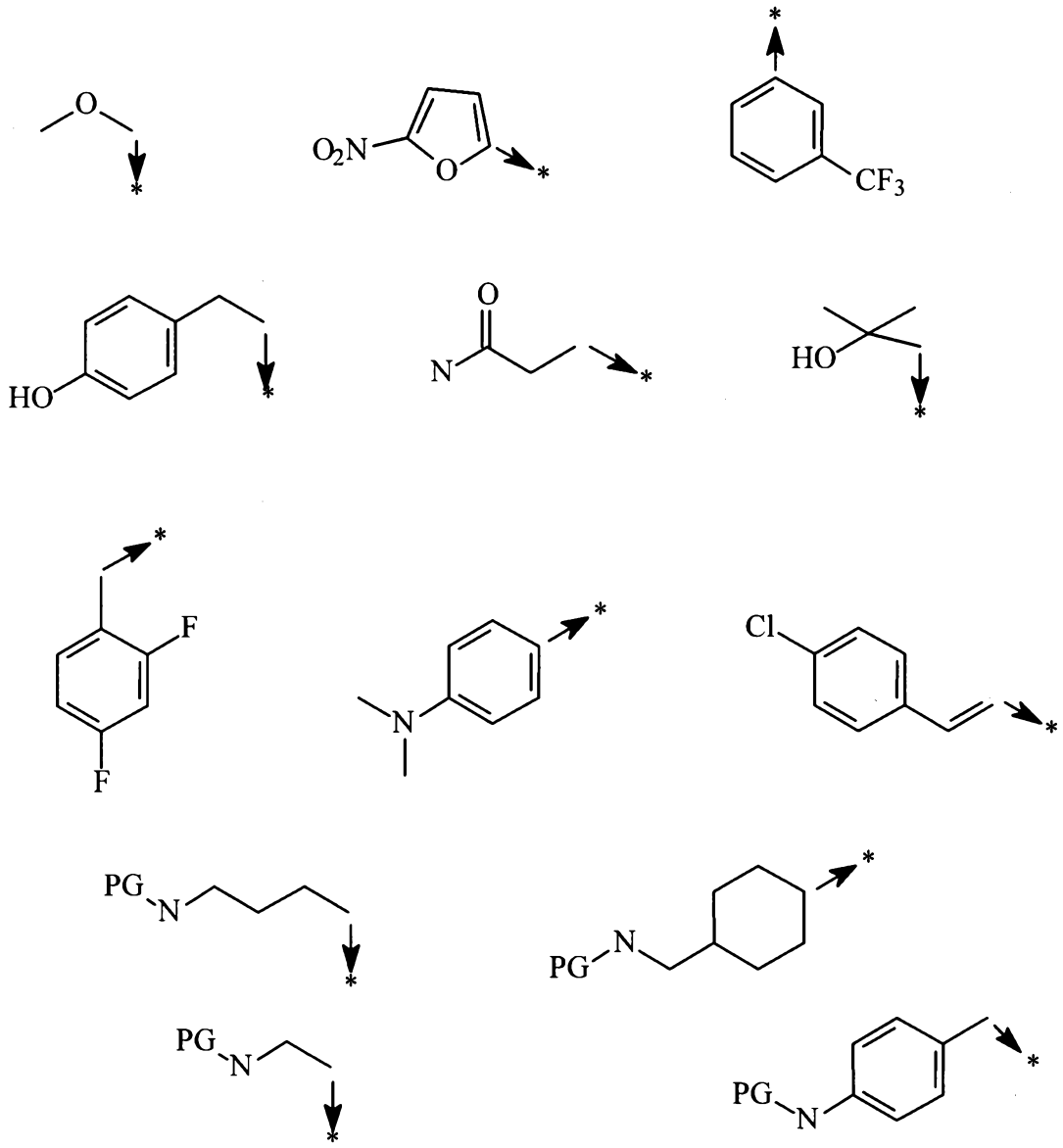

Br
Br







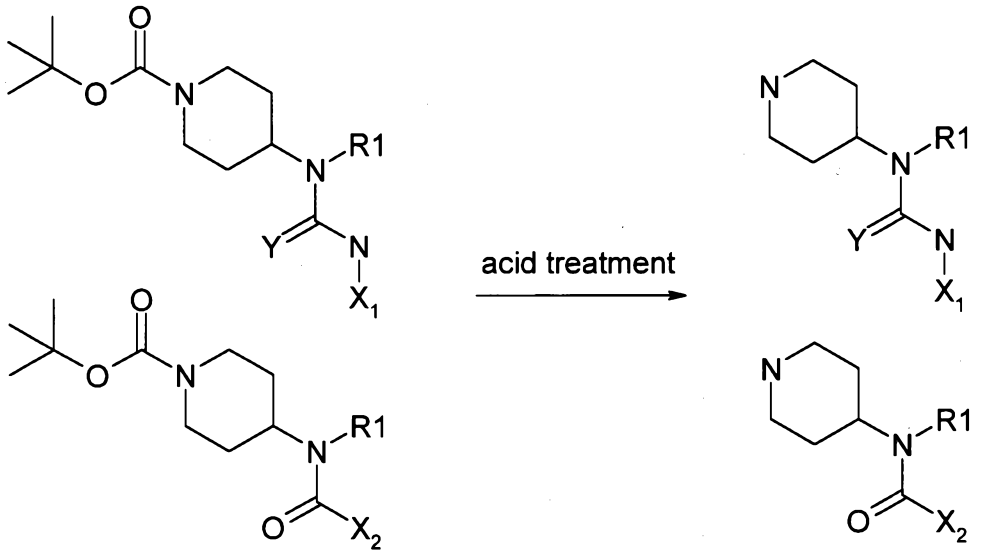




where the protective group (PG) represents H or *tert*-butyloxycarbonyl.

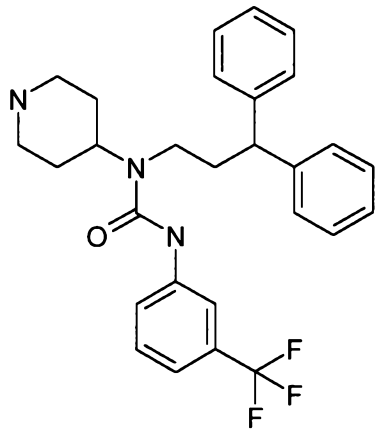
A3) Syntheses of 4-aminodisubstituted piperidines

The synthesis of 4-aminodisubstitueted piperidines according to the invention, can be carried out by acid treatment of the N-Boc compounds described previously, according to the following reaction diagram:



General procedure: two methods were used to carry out the deprotection in acid media of the ureas, thioureas and amides described previously. The first consists in dissolving the compound in dichloromethane and adding trifluoroacetic acid (5 to 20 eq.) whilst in the second a solution of dilute hydrochloric acid in solvents such as ethyl acetate, dioxane or diethylether (5 to 20 eq.) is used. The reaction medium is stirred for 1 to 4 hours at ambient temperature. In certain cases, dichloromethane is added and the organic phase is washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate, filtered and concentrated under vacuum in order to isolate the free base.

Example A3: N-(3,3-diphenylpropyl)-N-(4-piperidinyl)-N'-[3-(trifluoro methyl)phenyl] urea ($C_{28}H_{30}F_3N_3O$, M = 481.57)



1.6 ml (21 mmol, 20 eq.) of trifluoroacetic acid is added to a solution of *tert*-butyl 4-((3,3-diphenylpropyl) {[3-(trifluoromethyl)anilino]carbonyl}amino)-1-piperidine carboxylate (600 mg, 1.04 mmol) in dichloromethane. The reaction medium is stirred for 90 minutes then concentrated. Dichloromethane is added and the organic

phase is washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate, filtered and concentrated under vacuum in order to isolate 490 mg (yield = 98 %) of a white foam.

NMR ^1H (CD_3OD, 400 MHz) δ: 7.7 (s, 1H); 7.55 (d, 1H); 7.44 (t, 1H); 7.28 (m, 9H); 7.18 (m, 2H); 4.05 (m, 2H); 3.26 (m, 2H); 3.11 (d, J = 10.8Hz, 2H); 2.7 (td, J = 2.4 and 12.4Hz, 2H); 2.38 (q, J = 8Hz, 2H); 1.76 (d, J = 10Hz, 2H); 1.63 (qd, J = 4 and 12.4Hz, 2H). MS/LC: m/z = 482.2 (M+H).

A series of 4-aminopiperidines was synthesized according to this procedure. The R_1, X_1 and X_2 radicals which can be envisaged are those already illustrated in points A1 and A2 above.

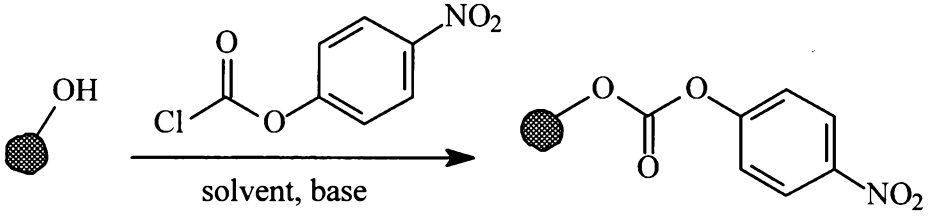
B) Synthesis in solid phase of 4-aminopiperidines

4-aminopiperidines were prepared by synthesis in solid phase starting with Wang resin.

B1) Preparation of the resin

B1a) Preparation of the *p*-nitrophenyl carbonate Wang resin

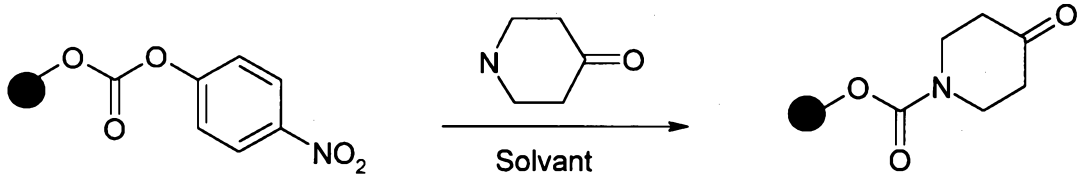
It is carried out according to the following diagram



This resin was prepared from Wang resin (supplied by Bachem or Novabiochem) with a load rate greater than 0.89 mmol/g, following the procedure described in the literature (Bunin, B.A. *The Combinatorial Index*, Academic Press, **1998**, p. 62-63; Dressman, B.A.; Spangle, L.A.; Kaldor, S.W. *Tetrahedron Lett.* **1996**, *37*, 937-940; Hauske, J.R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589-1592; Cao, J.; Cuny, G.D.; Hauske, J.R. *Molecular Diversity* **1998**, *3*, 173-179): N-methylmorpholine or pyridine and 4-nitrophenyl chloroformate are added successively to the Wang resin preswollen in dichloromethane or tetrahydrofuran at ambient temperature. The mixture is stirred overnight. The resin is washed with tetrahydrofuran, with diethylether and with dichloromethane then dried *in vacuo* at 50° C overnight.

B1b) Preparation of the piperidone carbamate resin

It is carried out according to the following diagram



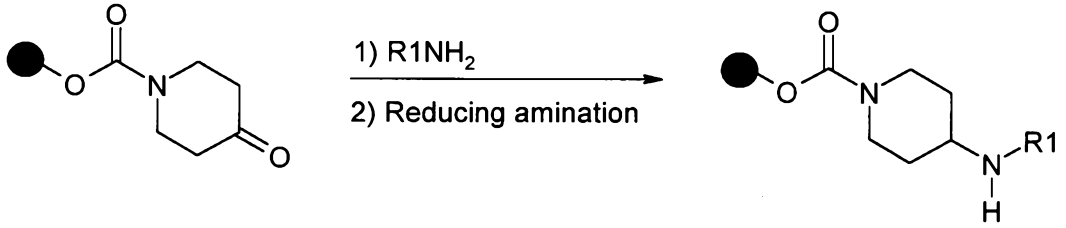
Triethylamine (1 eq.) and the molecular sieve are added to the hydrated piperidone hydrochloride diluted in dimethylformamide. The mixture is heated until complete dissolution of the ketone. This solution is added to the *p*-nitrophenyl carbonate Wang resin (0.05 eq.) preswollen in dimethylformamide. After stirring for 24 to 72 hours at ambient temperature, the resin is filtered then washed several times with dimethylformamide, tetrahydrofuran, diethylether and dichloromethane.

Preparation 2

2.5 g of *p*-nitrophenyl carbonate Wang resin (load rate of 0.88 mmol/g, 2.2 mmol) is preswollen in 100 ml of dimethylformamide. At the same time, 6.7 g (44 mmol, 20 eq.) of hydrated piperidone hydrochloride, 4.45 g (44 mmol, 20 eq.) of triethylamine and three spatulas of molecular sieve are heated in 100 ml of dimethylformamide until complete dissolution. The yellowish solution is poured warm onto the resin and the mixture is stirred for 40 hours at ambient temperature. The resin is filtered then washed with dimethylformamide, tetrahydrofuran, diethylether and dichloromethane (3 times with each solvent) then dried under vacuum. 2.4 g of pale yellow resin is isolated with a load rate of 0.88 mmol/g calculated after elementary analysis of the nitrogen.

B2) Reducing amination on solid support

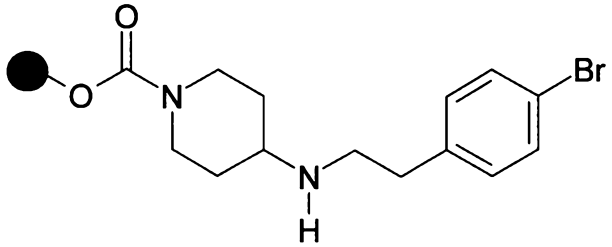
It is carried out according to the following diagram



The general procedure is the following: the primary amine (5 to 10 eq.) is added to the ketonic resin preswollen in trimethylorthoformate (TMOF) then the mixture is sonicated. Then, the borane pyridine complex (8M, 5 to 10 eq.) is added and the mixture is stirred for 12 to 72 hours. The resin is filtered, washed with solvents such as dichloromethane, dimethylformamide and tetrahydrofuran then dried under

vacuum (Pelter, A.; Rosser, R.M. *J. Chem. Soc. Perkin Trans I* **1984**, 717-720; Bomann, M.D.; Guch, I.C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995-5996; Khan, N.M.; Arumugam, V.; Balasubramanian, S. *Tetrahedron Lett.* **1996**, *37*, 4819-4822).

Preparation 3

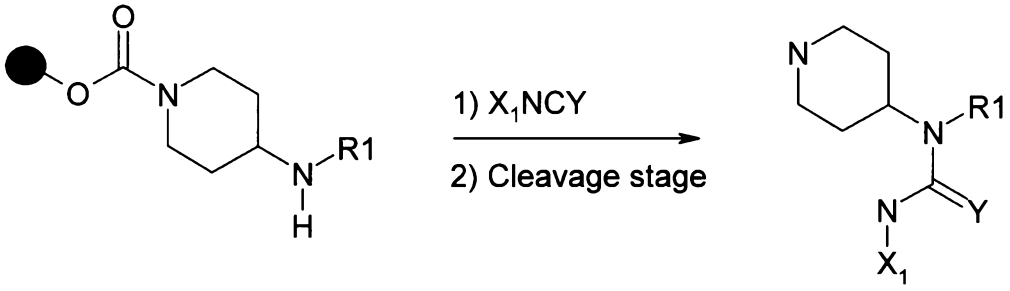


300 mg (load rate of 0.88 mmol/g, 0.27 mmol) of ketonic resin is preswollen in TMOF. Then 4-bromophenethylamine (540 mg, 420 µl, 2.7 mmol, 10 eq.) then the borane pyridine complex (8 M, 338 µl, 2.7 mmol, 10 eq.) are added. The mixture is stirred for 56 hours at ambient temperature. The resin is filtered, rinsed successively with dichloromethane, dimethylformamide, tetrahydrofuran and dichloromethane then dried under vacuum. 340 mg of pale yellow resin is thus obtained with a load rate of 0.81 mmol/g calculated after elementary analysis of the nitrogen.

B3) Functionalization

B3a) Functionalization with isocyanates or isothiocyanates

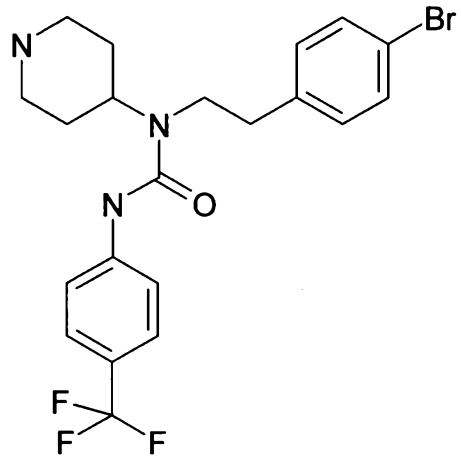
It is carried out according to the diagram



The general procedure is the following: the "secondary amine " resin is preswollen in a solvent such as dichloromethane or dimethylformamide before the addition of isocyanate or isothiocyanate (3 to 10 eq.). The mixture is stirred for 1 to 24 hours at ambient temperature. The resin is then filtered, washed with solvents such as dichloromethane, dimethylformamide and tetrahydrofuran then dried under vacuum. Cleavage of the resin is carried out in the presence of an equimolar mixture of dichloromethane and trifluoroacetic acid and stirring is carried out for 30 minutes to 4 hours. The resin is rinsed with dichloromethane then the filtrate is concentrated under vacuum. In certain cases the filtrate is redissolved in dichloromethane then

desalified with a saturated solution of sodium carbonate. The organic phase is evaporated under vacuum in order to produce the free base.

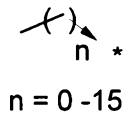
Example B3a: N-(4-bromophenethyl)-N-(4-piperidinyl)-N'-[4-(trifluoromethyl) phenyl] urea ($C_{21}H_{23}BrF_3N_3O$, M = 470.3)



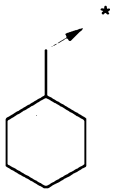
55 mg (50 µmol) of resin (see Preparation 3) is preswollen in anhydrous dichloromethane. Then 4-trifluorophenylisocyanate (28 mg, 150 µmol, 3 eq.) is added and the whole is stirred overnight. The resin is filtered, rinsed with tetrahydrofuran, with dimethylformamide, with tetrahydrofuran then with dichloromethane before being dried under vacuum. Then stirring is carried out for 1.5 hour in the presence of 800 µl of an equimolar mixture of dichloromethane and trifluoroacetic acid. The resin is filtered and rinsed with dichloromethane, the filtrate is concentrated, rediluted in dichloromethane and washed with a saturated solution of sodium bicarbonate. 6 mg of a brown oil (yield = 25 %) is thus isolated.

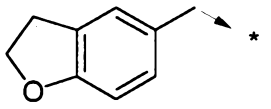
NMR ^1H (CD_3OD, 400 MHz) δ: 7.53 (m, 4H); 7.44 (d, J = 6.8Hz, 2H); 7.21 (d, J = 8.4Hz, 2H); 4.1 (m, 1H); 3.53 (t, J = 7.2Hz, 2H); 3.12 (d, J = 12.8Hz, 2H); 2.89 (t, J = 8Hz, 2H); 2.7 (m, 2H); 1.73 (m, 4H). MS/LC: m/z = 472.2 (M+H).

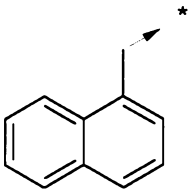
A series of ureas (Y = O) and thioureas (Y = S) was synthesized according to this procedure. The R_1 radicals which can be envisaged are the following:

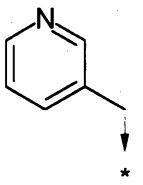


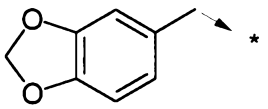
n = 0 -15

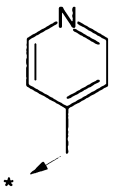


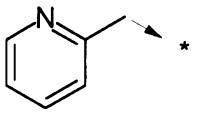


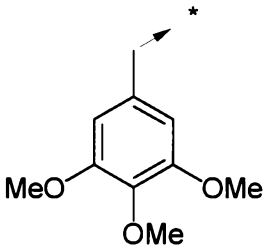


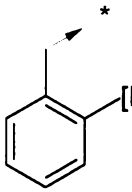




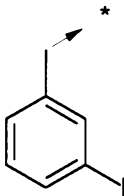




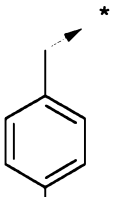




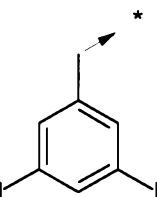
[H, F, Br, Cl, OMe, SMe, OEt, CF_3, OCF_3, Ph, Me]



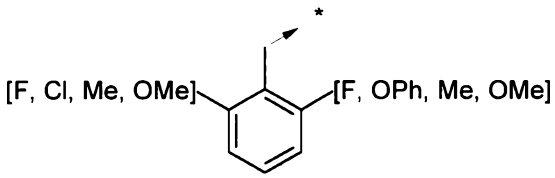
[F, Cl, OMe, Me, CF_3, OCF_3, Ph]



[F, Cl, OMe, SMe, Me, CF_3, OCF_3, Ph, OPh]



[Cl, F, OMe, Me, CF_3] [Cl, F, CF_3, OMe, Me]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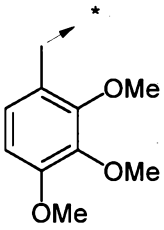
[F, OPh, Me, OMe]


OMe
OMe
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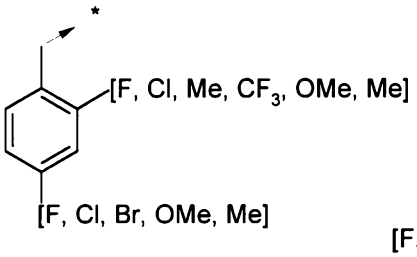
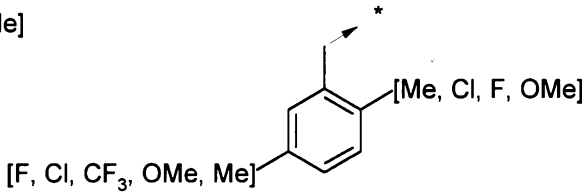
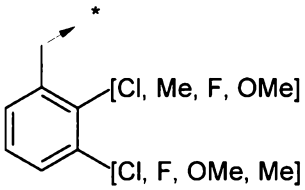

[F, Cl, Me, CF3, OMe, Me]
[F, Cl, Br, OMe, Me]


[Me, Cl, F, OMe]
[F, Cl, CF3, OMe, Me]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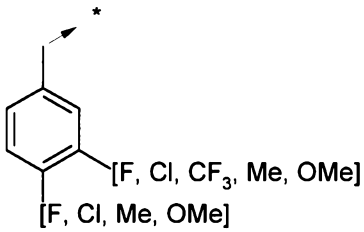
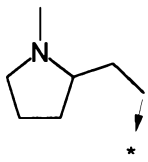
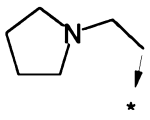
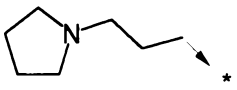
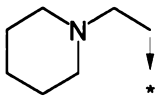
[Cl, F, OMe, Me]

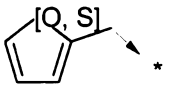

[F, Cl, CF3, Me, OMe]
[F, Cl, Me, OMe]

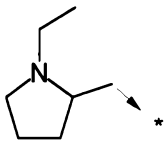


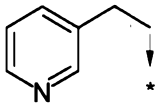


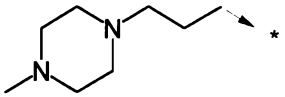


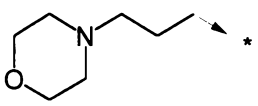


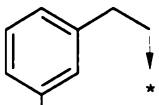


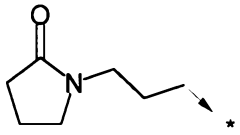




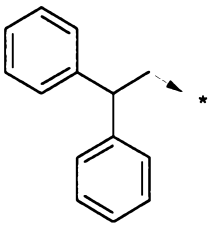


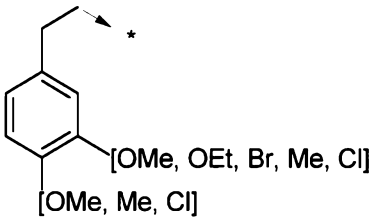


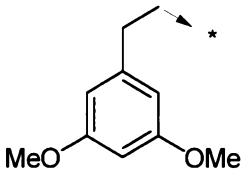


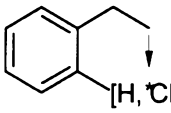


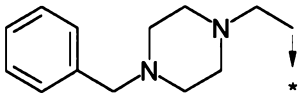
[OMe, CF_3, OEt, F, Cl, Me]

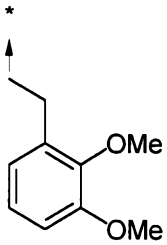


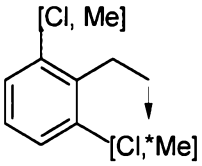


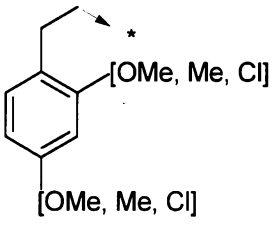


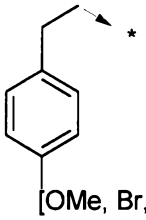




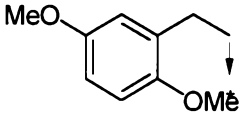


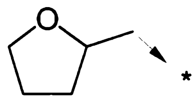


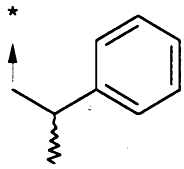


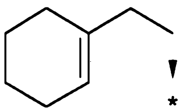


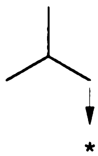
[OMe, Br, Me, SO_2NH_2, OEt, Et, OPh, F, Ph, Br, Cl]

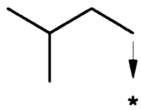


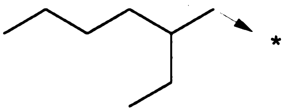


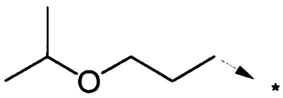


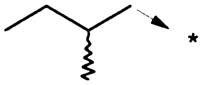


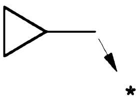


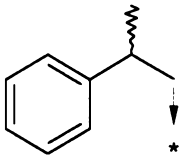


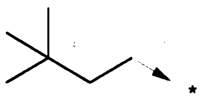


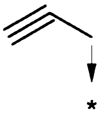


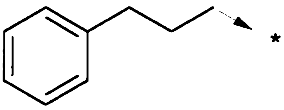


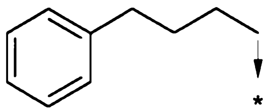


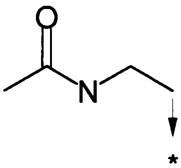


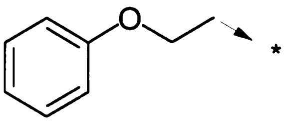


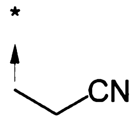




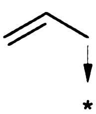


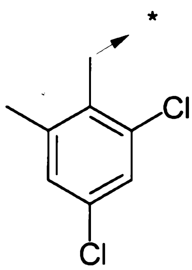


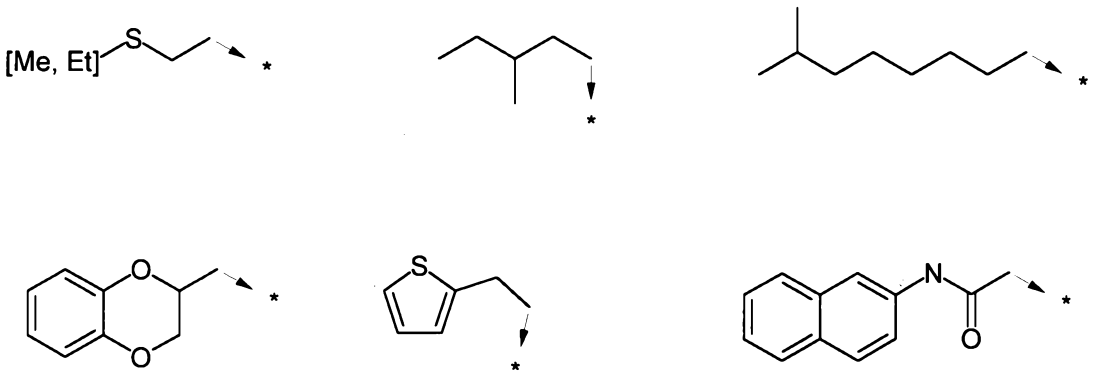



CN


[Me, Et]
[O, S]



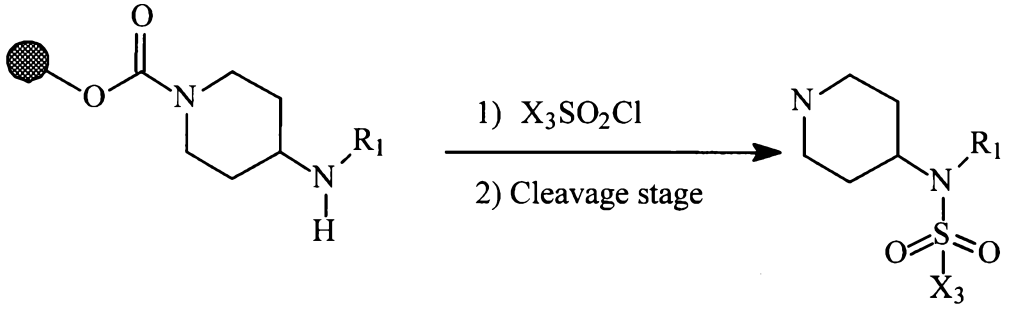

Cl
Cl



The X_1 radicals which can be envisaged are those illustrated in point A above.

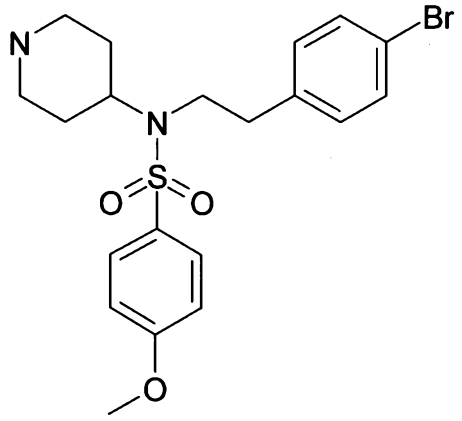
B3b) Functionalization with sulphonyl chlorides

It is carried out according to the following diagram



General procedure: the " secondary amine " resin is preswollen in solvents such as dichloromethane, dimethylformamide or tetrahydrofuran. Then sulphonyl chloride (5 to 10 eq.) and triethylamine (6 to 12 eq.) are added and the mixture is stirred for 12 to 24 hours at ambient temperature. The resin is filtered, washed with solvents such as dichloromethane, dimethylformamide and tetrahydrofuran, then dried under vacuum. Then the resin is stirred for 1 to 4 hours in the presence of an equimolar mixture of dichloromethane and trifluoroacetic acid. The resin is rinsed with dichloromethane then the filtrate is concentrated under vacuum. In certain cases the filtrate is redissolved in dichloromethane then desalified with a saturated solution of sodium carbonate. The organic phase is evaporated under vacuum in order to produce the free base.

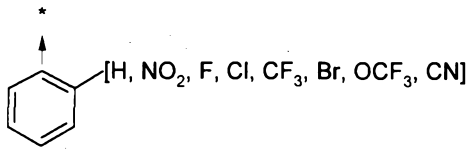
Example B3b: N-(4-bromophenethyl)-4-methoxy-N-(4-piperidinyl) phenyl sulphonamide ($C_{20}H_{25}BrN_2O_3S$, M = 453.4)

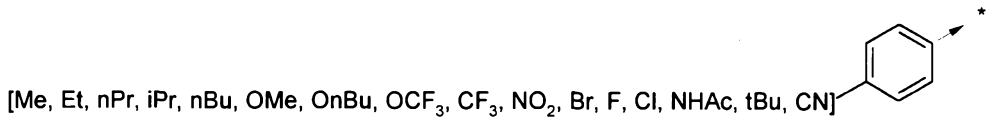


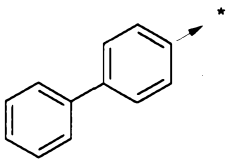
55 mg (50 µmol) of resin (see Preparation 3) is preswollen in anhydrous dichloromethane. Then triethylamine (42 µl, 300 µmol, 6 eq.) then 4-methoxybenzene sulphonyl chloride (51.5 mg, 250 µmol, 5 eq.) are added and the whole is stirred overnight. The resin is filtered, rinsed with tetrahydrofuran, with dimethylformamide, with tetrahydrofuran then with dichloromethane before being dried under vacuum. The reaction is repeated a second time in order to have a complete substitution. 800 µl of an equimolar mixture of dichloromethane and trifluoroacetic acid is added and stirring is carried out for 1.5 hour at ambient temperature. The resin is filtered and rinsed with dichloromethane. The filtrate is concentrated, rediluted in dichloromethane and washed with a saturated solution of sodium bicarbonate. 14 mg of a brown oil (yield = 63%) is thus isolated.

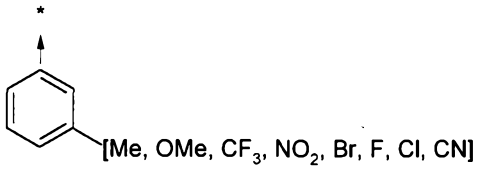
NMR ^1H (CD_3OD, 400 MHz) δ: 7.8 (dd, J = 2.8 and 10Hz, 2H); 7.44 (dd, J = 1.2 and 6.8Hz, 2H); 7.17 (d, J = 8.4Hz, 2H); 7.07 (dd, J = 3.2 and 10Hz, 2H); 3.87 (s, 3H, OCH_3); 3.72 (m, 1H); 3.3 (m, 2H); 3.04 (d, J = 12.8Hz, 2H); 2.92 (t, J = 8.4Hz, 2H); 2.6 (t, J = 12.4Hz, 2H); 1.58 (m, 2H); 1.47 (broad d, J = 10Hz, 2H). MS/LC: m/z = 455 (M+H).

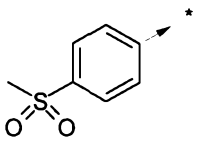
A series of sulphonamides was synthesized according to this procedure. The R_1 radicals which can be envisaged are those illustrated in points A and B3a above. The X_3 radicals which can be envisaged are the following:

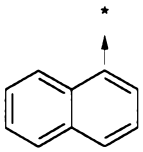

[H, NO2, F, Cl, CF3, Br, OCF3, CN]

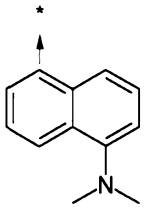

[Me, Et, nPr, iPr, nBu, OMe, OnBu, OCF3, CF3, NO2, Br, F, Cl, NHAc, tBu, CN]

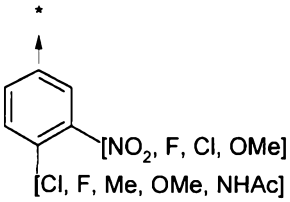


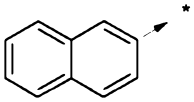

[Me, OMe, CF3, NO2, Br, F, Cl, CN]

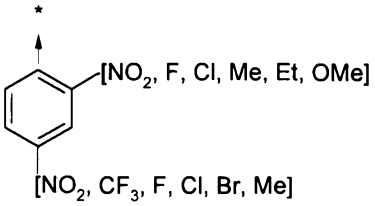

S
O
O

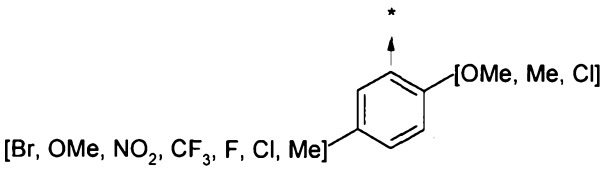


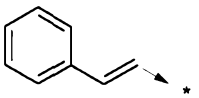

N

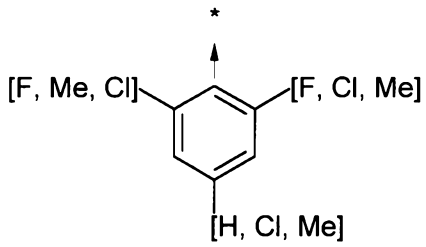

[NO2, F, Cl, OMe]
[Cl, F, Me, OMe, NHAc]

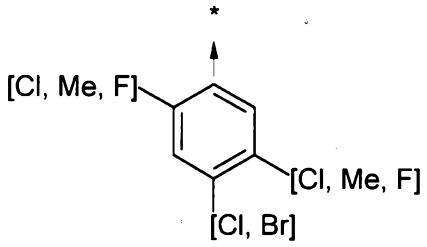


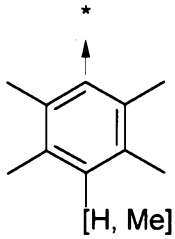

[NO2, F, Cl, Me, Et, OMe]
[NO2, CF3, F, Cl, Br, Me]

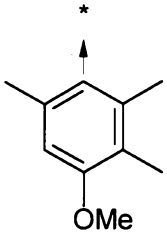

[OMe, Me, Cl]
[Br, OMe, NO2, CF3, F, Cl, Me]

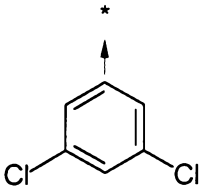


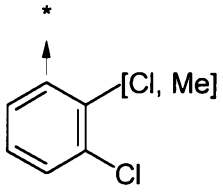

[F, Me, Cl]
[F, Cl, Me]
[H, Cl, Me]

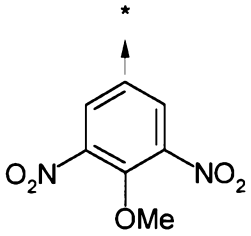

[Cl, Me, F]
[Cl, Me, F]
[Cl, Br]

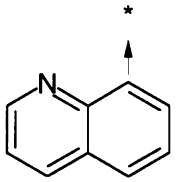

[H, Me]

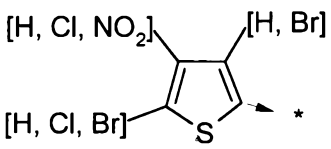

OMe

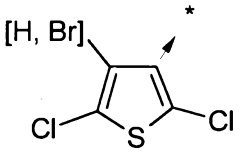

Cl
Cl

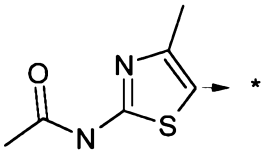

[Cl, Me]
Cl

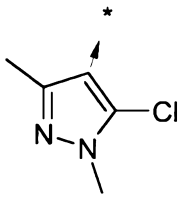

O2N
NO2
OMe

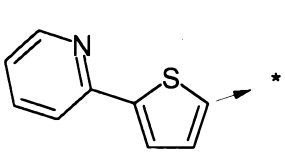

N

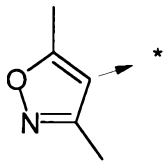

[H, Cl, NO2]
[H, Br]
[H, Cl, Br]
S

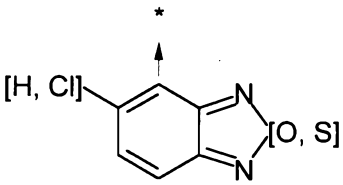

[H, Br]
Cl
Cl
S

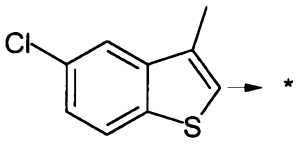

O
N
N
S

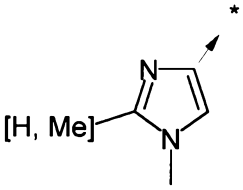

Cl
N
N

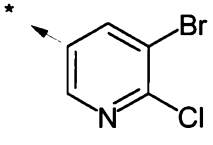

N
S

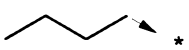

O
N

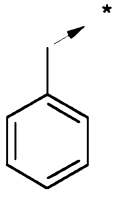

[H, Cl]
N
[O, S]
N

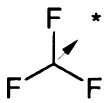

Cl
S


[H, Me]
N
N


Br
N
Cl

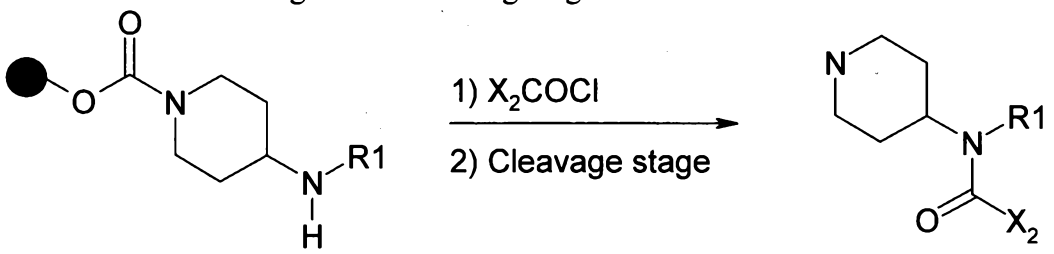





F
F
F

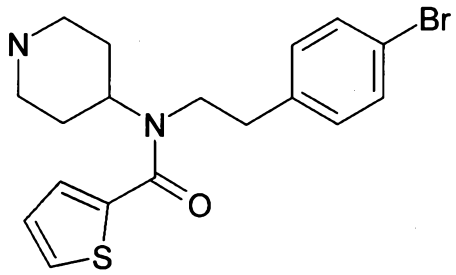
B3c) Functionalization with acid chlorides

It is carried out according to the following diagram



General procedure: the "secondary amine" resin is preswollen in solvents such as dichloromethane, dimethylformamide or tetrahydrofuran. Then the acid chloride (5 to 10 eq.) and triethylamine (6 to 12 eq.) are added and the mixture is stirred for 12 to 24 hours at ambient temperature. The resin is filtered, washed with solvents such as dichloromethane, dimethylformamide and tetrahydrofuran, then dried under vacuum. The resin is then stirred for 1 to 4 hours in the presence of an equimolar mixture of dichloromethane and trifluoroacetic acid. The resin is rinsed with dichloromethane then the filtrate is concentrated under vacuum. In certain cases the filtrate is redissolved in dichloromethane then desalified with a saturated solution of sodium carbonate. The organic phase is evaporated under vacuum in order to produce the free base.

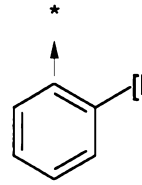
Example B3c: N-(4-bromophenethyl)-N-(4-piperidinyl)-2-thiophene carboxamide ($C_{18}H_{21}BrN_2OS$, M = 393.3)

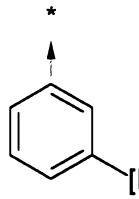


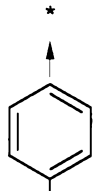
55 mg (50 µmol) of resin (see Preparation 3) is preswollen in anhydrous tetrahydrofuran. Then triethylamine (42 µl, 300 µmol, 6 eq.) then 2-thiophene carbonyl chloride (37 mg, 250 µmol, 5 eq.) are added and the whole is stirred overnight. The resin is filtered, rinsed with tetrahydrofuran, with dimethylformamide, with tetrahydrofuran then with dichloromethane before being dried under vacuum. 800 µl of an equimolar mixture of dichloromethane and trifluoroacetic acid is added and stirring is carried out for 1.5 hour at ambient temperature. The resin is filtered and rinsed with dichloromethane. The filtrate is concentrated, rediluted in dichloromethane and washed with a saturated solution of sodium bicarbonate in order to obtain 10 mg of a brown oil (yield = 50 %).

NMR ^1H (CD_3OD, 400 MHz) δ: 7.64 (dd, J = 0.8 and 4.8Hz, 1H); 7.44 (d, J = 8.4Hz, 2H); 7.36 (d, J = 3.6Hz, 1H); 7.14 (m, 3H); 4.11 (m, 1H); 3.61 (t, J = 8Hz, 2H); 3.09 (d, J = 12Hz, 2H); 2.92 (m, 2H); 2.54 (m, 2H); 1.82 (m, 2H); 1.7 (m, 2H). MS/LC: m/z = 393.1 (M+H).

A series of amides was synthesized according to this procedure. The R_1 groups envisaged are those illustrated in points A and B3 above. The X_2 groups are illustrated below.


[H, F, Cl, Br, I, CN, OCF_3, NO_2, Me, CF_3, OMe]


[F, Cl, Br, CF_3, Me, CN, NO_2, OMe, OEt]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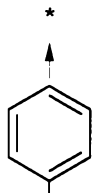
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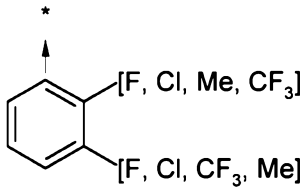
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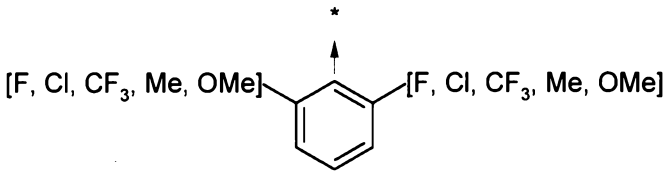
[F, Cl, CF3, Me]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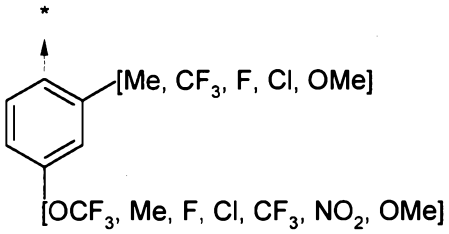
[F, Cl, CF3, Me, OMe]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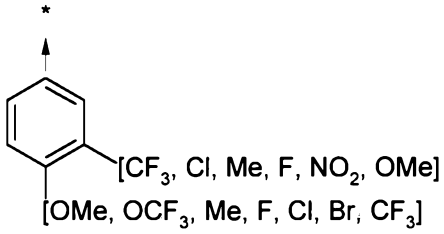
[OCF3, Me, F, Cl, CF3, NO2, OMe]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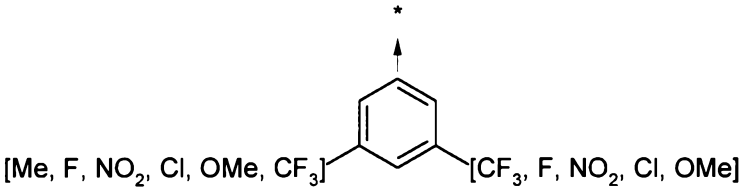
[OMe, OCF3, Me, F, Cl, Br, CF3]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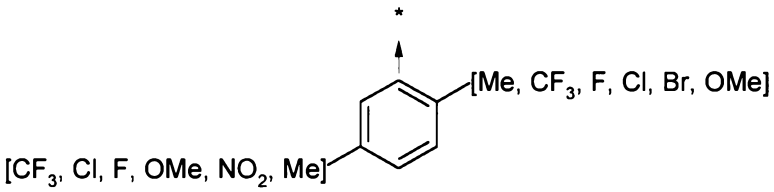
[Me, F, NO2, Cl, OMe, CF3]
[CF3, F, NO2, Cl, OMe]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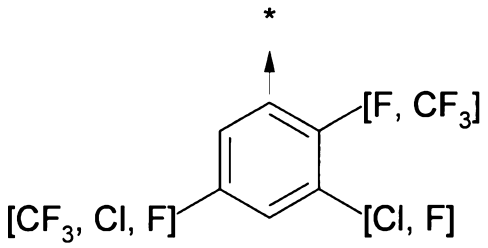
[CF3, Cl, F, OMe, NO2, Me]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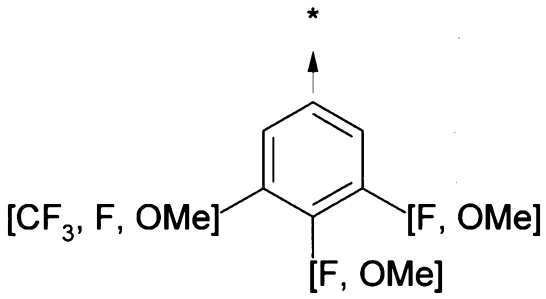
[CF3, Cl, F]
[Cl, F]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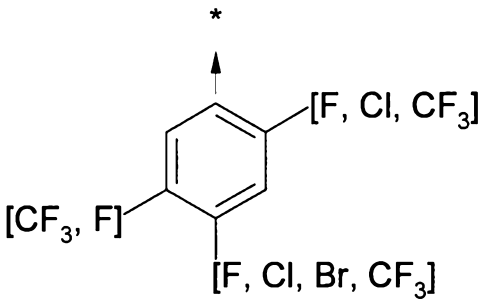
[CF3, F, OMe]
[F, OMe]
[F, OMe]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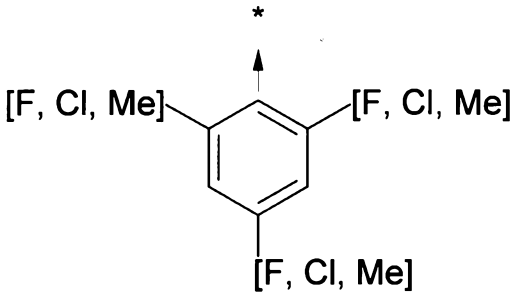
[CF3, F]
[F, Cl, Br, CF3]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[F, Cl, Me]
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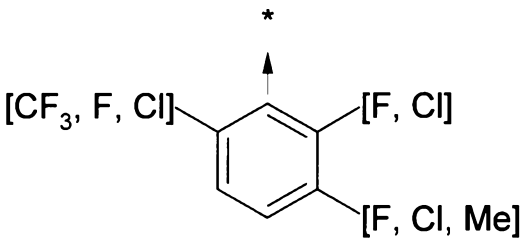
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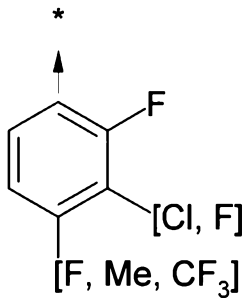
[F, Cl]
[F, Cl, Me]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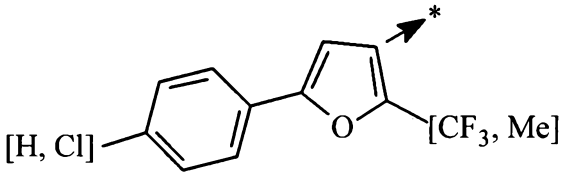
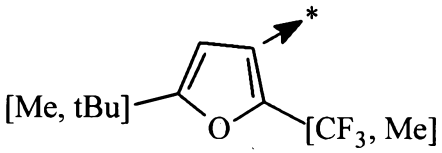
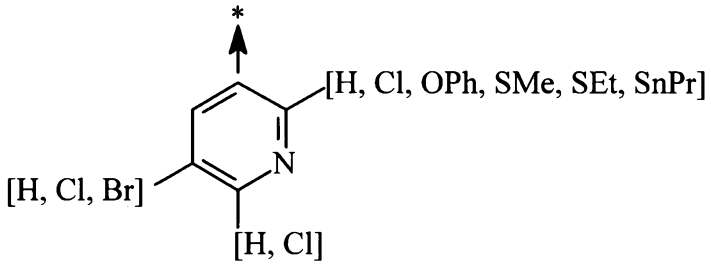
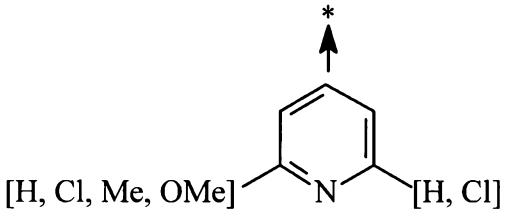
[F, Me, CF3]


[H, Cl]
O
[CF3, Me]


[Me, tBu]
O
[CF3, Me]


[H, Cl, OPh, SMe, SEt, SnPr]
N
[H, Cl, Br]
[H, Cl]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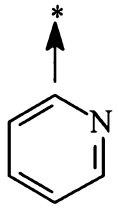
[H, Cl]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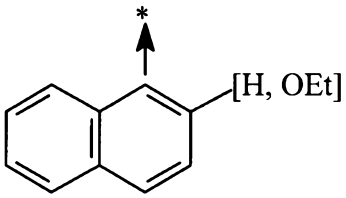
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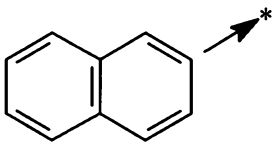

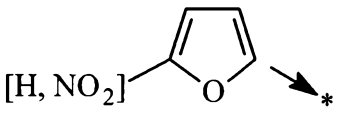
[H, NO2]
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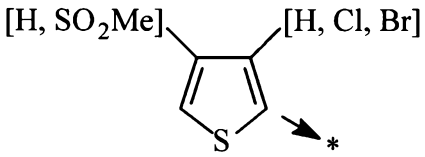
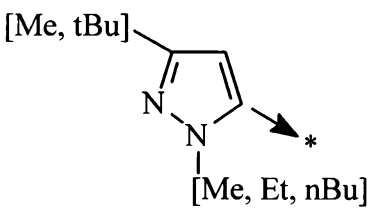
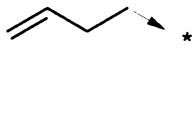
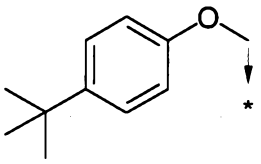
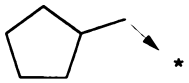
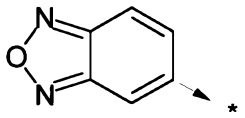

[H, SO2Me]
[H, Cl, Br]
S

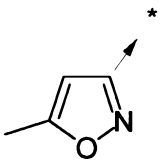

[Me, tBu]
N
N
[Me, Et, nBu]

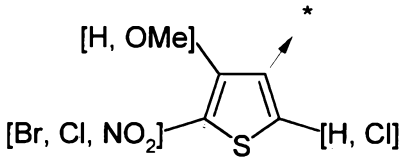


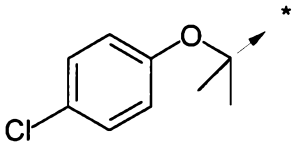









[H, OMe]
[Br, Cl, NO2]
S
[H, Cl]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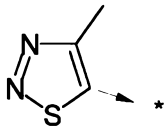
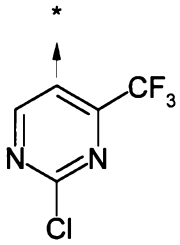
Cl




CF3
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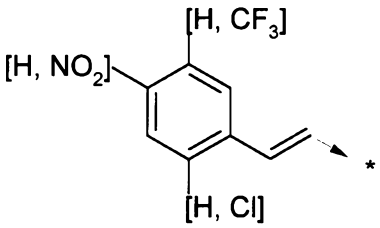
N
Cl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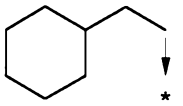
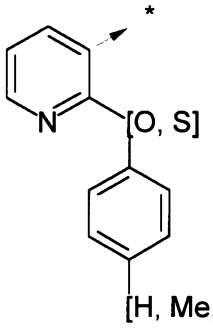
[H, NO2]
[H, Cl]

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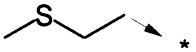
[O, S]
[H, Me, Cl]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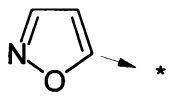
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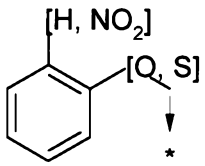
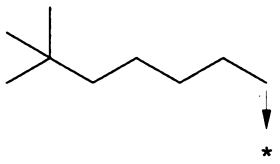
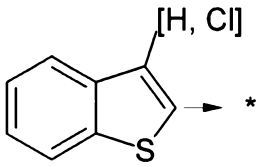

[H, NO2]
[O, S]




[H, Cl]
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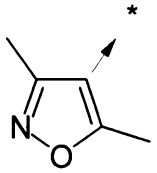
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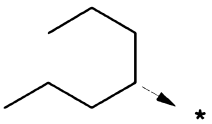

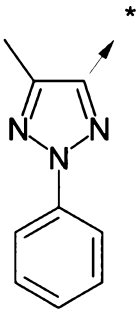
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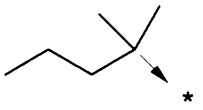

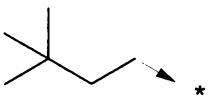

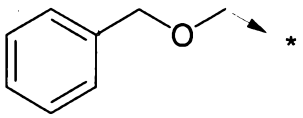
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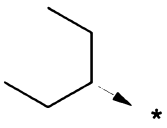
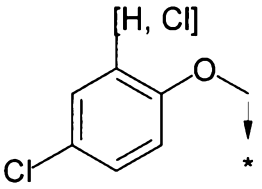
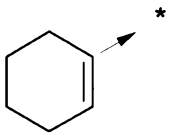
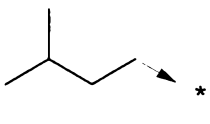
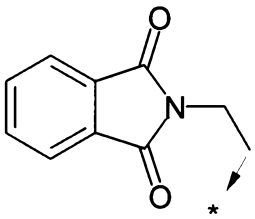



[H, Cl]
O
Cl



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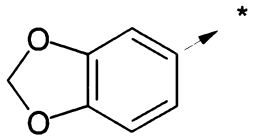
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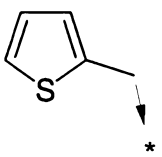
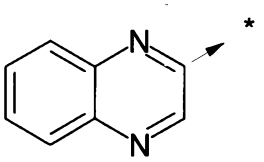
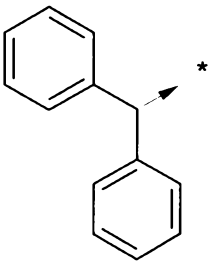
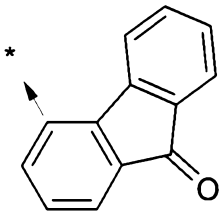

S


N
N

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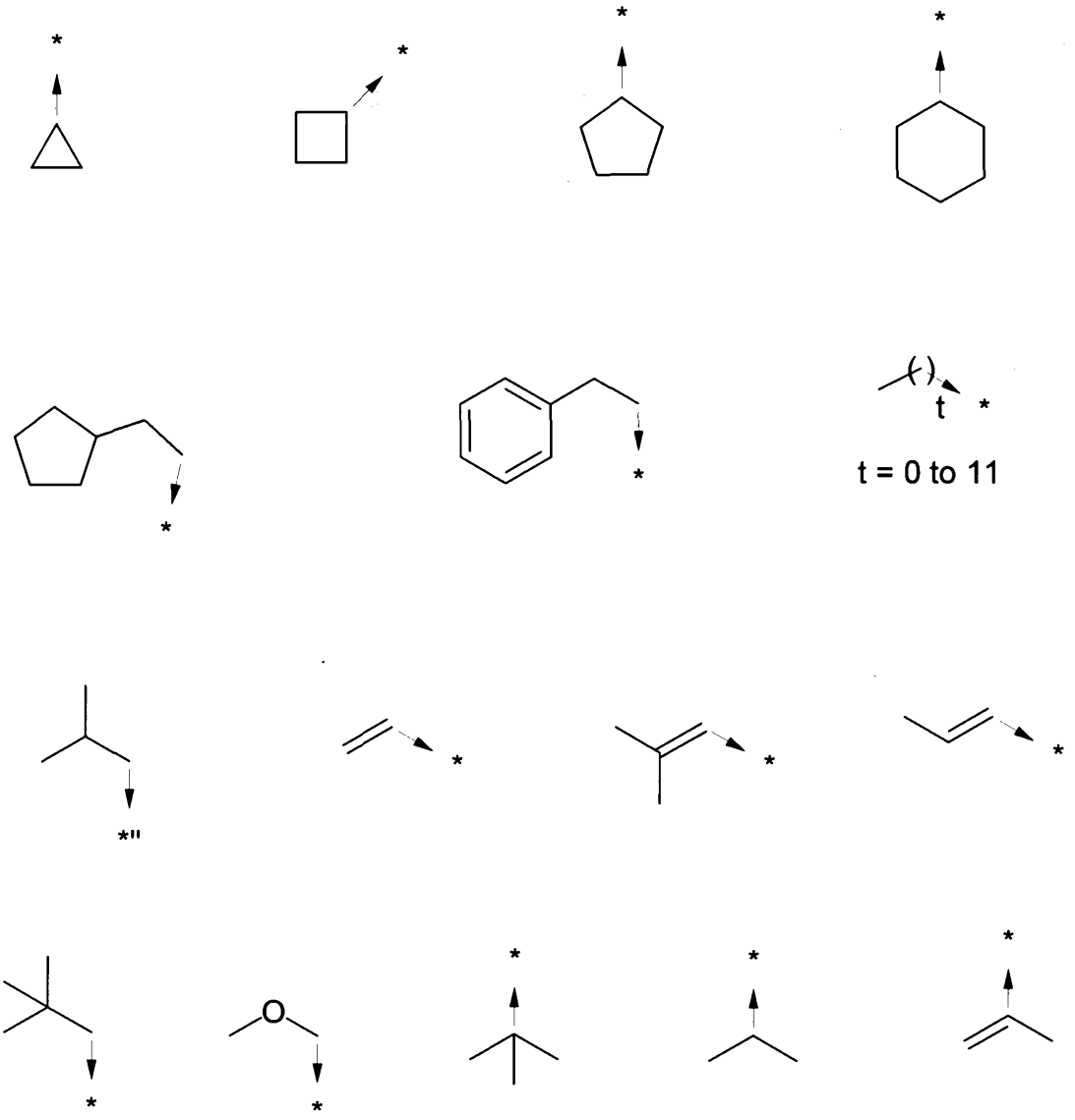
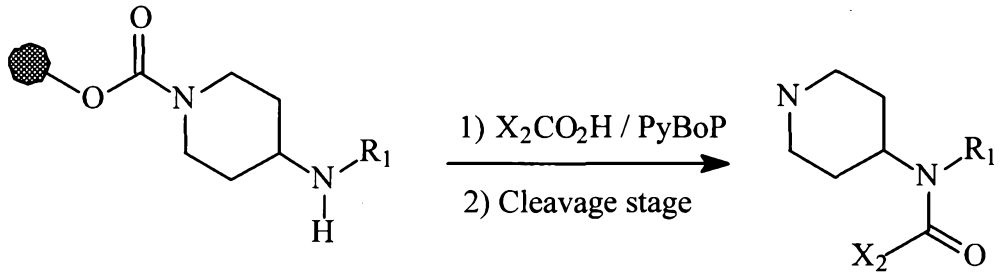


B3d) Functionalization with carboxylic acids

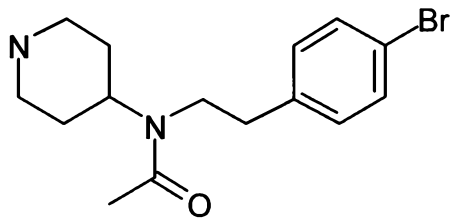
It is carried out according to the procedure described in the literature (Kobayashi, S; Aoki, Y., *J. Comb. Chem.* **1999**, *1*, 371-372) according to the following diagram:



General procedure: the "secondary amine" resin is preswollen in solvents such as dichloromethane, dimethylformamide or tetrahydrofuran. Then the carboxylic acid (3 to 5 eq.), benzo-triazol-1-yl-oxy-tris-pyrrolidino phosphonium

hexafluorophosphate (PyBoP, 3 to 5 eq.) and diisopropylethylamine (6 to 10 eq.) are added and the mixture is stirred for 24 hours at ambient temperature. The resin is filtered, washed with solvents such as dichloromethane, dimethylformamide and tetrahydrofuran, then dried under vacuum. Then the resin is stirred for 1 to 4 hours in the presence of an equimolar mixture of dichloromethane and trifluoroacetic acid. The resin is rinsed with dichloromethane then the filtrate is concentrated under vacuum. In certain cases the filtrate is redissolved in dichloromethane then desalified with a saturated solution of sodium carbonate. The organic phase is evaporated under vacuum in order to produce the free base.

Example B3d: N-[2-(4-bromophenyl)ethyl]-N-(4-piperidinyl) acetamide ($C_{15}H_{21}BrN_2O$, M = 325.25)



55 mg (50 µmol) of resin (see Preparation 3) is preswollen in anhydrous dimethylformamide. Then acetic acid (8.8 mg, 150 µmol, 3 eq.) PyBoP (76 mg, 150 µmol, 3 eq.) then diisopropylethylamine (38 mg, 300 µmol, 6 eq.) are added and the whole is stirred overnight. The resin is filtered, rinsed with dimethylformamide, with tetrahydrofuran then with dichloromethane before being dried under vacuum. 800 µl of an equimolar mixture of dichloromethane and trifluoroacetic acid is added and stirring is carried out for 1.5 hour at ambient temperature. The resin is filtered and rinsed with dichloromethane. The filtrate is concentrated, rediluted in dichloromethane and washed with a saturated solution of sodium bicarbonate in order to obtain 11 mg of a brown oil (yield = 68 %).

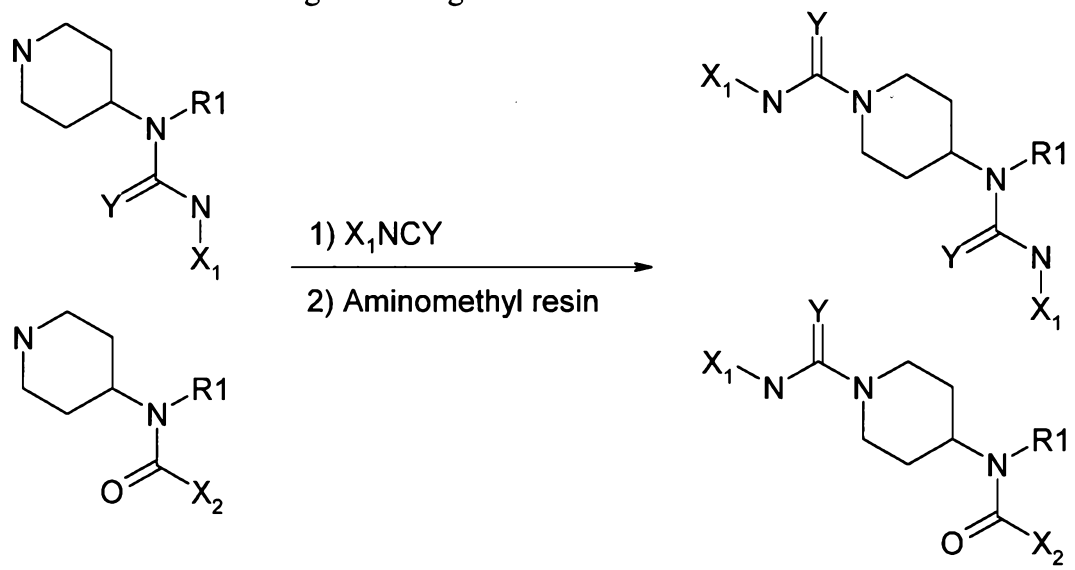
NMR ^1H (CD_3OD, 400 MHz) δ: 7.44 (m, 2H); 7.20 (m, 2H); 4.05 (m,1H); 3.45 (m, 2H); 3.10 (m, 2H); 2.83 (m, 2H); 2.64 (m, 2H); 2.13 (s,3H); 1.73 (m, 4H). MS/LC: m/z = 325.2 (M+H).

A series of amides was synthesized according to this procedure. The R_1 groups envisaged are those illustrated in points A and B3a above. The X_2 groups are illustrated in point A above.

C) Functionalization of the piperidine part in solution

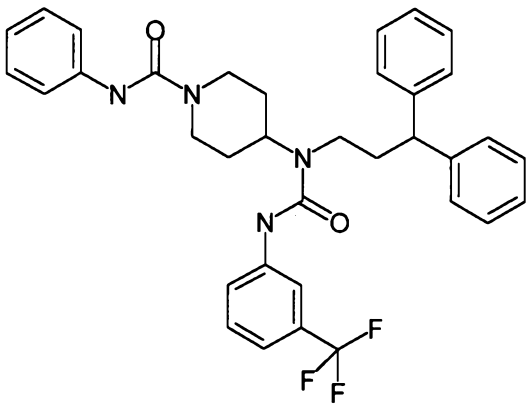
C1) Obtaining piperidine with R_3= -C(Y)NHX_1

It is carried out according to the diagram



General procedure: An isocyanate or isothiocyanate (1.1 to 1.5 eq.) is added to piperidine in the form of the free base diluted in dichloromethane. The mixture is stirred for one to 18 hours at ambient temperature. The aminomethyl resin (0.2 to 1 eq.) is added and the mixture is again stirred for 2 to 18 hours. In certain cases, ion exchange resin such as IRA68 or SAX is added. The resins are filtered and the filtrate is concentrated. In certain cases, the product is dissolved in dichloromethane or ethyl acetate then filtered on a silica gel or basic alumina cartridge (500 mg, Interchim).

Example C1: 4-((3,3-diphenylpropyl){[3-(trifluoromethyl)anilino] carbonyl}amino)-N-phenyl-1-piperidine carboxamide
($C_{35}H_{35}F_3N_4O_2$, M = 600.68)



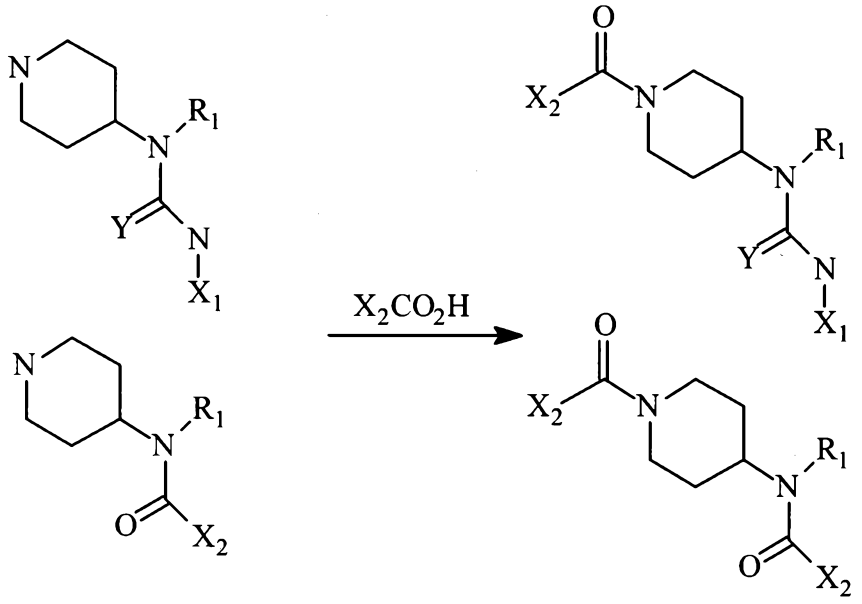
N-(3,3-diphenylpropyl)-N-(4-piperidinyl)-N'-[3-(trifluoromethyl)phenyl] urea (24 mg, 0.05 mmol) is dissolved in dichloromethane. Phenylisocyanate (9 mg, 0.075 mmol, 1.5 eq.) is added and the mixture is stirred for 2.5 hours. The aminomethyl resin (0.02 mmol) is added and the reaction is again stirred overnight. The resin is filtered, rinsed with dichloromethane and the filtrate is concentrated. The oil obtained is passed through a silica gel cartridge eluting with an equimolar mixture of heptane and ethyl acetate in order to obtain 12 mg (yield = 40 %) of a yellow oil after concentration.

NMR ^1H (CD_3OD, 400 MHz) δ: 7.72 (s, 1H); 7.58 (d, 1H); 7.44 (m, 1H); 7.38 (m, 2H); 7.29 (m, 12H); 7.12 (m, 2H); 7.07 (m, 1H); 4.2 (d, J = 12.4Hz, 3H); 3.21 (t, J = 8Hz, 2H); 2.9 (t, J = 12.4Hz, 2H); 2.38 (q, J = 8Hz, 2H); 1.73 (d, J = 10Hz, 2H); 1.54 (qd, J = 3.6 and 12Hz, 2H). MS/LC: m/z = 601.4 (M+H).

A series of ureas (Y = O) and thioureas (Y = S) was synthesized according to this procedure. The R_1, X_1 and X_2 groups which can be envisaged, are those illustrated in the above points (A and B3a), A, and (A and B3c) respectively.

C2) Functionalization with carboxylic acids

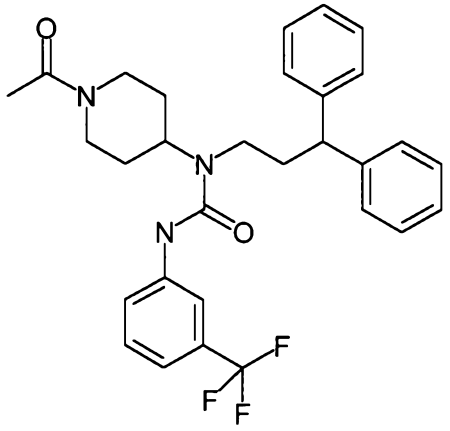
It is carried out according to the following diagram



General procedure: the P-EDC resin (1.3 to 3 eq.) is preswollen in anhydrous dichloromethane. Carboxylic acid (1.1 to 2.5 eq.) is dissolved in an anhydrous solvent such as dichloromethane, dimethylformamide or tetrahydrofuran and is added to the resin. This mixture is stirred for 5 to 30 minutes at ambient temperature. The 4-aminodisubstituted piperidine, in the form of the free base, in

solution in an anhydrous solvent such as dichloromethane, dimethylformamide or tetrahydrofuran is then added to this mixture and the whole is stirred for 1 to 18 hours at ambient temperature. In certain cases, ion exchange resin such as IRA68 or SAX is added and the mixture is again stirred at ambient temperature for 1 to 18 hours. The resins are filtered on frit, on a SAX ion exchange resin cartridge (500 mg, Interchim) or on a basic alumina cartridge (500 mg, Interchim).

Example C2: N-(1-acetyl-4-piperidinyl)-N-(3,3-diphenylpropyl)-N'-[3-(trifluoromethyl) phenyl] urea ($C_{30}H_{32}F_3N_3O_2$, M = 523.60)



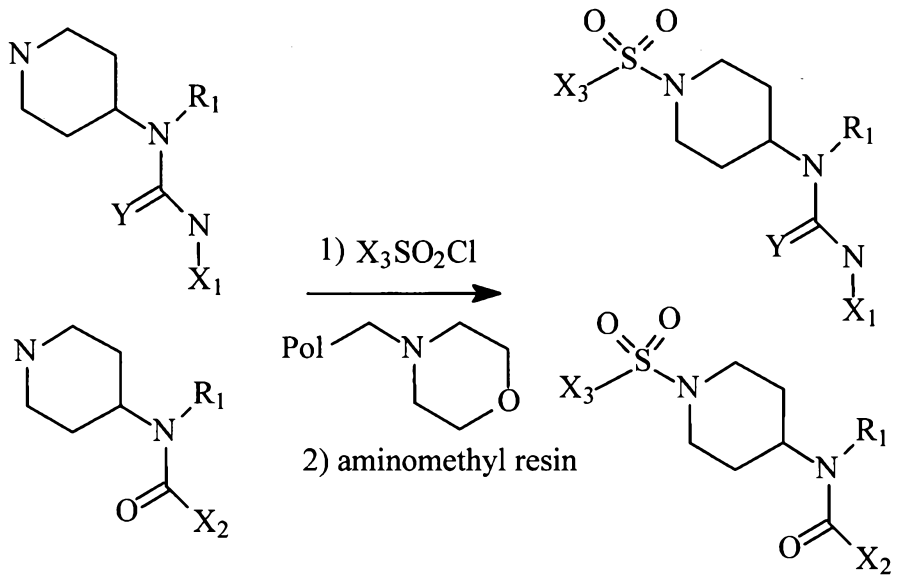
117 mg (175 µmol, 3.5 eq.) of P-EDC resin is preswollen in 1.5 ml of anhydrous dichloromethane. Acetic acid (7.5 mg, 125 µmol, 2.5 eq.) is added and the mixture is stirred for 10 minutes. Then N-(3,3-diphenylpropyl)-N-(4-piperidinyl)-N'-[3-(trifluoromethyl)phenyl] urea (24.3 mg, 50 µmol) is added in its turn and the mixture is stirred overnight. The resin is filtered and the filtrate is concentrated. The oil obtained is passed through a silica gel cartridge eluting with an equimolar mixture of heptane and ethyl acetate in order to obtain 16 mg (yield = 62 %) of a white foam after concentration.

NMR ^1H (CD_3OD, 400 MHz) δ: 7.71 (s, 1H); 7.58 (d, J = 8.4Hz, 1H); 7.43 (t, J = 8Hz, 1H); 7.28 (m, 9H); 7.17 (m, 2H); 4.56 (dd, J = 2 and 11.2Hz, 1H); 4.17 (m, 1H); 3.96 (t, J = 7.6Hz, 1H); 3.88 (d, J = 12Hz, 1H); 3.19 (q, J = 4 and 8Hz, 2H); 3.1 (t, J = 12Hz, 1H); 2.58 (t, J = 12Hz, 1H); 2.37 (m, 2H); 2.06 (s, 3H, CH_3); 1.72 (t, J = 14.4Hz, 2H); 1.43 (qd, J = 4 and 12.4Hz, 2H).
MS/LC: m/z = 524.3 (M+H).

A series of amides was synthesized according to this procedure. The R_1, X_1 and X_2 groups which can be envisaged, are those illustrated in points (A and B3a), A, (A and B3c) respectively.

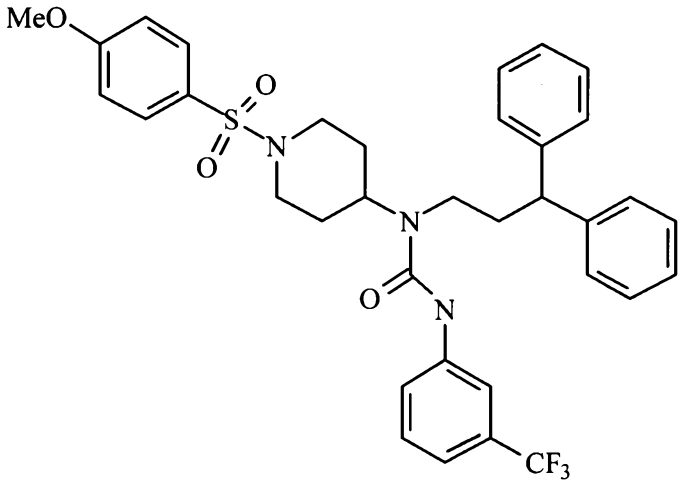
C3) Functionalization with sulphonyl chlorides

It is carried out according to the following diagram



General procedure: the morpholinomethyl resin (Novabiochem, 2 to 3 eq.) is preswollen in anhydrous solvents such as dichloromethane, dimethylformamide or tetrahydrofuran. Sulphonyl chloride (1.1 to 2 eq.) dissolved in anhydrous solvents such as dichloromethane, dimethylformamide or tetrahydrofuran is added, followed by 4-aminodisubstituted piperidine. The mixture is stirred for 16 to 48 hours. The aminomethyl resin (0.1 to 1.5 eq.) is added and the reaction medium is stirred overnight. In certain cases, ion exchange resin such as IRA68 or SAX is added and the mixture is stirred at ambient temperature for 1 to 18 hours. The resins are filtered on frit, on a SAX ion exchange resin cartridge (500 mg, Interchim) or on a basic alumina cartridge (500 mg, Interchim).

Example C3: N-(3,3-diphenylpropyl)-N-{1-[(4-methoxyphenyl)sulphonyl]-4-piperidinyl}-N'-[3-(trifluoromethyl)phenyl] urea ($C_{35}H_{36}F_3N_3O_4S$, M = 651.75)



27.5 mg (100 µmol, 2 eq.) of morpholinomethyl resin is preswollen in anhydrous tetrahydrofuran, then 4-methoxyphenylsulphonyl chloride (15.5 mg, 0.075 mmol, 1.5 eq.) then N-(3,3-diphenylpropyl)-N-(4-piperidinyl)-N'-[3-(trifluoromethyl)phenyl] urea (24.3 mg, 0.05 mmol) are added. The mixture is stirred overnight. The aminomethyl (20 mg) and SAX ion exchange resins are added and the mixture is stirred overnight. The resins are filtered and rinsed with dichloromethane. The oil obtained after evaporation is passed through a silica gel cartridge (500 mg, Interchim) eluting with ethyl acetate in order to obtain 18 mg (yield = 56 %) of a white solid after concentration.

NMR ^{1}H (CD_3OD, 400 MHz) δ: 7.71 (d, J = 9.2Hz, 2H); 7.65 (s, 1H); 7.51 (d, 1H); 7.41 (t, J = 7.6Hz, 1H); 7.29 (m, 9H); 7.20 (m, 2H); 7.11 (dd, J = 1.6 and 6.8Hz, 2H); 3.88 (s, 3H, OCH_3); 3.77 (d, J = 12.4Hz, 2H); 3.16 (t, J = 8Hz, 2H); 2.33 (m, 4H); 1.71 (d, J = 10Hz, 2H); 1.62 (qd, J = 4 and 12Hz, 2H); 1.3 (m, 2H). MS/LC: m/z = 652.4 (M+H).

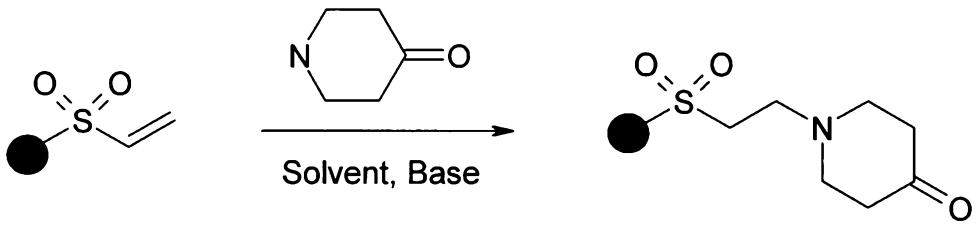
A series of sulphonamides was synthesized according to this procedure. The R_1, X_1, X_2 and X_3 groups which can be envisaged are those illustrated in points (A and B3a), A, (A and B3c) and B3b respectively.

D) Synthesis of tri-substituted piperidines in solid phase

It is carried out starting from vinyl sulphone resin (Kroll, F.E.K.; Morphy, R.; Rees, D.; Gani, D. *Tetrahedron Lett.* **1997**, *38*, 8573-8576; Brown, A.R. *J. Comb. Chem.* **1999**, *1*, 283-285) according to the following diagram:

D1) Preparation of the resin

It is carried out according to the following diagram:



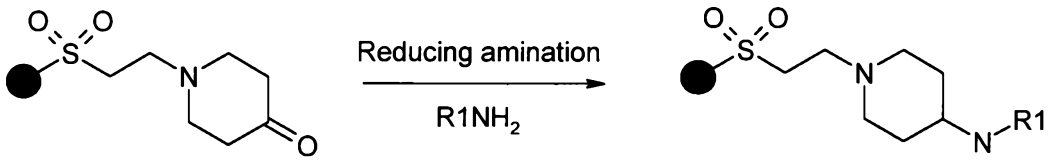
Triethylamine (1 eq.) is added to hydrated piperidone hydrochloride diluted in dimethylformamide. The mixture is heated until complete dissolution of the ketone. This solution is added to the vinyl sulphone resin (0.05 eq.) preswollen in dimethylformamide. After stirring for 24 to 72 hours at ambient temperature, the resin is filtered then washed several times with dimethylformamide, tetrahydrofuran, diethylether and dichloromethane.

Preparation 4

1.5 g of vinyl sulphone resin (Novabiochem, load rate of 1 mmol/g, 1.5 mmol) is preswollen in 50 ml of dimethylformamide. At the same time, 2.3 g (15 mmol, 10 eq.) of hydrated piperidone hydrochloride and 1.8 g (15 mmol, 10 eq.) of triethylamine are heated in 100 ml of dimethylformamide until complete dissolution. The yellowish solution is poured warm onto the resin and the mixture is stirred for 24 hours at ambient temperature. The resin is filtered then washed with dimethylformamide, tetrahydrofuran, diethylether and dichloromethane (3 times with each solvent) then dried under vacuum. 1.7 g of pale yellow resin is isolated with a load rate of 1mmol/g calculated after elementary analysis of the nitrogen.

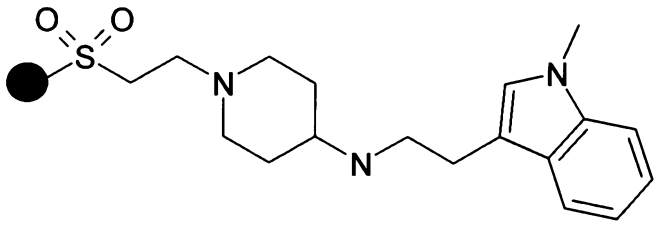
D2) Reducing amination on solid support

It is carried out according to the procedure described in the literature (Pelter, A.; Rosser, R.M. *J. Chem. Soc. Perkin Trans I* **1984**, 717-720; Bomann, M.D.; Guch, I.C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995-5996; Khan, N.M.; Arumugam, V.; Balasubramanian, S. *Tetrahedron Lett.* **1996**, *37*, 4819-4822) following the diagram:



General procedure: The primary amine (5 to 10 eq.) is added to the ketonic resin preswollen in trimethylorthoformate (TMOF) then the mixture is sonicated. Then the borane pyridine complex (8 M, 5 to 10 eq.) is added and the mixture is stirred for 12 to 72 hours. The resin is filtered, washed with solvents such as dichloromethane, dimethylformamide, methanol and tetrahydrofuran then dried under vacuum.

Preparation 5

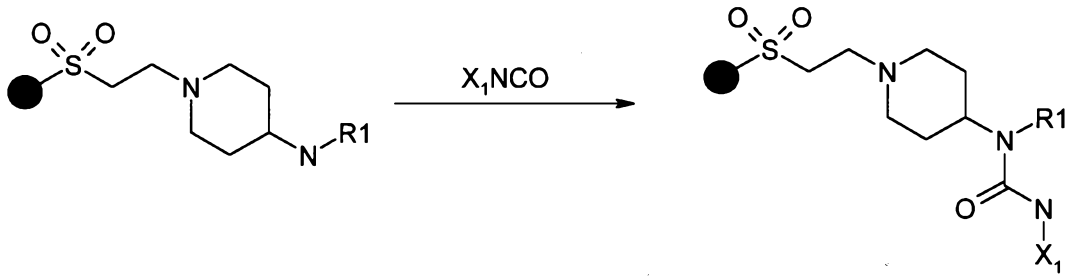


1 g (load rate of 1mmol/g, 1mmol) of ketonic resin is preswollen in TMOF. Then 2-(1-methyl-1*H*-indol-3-yl)ethylamine (1.01 g, 10 mmol, 10 eq.) then the borane pyridine complex (8M, 1.25 ml, 10 mmol, 10 eq.) are added. The mixture is stirred for 48 hours at ambient temperature. The resin is filtered, rinsed successively with

dichloromethane, dimethylformamide, methanol, tetrahydrofuran and dichloromethane then dried under vacuum. 1.05 g of pale yellow resin is thus obtained with a load rate of 0.91 mmol/g calculated after elementary analysis of the nitrogen.

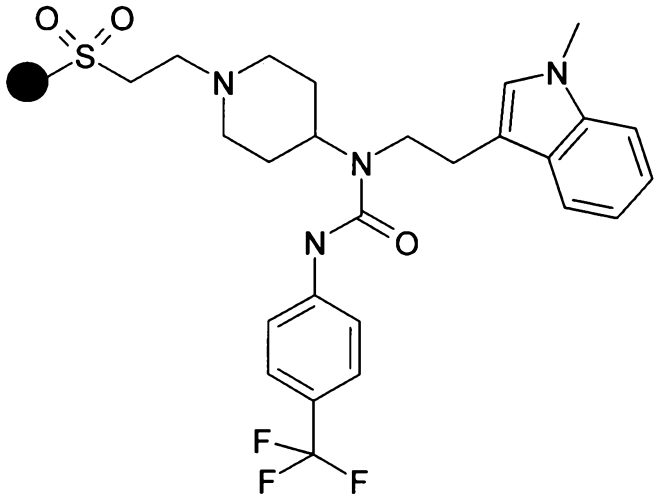
D3) Functionalization of the secondary amine

D3a) Functionalization with isocyanates



General procedure: the "secondary amine" resin is preswollen in a solvent such as dichloromethane or dimethylformamide before the addition of isocyanate (3 to 10 eq.). The mixture is stirred for 1 to 24 hours at ambient temperature. The resin is then filtered, washed with solvents such as dichloromethane, dimethylformamide and tetrahydrofuran then dried under vacuum.

Preparation 6



55 mg (50 µmol) of resin (see Preparation 5) is preswollen in anhydrous dichloromethane. Then 4-trifluorophenylisocyanate (28 mg, 150 µmol, 3 eq.) is added and the whole is stirred for 2 hours at ambient temperature. The resin is filtered, rinsed with tetrahydrofuran, with dimethylformamide, with tetrahydrofuran then with dichloromethane before being dried under vacuum.

D3b) Functionalization with sulphonyl chlorides

The functionalization operating method is identical to that stated in point B3b.

D3c) Functionalization with acid chlorides

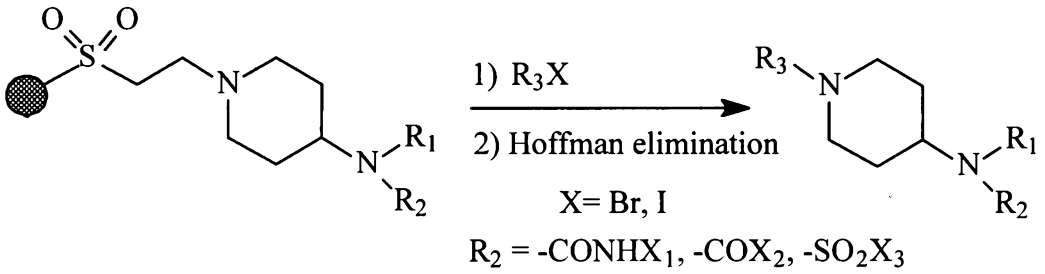
The functionalization operating method is identical to that stated in point B3c.

D3d) Functionalization with carboxylic acids

The functionalization operating method is identical to that stated in point B3d.

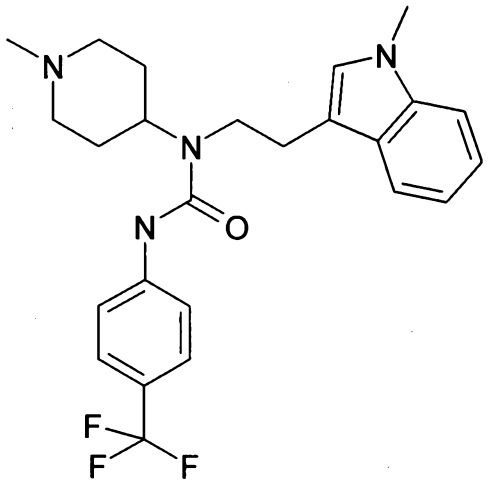
D4) Cleavage stage

The cleavage stage described below is valid whatever the functionalization carried out beforehand on the secondary amine:



General procedure: The disubstituted resin is swollen in solvents such as dichloromethane, dimethylformamide or tetrahydrofuran then the halide R_3X is added in which R_3 has the meaning indicated previously and X represents a halogen atom (5 eq.) and the mixture is stirred overnight at a temperature comprised between 20 and 60° C. The resin is filtered, followed by rinsing with solvents such as dimethylformamide, tetrahydrofuran, methanol and dichloromethane then drying under vacuum. The resin is swollen again in dichloromethane and basic ion exchange resin (Ouyang, X.; Armstrong, R.W.; Murphy, M.M. *J. Org. Chem.* **1998**, *63*, 1027-1032) is added. The whole is stirred for 48 hours at ambient temperature. The resins are filtered, rinsed with dichloromethane and the filtrate is concentrated under vacuum.

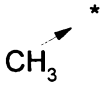
Example D4: *N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[4-(trifluoromethyl)phenyl] urea ($C_{25}H_{29}F_3N_4O$, M = 458.5)



55 mg (50 µmol) of the urea resin is swollen in dimethylformamide then 35 mg (250 µmol, 5 eq.) of iodomethane is added and the mixture is stirred for 18 hours at ambient temperature. The resin is filtered, rinsed with dimethylformamide, with tetrahydrofuran, with methanol and with dichloromethane then dried under vacuum. The resin is swollen again in dichloromethane then approximately 100 mg of amberlite IRA68 resin is added and the mixture is stirred for 48 hours. The resins are filtered, rinsed with dichloromethane and the filtrate is concentrated in order to produce 18 mg (yield = 78 %) of a colourless oil.

NMR ^{1}H (CD_3OD, 400 MHz) δ: 7.65 (m, 2H); 7.40 (m, 2H); 7.31 (m, 1H); 7.20 (t, 1H); 7.10 (m, 1H); 7.06 (m, 2H); 4.04 (m, 1H); 3.68 (s, 3H); 3.60 (t, 2H); 3.04 (t, 2H); 2.94 (m, 2H); 2.29 (s, 3H); 2.14 (m, 2H); 1.91 (m, 2H); 1.76 (m, 2H). MS/LC: m/z = 459.3 (M+H).

For the R_1, X_1, X_2 and X_3 groups as illustrated in points A and B above, the R_3 groups which can be envisaged for the synthesis of trisubstituted 4-aminopiperidines according to the above procedure, are the following: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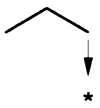
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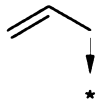
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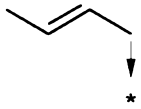
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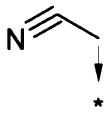
N
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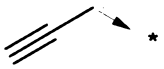
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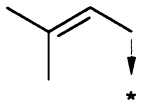
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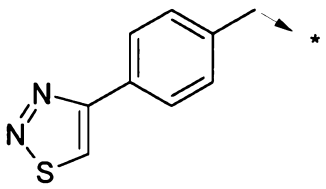
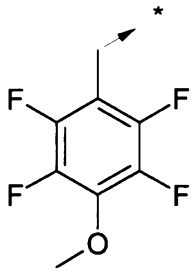
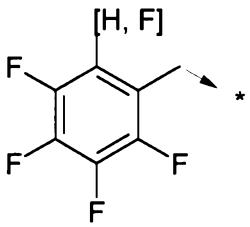
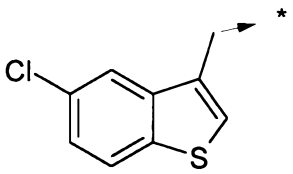
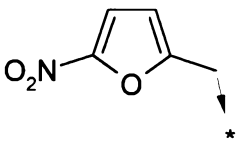

N
N
S
*


F
F
F
F
O
*


[H, F]
F
F
F
F
F
*


Cl
S
*


O2N
O
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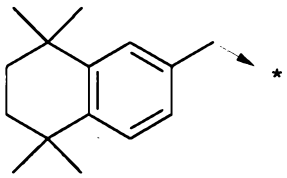
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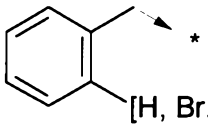
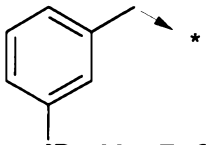
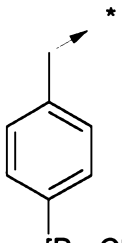


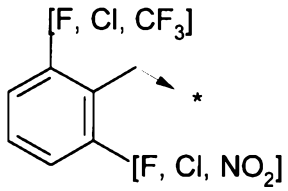
[H, Br, Me, F, Cl, CN, NO_2, CF_3, Ph, $OCHF_2$, I, OCF_3, SCF_3, $SCHF_2$]



[Br, Me, F, Cl, I, CF_3, CN, NO_2, OCF_3, OMe, $OCHF_2$, SCF_3, $SCHF_2$, CO_2Me]

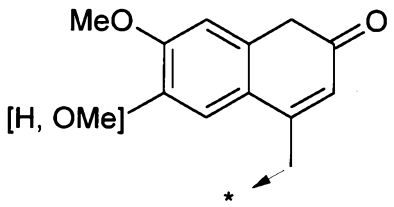


[Br, Cl, tBu, Me, F, CF_3, CN, NO_2, Ph, CO_2Me, OCF_3, $OCHF_2$, SCF_3, SO_2Me, I]



[F, Cl, CF_3]

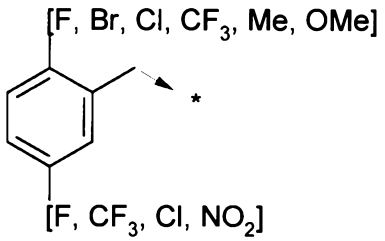
[F, Cl, NO_2]



MeO

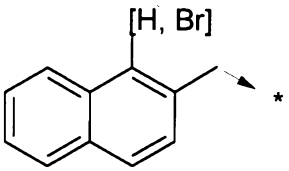
O

[H, OMe]

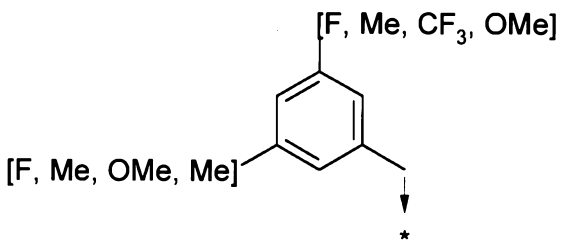


[F, Br, Cl, CF_3, Me, OMe]

[F, CF_3, Cl, NO_2]

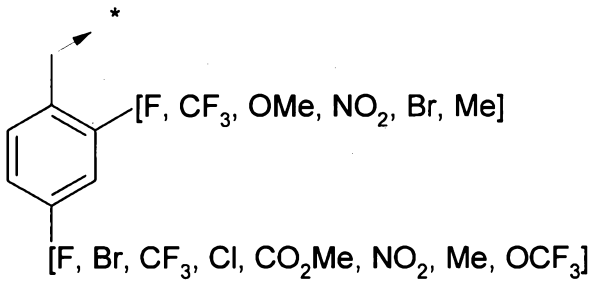


[H, Br]



[F, Me, CF_3, OMe]

[F, Me, OMe, Me]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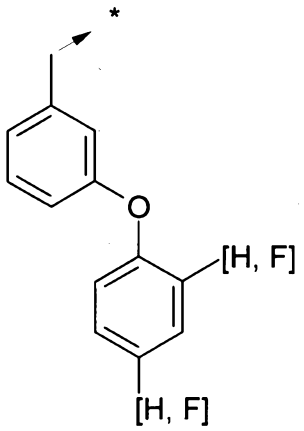
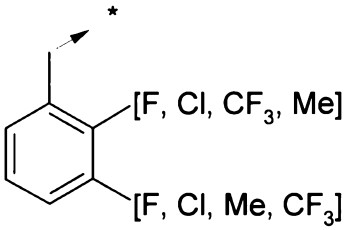
[F, CF3, OMe, NO2, Br, Me]
[F, Br, CF3, Cl, CO2Me, NO2, Me, OCF3]


*
O
[H, F]
[H, F]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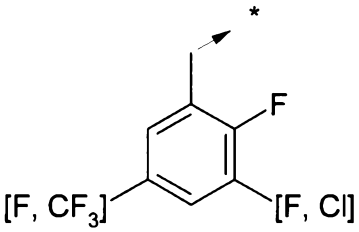
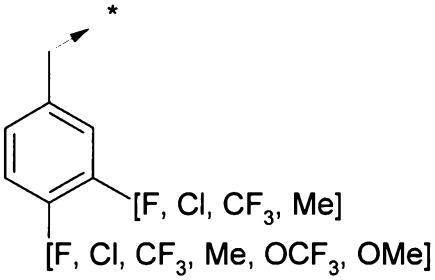
[F, Cl, CF3, Me]
[F, Cl, Me, CF3]


*
F
[F, CF3]
[F, Cl]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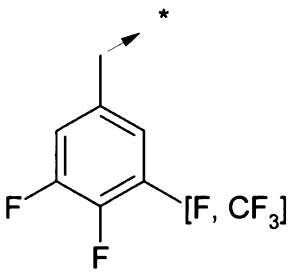
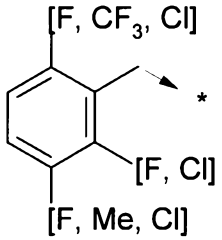
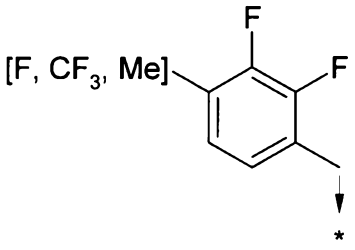
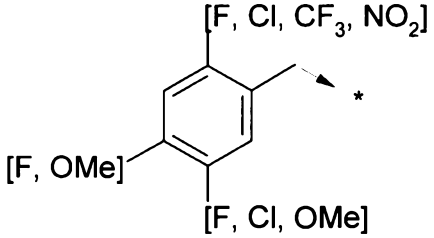
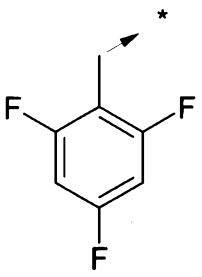
[F, Cl, CF3, Me]
[F, Cl, CF3, Me, OCF3, OMe]


*
F
[F, CF3]
F


[F, CF3, Cl]
*
[F, Cl]
[F, Me, Cl]


F
[F, CF3, Me]
F
*


[F, Cl, CF3, NO2]
*
[F, OMe]
[F, Cl, OMe]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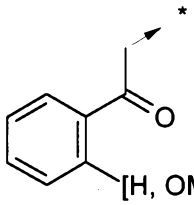
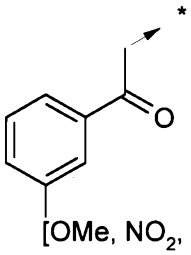
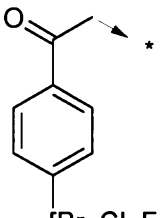
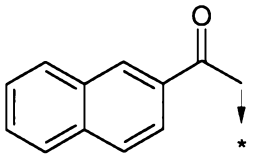
F
F
F


O
*
[H, OMe, NO2, Cl]


O
*
[OMe, NO2, Br, F, Cl, CN]


O
*
[Br, Cl, F, OMe, Ph, Me, NO2, N3, OCF3, CN, CF3, NEt2, nC4H9, nC5H11, OCH2Ph]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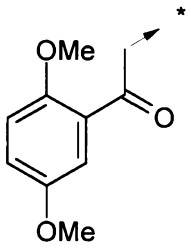
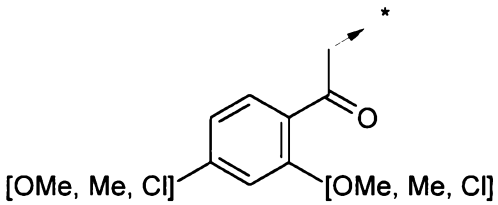

OMe
O
OMe
*


O
*
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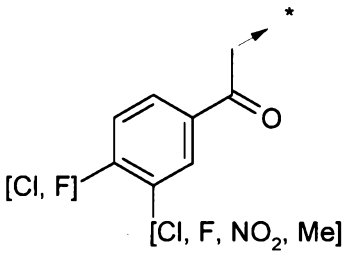
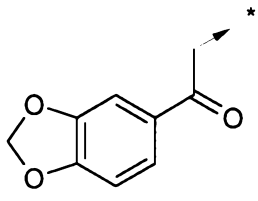
[OMe, Me, Cl]


O
*
[Cl, F]
[Cl, F, NO2, Me]


O
O
O
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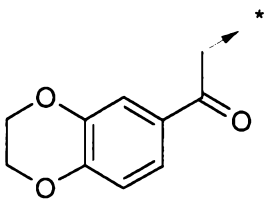
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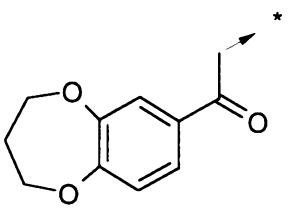
O
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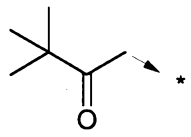
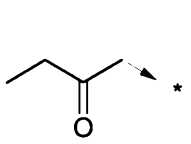
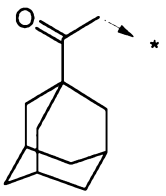
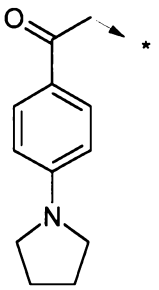
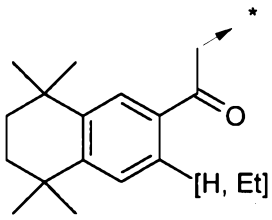
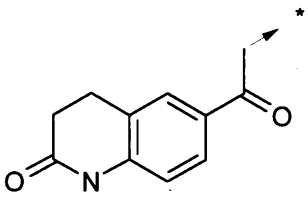
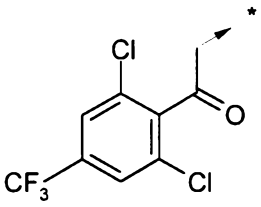
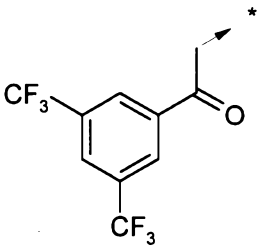
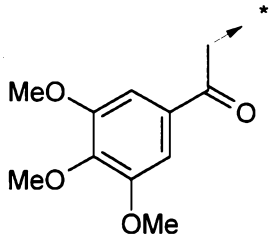
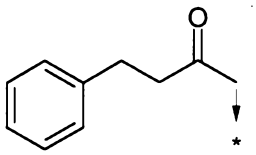
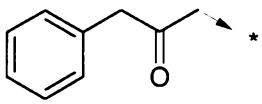
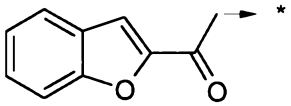
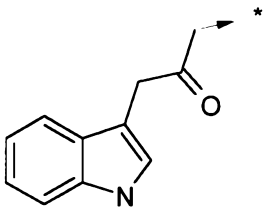
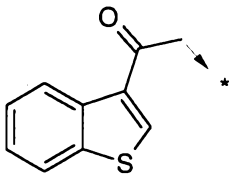
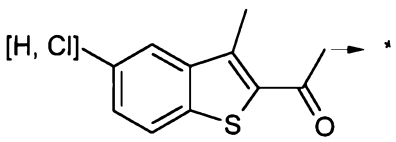
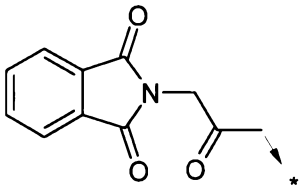
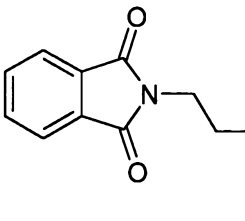
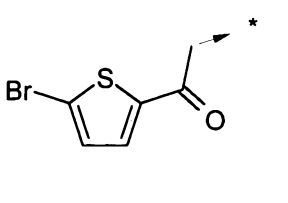
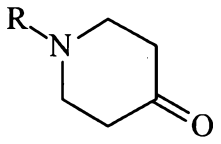
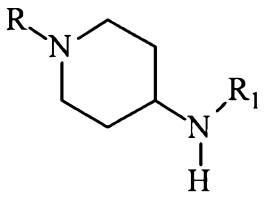



















A more particular subject of the invention is a process for the preparation, in liquid phase, of compounds of formula I as defined above, characterized in that it comprises

the reducing amination of the following N-substituted piperidone



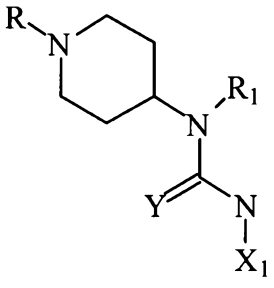
in which R represents the methyl or Boc radical, in the presence of an amine of formula R_1NH_2 in which R_1 has the meaning indicated above, in order to obtain the compound of formula 1



(1)

which compound of formula (1) is reacted with

A) either a compound of formula $X_1NC(Y)$ in which X_1 and Y have the meaning indicated above, in order to obtain a compound of formula (2)



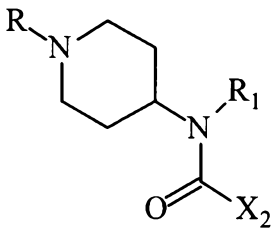
(2)

which compound of formula (2) represents the corresponding compound of formula (I) in which R_3 represents Me or Boc and which, when R_3 represents Boc, can be subjected to an acid treatment in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

which compound of formula (I) thus obtained can be reacted with a compound of formula $X_1NC(Y)$, X_2CO_2H or X_3SO_2Cl in which X_1, Y, X_2 and X_3 have the

meaning indicated above, in order to obtain the corresponding compound of formula I in which R_2 represents a radical of formula $-C(Y)NHX_1$ and R_3 the $-C(Y)-NHX_1$, $-C(O)X_2$ or SO_2X_3 radical respectively;

B) or a compound of formula X_2CO_2H in which X_2 has the meaning indicated above, in order to obtain a compound of formula (3)



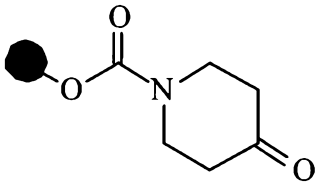
(3)

which compound of formula (3) represents the corresponding compound of formula (I) in which R_3 represents Me or Boc and which, when R_3 represents Boc, can be subjected to an acid treatment in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

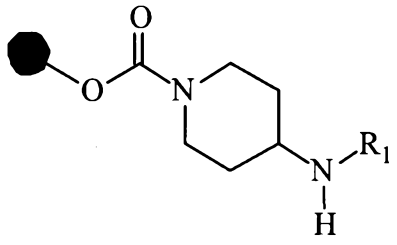
which compound of formula (I) thus obtained can be reacted with a compound of formula $X_1NC(Y)$, X_2CO_2H or X_3SO_2Cl in which X_1, Y, X_2 and X_3 have the meaning indicated above, in order to obtain the corresponding compound of formula I in which R_2 represents a radical of formula $-C(O)X_2$ and R_3 the $-C(Y)-NHX_1$, $-C(O)X_2$ or SO_2X_3 radical respectively.

A more particular subject of the invention is also a preparation process, in solid phase, for compounds of formula I as defined above, characterized in that it comprises

the reducing amination of the ketonic resin



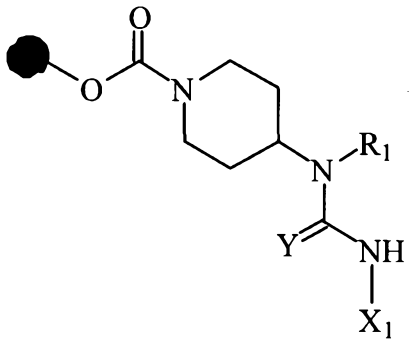
in the presence of an amine of formula R_1NH_2 in which R_1 has the meaning indicated above, in order to obtain the compound of formula (4)



(4)

which compound of formula (4) is reacted with

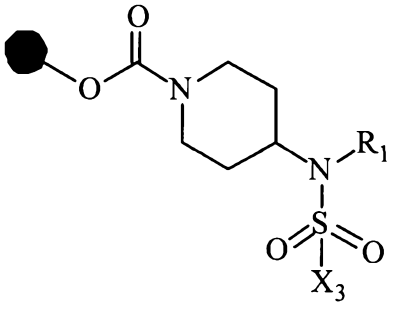
A) either a compound of formula $X_1NC(Y)$ in which X_1 and Y have the meaning indicated above, in order to obtain a compound of formula (5)



(5)

followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

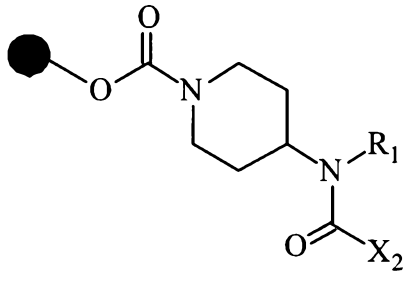
B) or a compound of formula X_3SO_2Cl in which X_3 has the meaning indicated above, in order to obtain a compound of formula (6)



(6)

followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

C) or a compound of formula X_2CO_2Cl in which X_2 has the meaning indicated above, in order to obtain a compound of formula (7)



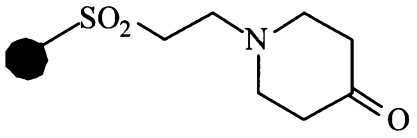
(7)

followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom;

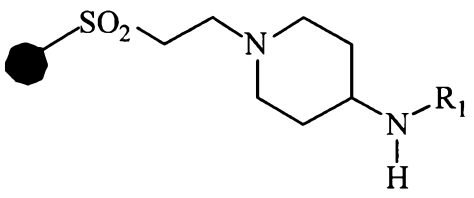
D) or a compound of formula X_2CO_2H in which X_2 has the meaning indicated above, in order to obtain a compound of formula (7) as defined above, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom.

Finally a more particular subject of the invention is a preparation process, in solid phase, for compounds of formula I as defined above, characterized in that it comprises

the reducing amination of the ketonic resin



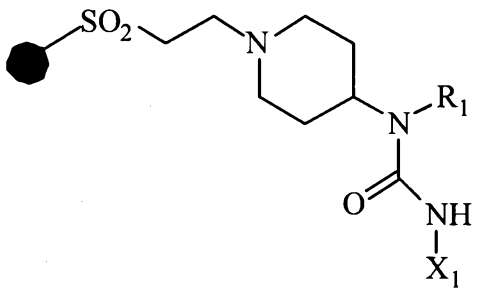
in the presence of an amine of formula R_1NH_2 in which R_1 has the meaning indicated above, in order to obtain the compound of formula (8)



(8)

which compound of formula (8) is reacted with

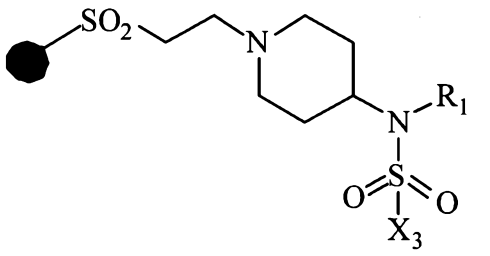
A) either a compound of formula $X_1NC(O)$ in which X_1 has the meaning indicated above, in order to obtain a compound of formula (9)



(9)

which compound (9) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined above and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I);

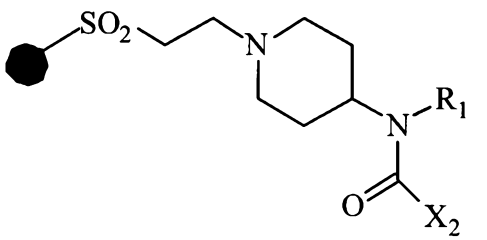
B) or a compound of formula X_3SO_2Cl in which X_3 has the meaning indicated above, in order to obtain a compound of formula (10)



(10)

which compound (10) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined above and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I);

C) or a compound of formula X_2CO_2Cl in which X_2 has the meaning indicated above, in order to obtain a compound of formula (11)



(11)

which compound (11) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined above and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I);

D) or a compound of formula X_2CO_2H in which X_2 has the meaning indicated above, in order to obtain a compound of formula (11) as defined above,

which compound (11) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined above and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I).

Compounds I of the present invention have useful pharmacological properties. Thus it has been discovered that compounds I of the present invention have a high affinity for one (or more) of the somatostatin receptors. They can be used as non-peptide agonists or antagonists of somatostatin in a selective or non-selective manner.

The compounds of the present invention can therefore be used in different therapeutic applications. They can advantageously be used to treat the pathological states or the diseases as presented above and in which one (or more) of the somatostatin receptors are involved.

An illustration of the pharmacological properties of the compounds of the invention will be found hereafter in the experimental part.

A subject of the present Application is also, as medicaments, the products of formula I as defined above, as well as the addition salts with pharmaceutically acceptable mineral or organic acids of said products of formula I, as well as the pharmaceutical compositions containing, as active ingredient, at least one of the medicaments as defined above, in combination with a pharmaceutically acceptable support.

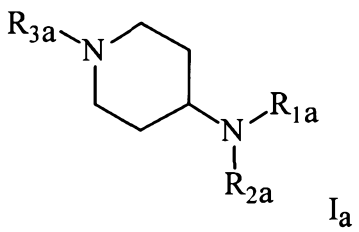
The pharmaceutical composition can be in the form of a solid, for example, powders, granules, tablets, gelatin capsules or suppositories. Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax.

The pharmaceutical compositions containing a compound of the invention can also be presented in liquid form, for example, solutions, emulsions, suspensions or syrups. Appropriate liquid supports can be, for example, water, organic solvents

such as glycerol or glycols, similarly their mixtures, in varying proportions, in water, with added pharmaceutically acceptable oils or fats. The sterile liquid compositions can be used for intramuscular, intraperitoneal or subcutaneous injections and the sterile compositions can also be administered intravenously.

Certain compounds of general formula I described previously are covered by the Application DE 2751138. This DE application describes compounds which antagonise the effects of dopamine and of endogenous or exogenous dopaminergic agents and activate the serotoninergic mechanism, very different activities from that described in the present Application.

A subject of the present invention is also the use of the compounds of general formula I_a



I_a

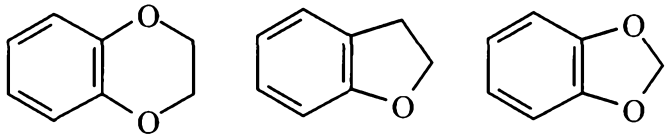
in racemic, enantiomeric form or all combinations of these forms, in which:

R_{1a} represents a linear or branched $(C_1\text{-}C_{16})$alkyl, alkenyl, alkynyl, $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $-(CH_2)_m\text{-}Z_{12}$ radical in which

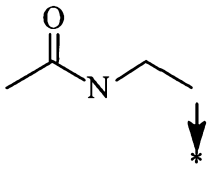
Z_{11} represents an optionally substituted $(C_1\text{-}C_6)$alkyl or aryl,

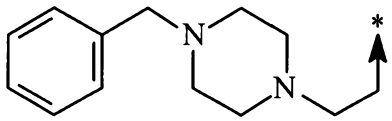
Z_{12} represents cyano, cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl optionally substituted, aryl optionally substituted or heteroaryl optionally substituted,

or Z_{12} represents a radical of formula



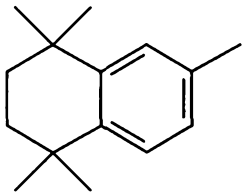
or R_{1a} represents a radical of formula

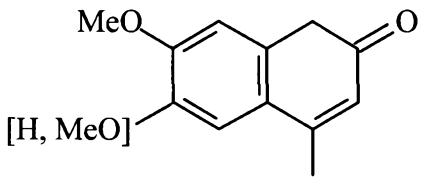




R_{2a} represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3;

R_{3a} represents the hydrogen atom, an optionally substituted alkyl, alkenyl, alkynyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl radical, or a radical of formula $-C(Y)-NHX_1$, $-(CH_2)_n-C(O)X_2$, SO_2X_3 or



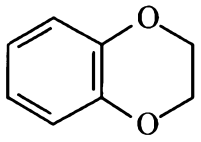


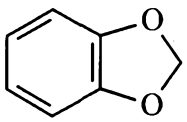
X_1 represents a linear or branched (C_1-C_{15})alkyl, alkenyl, alkynyl, $-(CH_2)_m-Y-Z_{21}$ or $-(CH_2)_pZ_{22}$ radical in which

Z_{21} represents a (C_1-C_6)alkyl

Z_{22} represents cyclohexenyl, indanyl, *bis*-phenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl or heteroaryl optionally substituted,

or Z_{22} represents a radical of formula



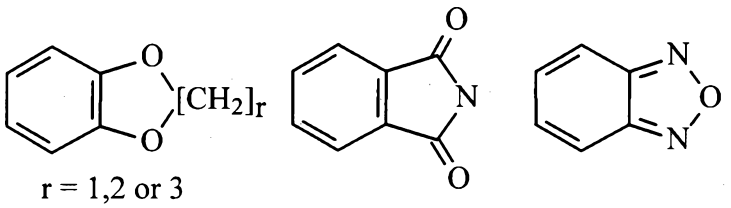


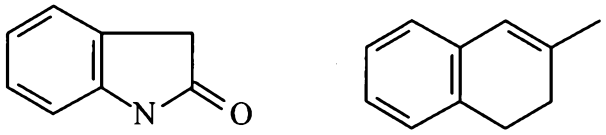
X_2 represents a linear or branched (C_1-C_{10})alkyl, alkenyl optionally substituted by a phenyl radical (the phenyl radical itself being optionally substituted), alkynyl radical, or a radical of formula $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ or $-(CH_2)_p-U-Z_{24}$ in which

Z_{23} represents a (C_1-C_6)alkyl or aryl optionally substituted;

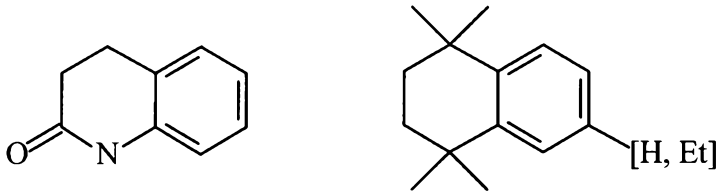
Z_{24} represents alkyl, cyclohexenyl, *bis*-phenyl, (C_3-C_7)cycloalkyl optionally substituted, (C_3-C_7)heterocycloalkyl, cyano, amino, mono or di-alkylamino, or aryl or heteroaryl optionally substituted,

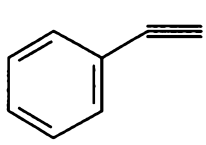
or Z_{24} represents a radical of formula

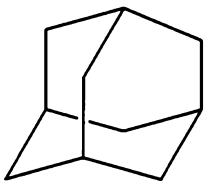


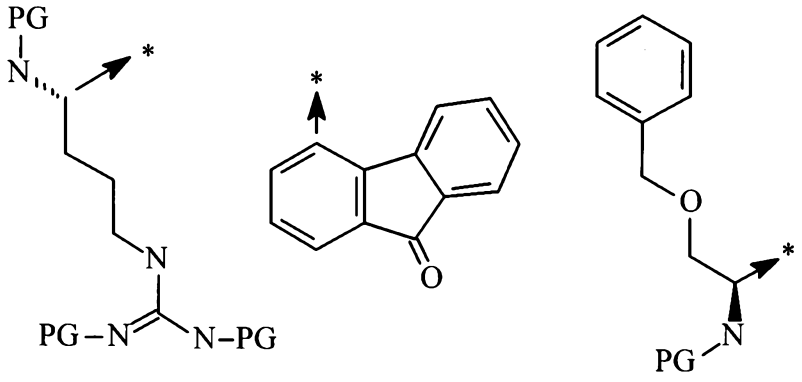


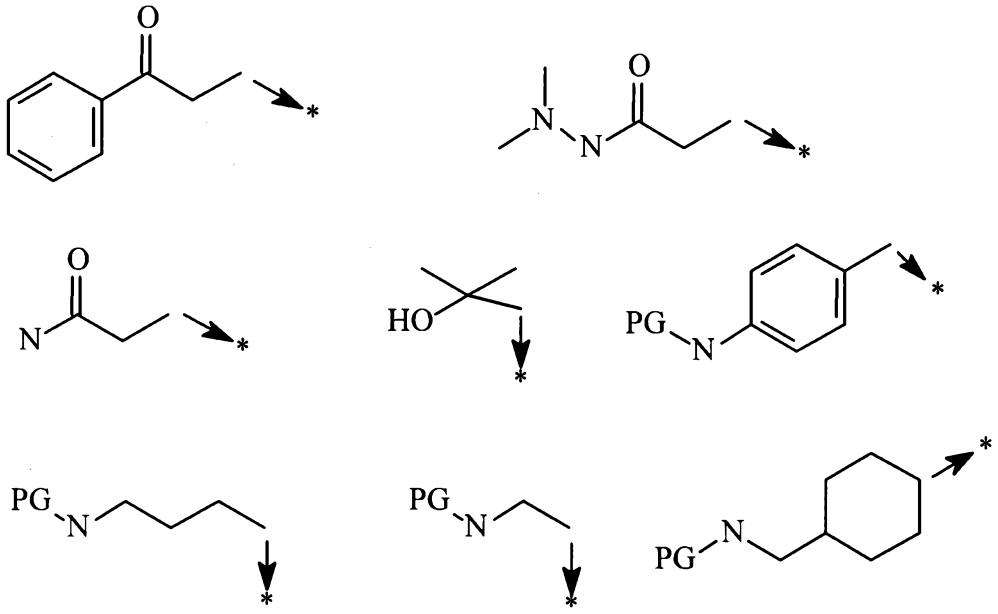
or X_2 represents a radical shown below:









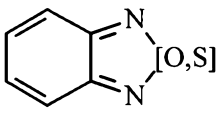


where the protective group (PG) represents H or *tert*-butyloxycarbonyl;

X_3 represents a linear or branched (C_1-C_{10})alkyl, alkenyl optionally substituted by a phenyl radical (the phenyl radical itself being optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ radical in which

Z_{25} represents aryl or heteroaryl optionally substituted,

or X_3 represents a radical of formula

 optionally substituted by one or more identical or different

halo radicals;

Y represents an oxygen or sulphur atom;

W represents an oxygen, sulphur or SO_2 atom;

U represents a covalent bond or the oxygen atom;

n is an integer from 0 to 4;

m is an integer from 1 to 6;

p is an integer from 0 to 6;

q is an integer from 0 to 2,

or their addition salts with pharmaceutically acceptable mineral or organic acids, for the preparation of a medicament intended to treat pathological states or diseases in which one or more somatostatin receptors is (are) involved.

A more particular subject of the invention is the use of products of general formula I_a as defined above, characterized in that

i) the substituent(s) which can be carried by the aryl radicals represented by Z_{11} and Z_{12} and heteroaryl represented by Z_{12} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phenyl, phenoxy, aminosulphonyl radicals;

ii) the substituent(s) which can be carried by the heterocycloalkyl radical represented by Z_{12} are chosen independently from the oxy and alkyl radicals;

iii) the substituent(s) which can be carried by the aryl and heteroaryl radicals represented by Z_{22} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkenyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, aminosulphonyl, piperidinosulphonyl, mono- or di-alkylamino, -C(O)-O-alkyl, -C(O)-alkyl radicals, or phenyl, phenoxy, phenylthio, benzyloxy, the phenyl radical being able to be substituted;

iv) the substituent(s) which can be carried by the aryl radicals represented by Z_{23} and Z_{24}, cycloalkyl and heteroaryl represented by Z_{24} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, $OCHF_2$, SCF_3, nitro, cyano, azido, hydroxy, -C(O)O-alkyl, -O-C(O)-alkyl, -NH-C(O)-alkyl, alkylsulphonyl, mono- or di-alkylamino, amino, aminoalkyl, pyrrolyl, pyrrolydinyl radicals or the phenyl, phenoxy, phenylthio, benzyl, benzyloxy radicals the aryl radical of which is optionally substituted by one or more alkyl, CF_3 or halo radicals;

v) the substituent(s) which can be carried by the aryl and heteroaryl radicals represented by Z_{25} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, nitro, cyano, -NH-C(O)-alkyl, alkylsulphonyl, amino, mono- and di-alkylamino, phenyl, pyridino radicals;

vi) the substituent which can be carried by the alkyl radical represented by R_3 is the cyano radical.

vii) the substituent(s) which can be carried by the aralkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, nitro, cyano, -C(O)O-alkyl, alkylsulphonyl,

thiadiazolyl radicals, or the phenyl and phenoxy radicals the phenyl radical of which is optionally substituted by one or more halo radicals.

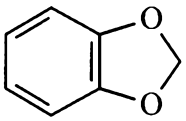
viii) the substituent(s) which can be carried by the heteroarylalkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo or nitro radicals.

A more particular subject of the present invention is the use of the compounds of general formula I_a as defined above, in which R_{1a} represents a linear or branched $(C_1\text{-}C_6)$alkyl radical, the $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $-(CH_2)_m\text{-}Z_{12}$ radical in which

Z_{11} represents a $(C_1\text{-}C_6)$alkyl,

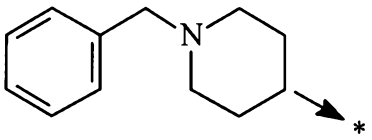
Z_{12} represents *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl optionally substituted, or aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy radicals,

or Z_{12} represents



Y represents the oxygen atom,

or R_{1a} represents a radical of formula

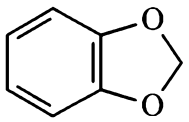


A more particular subject of the present invention is the use of compounds of general formula I_a as defined above, in which R_{2a} represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{15})$alkyl, or $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl or heteroaryl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, –C(O)-O-alkyl, -C(O)-alkyl, or phenyl radicals,

or Z_{22} represents a radical of formula



X_2 represents a linear or branched $(C_1\text{-}C_{10})$alkyl, alkynyl, $\text{-}(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $\text{–}(CH_2)_p\text{-}U\text{-}Z_{24}$ radical in which

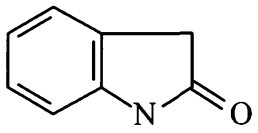
W represents SO_2,

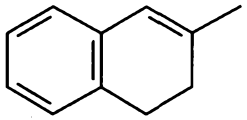
U represents a covalent bond,

Z_{23} represents an aryl radical;

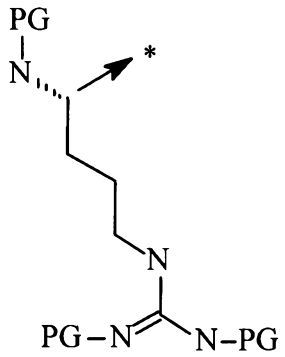
Z_{24} represents cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl optionally substituted by an aminoalkyl radical, or aryl or heteroaryl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, $\text{-}CF_3$, $\text{-}OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyl, mono- or di-alkylamino, amino

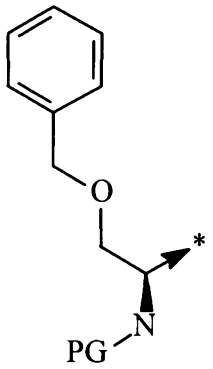
or Z_{24} represents a radical of formula





or X_2 represents





X_3 represents a $\text{–}(CH_2)_pZ_{25}$ radical in which Z_{25} represents an aryl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3.

A more particular subject of the present invention is the use of the compounds of general formula I_a as defined above, in which R_{3a} represents the hydrogen atom, an alkyl, alkenyl, heteroarylalkyl radical or a radical optionally substituted of formula $\text{-}C(Y)\text{-}NHX_1$, $\text{-}C(O)X_2$ or SO_2X_3 in which

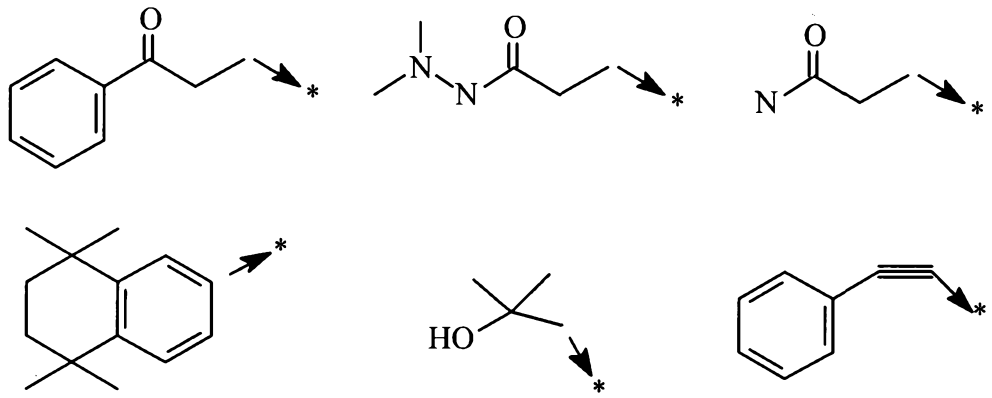
X_1 represents a $\text{–}(CH_2)_pZ_{22}$ radical in which

Z_{22} represents an aryl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals;

X_2 represents the vinyl radical substituted by a phenyl, the phenyl radical itself being optionally substituted by one or more halo, or $-(CH_2)_p$-U-Z_{24} radicals in which

Z_{24} represents alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, *bis*-phenyl, amino, mono or di-alkylamino, or aryl or heteroaryl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, hydroxy, CF_3, nitro, amino, mono- and di-alkylamino, pyrrolyl,

or X_2 represents a radical of formula



X_3 represents a linear or branched (C_1-C_{10})alkyl radical, the vinyl radical substituted by a radical (the phenyl radical itself being optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ in which

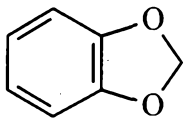
Z_{25} represents aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals.

Preferentially, R_{1a} represents a linear or branched (C_1-C_6)alkyl radical, the $-(CH_2)_m$-Y-Z_{11} or $-(CH_2)_m$-Z_{12} radical in which

Z_{11} represents a (C_1-C_6)alkyl,

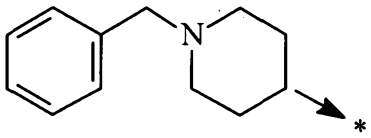
Z_{12} represents naphthyl, morpholino, *bis*-phenyl, pyrrolidinyl substituted by the oxy radical, or the phenyl, piperazinyl, pyridinyl and indolyl radicals which are optionally substituted by one or more substituents chosen independently from the bromo, fluoro, chloro, alkyl, alkoxy, -CF_3, -OCF_3 radicals;

or Z_{12} represents



Y represents the oxygen atom,

or R_{1a} represents a radical of the following formula:

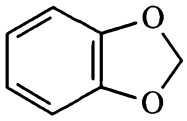


Preferentially, R_{2a} represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{10})$alkyl, or $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents cyclohexyl, cyclohexenyl, *bis*-phenyl, morpholino, piperidino, mono- or di-alkylamino, -C(O)-O-alkyl, or phenyl, naphthyl or furyl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, –C(O)-O-alkyl, -C(O)-alkyl or phenyl radicals,

or Z_{22} represents a radical of formula



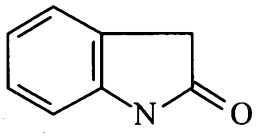
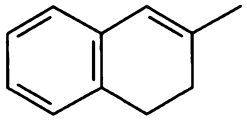
X_2 represents an alkyl, alkynyl, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $-(CH_2)_pZ_{24}$ radical in which

W represents SO_2;

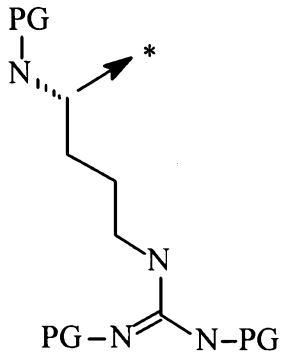
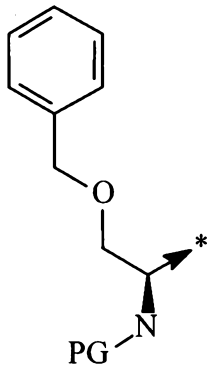
Z_{23} represents the phenyl radical;

Z_{24} represents cyclohexenyl, *bis*-phenyl, cyclohexyl optionally substituted by an aminoalkyl radical, or phenyl, naphthyl, benzothienyl, thienyl or indolyl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyl, -NH-C(O)-alkyl, mono- or di-alkylamino, amino, or

Z_{24} represents a radical of formula

or X_2 represents

X_3 represents a–$(CH_2)_pZ_{25}$ radical in which Z_{25} represents the phenyl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3,

Preferentially, R_{3a} represents the hydrogen atom, an alkyl, alkenyl or furyl-methyl radical substituted by one or more nitro radicals, or a radical of formula –C(Y)-NHX_1, -$C(O)X_2$ or SO_2X_3 in which

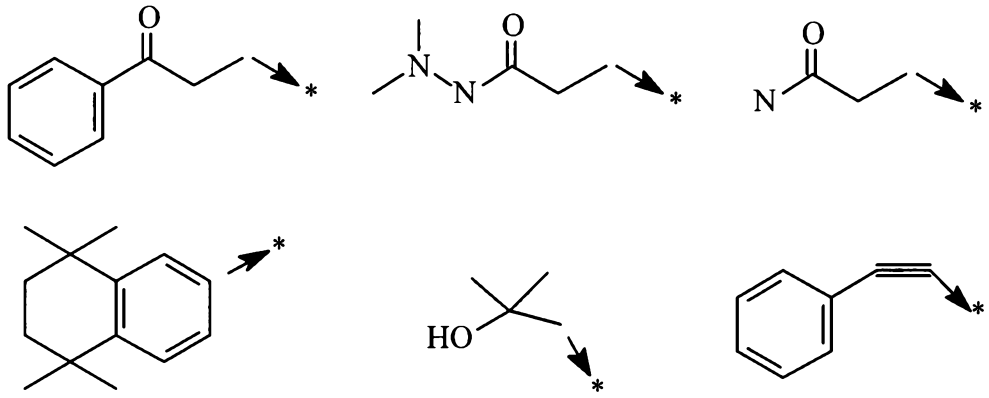
X_1 represents a –$(CH_2)_pZ_{22}$ radical in which

Z_{22} represents the phenyl or naphthyl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals,

X_2 represents the vinyl radical substituted by a phenyl radical itself optionally substituted by one or more halo, or –$(CH_2)_p$-U-Z_{24} radicals in which

Z_{24} represents alkyl, cyclohexyl, tetrahydrofuryl, *bis*-phenyl, amino, mono or di-alkylamino, or phenyl, indolyl, thienyl, pyridinyl, benzothienyl and furyl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, amino, mono- and di-alkylamino, nitro, hydroxy, pyrrolyl

or X_2 represents a radical of formula



X_3 represents a linear or branched (C_1-C_{10})alkyl radical, the vinyl radical substituted by a phenyl, CF_3, or $-(CH_2)_pZ_{25}$ radical in which

Z_{25} represents a phenyl, naphthyl, thienyl, pyrazolyl or thiazolyl radical optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals;

Very preferentially, R_{1a} represents the $-(CH_2)_mZ_{12}$ radical in which m = 2 and Z_{12} represents *bis*-phenyl or the indolyl radical substituted by one or more substituents chosen independently from the alkyl and alkoxy radicals.

Very preferentially, R_{2a} represents the radicals of formula $-C(Y)NHX_1$ and $-C(O)X_2$ in which

Y represents S;

X_1 represents a phenyl radical optionally substituted by one or more azido radicals,

X_2 represents $-(CH_2)_pZ_{24}$ in which

p is equal to 1, 2 or 3,

Z_{24} represents cyclohexyl, or phenyl or benzothienyl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo or $-CF_3$.

Very preferentially, R_{3a} represents the hydrogen atom or the methyl radical.

All the technical and scientific terms used in the present text have the meaning known to a person skilled in the art. Furthermore, all patents (or patent applications) as well as other bibliographical references are incorporated by way of reference.

Experimental part:

Other compounds according to the invention obtained according to the procedures of Examples A, B, C and D described previously, are set out in the table below.

The compounds are characterized by their retention time (rt), expressed in minutes, and their molecular peak (M+H+) determined by mass spectroscopy (MS).

For the mass spectroscopy, a single quadripole mass spectrometer (Micromass, Platform model) equipped with an electrospray source is used with a resolution of 0.8 Da at 50% valley. The conditions for Examples 1 to 778 below, are as follows:

Conditions C1 and C2

Eluent: A: Water + 0.02 % trifluoracetic acid; B: acetonitrile

T (min)	*A %*	*B %*
0	100	0
1	100	0
10	15	85
12	15	85

Condition C1	Condition C2
Flow rate: 1.1 ml/min Injection: 5 µl Temp: 40° C Wavelength (% UV): 210 nm Column: Uptisphere ODS 3 µm 33 * 4.6 mm i.d	Flow rate: 1.1 ml/min Injection: 20 µl Temp: 40° C Wavelength (% UV): 210 nm Column: Kromasyl ODS 3.5 µm 50 * 4.6 mm i.d

Conditions C3

Eluent: A: Water + 0.02 % trifluoracetic acid; B: acetonitrile

T (min)	*A %*	*B %*
0	90	10
6	15	85
10	15	85

Flow rate: 1 ml/min

Injection: 5 µl

Column: Uptisphere ODS 3 µm 50 * 4.6 mm i.d

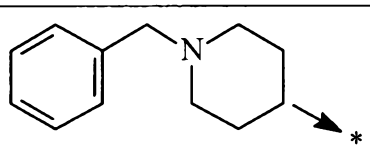
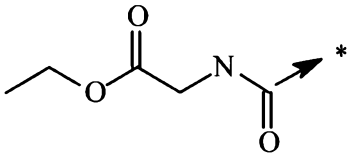
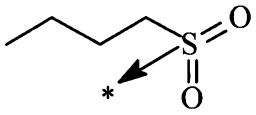
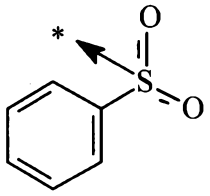
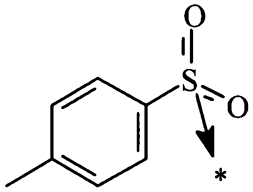
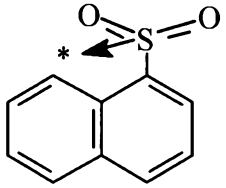
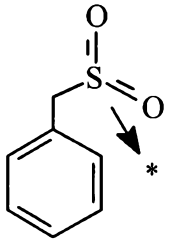
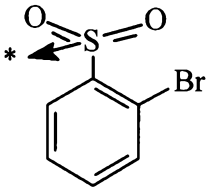
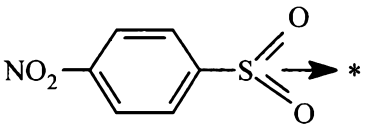
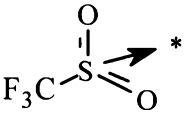
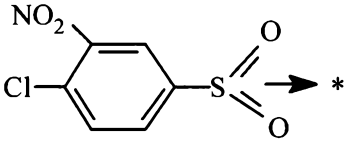
Temp: 40° C

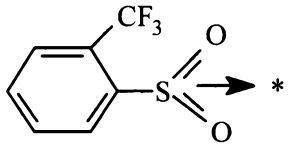
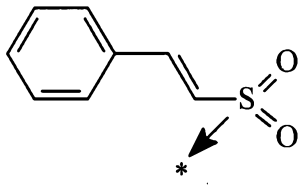
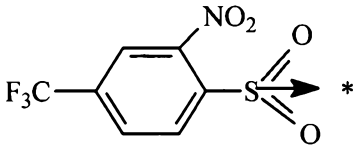
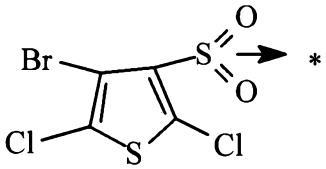
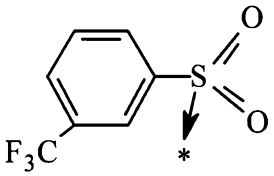
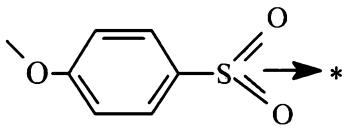
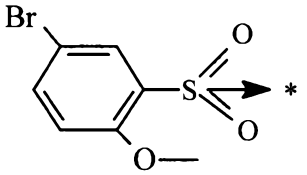
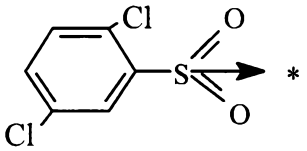
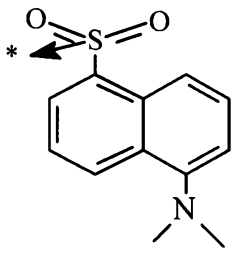
Wavelength (% UV): 220 nm

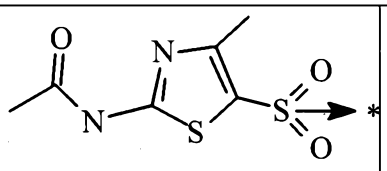
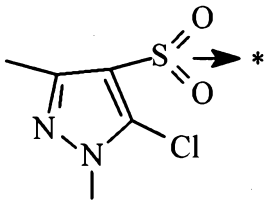
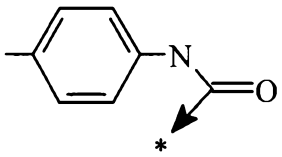
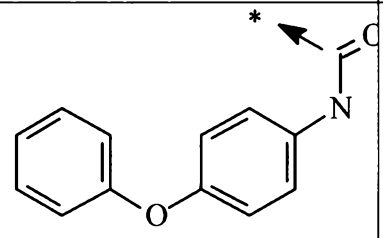
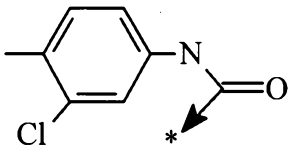
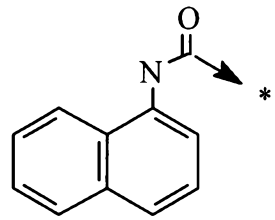
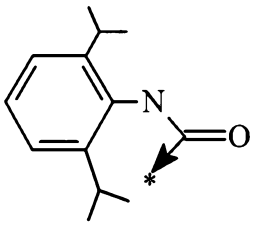
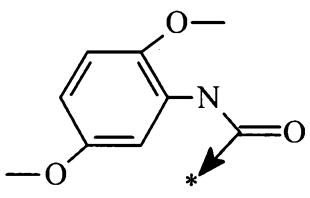
The conditions depending on the examples, are as follows:

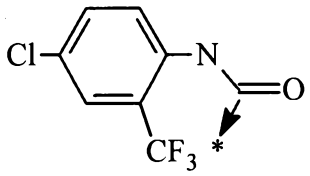
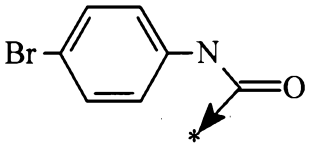
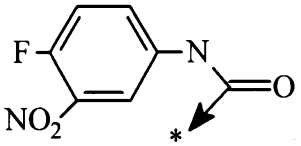
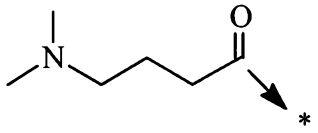
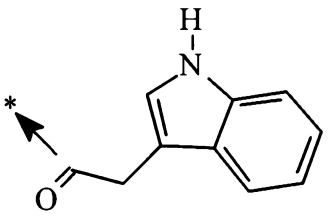
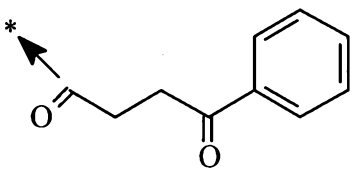
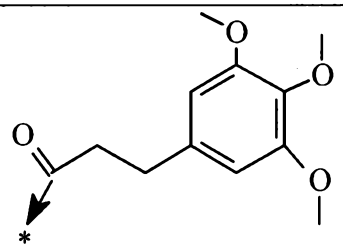
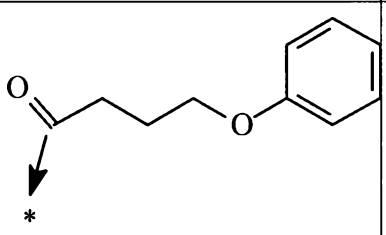
Examples	Conditions
1 to 29	C2
30 to 263	C1
264 to 425	C3
426 to 456	C2
457 to 503	C3
504 to 586	C1
587 to 778	C3

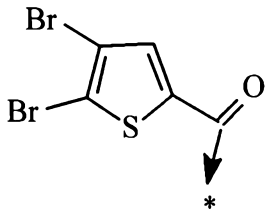
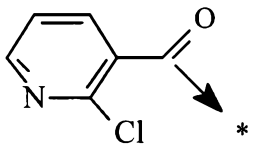
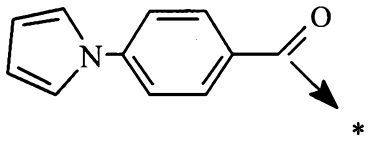
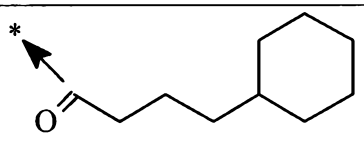
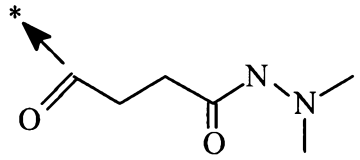
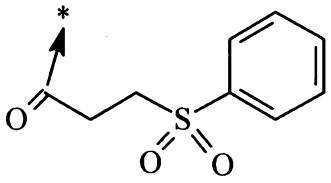
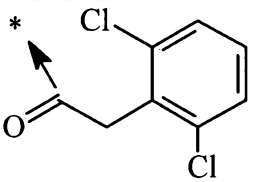
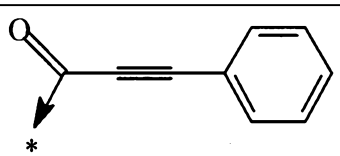
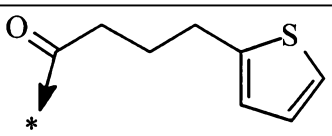
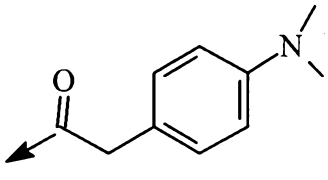
These examples are presented to illustrate the above procedures and should in no way be considered as limiting the scope of the invention.

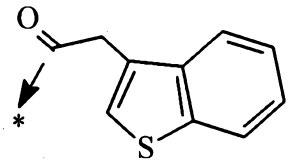
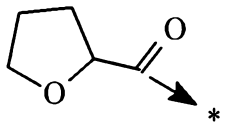
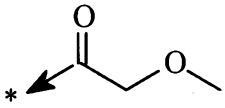
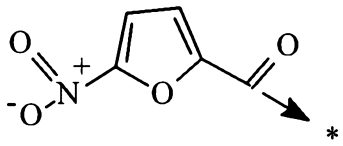
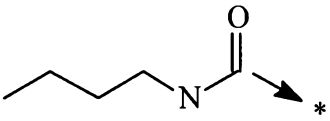
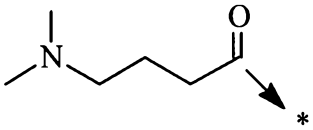
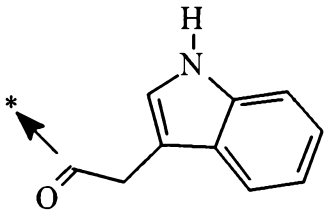
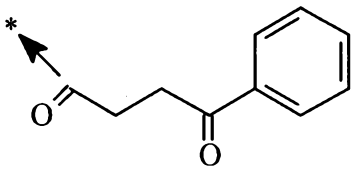
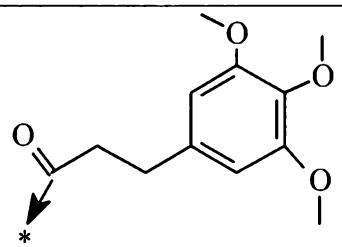
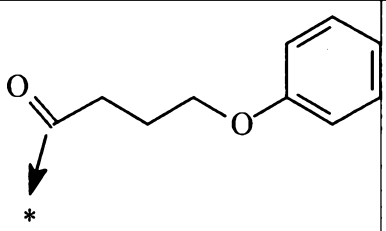
Ex	R_1	R_2	R_3	Purity (in %)	rt	M+H+
1				66	7.6	523.3
2	"	"		94	7.7	543.2
3	"	"		96	8.1	557.2
4	"	"		98	8.5	593.2
5	"	"		95	7.8	557.2
6	"	"		97	8.1	623.1
7	"	"		95	8.1	588.2
8	"	"		19	8.1	535.2
9	"	"		99	8.5	622.2

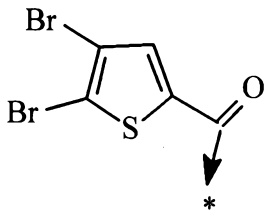
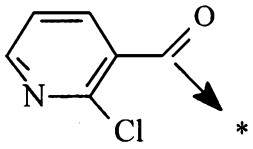
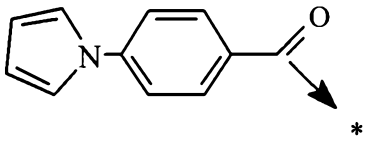
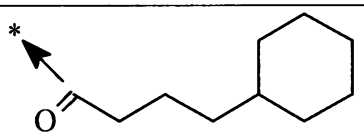
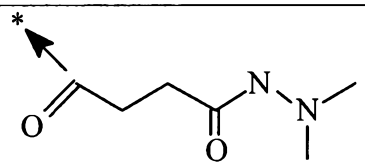
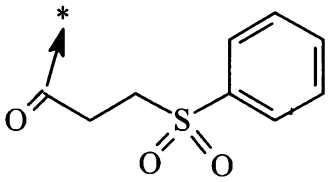
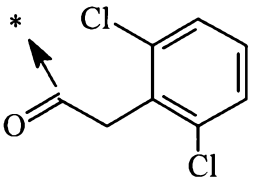
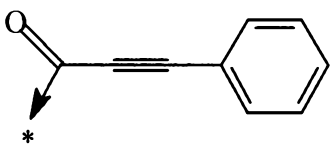
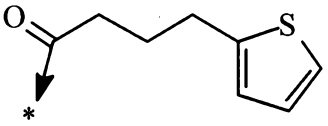
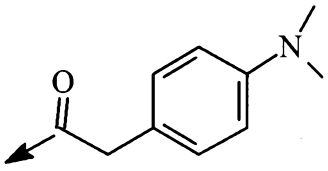
10	"	"		80	8.4	611.2
11	"	"		99	8.2	569.2
12	"	"		93	8.9	656.2
13	"	"		85	9.1	697.0
14	"	"		95	8.7	611.2
15	"	"		87	7.8	573.2
16	"	"		100	8.4	653.2
17	"	"		97	8.6	611.1
18	"	"		99	8.7	636.3

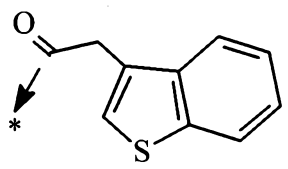
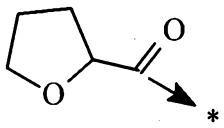
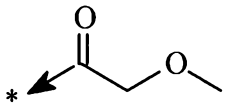
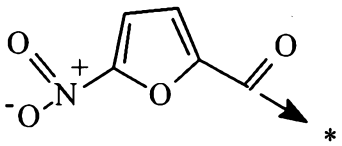
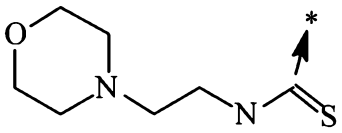
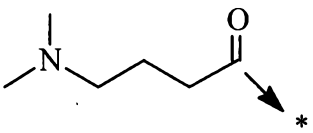
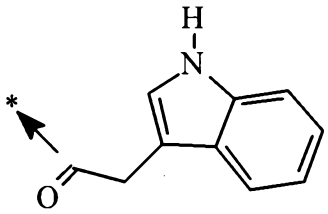
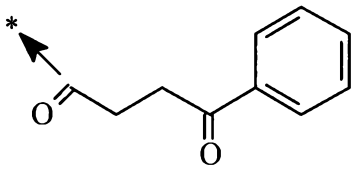
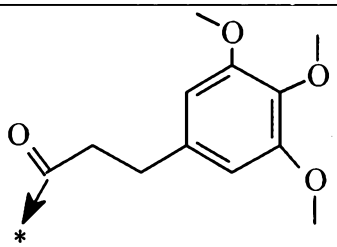
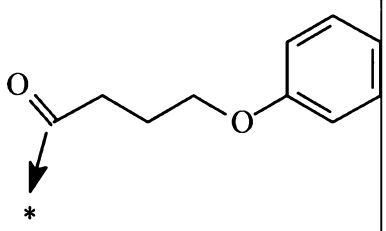
19	"	"		83	7.2	621.2
20	"	"		98	7.4	595.2
21	"	"		84	7.4	536.3
22	"	"		99	8.4	614.3
23	"	"		63	8.2	570.2
24	"	"		92	7.5	572.3
25	"	"		93	8.4	606.4
26	"	"		96	7.4	582.3

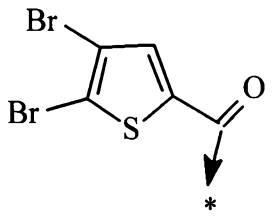
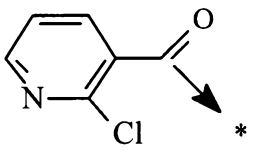
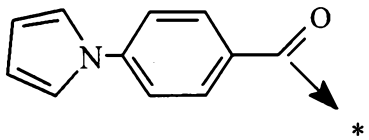
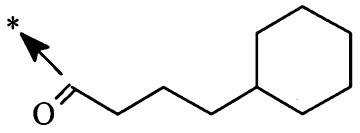
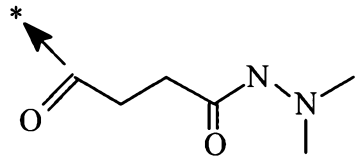
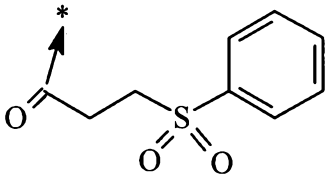
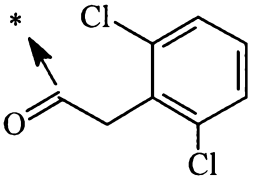
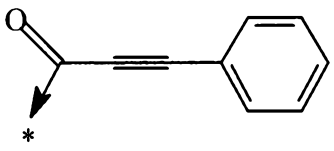
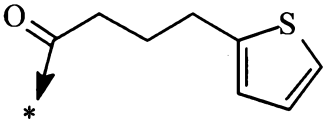
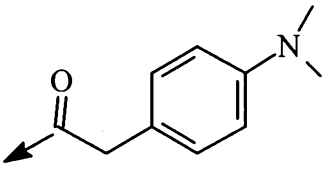
27	"	"		93	8.1	624.2
28	"	"		93	7.8	602.2
29	"	"		95	7.4	585.2
30	"	"		87.39	4.0	516.4
31	"	"		92	5.5	560.3
32	"	"		90	5.7	563.3
33	"	"		87.73	5.6	625.4
34	"	"		85.41	6.0	565.4

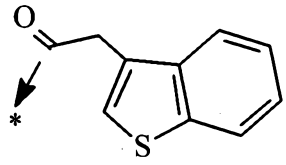
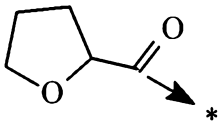
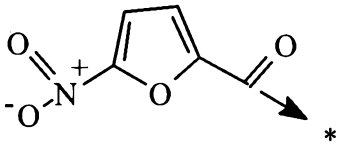
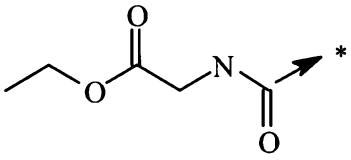
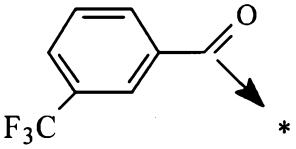
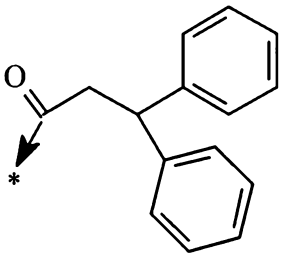
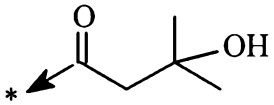
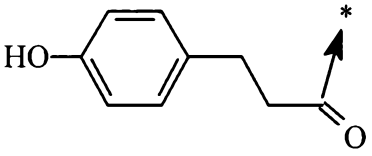
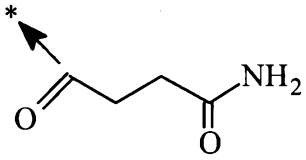
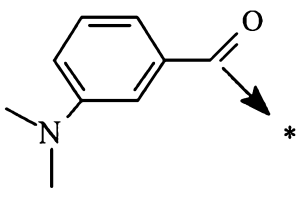
35	"	"		98.4	6.4	671.1
36	"	"		86	4.9	542.3
37	"	"		89	6.1	572.3
38	"	"		77.61	6.8	555.4
39	"	"		89.16	4.2	545.4
40	"	"		92.32	5.3	599.3
41	"	"		83	6.0	589.2
42	"	"		36.3	5.9	531.2
43	"	"		83.27	5.9	555.3
44	"	"		82	4.5	564.4

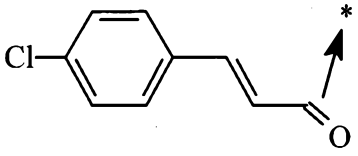
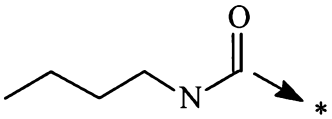
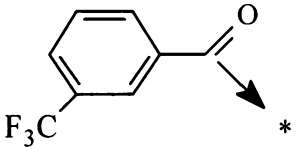
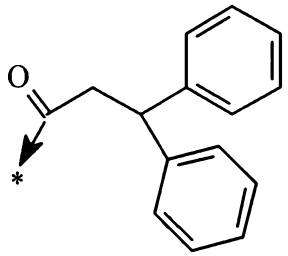
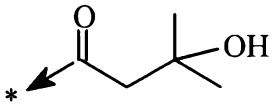
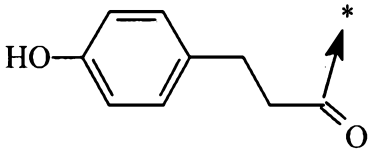
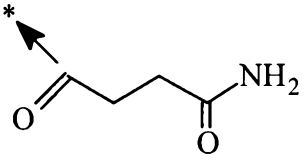
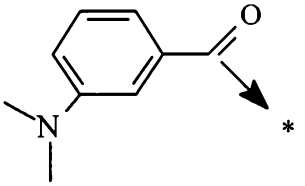
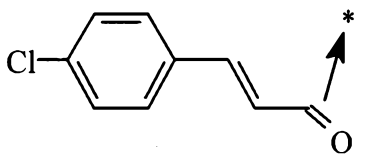
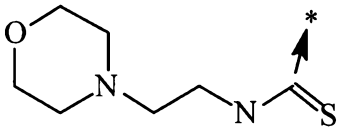
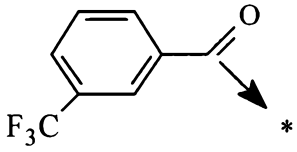
45	"	"		86.75	6.0	577.3
46	"	"		91.95	4.7	501.4
47	"	"		88.94	4.5	475.3
48	"	"		73	5.3	542.3
49	"			90.96	4.4	486.4
50	"	"		95.5	5.9	530.4
51	"	"		94.51	6.1	533.4
52	"	"		93.64	6.0	595.4
53	"	"		96.05	6.5	535.4

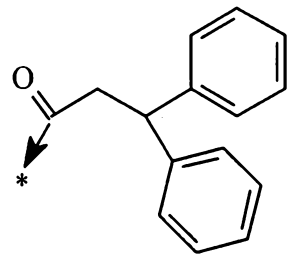
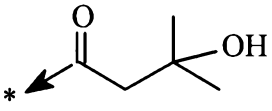
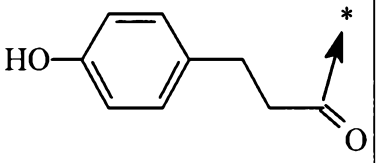
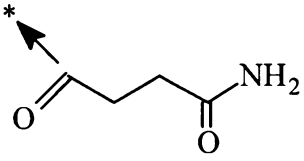
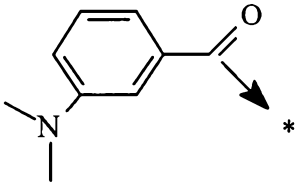
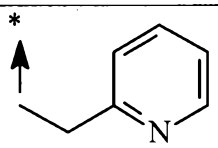
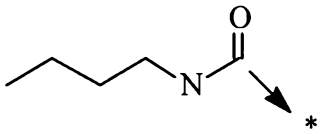
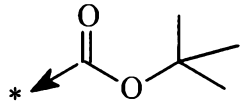
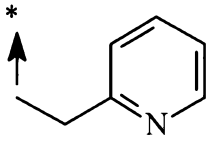
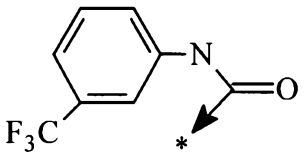
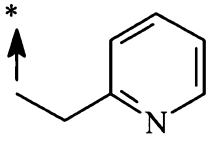
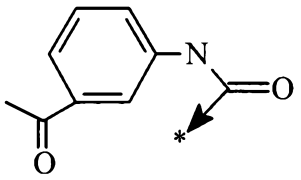
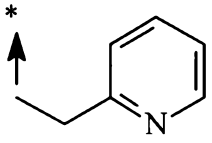
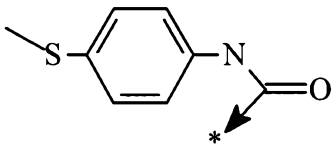
54	"	"		84.68	6.9	641.1
55	"	"		86	5.5	512.3
56	"	"		92	6.5	542.4
57	"	"		91.29	7.2	525.5
58	"	"		94.7	4.7	515.4
59	"	"		94	5.8	569.3
60	"	"		89.43	6.6	559.3
61	"	"		32	6.9	501.5
62	"	"		93.53	6.4	525.4
63	"	"		94.7	4.9	534.4

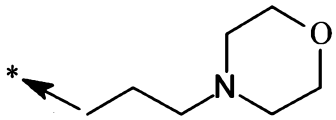
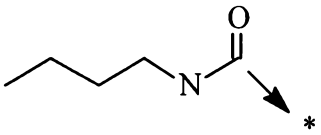
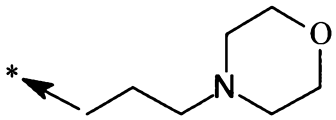
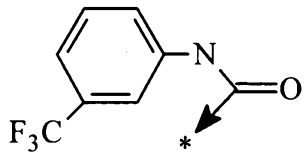
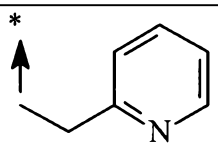
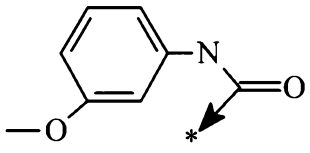
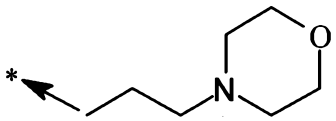
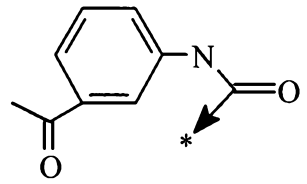
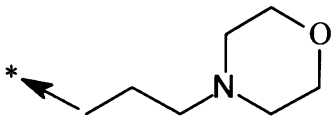
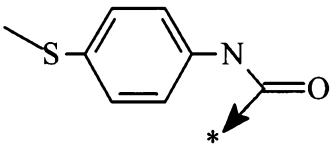
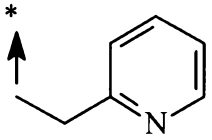
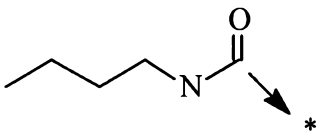
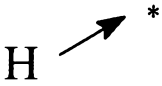
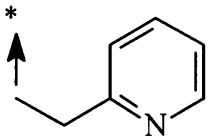
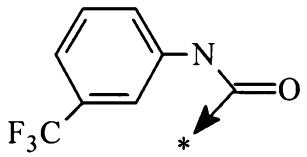
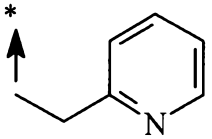
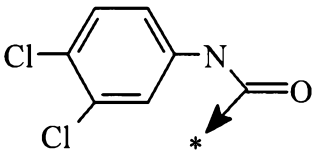
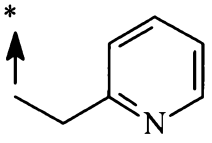
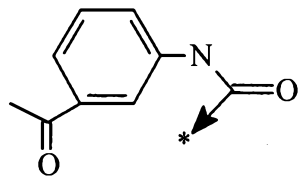
64	"	"		94.32	6.4	547.3
65	"	"		91.71	5.2	471.4
66	"	"		92.47	5.0	445.4
67	"	"		58	5.9	512.3
68	"			84.55	3.6	559.4
69	"	"		87.7	4.7	603.4
70	"	"		90.77	4.8	606.4
71	"	"		72.34	4.8	668.4
72	"	"		87.18	5.1	608.4

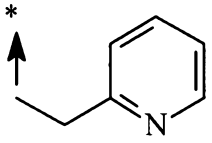
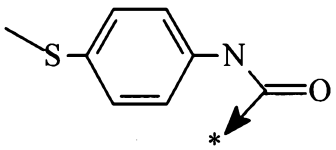
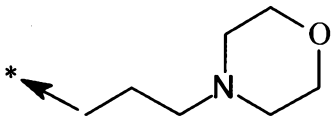
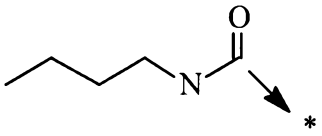
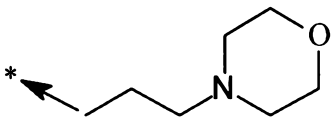
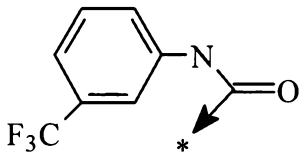
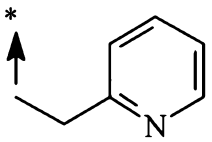
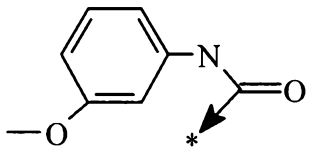
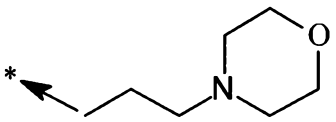
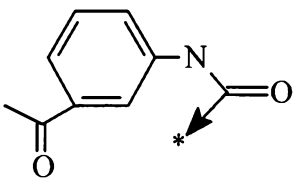
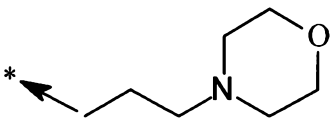
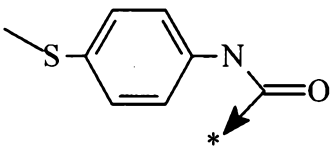
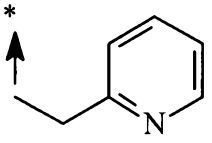
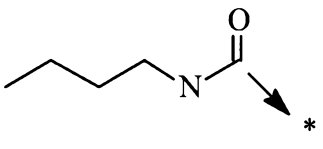
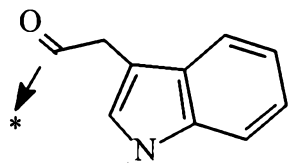
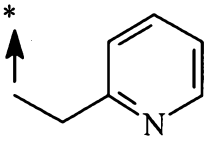
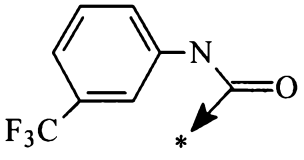
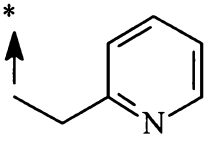
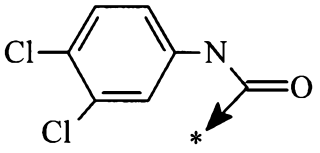
73	"	"		69.52	5.4	714.1
74	"	"		63.39	4.2	585.3
75	"	"		54.46	5.1	615.4
76	"	"		87.3	5.7	598.4
77	"	"		96.1	3.8	588.4
78	"	"		89.9	4.5	642.3
79	"	"		61.5	5.1	632.3
80	"	"		43.65	5.0	574.3
81	"	"		88.18	5.0	598.3
82	"	"		88.6	4.0	607.4

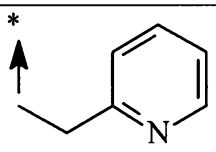
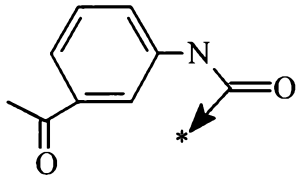
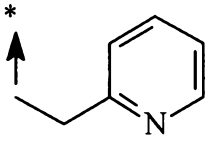
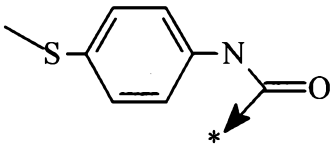
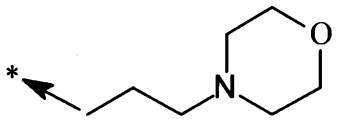
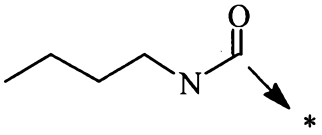
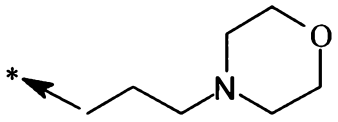
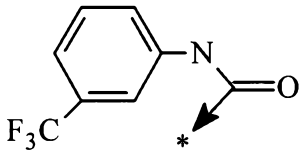
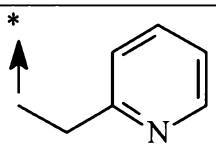
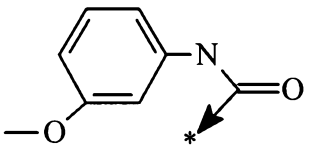
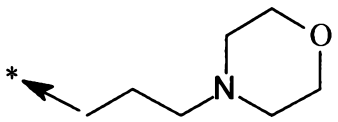
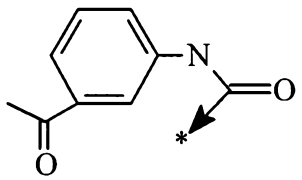
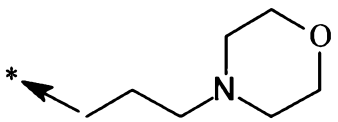
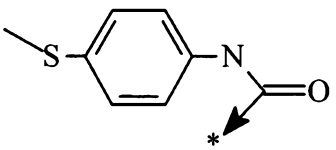
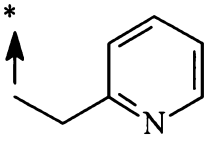
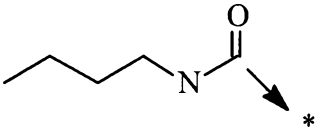
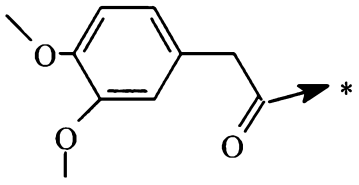
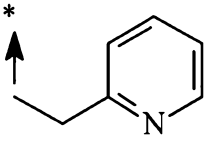
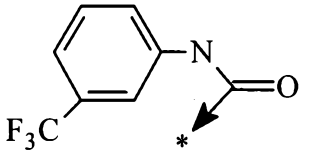
83	"	"		90.08	5.1	620.3
84	"	"		85.57	4.0	544.3
85	"	"		48.41	4.5	585.3
86	"			82.68	6.1	589.3
87	"	"		79.99	6.5	611.4
88	"	"		86.07	4.8	503.4
89	"	"		82	5.1	551.4
90	"	"		19.44	4.4	502.4
91	"	"		86.48	5.1	550.4

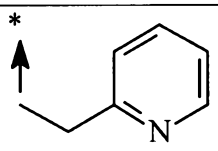
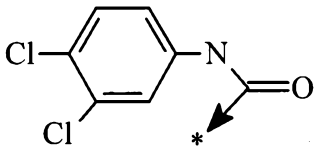
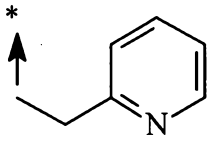
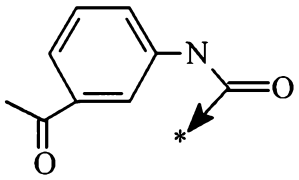
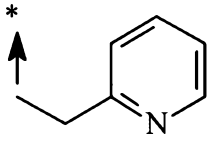
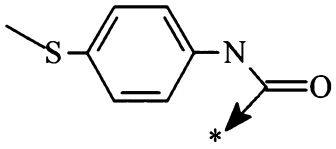
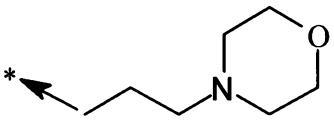
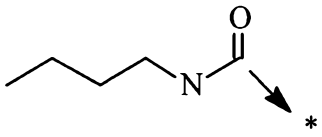
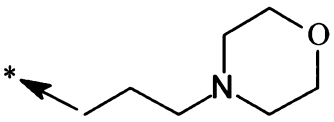
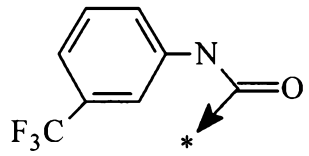
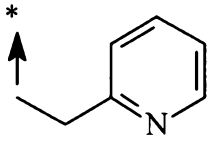
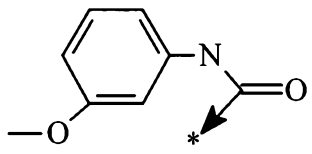
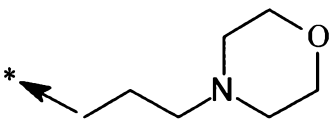
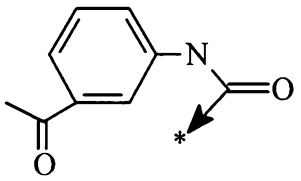
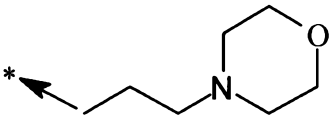
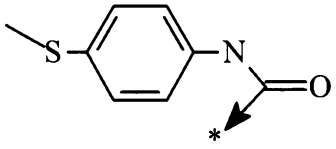
92	"	"		80	6.3	567.3
93	"			94.62	6.6	559.3
94	"	"		57..01	6.9	581.4
[redacted]	"	"		92	5.2	473.4
96	"	"		87.4	5.6	521.4
97	"	"		20.99	5.0	472.4
98 [redacted]	"	"		88.63	5.7	520.4
99	"	"		84	6.7	537.3
100	"			89.71	5.2	632.3

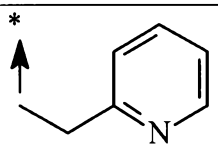
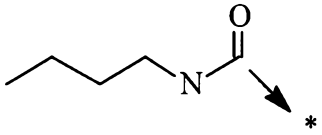
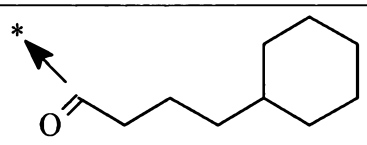
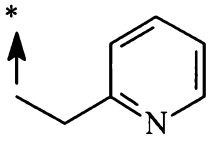
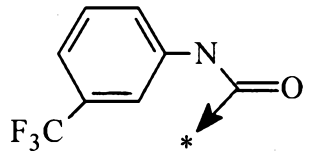
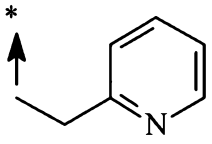
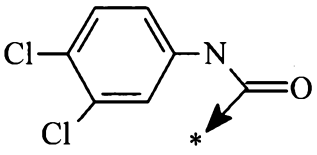
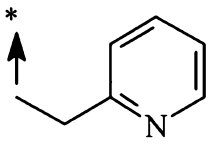
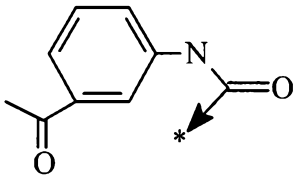
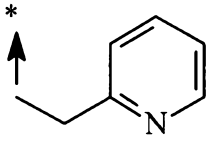
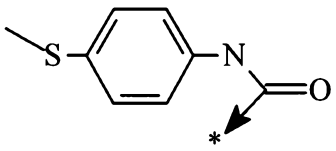
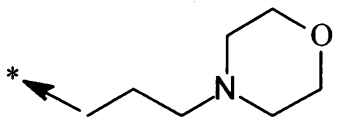
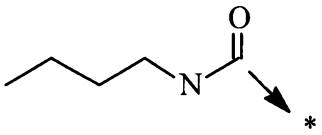
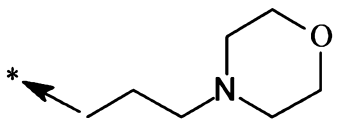
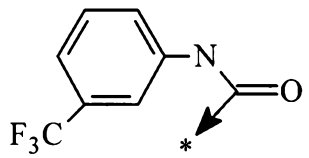
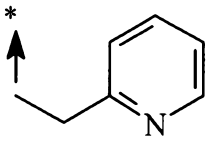
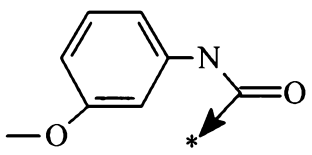
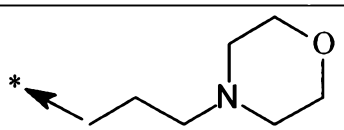
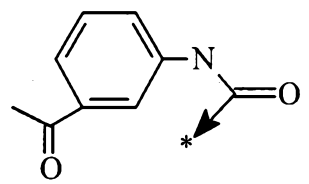
101	"	"		90.25	5.5	654.4
102	"	"		90.09	4.0	546.4
103	"	"		71	4.4	594.3
104	"	"		37.19	3.8	545.3
105	"	"		76.55	4.5	593.4
106				69.62	5.9	405.2
107			"	98	7.1	493.2
108			"	80	6.0	467.3
109			"	88	6.5	471.2

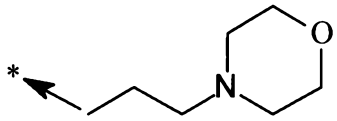
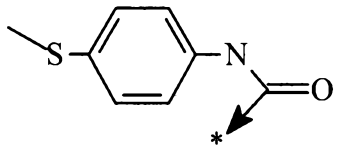
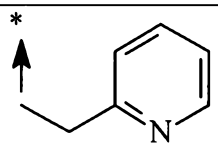
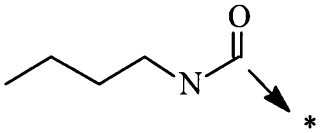
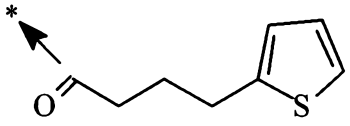
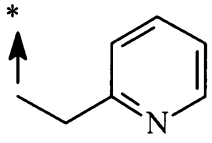
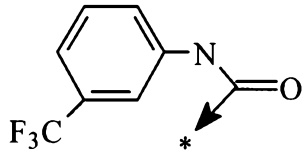
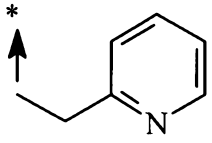
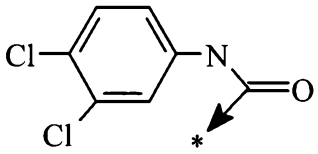
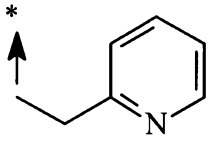
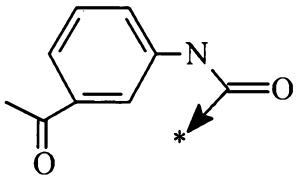
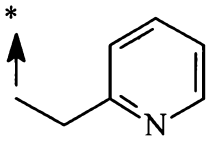
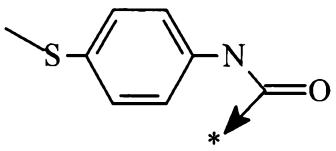
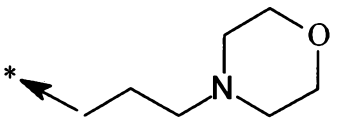
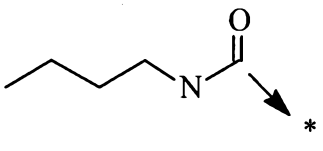
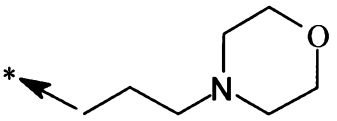
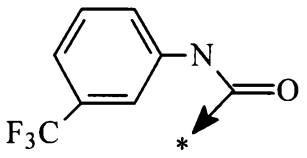
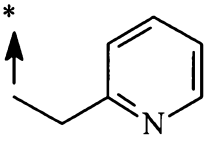
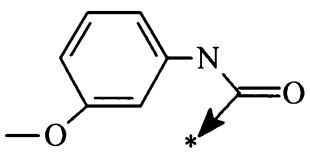
110			"	60.04	5.7	427.3
111			"	78	6.5	515.2
112			"	97	6.2	455.2
113			"	70	5.7	489.3
114			"	90	6.2	493.3
115				62.88	3.6	305.3
116			"	82.99	4.7	393.2
117			"	74.42	5.0	393.1
118			"	10.53	5.4	367.3

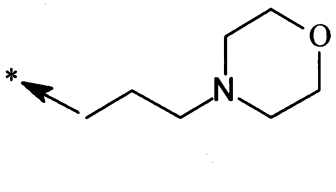
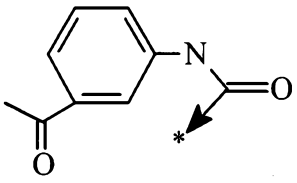
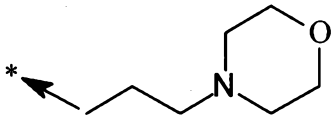
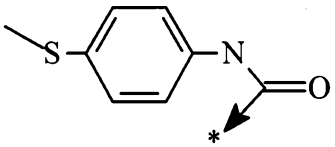
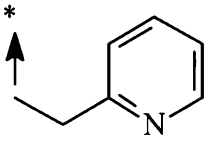
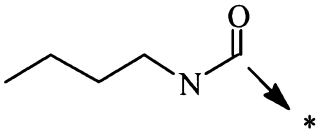
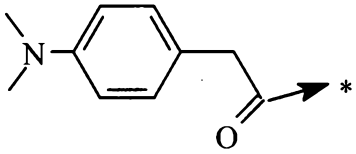
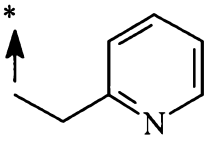
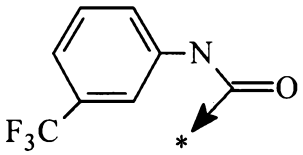
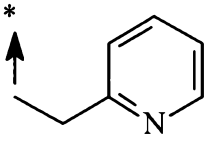
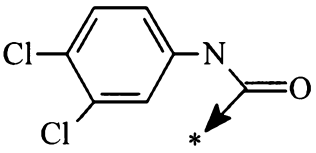
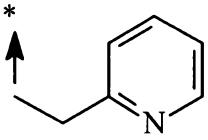
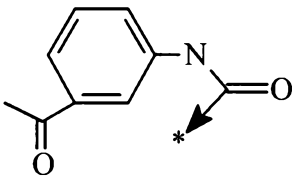
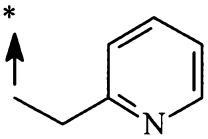
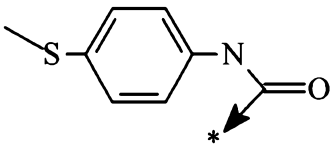
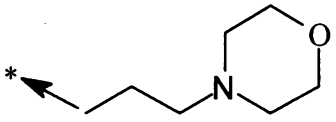
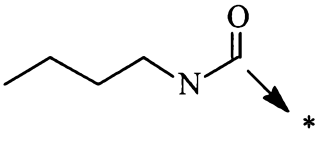
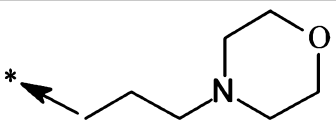
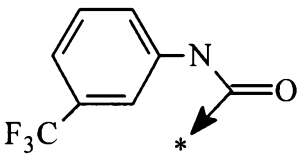
119			"	74.79	4.3	371.2
120			"	50.14	3.4	327.3
121			"	70	4.3	415.2
122			"	84	3.9	355.3
123			"	66	3.5	389.3
124			"	94.61	3.9	393.2
125				71	5.5	462.3
126			"	52	6.6	550.2
127			"	57	6.8	550.1

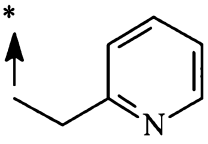
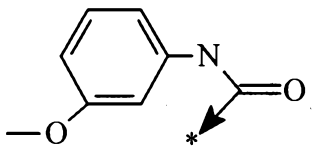
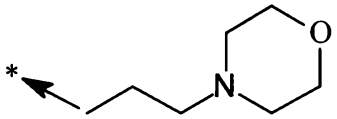
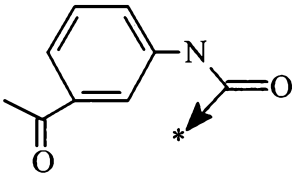
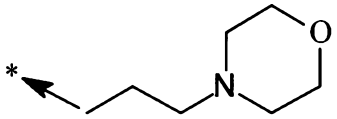
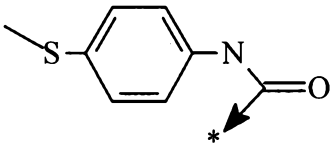
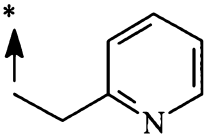
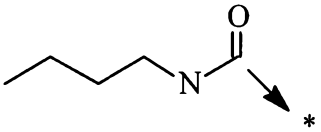
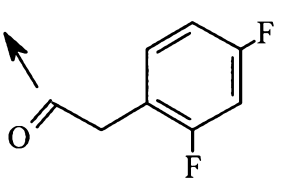
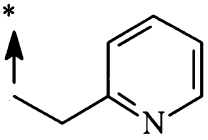
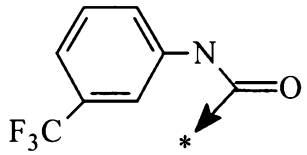
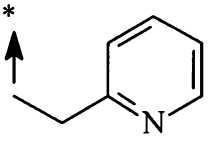
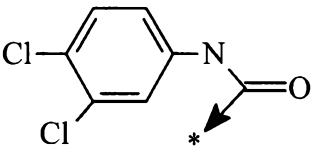
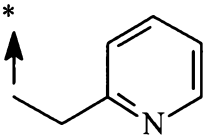
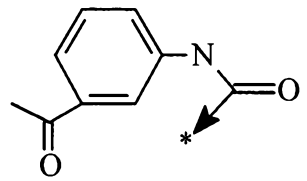
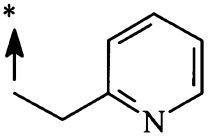
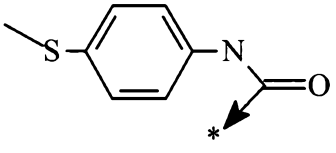
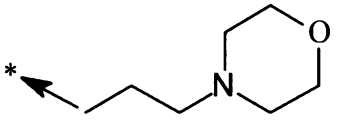
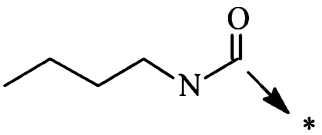
128			"	60	5.6	524.2
129			"	64	6.1	528.2
130			"	27	5.4	484.3
131			"	51	6.2	572.2
132			"	73	5.7	512.2
133			"	61	5.4	546.2
[redacted]			"	43	5.8	550.2
135				76	5.3	483.3
136			"	49	6.4	571.2

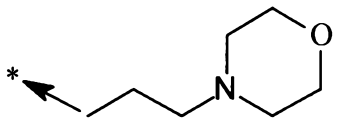
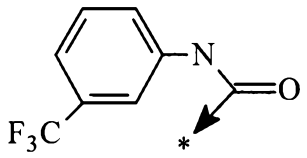
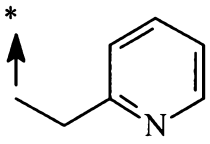
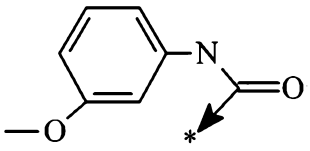
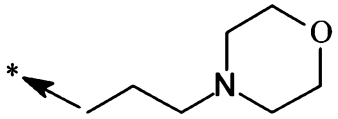
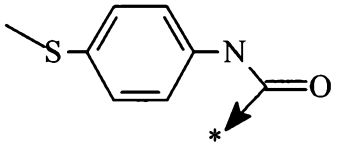
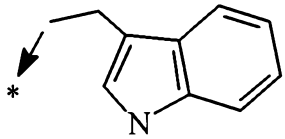
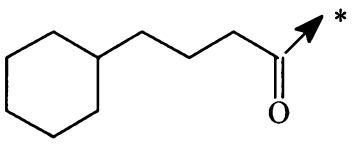
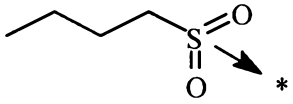
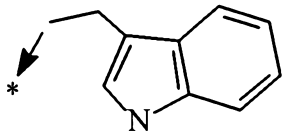
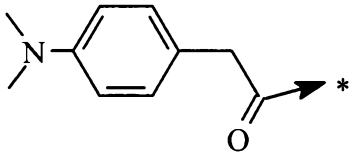
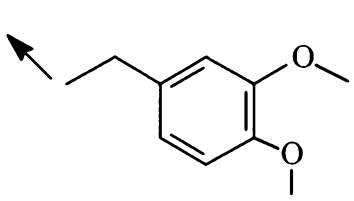
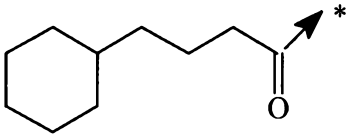
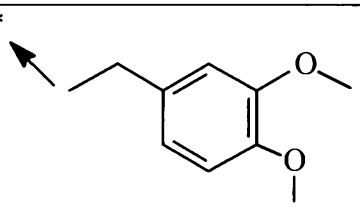
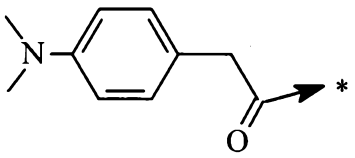
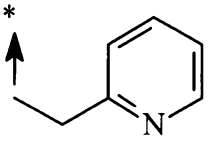
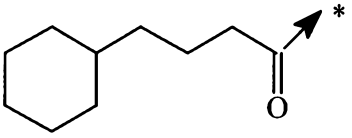
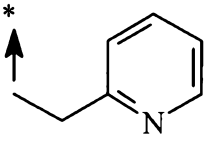
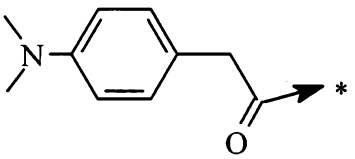
137			"	63	6.6	571.1
138			"	79	5.4	545.2
139			"	57	5.9	549.2
140			"	66.58	5.2	505.3
141			"	61	6.0	593.2
142			"	67	5.5	533.2
143			"	61	5.2	567.3
144			"	51	5.6	571.2

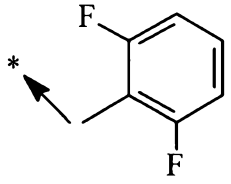
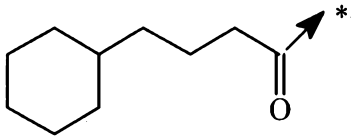
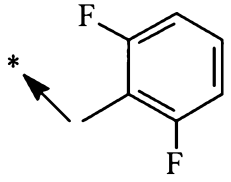
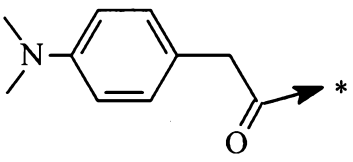
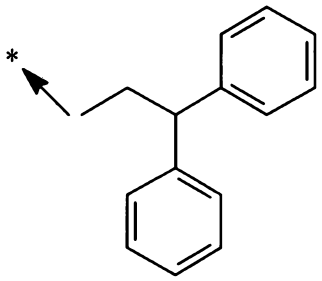
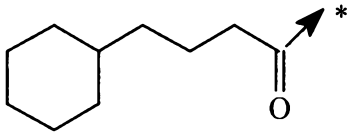
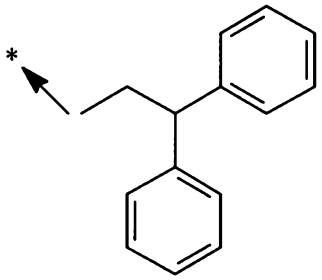
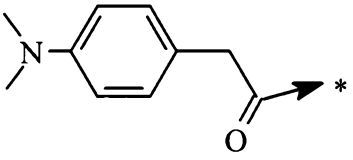
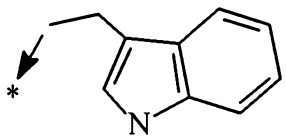
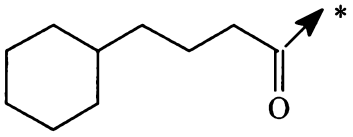
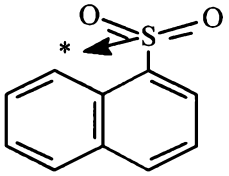
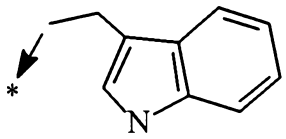
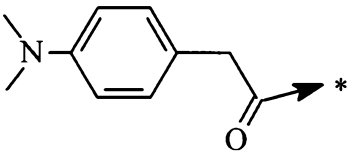
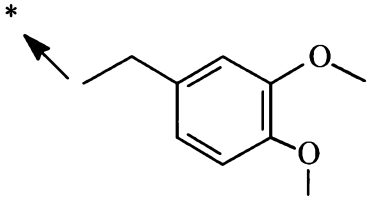
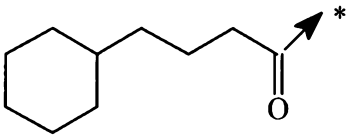
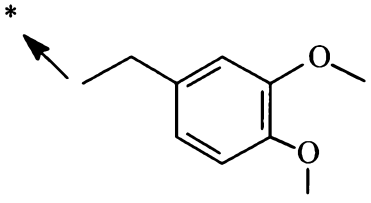
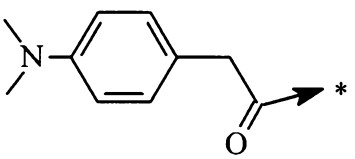
145				56	7.0	457.3
146			"	64	8.1	545.2
147			"	52	8.3	545.2
148			"	69	7.1	519.3
149			"	70	7.6	523.3
150			"	63.77	6.7	479.4
151			"	50	7.3	567.3
152			"	46	7.3	507.3
153			"	78	6.7	541.3

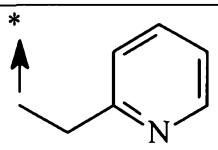
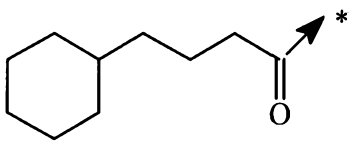
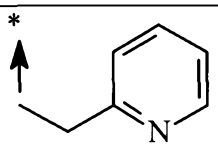
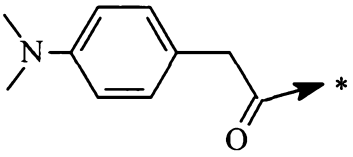
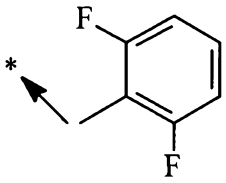
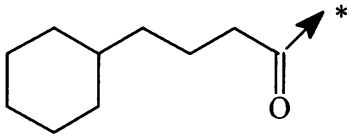
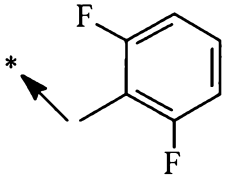
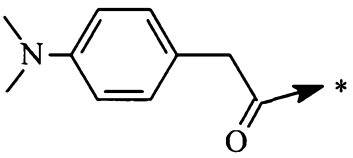
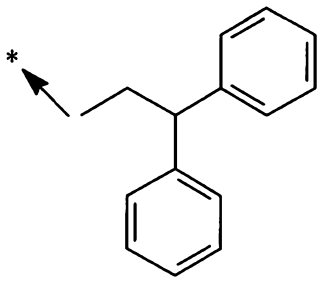
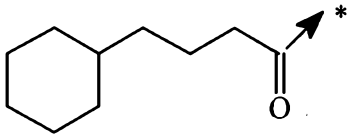
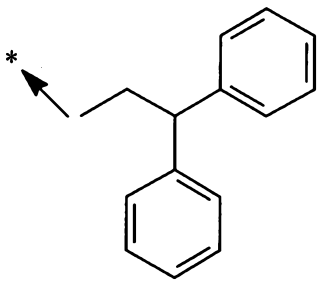
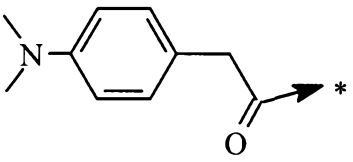
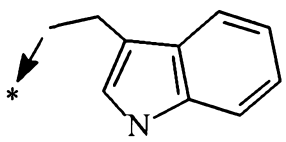
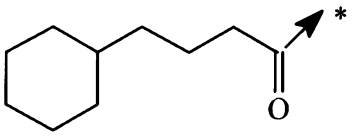
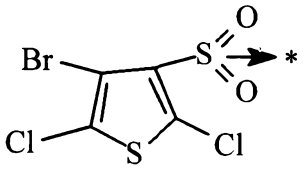
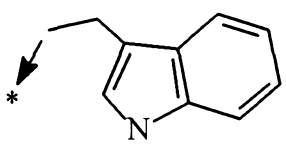
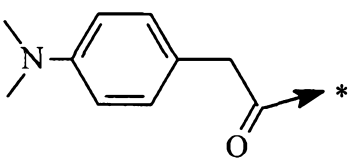
154			"	66	7.0	545.3
155				68	6.0	457.2
156			"	65	7.1	545.2
157			"	67	7.3	545.1
158			"	66	6.1	519.2
159			"	77	6.6	523.2
160			"	60.49	5.8	479.3
161			"	60	6.6	567.3
162			"	69	6.2	507.2

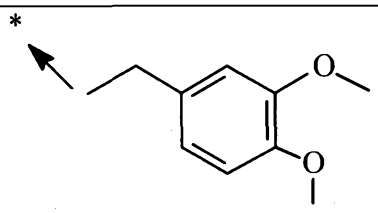
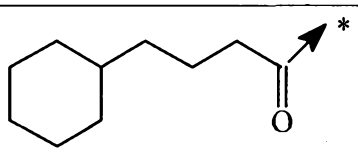
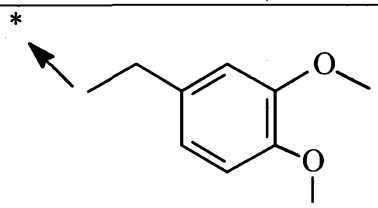
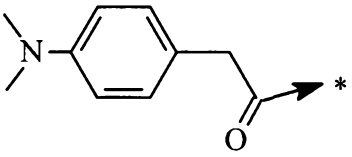
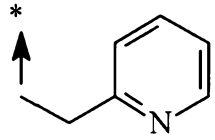
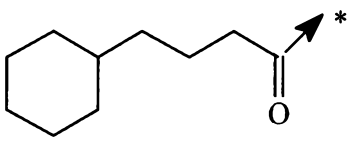
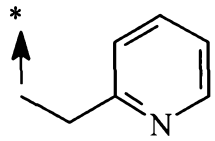
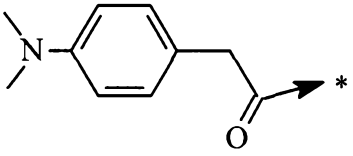
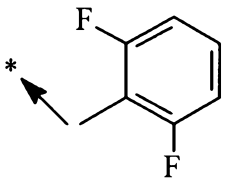
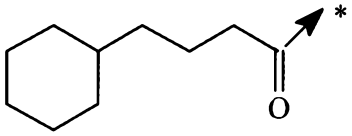
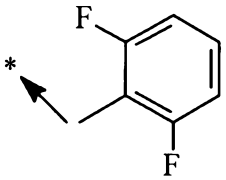
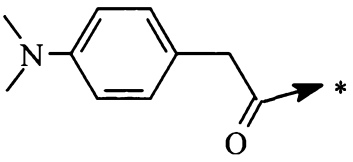
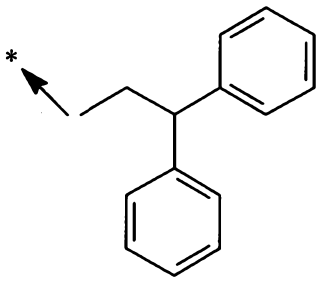
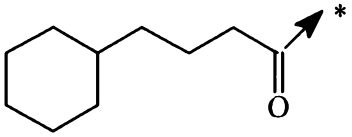
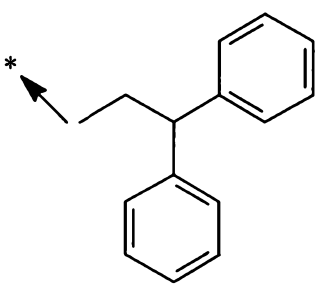
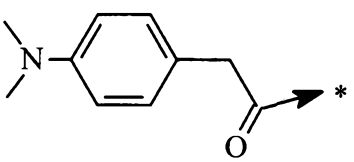
163			"	50	5.8	541.2
164			"	49	6.2	545.2
165				67	4.4	466.3
166			"	45	5.5	554.2
167			"	65.89	5.7	554.1
168			"	5	5.4	528.2
169			"	64.08	5.0	532.2
170			"	62.51	4.3	488.3
171			"	55	5.2	576.3

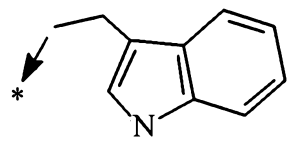
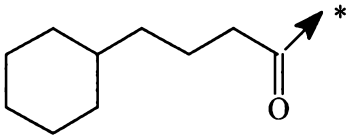
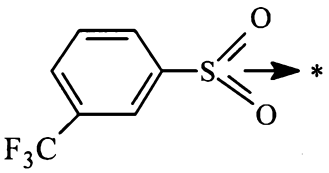
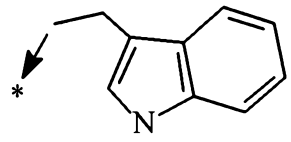
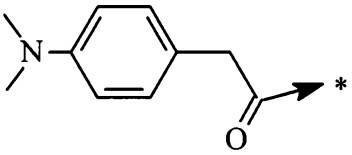
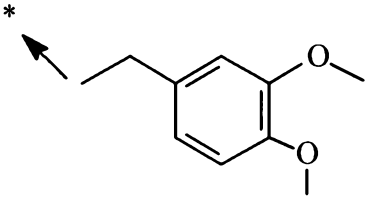
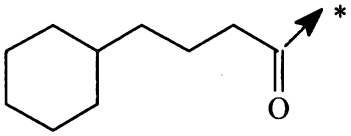
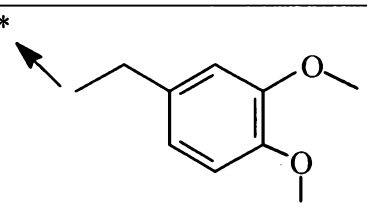
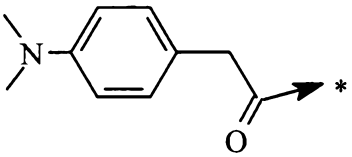
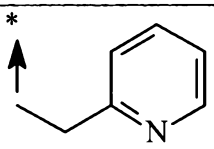
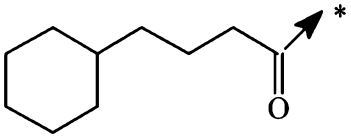
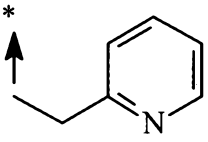
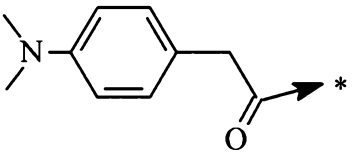
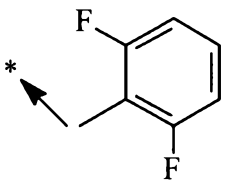
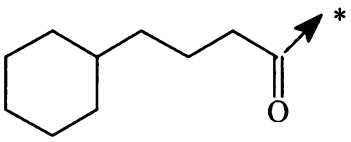
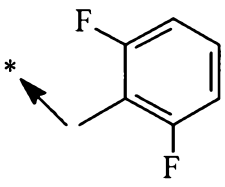
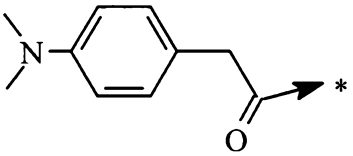
172			"	50.35	4.7	516.3
173			"	7	5.2	550.3
174			"	48.63	4.8	554.3
175				53	5.7	459.2
176			"	49	6.9	547.2
177			"	61	7.1	547.1
178			"	57	5.9	521.2
179			"	65	6.4	525.2
180			"	88.99	5.6	481.3

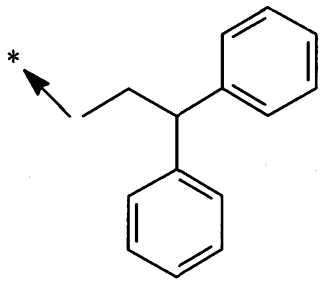
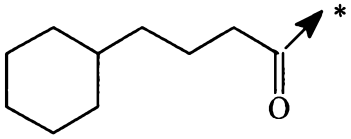
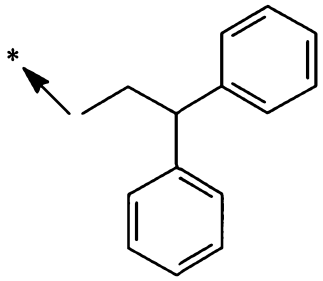
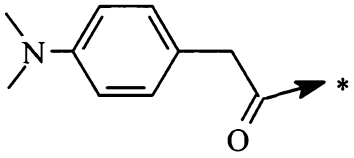
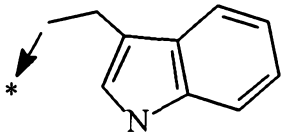
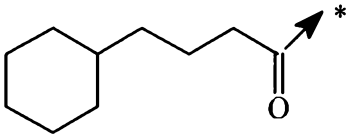
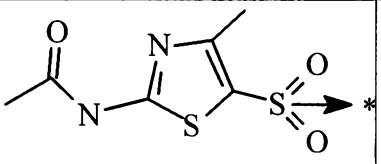
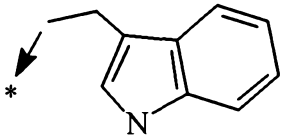
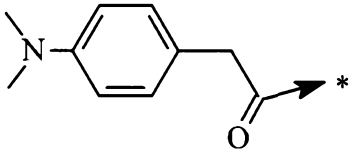
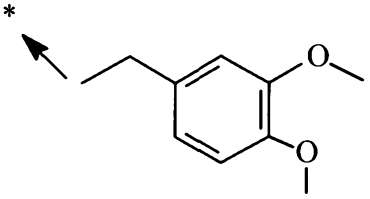
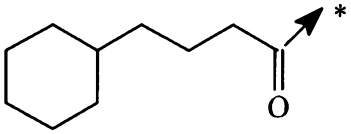
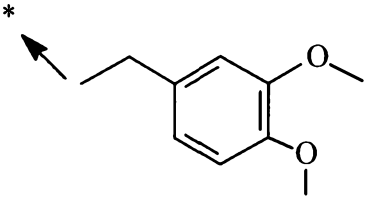
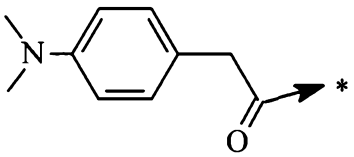
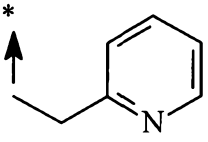
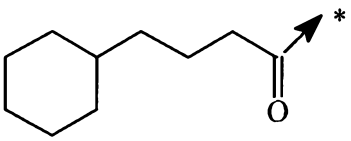
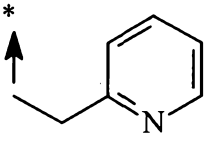
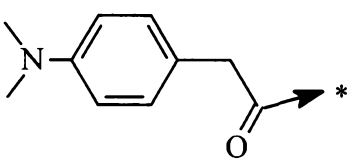
181			"	58	6.4	569.2
182			"	64	6.0	509.2
183			"	63	6.0	547.2
184				67.83	10.1	516.3
185			"	61.66	6.7	525.3
186			"	40.48	9.9	537.3
187			"	50	6.4	546.3
188			"	42.57	7.4	478.4
189			"	29	4.8	487.3

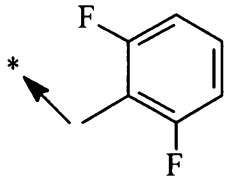
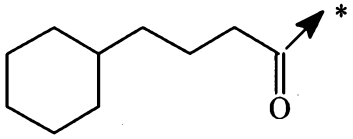
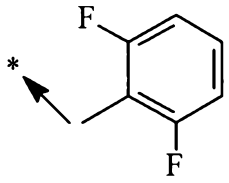
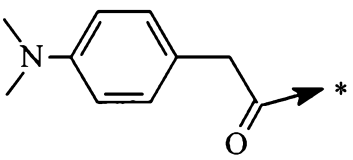
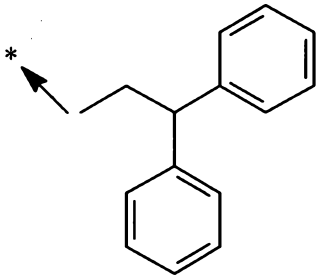
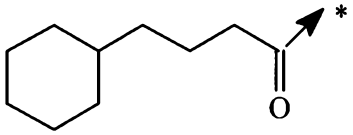
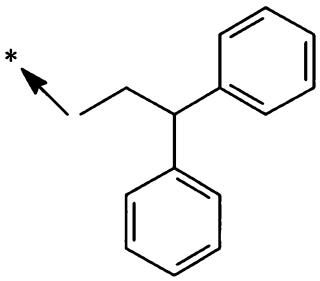
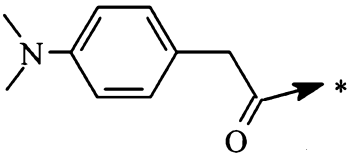
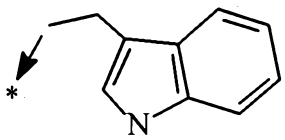
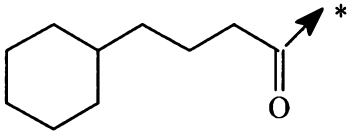
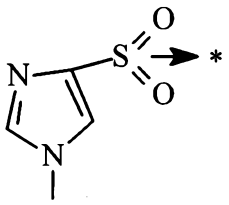
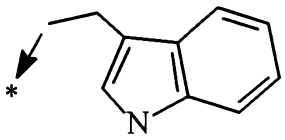
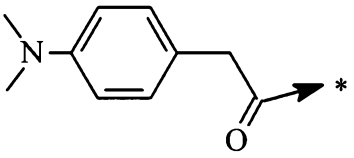
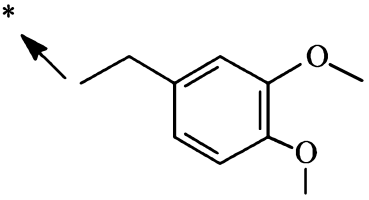
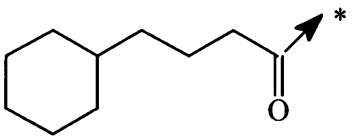
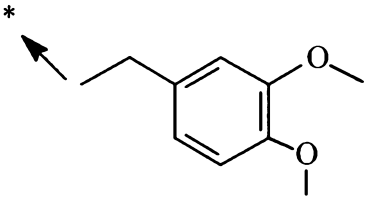
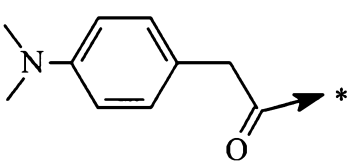
190			"	55	10.3	499.3
191			"	19.39	6.7	508.3
192			"	67	11.1	567.3
193			"	64.73	7.9	576.3
194				92	10.6	586.3
195			"	85	7.3	595.3
196			"	96	10.5	607.3
197			"	89.25	7.2	616.3

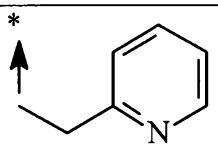
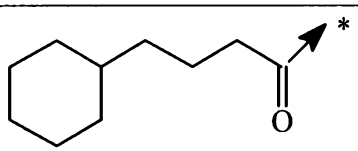
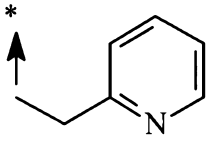
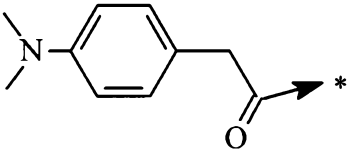
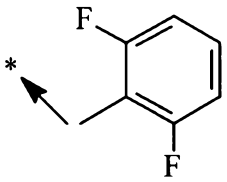
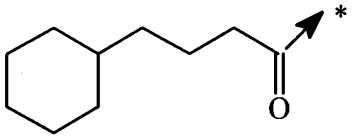
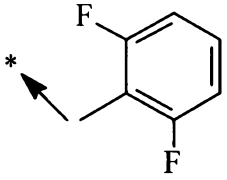
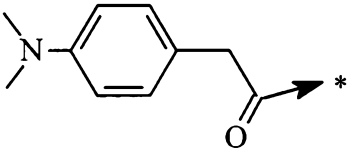
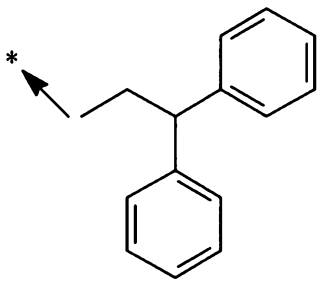
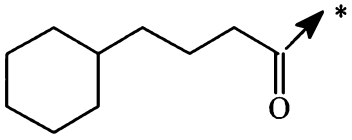
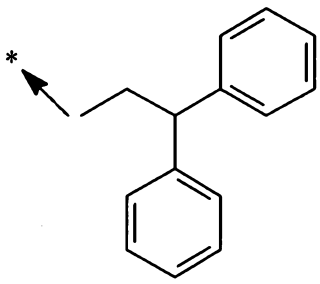
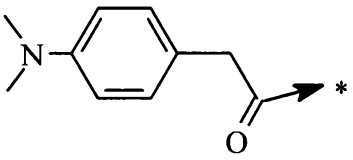
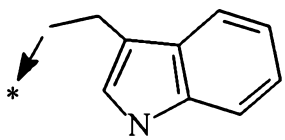
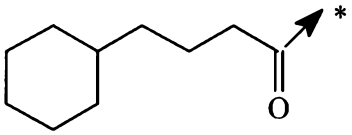
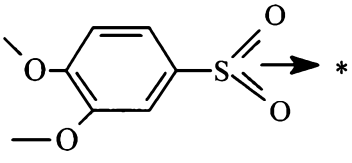
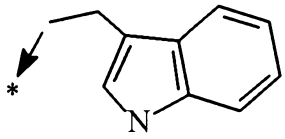
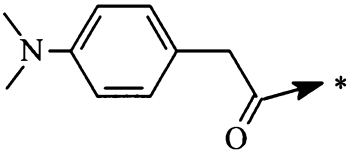
198			"	98.24	7.9	548.3
199			"	94	5.6	557.3
200			"	98	10.8	569.2
201			"	93.17	7.3	578.2
202			"	97.82	11.7	637.3
203			"	88.11	8.5	646.3
204				73	11.2	690.0
205			"	60.44	7.9	699.0

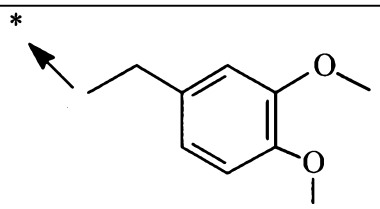
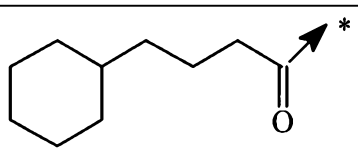
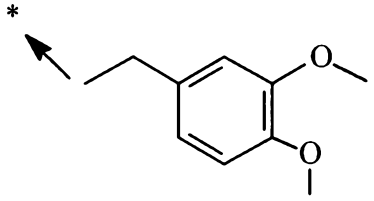
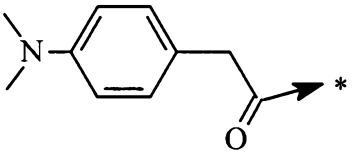
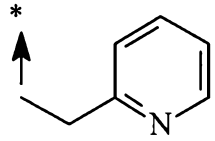
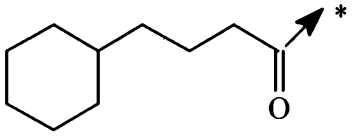
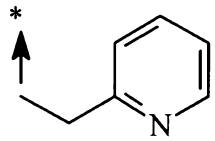
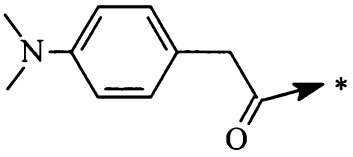
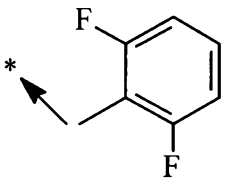
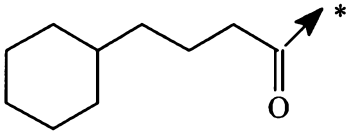
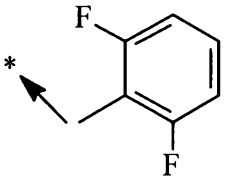
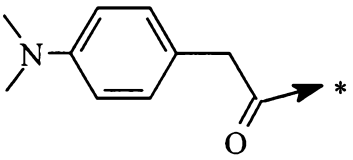
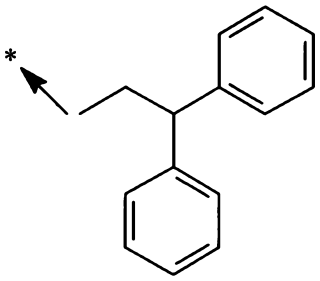
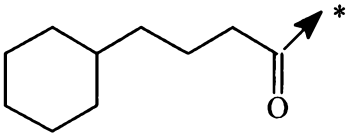
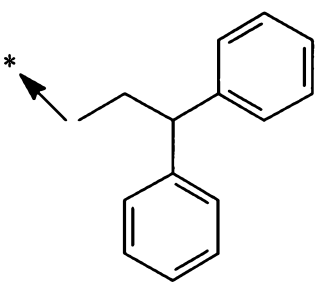
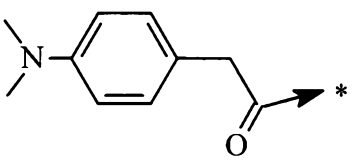
206			"	76	11.1	711.0
207			"	72.2	7.8	720.0
208			"	89.42	8.5	652
209			"	48	6.2	659.0
210			"	78.2	11.6	673.0
211			"	66.1	7.9	682.0
212			"	78	12.6	739.1
213			"	88.77	9.1	750.0

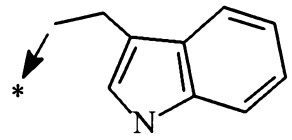
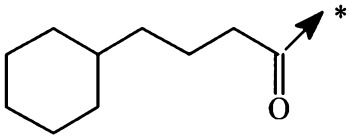
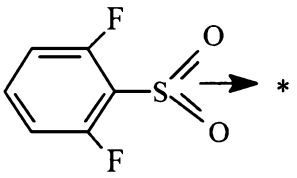
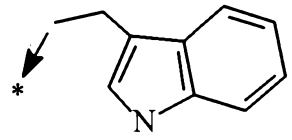
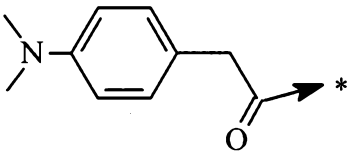
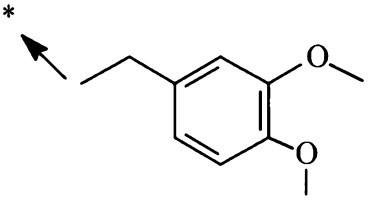
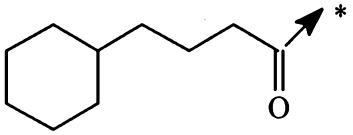
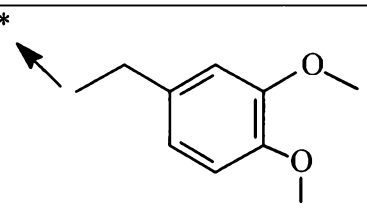
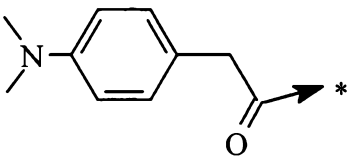
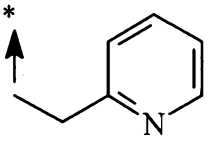
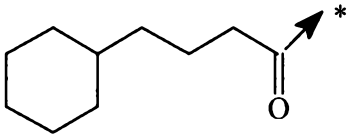
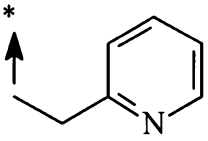
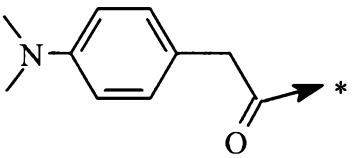
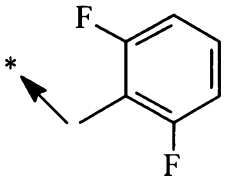
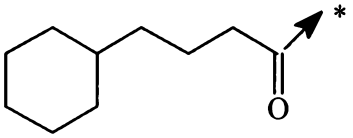
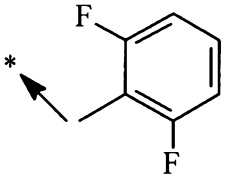
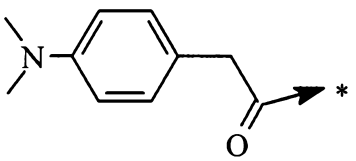
214				73	10.6	604.3
215			"	67	7.5	613.2
216			"	73	10.5	625.3
217			"	83	7.3	634.2
218			"	87.32	7.9	566.3
219			"	79	5.7	575.2
220			"	89	10.7	587.2
221			"	78.75	7.4	596.2

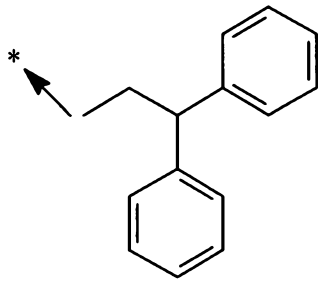
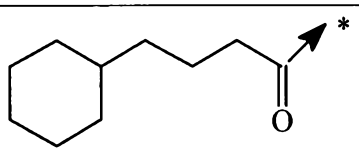
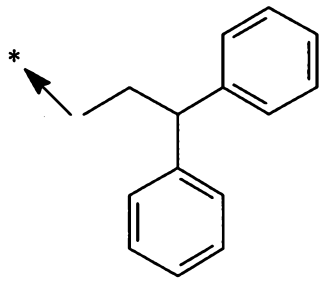
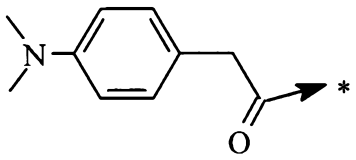
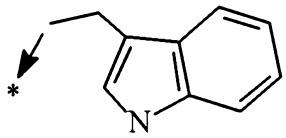
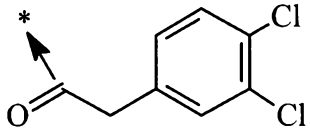
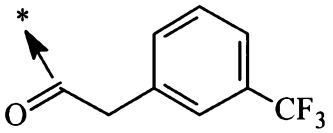
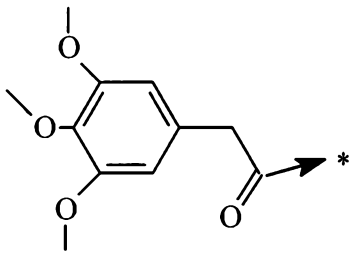
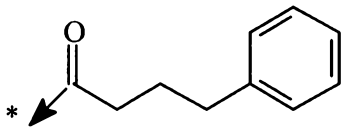
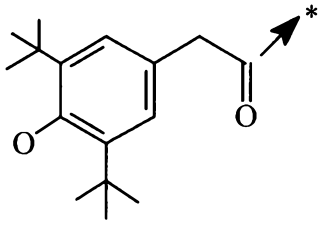
222			"	95	11.6	655.3
223			"	79	8.6	664.3
224				58	9.4	614.2
225			"	78	6.4	623.2
226			"	75	9.2	635.3
227			"	88	6.1	644.3
228			"	86	6.7	576.3
229			"	80	4.6	585.2

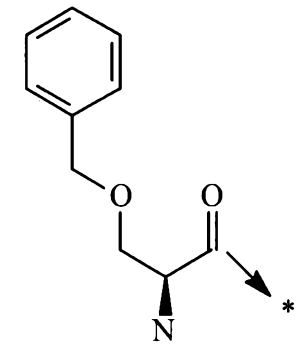
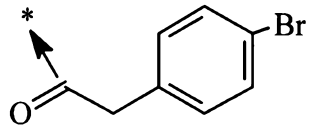
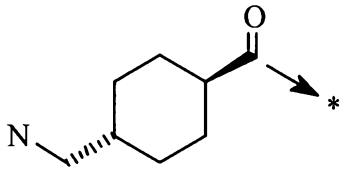
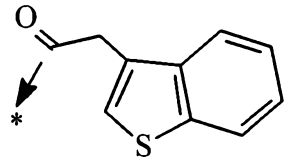
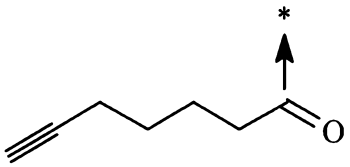
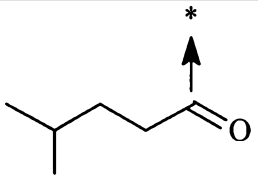
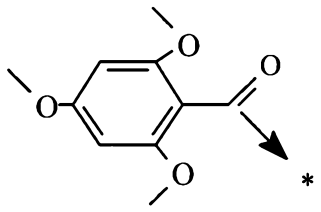
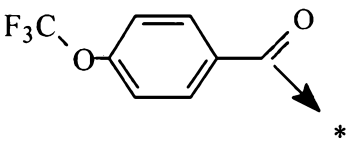
230			"	73	9.5	597.2
231			"	66	6.2	606.2
232			"	62	10.5	665.3
233			"	81	7.5	674.3
234				92	8.9	540.3
235			"	86	5.6	549.2
236			"	91	8.7	561.3
237			"	94.51	5.4	570.2

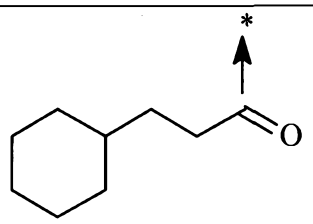
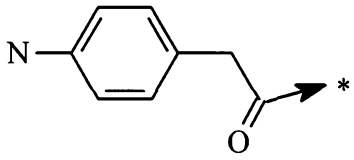
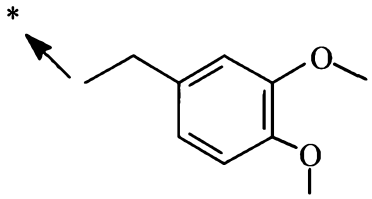
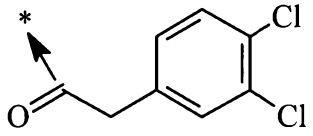
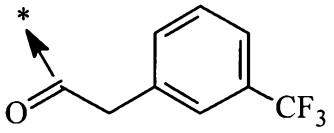
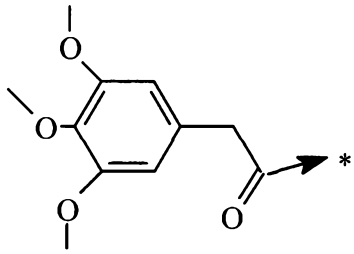
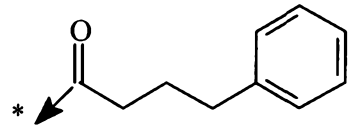
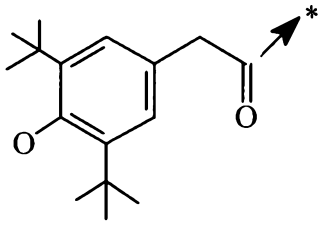
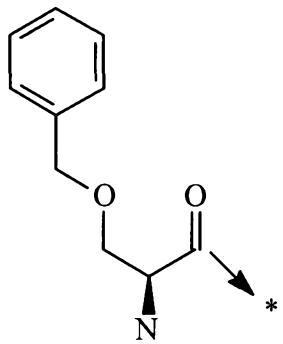
238			"	93.36	6.2	502.3
239			"	97	3.8	511.3
240			"	98.13	9.0	523.3
241			"	82	5.4	532.2
242			"	99	10.1	591.3
243			"	94.74	6.8	600.3
244				89	9.8	596.3
245			"	81	6.6	605.3

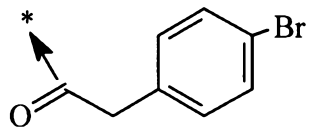
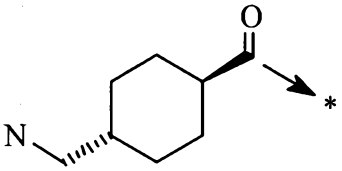
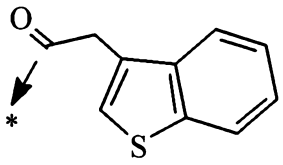
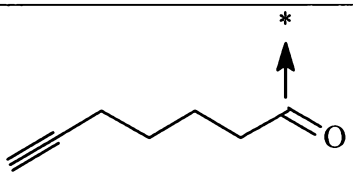
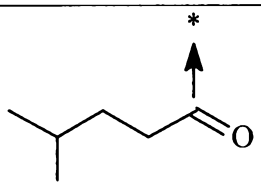
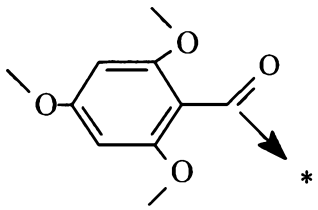
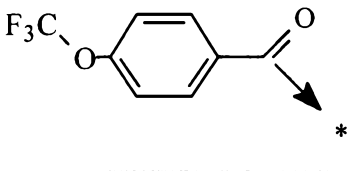
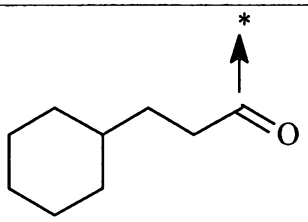
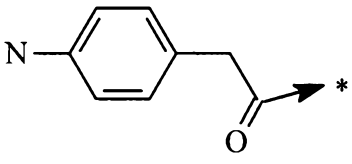
246			"	96	9.7	617.3
247			"	85.68	6.4	626.3
248			"	98.65	7.1	558.3
249			"	92	4.8	567.2
250			"	96	10.0	579.2
251			"	88.12	6.5	588.2
252			"	97	10.9	647.3
253			"	86	7.8	656.3

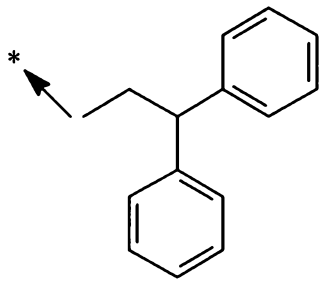
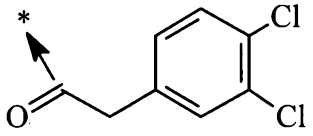
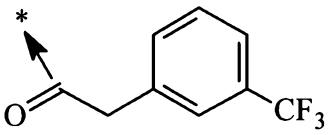
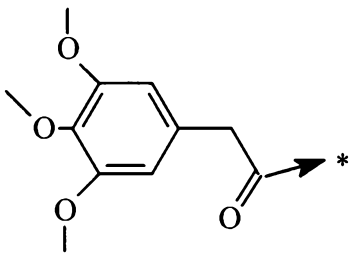
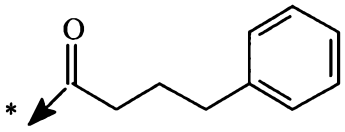
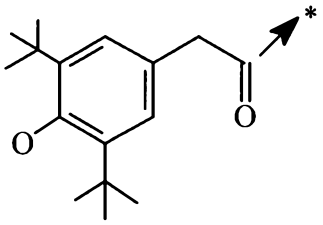
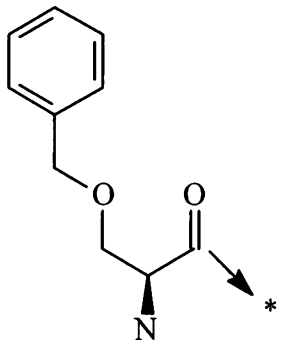
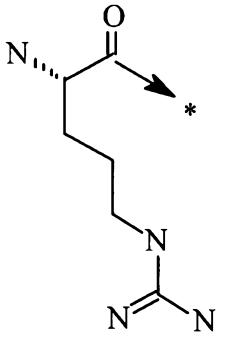
254				79	10.1	572.2
255			"	79	7.0	581.2
256			"	71	10.0	593.3
257			"	72.74	6.6	602.2
258			"	79.1	7.4	534.3
259			"	74	4.9	543.2
260			"	84.17	10.3	555.2
261			"	76.16	6.7	564.2

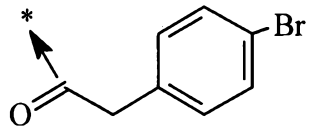
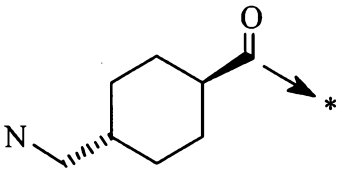
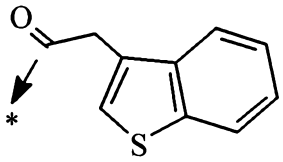
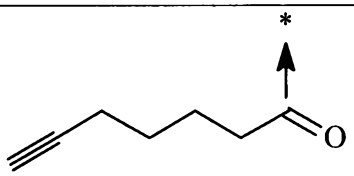
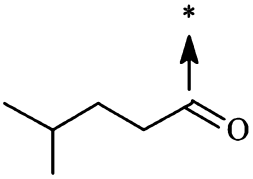
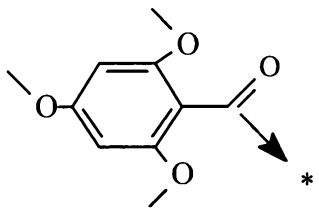
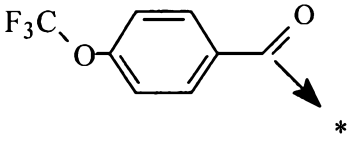
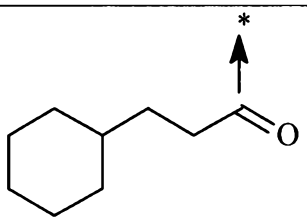
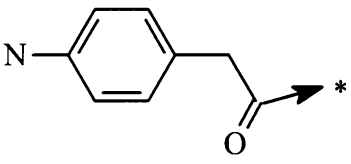
262			"	95	11.1	623.3
263			"	78.91	8.0	632.3
264				75.26	5.1	430.2
265	"		"	90.43	5.0	430.3
266	"		"	74.93	4.3	452.3
267	"		"	79.62	4.9	390.3
268	"		"	92.82	5.6	490.4

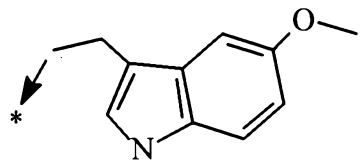
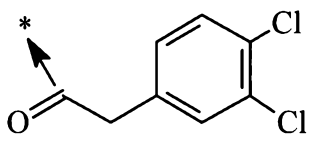
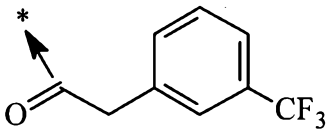
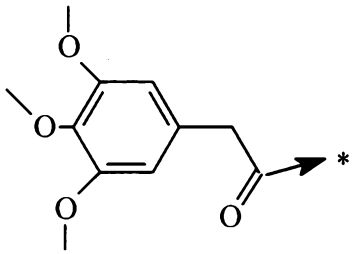
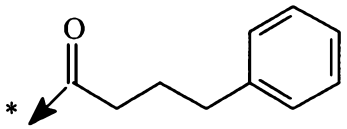
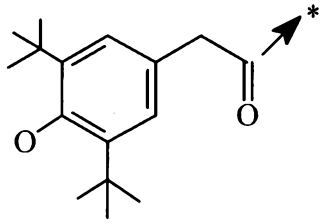
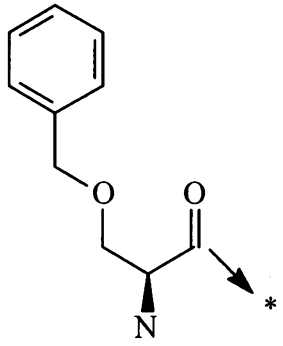
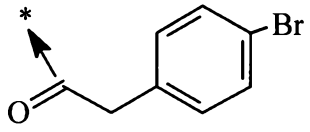
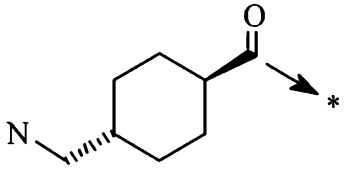
269	"		"	68.87	3.6	421.3
270	"		"	79.07	4.9	440.2
271	"		"	84.22	3.0	392.3
272	"		"	67.34	4.9	418.2
273	"		"	81.63	4.4	352.3
274	"		"	90.11	4.7	342.3
275	"		"	54.36	4.3	438.3
276	"		"	81.69	4.9	432.2

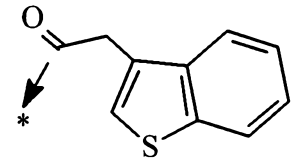
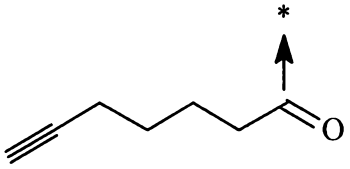
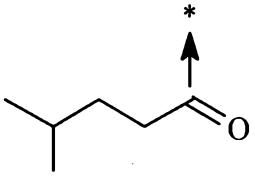
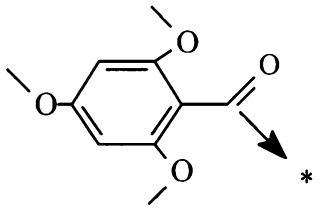
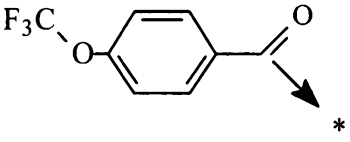
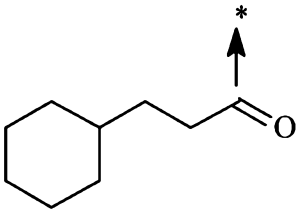
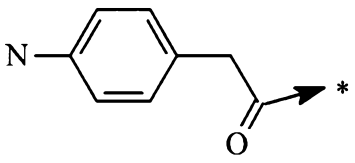
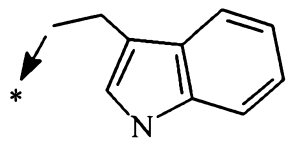
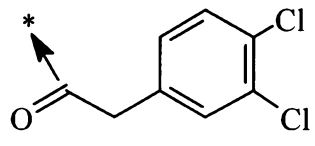
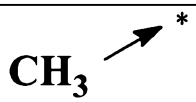
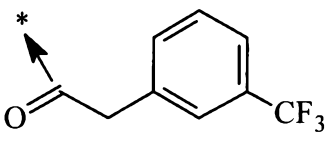
277	"		"	85.62	5.2	382.3
278	"		"	86.19	3.2	377.3
279			"	94.76	4.9	451.2
[illegible]	"		"	99.42	4.7	451.3
281	"		"	90.55	4.0	473.3
282	"		"	93.80	4.6	411.3
[illegible]	"		"	82.71	5.4	511.4
284	"		"	90.85	3.4	442.3

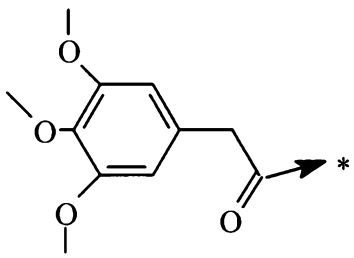
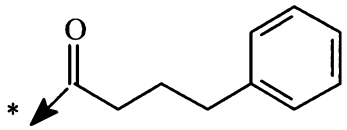
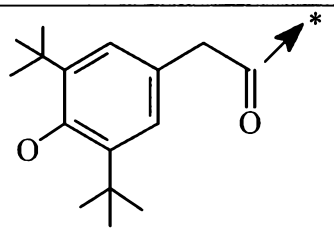
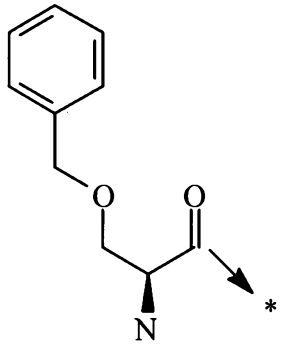
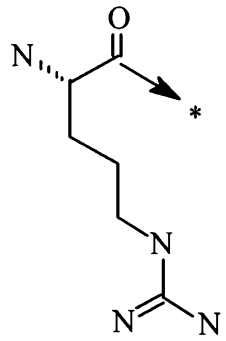
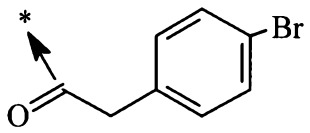
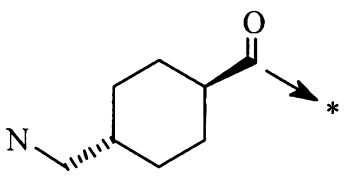
285	"		"	98.65	4.6	461.2
286	"		"	98.80	2.8	404.3
287	"		"	86.02	4.6	439.3
288	"		"	97.47	4.1	373.3
289	"		"	99.31	4.4	363.3
290	"		"	45.77	4.1	459.3
291	"		"	94.07	4.6	453.3
292	"		"	95.65	5.0	403.4
293	"		"	94.30	2.9	398.3

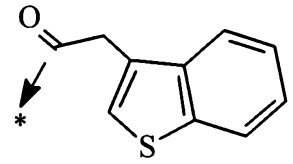
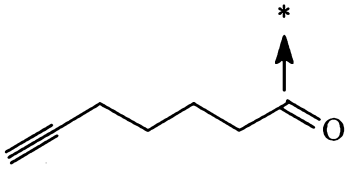
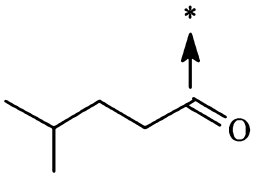
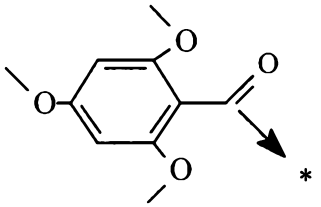
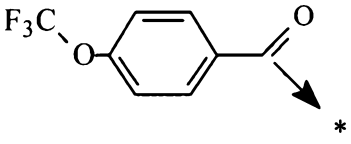
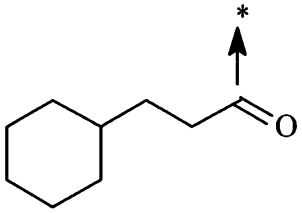
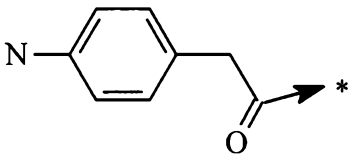
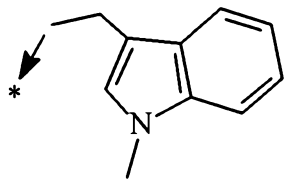
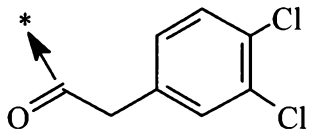
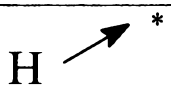
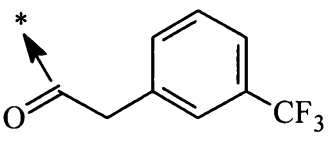
294			"	80.64	5.9	481.2
295	"		"	98.05	5.7	481.3
296	"		"	94.93	5.0	503.4
297	"		"	96.81	5.6	441.3
298	"		"	95.00	6.3	541.4
299	"		"	95.13	4.2	472.4
300	"		"	52.68	3.2	452.4

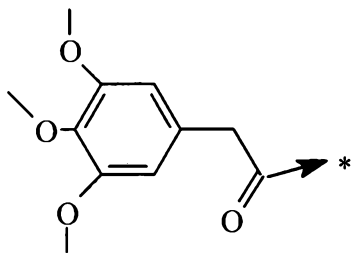
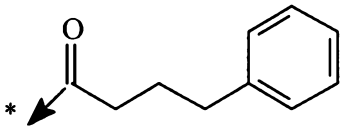
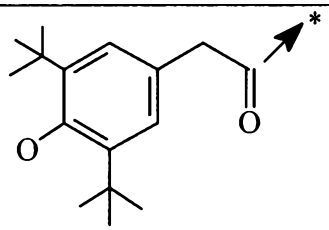
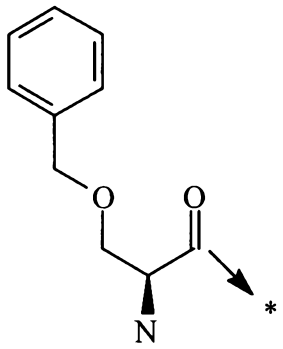
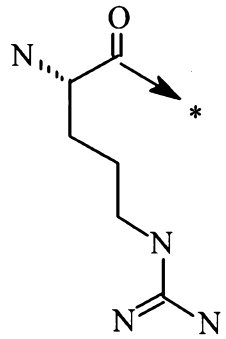
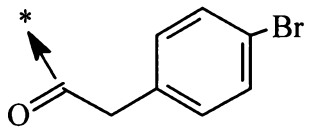
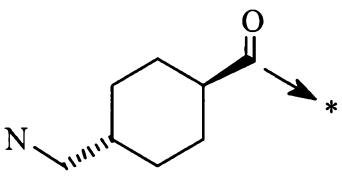
301	"		"	98.03	5.6	491.2
302	"		"	96.44	3.7	217.9
303	"		"	97.22	5.6	469.3
304	"		"	96.97	5.2	403.3
305	"		"	99.05	5.4	393.4
306	"		"	32.67	5.1	489.3
307	"		"	84.51	5.6	483.3
308	"		"	98.44	6.0	433.4
309	"		"	97.78	4.0	428.3

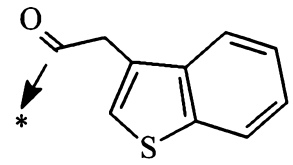
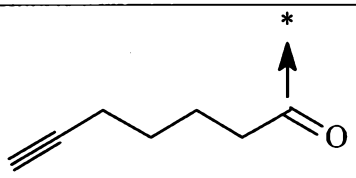
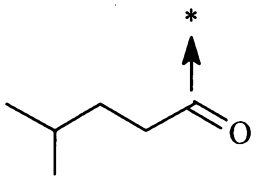
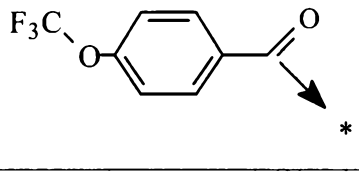
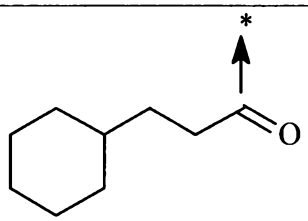
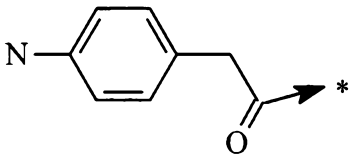
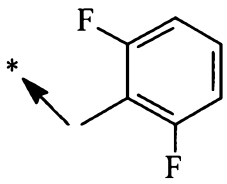
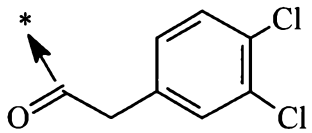
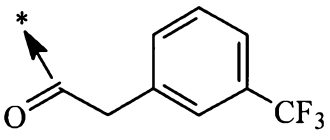
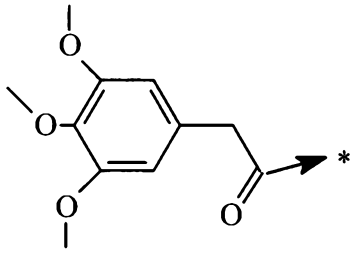
310			"	79.54	5.0	460.2
311	"		"	78.59	4.9	460.3
312	"		"	66.24	4.2	482.3
[illegible]	"		"	70.15	4.8	420.3
314	"		"	57.87	5.5	520.4
315	"		"	71.26	3.6	451.3
316	"		"	81.16	4.8	470.2
317	"		"	74.96	2.9	413.3

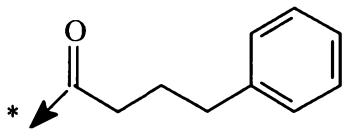
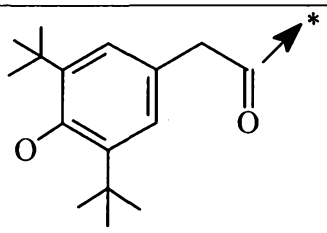
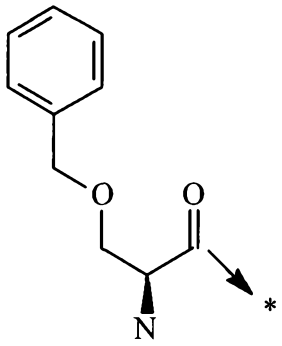
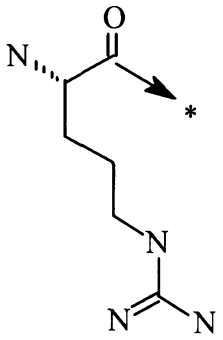
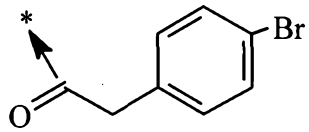
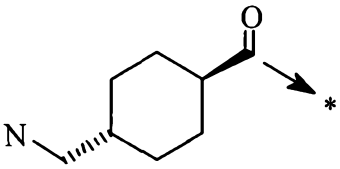
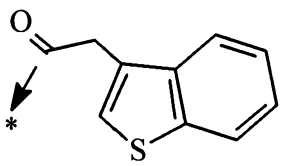
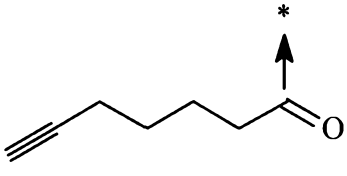
318	"		"	53.47	4.8	448.3
319	"		"	87.88	4.3	382.3
320	"		"	91.41	4.6	372.3
321	"		"	1.59	5.0	468.3
322	"		"	77.81	4.8	462.3
323	"		"	76.59	5.1	412.3
324	"		"	83.35	3.1	407.3
325				87.42	5.2	444.2
326	"		"	98.89	5.1	444.3

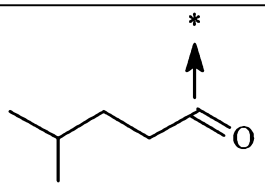
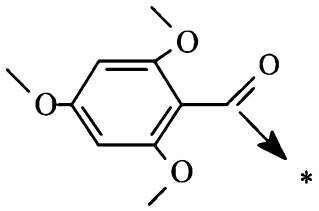
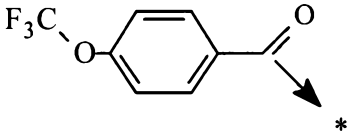
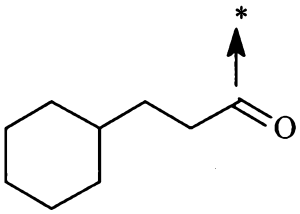
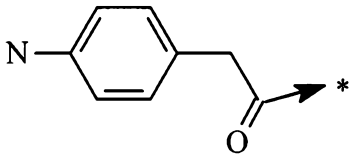
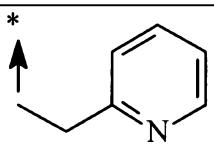
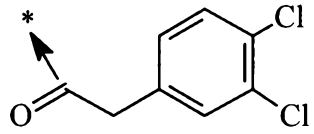
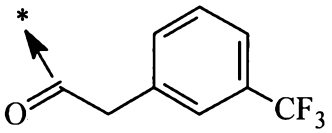
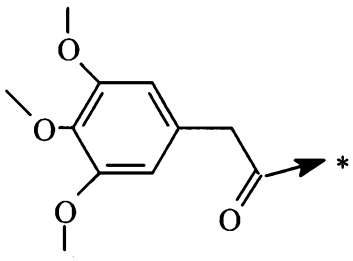
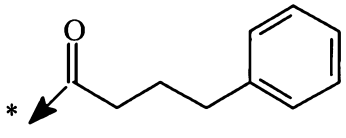
327	"		"	95.68	4.3	466.3
328	"		"	97.27	4.9	404.3
329	"		"	95.73	5.7	504.4
330	"		"	83.37	3.7	435.3
331	"		"	71.88	3.2	413.3
332	"		"	98.33	5.0	454.2
333	"		"	83.73	3.0	397.3

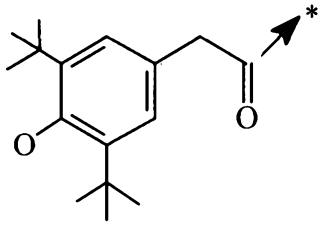
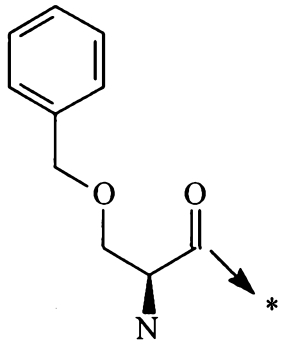
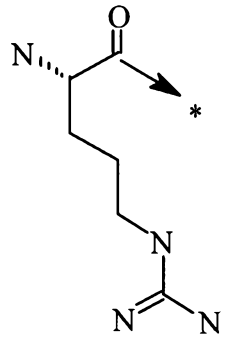
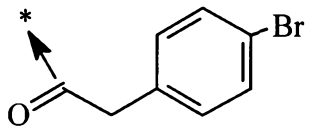
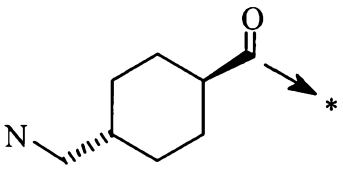
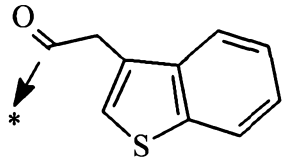
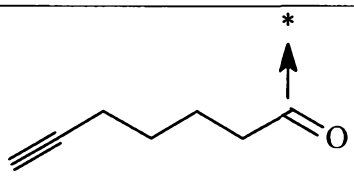
334	"		"	94.77	5.0	432.3
335	"		"	95.88	4.5	366.3
336	"		"	98.9	4.7	356.3
337	"		"	50.74	4.4	452.3
338	"		"	95.39	5.0	446.3
339	"		"	98.2	5.3	396.3
340	"		"	92.35	3.2	391.3
341				90.41	5.1	444.2
342	"		"	87.41	5.0	444.3

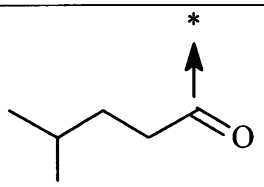
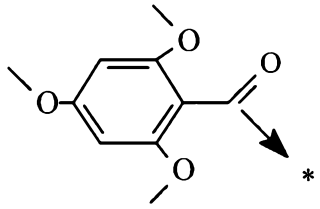
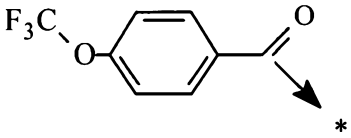
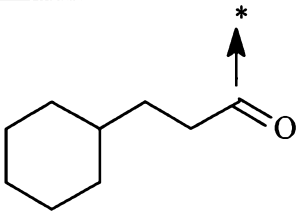
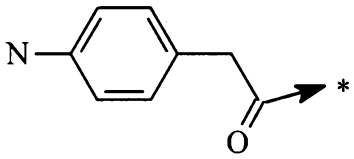
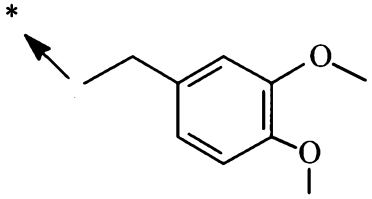
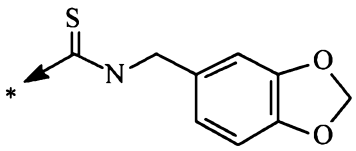
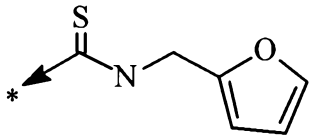
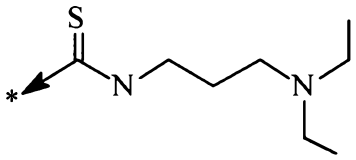
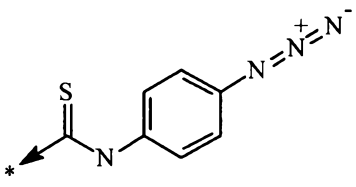
343	"		"	87.37	4.3	466.3
344	"		"	83.01	4.9	404.3
345	"		"	89.47	5.6	504.4
346	"		"	77.55	3.6	435.3
347	"		"	49.49	2.4	414.3
348	"		"	85.63	4.9	454.2
349	"		"	88.12	2.9	397.3

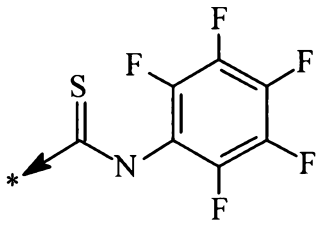
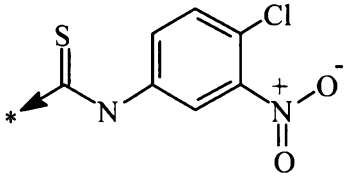
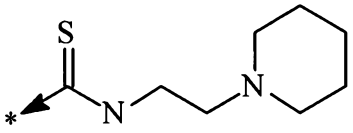
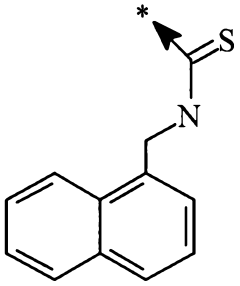
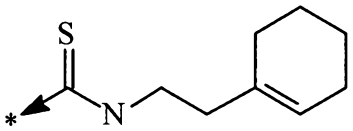
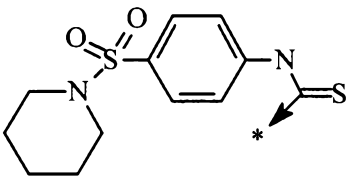
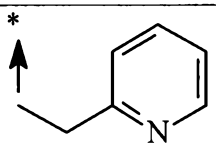
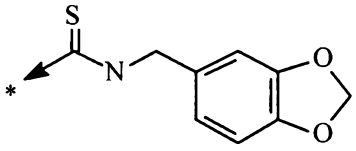
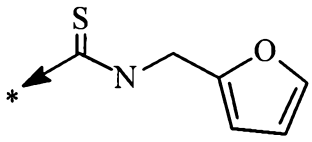
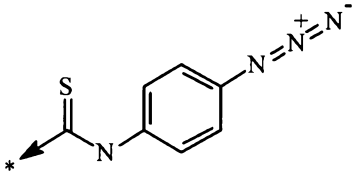
350	"		"	87.73	4.9	432.3
351	"		"	84.48	4.4	366.3
352	"		"	82.03	4.7	356.3
353	"		"	82.93	4.9	446.3
354	"		"	72.6	5.3	396.3
355	"		"	86.75	3.2	391.3
356			"	93.75	4.7	413.1
357	"		"	96.13	4.6	413.2
358	"		"	98.3	3.8	435.2

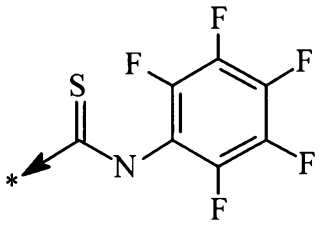
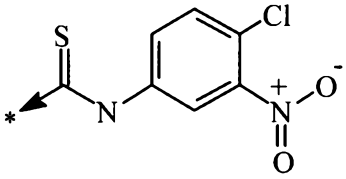
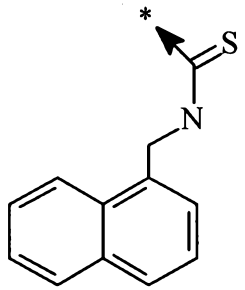
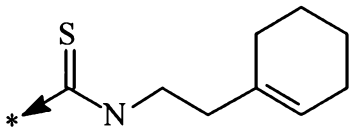
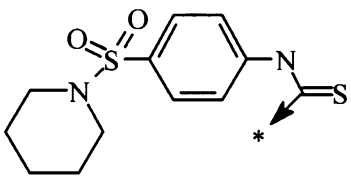
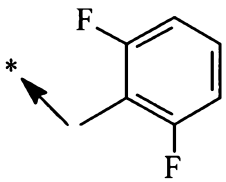
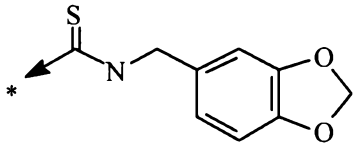
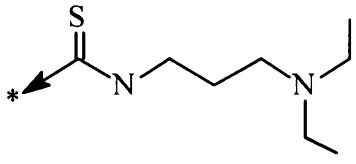
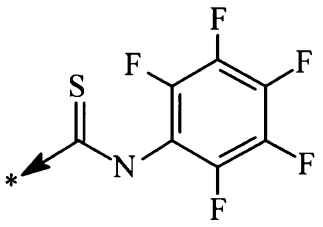
359	"		"	96.45	4.5	373.2
360	"		"	97.9	5.3	473.4
361	"		"	97.57	3.0	404.3
362	"		"	78.0	2.5	383.2
363	"		"	98.96	4.5	423.1
364	"		"	93.98	2.4	366.3
365	"		"	97.98	4.5	401.2
366	"		"	93.33	4.0	335.2

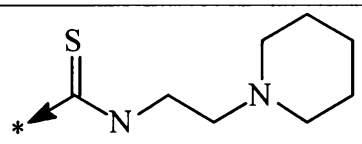
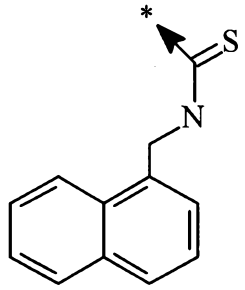
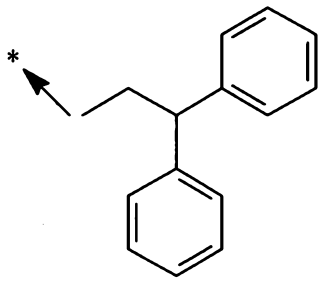
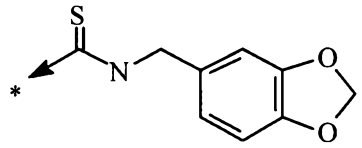
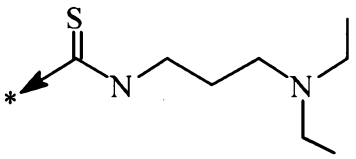
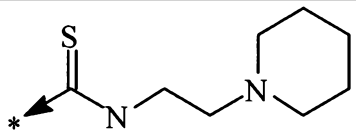
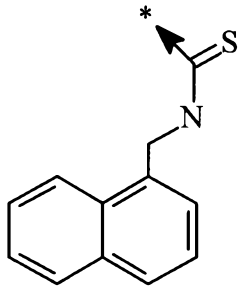
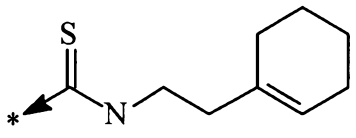
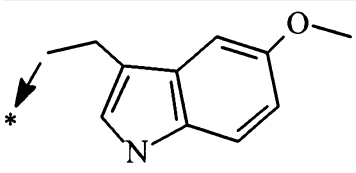
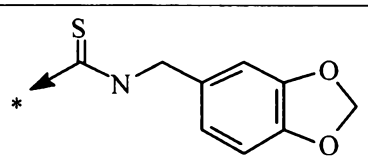
367	"		"	95.73	4.3	325.3
368	"		"	1.21	3.9	421.3
369	"		"	88.55	4.6	415.2
370	"		"	95.93	4.9	365.3
371	"		"	99.1	2.6	360.2
372			"	90.59	3.4	392.1
373	"		"	93.57	3.3	392.2
374	"		"	97.23	2.6	414.2
375	"		"	93.83	3.1	352.3

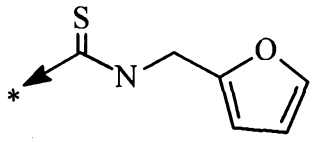
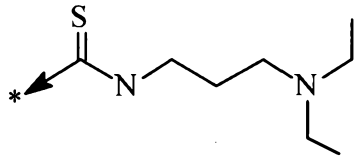
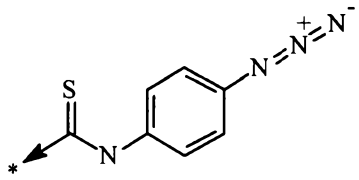
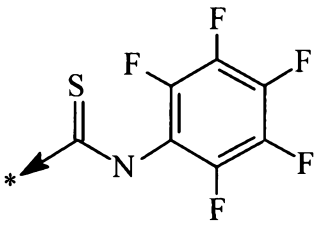
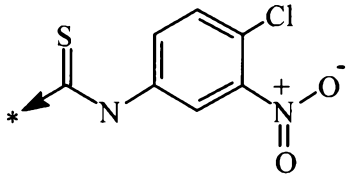
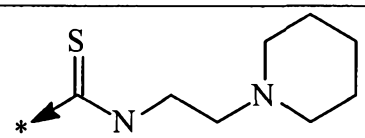
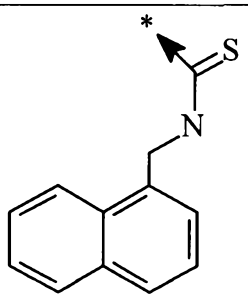
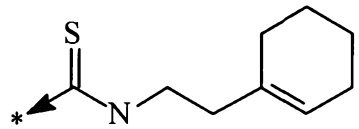
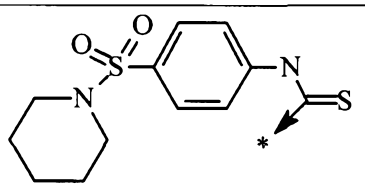
376	"		"	96.81	4.0	452.4
377	"		"	97.7	2.2	383.3
378	"		"	53.69	2.3	362.2
379	"		"	97.1	3.1	402.1
380	"		"	70.3	2.5	345.3
381	"		"	97.59	3.1	380.2
382	"		"	86.74	2.4	314.2

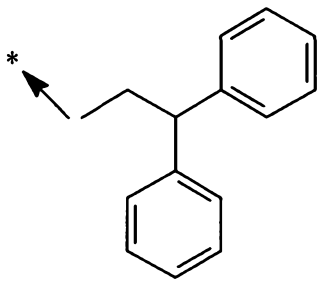
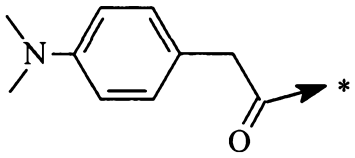
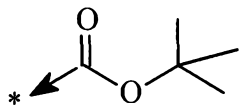
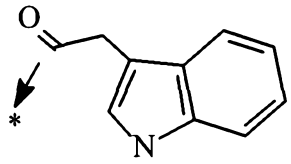
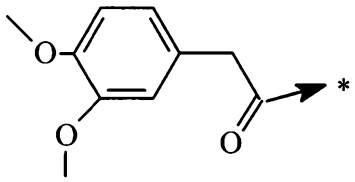
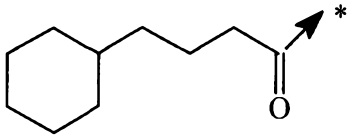
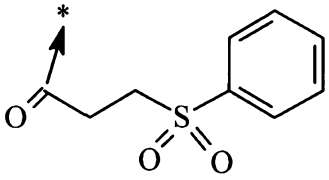
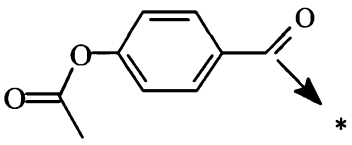
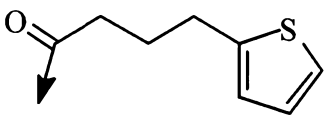
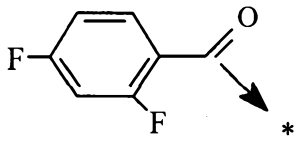
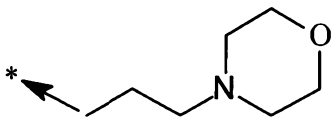
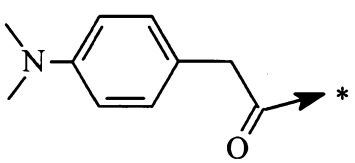
383	"		"	87.28	2.6	304.3
384	"		"	10.27	3.1	400.2
385	"		"	93.38	3.1	394.2
386	"		"	88.99	3.4	344.3
387	"		"	89.43	2.5	339.3
388				86.18	4.2	458.3
[illegible]	"		"	37.01	3.9	404.3
390	"		"	57.02	2.7	437.4
391	"		"	78.70	4.3	441.3

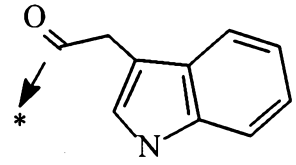
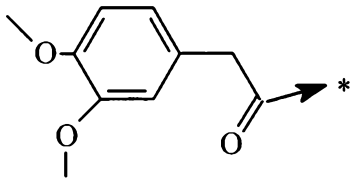
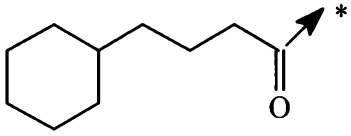
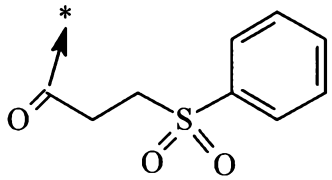
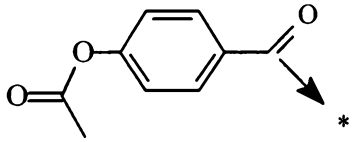
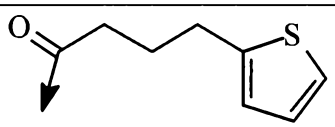
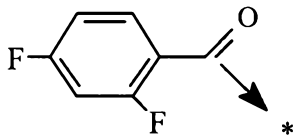
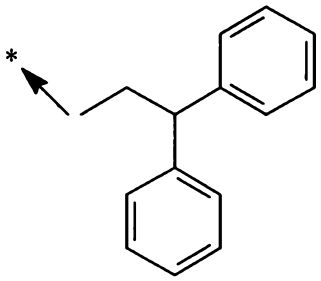
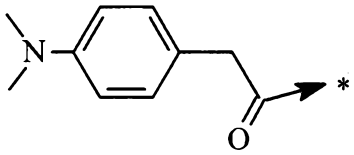
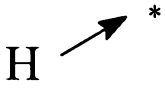
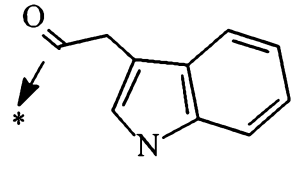
392	"		"	67.94	4.6	490.3
393	"		"	39.75	4.5	479.3
394	"		"	94.48	2.8	435.4
[illegible]	"		"	83.7	3.4	432.3
396	"		"	96.5	4.7	464.4
397	"		"	43.75	4.5	547.3
398			"	86.87	3.3	399.3
399	"		"	47.77	2.9	345.3
400	"		"	82	3.4	382.3

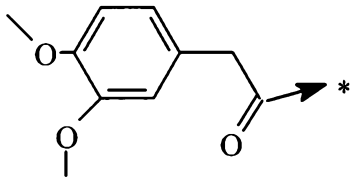
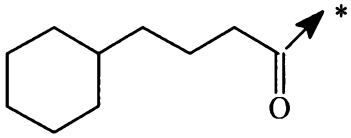
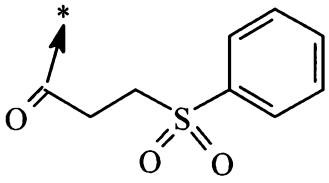
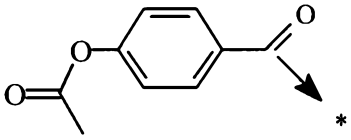
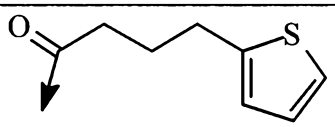
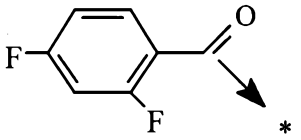
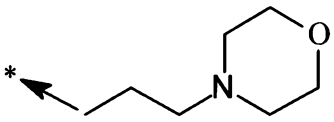
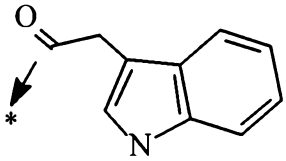
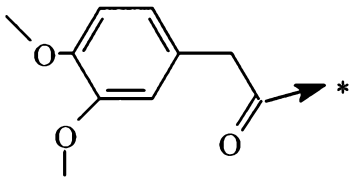
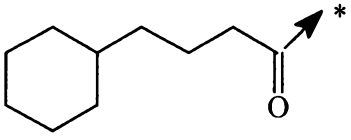
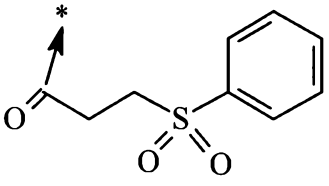
401	"		"	97.10	3.8	431.2
402	"		"	76.92	3.8	420.2
403	"		"	97.3	2.8	373.3
404	"		"	95.9	4.0	405.3
405	"		"	69.50	3.7	488.3
406			"	90.79	4.1	420.3
407	"		"	86.38	2.5	399.3
408	"		"	67.52	4.6	452.2

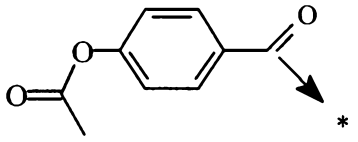
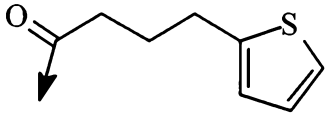
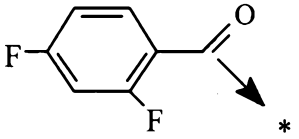
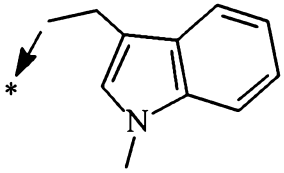
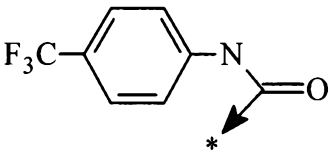
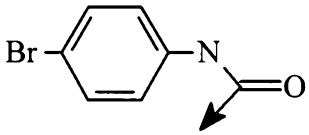
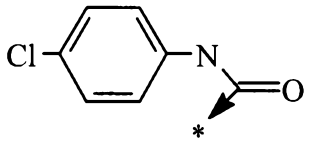
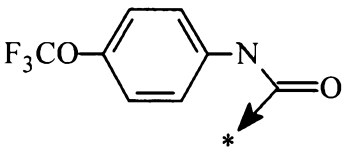
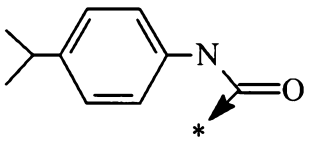
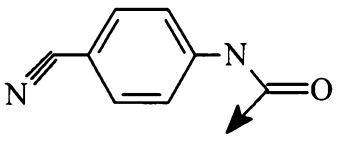
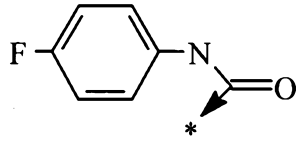
409	"		"	99.8	2.7	397.3
410	"		"	97.7	3.3	394.3
411			"	87.97	5.0	488.3
412	"		"	97.23	3.6	467.4
413	"		"	99.29	3.7	465.4
414	"		"	96.2	4.2	462.4
415	"		"	72.0	5.5	494.3
416			"	85.09	4.3	467.3

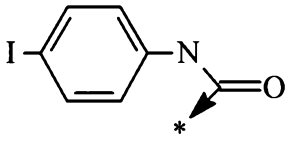
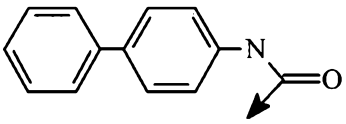
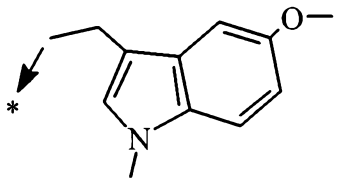
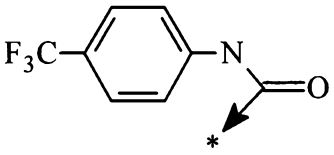
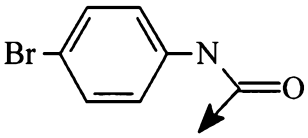
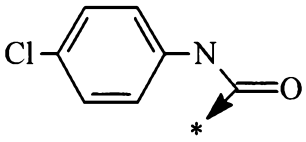
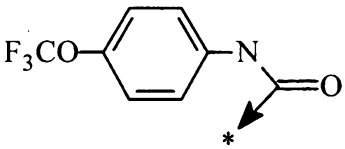
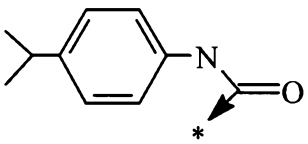
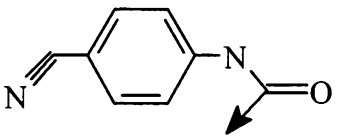
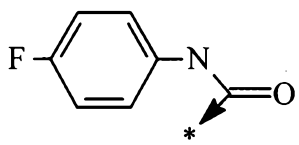
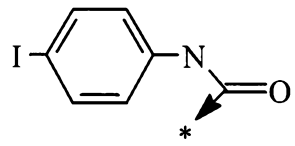
417	"		"	68.52	4.1	413.3
418	"		"	98.76	2.8	446.4
419	"		"	73.21	4.4	450.3
420	"		"	76.94	4.7	499.2
421	"		"	85.12	4.6	488.2
422	"		"	98.15	2.9	444.4
423	"		"	58	5.1	477.3
424	"		"	25	3.6	410.3
425	"		"	69.90	4.6	556.3

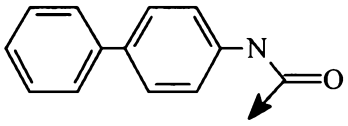
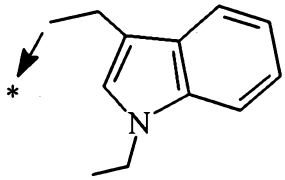
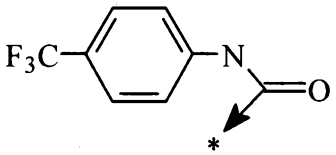
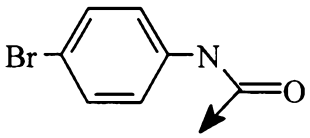
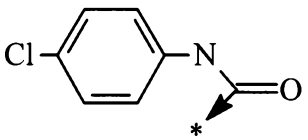
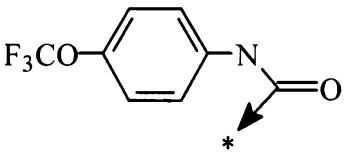
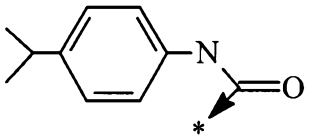
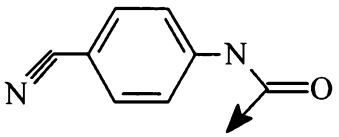
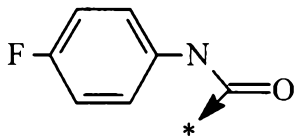
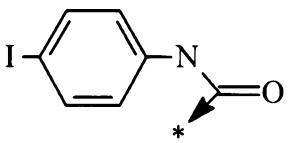
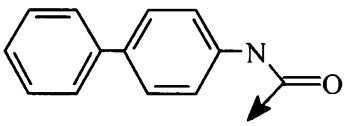
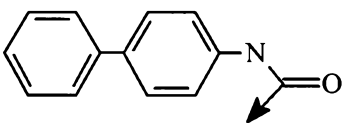
426				90.11	8.2	556.3
427	"		"	95.30	9.7	552.3
428	"		"	89.35	9.6	573.3
429	"		"	97.48	11.8	547.4
430	"		"	91.35	9.6	591.3
431	"		"	66.60	9.7	557.3
432	"		"	97.25	10.5	547.3
433	"		"	98.20	10.2	549.3
434			"	88.28	4.7	489.3

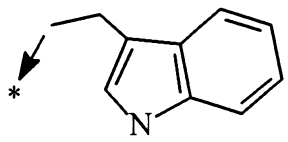
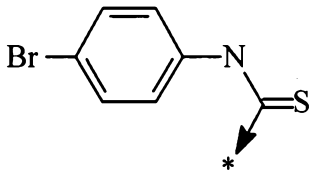
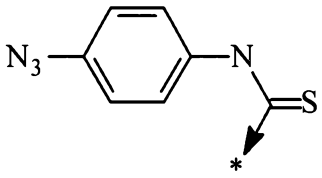
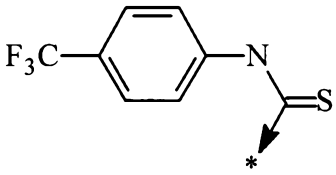
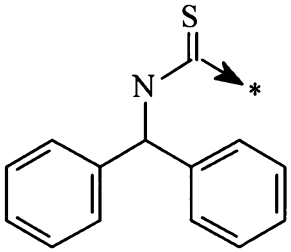
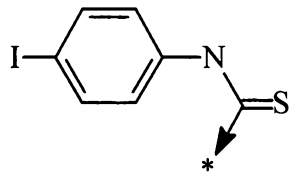
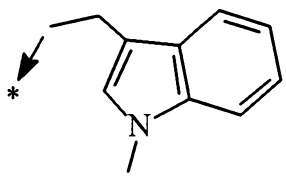
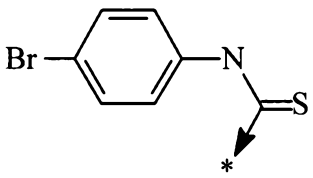
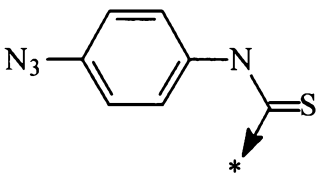
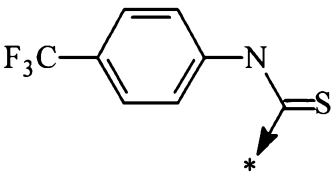
435	"		"	94.30	5.8	485.3
436	"		"	92.92	5.6	506.3
437	"		"	95.73	7.1	480.4
438	"		"	89.80	5.6	524.3
439	"		"	69.38	5.6	490.3
440	"		"	95.21	6.2	480.3
441	"		"	96.98	6.0	482.3
442				85.00	5.4	456.3
443	"		"	94.40	6.5	452.3

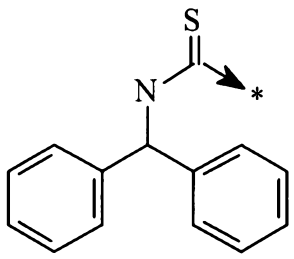
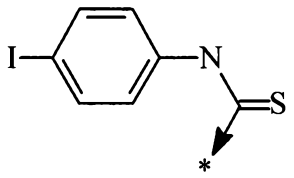
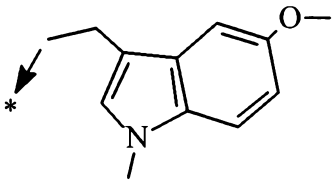
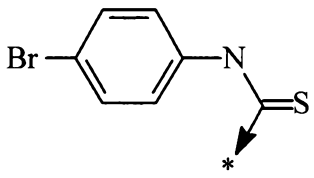
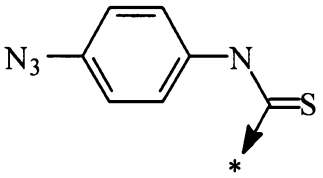
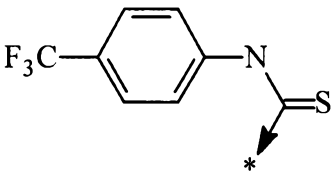
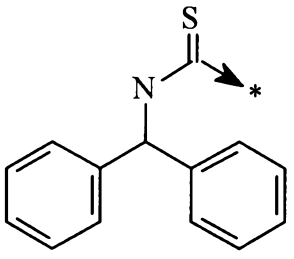
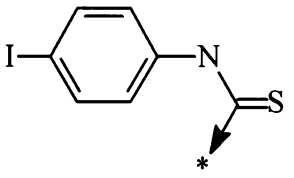
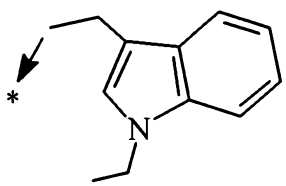
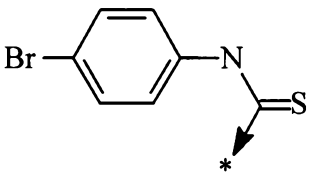
444	"		"	91.10	6.3	473.3
445	"		"	96.60	7.7	447.3
446	"		"	92.80	6.3	491.2
447	"		"	85.40	6.3	457.2
448	"		"	96.70	6.9	447.2
449	"		"	98	6.7	449.2
450			"	38.17	3.6	385.2
451	"		"	92.70	3.4	406.2
452	"		"	89.50	4.7	380.3
453	"		"	86.24	3.4	424.2

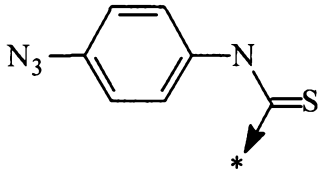
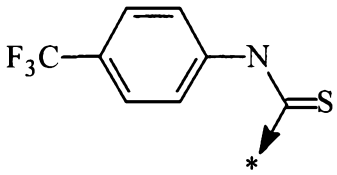
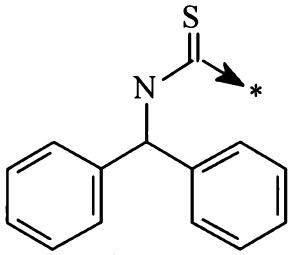
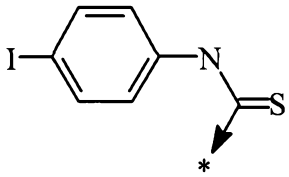
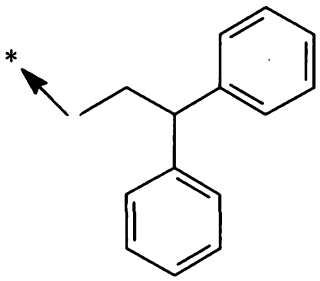
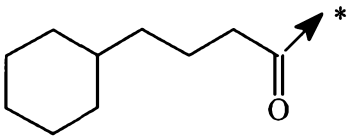
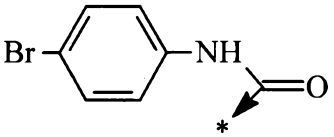
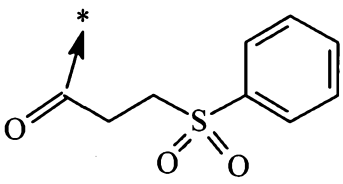
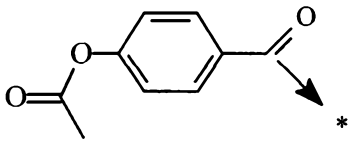
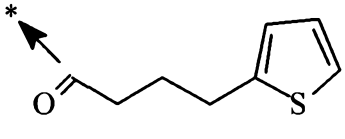
454	"		"	71.20	3.3	390.2
455	"		"	88.60	3.8	380.2
456	"		"	89.26	3.5	382.2
457			"	96.55	4.9	445.3
458	"		"	94.46	4.8	455.2
459	"		"	95.6	4.7	411.3
460	"		"	98.1	5.0	461.3
461	"		"	93.31	5.1	419.4
462	"		"	97.08	4.2	402.3
463	"		"	94.61	4.4	395.3

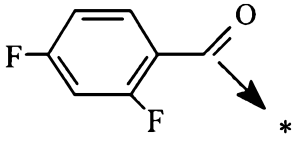
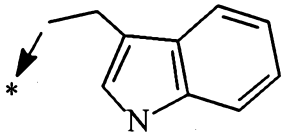
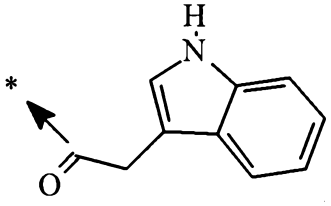
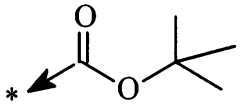
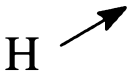
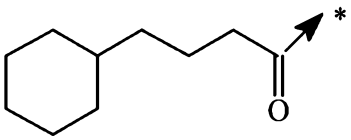
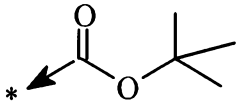
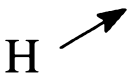
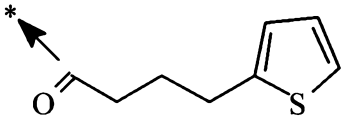
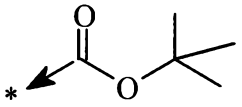
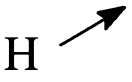
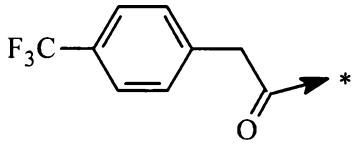
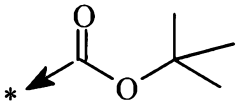
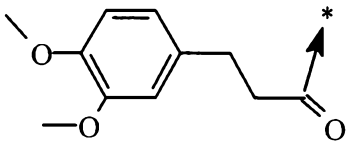
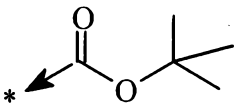
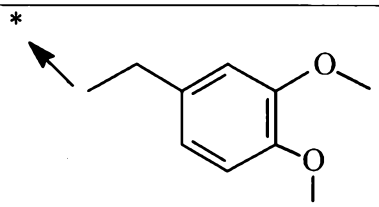
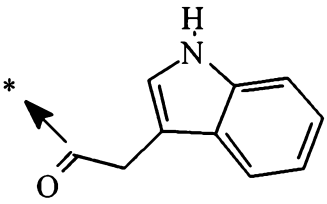
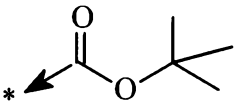
464	"		"	97.05	4.9	503.2
465	"		"	95.13	5.1	453.4
466			"	93.21	4.8	475.3
467	"		"	94.08	4.7	485.2
468	"		"	93.08	4.6	441.3
469	"		"	95.17	4.9	491.3
470	"		"	89.99	5.0	449.4
[illegible]	"		"	92	4.1	432.3
472	"		"	94.71	4.3	425.3
473	"		"	95.3	4.8	533.2

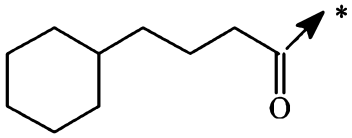
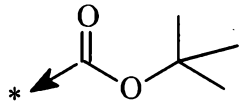
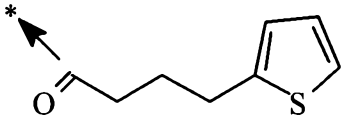
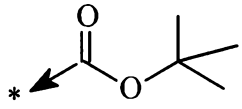
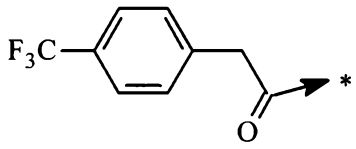
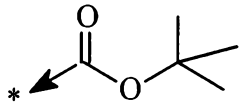
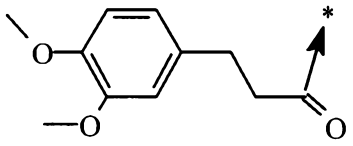
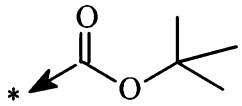
474	"		"	94.13	5.0	483.4
475			"	95	5.1	459.3
476	"		"	94.69	5.0	469.2
477	"		"	94.44	4.9	425.3
478	"		"	98	5.2	475.3
479	"		"	96.2	5.3	433.4
480	"		"	93	4.4	416.3
	"		"	94.59	4.6	409.3
482	"		"	95.22	5.1	517.2
483	"		"	95.7	5.3	467.4
483	"		"	95.7	5.3	467.4

484			"	94.8	4.6	457.2
485	"		"	86.7	4.5	420.3
486	"		"	88.5	4.8	447.3
	"		"	96.9	5.1	483.4
488	"		"	92.3	4.7	505.2
489			"	65.4	4.9	471.2
490	"		"	62.6	4.7	434.3
491	"		"	57.9	5.0	461.3

492	"		"	94.2	5.3	497.4
493	"		"	54.0	5.0	519.2
494			"	54.6	4.8	501.3
495	"		"	64.9	4.7	464.3
496	"		"	70.4	4.9	491.3
497	"		"	96.5	5.2	527.4
498	"		"	55.7	4.9	549.2
499			"	57.4	5.1	485.3

500	"		"	59.3	4.9	448.4
501	"		"	53.6	5.2	475.3
502	"		"	97.8	5.4	511.4
503	"		"	10 +36.87	5.2	533.2
504				96.33	11.2	646.3
505	"		"	92.67	9.4	690.1
506	"		"	41.11	9.5	656.2
507	"		"	97.65	10.1	646.2

508	"		"	96.29	9.9	648.2
509				90.89	8.5	501.3
510	"	"		61.04	5.8	401.2
511	"			99.16	10.5	496.4
512	"	"		95.73	7.1	396.3
513	"			66	9.3	496.3
514	"	"		95.00	8.9	396.2
515	"			96.61	9.5	530.3
516	"	"		94.05	6.4	430.3
517	"			87	8.6	536.3
518	"	"		91.59	5.6	436.3
519				86.84	8.4	522.3

520	"	"		94.18	5.4	422.3
521	"			99.75	10.4	517.4
522	"	"		96.8	6.8	417.4
523	"			70.34	9.1	517.3
524	"	"		93.49	5.8	417.3
	"			93.03	9.3	551.3
526	"	"		97.13	6.1	451.3
527	"			74.37	8.4	557.3
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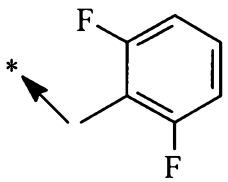
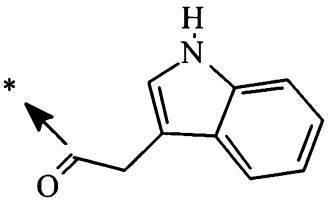
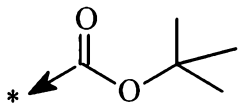
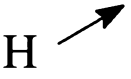
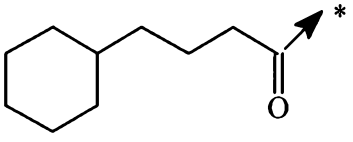
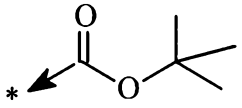
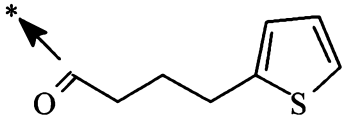
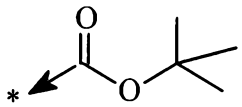
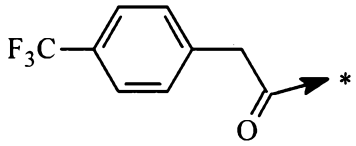
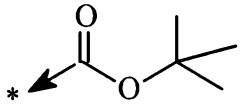
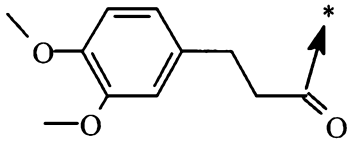
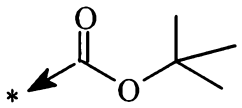
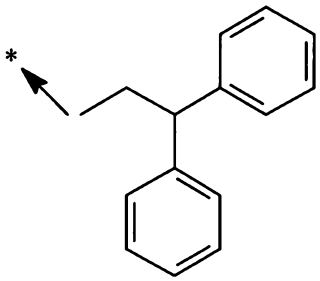
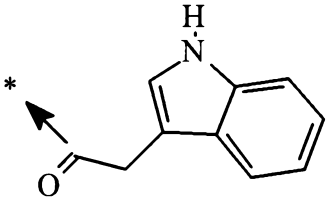
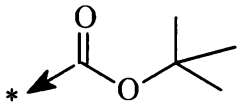
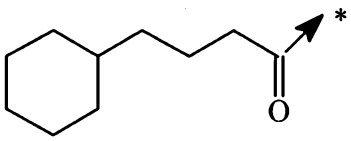
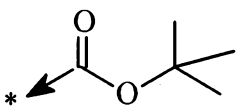
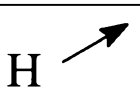
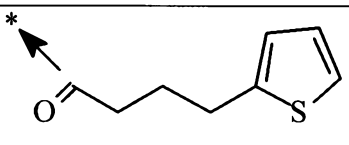
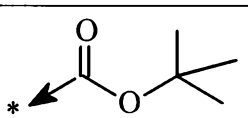
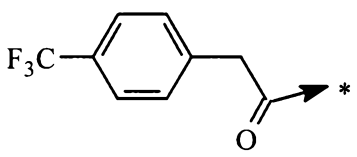
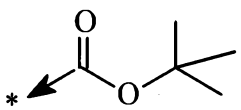
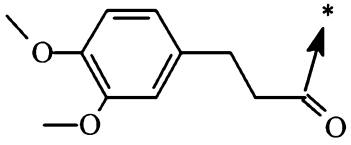
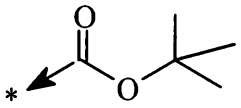
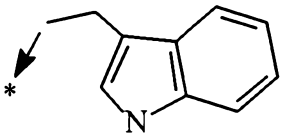
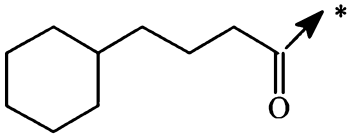
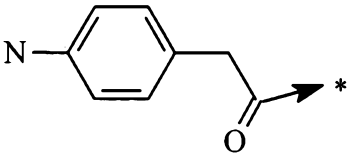
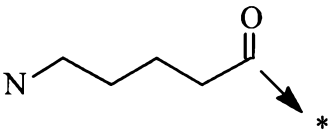
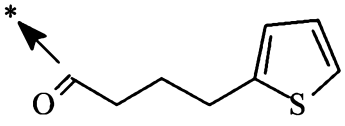
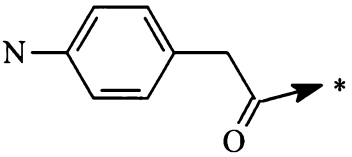
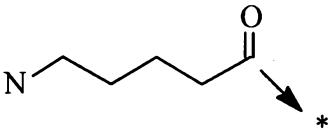
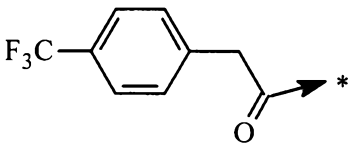
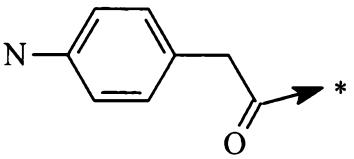
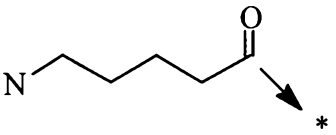
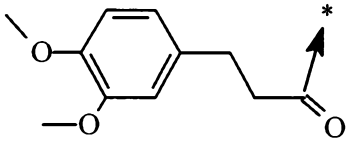
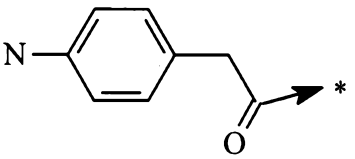
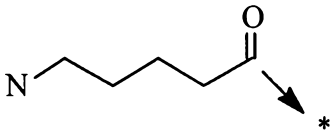
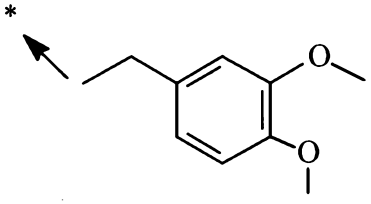
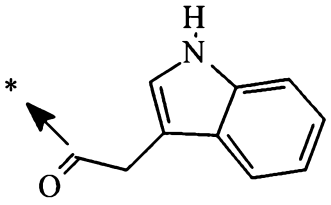
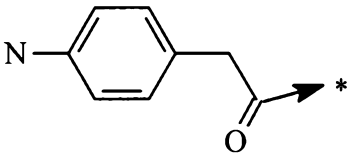
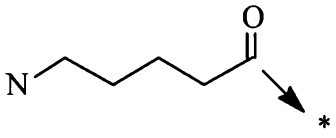
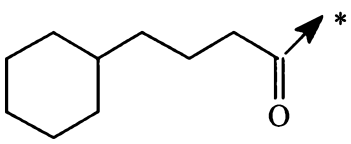
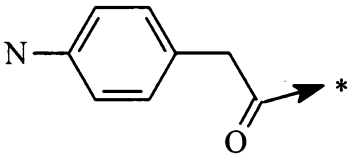
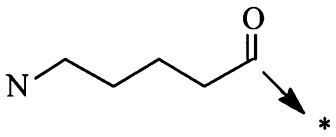
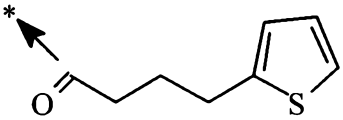
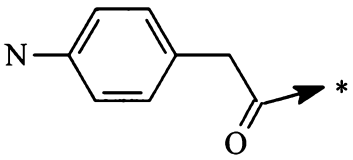
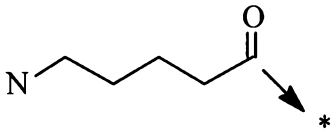
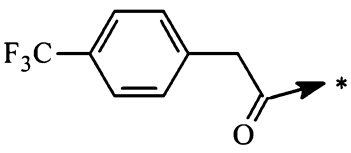
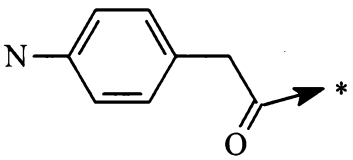
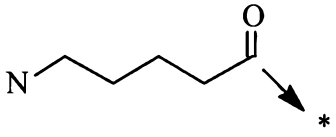
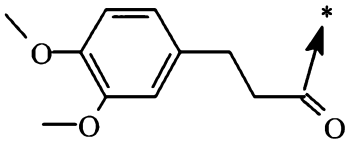
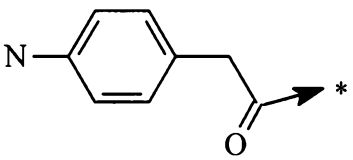
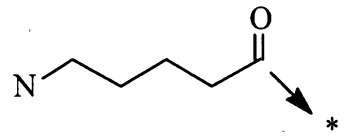
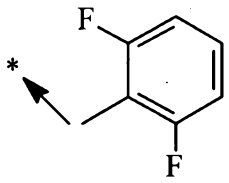
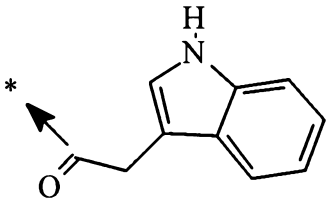
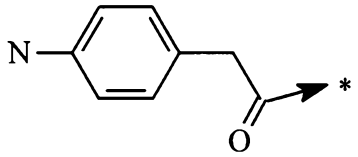
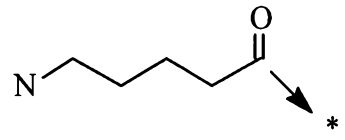
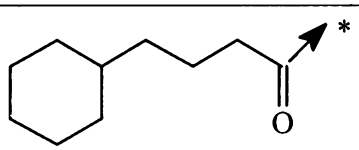
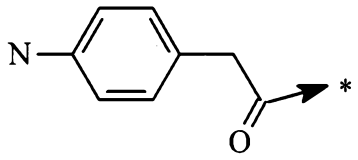
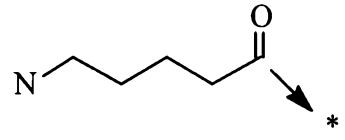
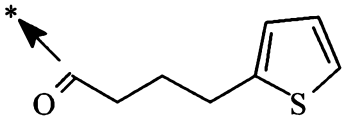
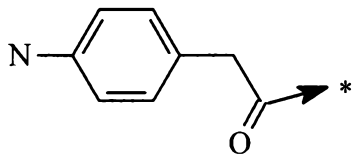
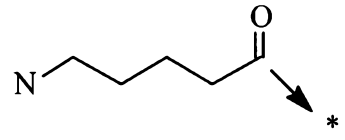
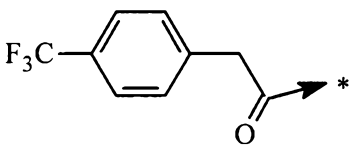
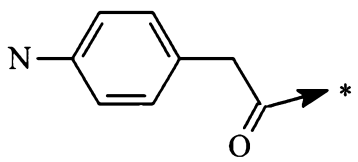
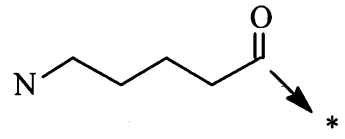
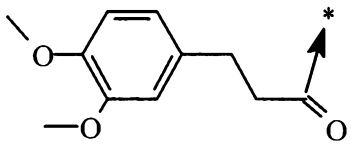
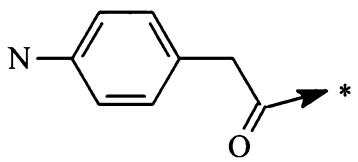
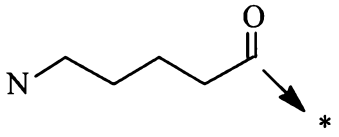
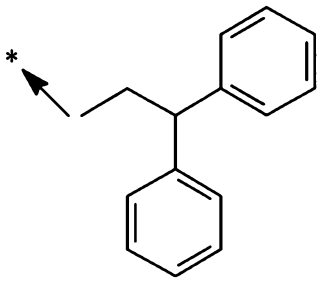
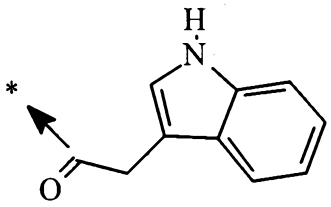
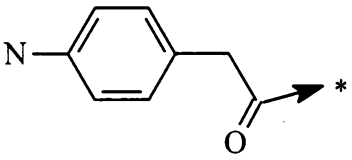
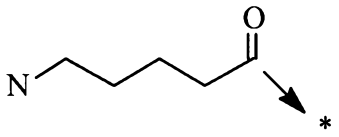
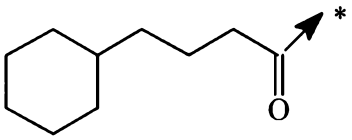
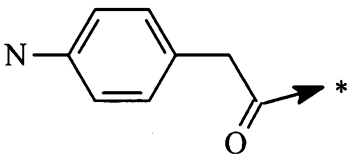
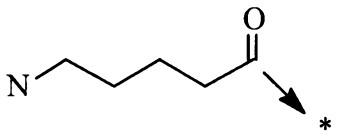
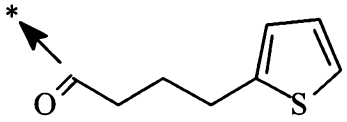
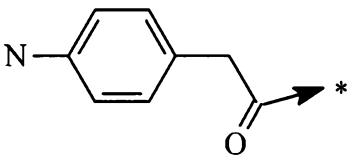
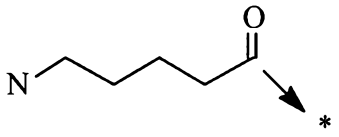
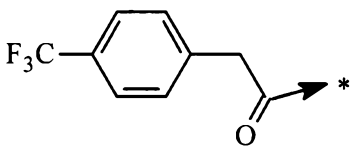
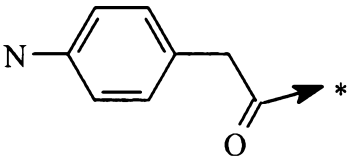
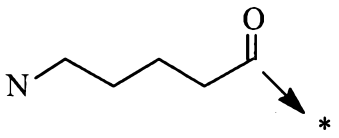
				92.92	8.8	484.3
530	"	"		92.68	5.5	384.2
531	"			98.29	10.8	479.3
532	"	"		96.39	7.0	379.3

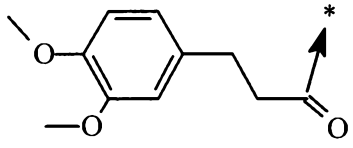
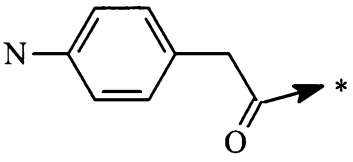
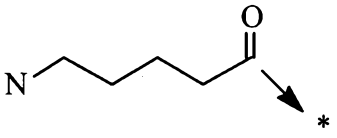
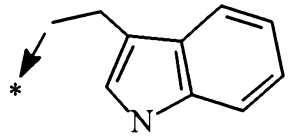
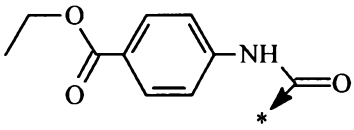
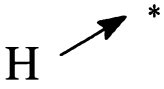
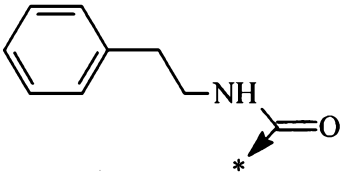
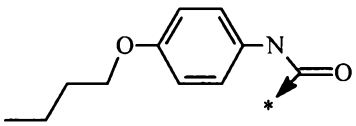
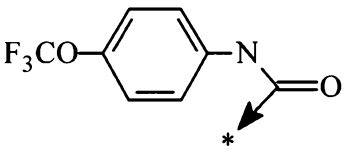
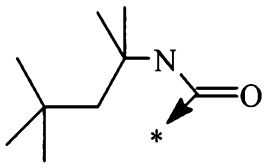
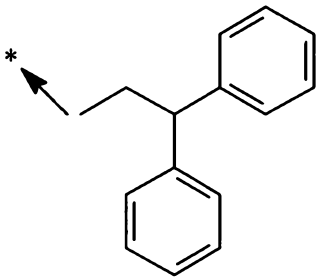
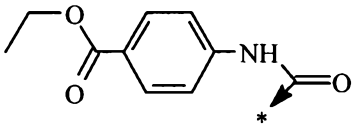
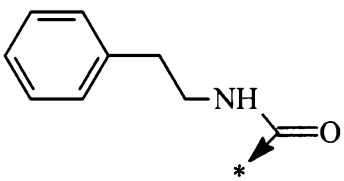
533	"			99	9.5	479.2
534	"	"		99.76	6.0	379.2
535	"			99.17	9.7	513.2
536	"	"		99.74	6.3	413.2
537	"			68.71	8.7	519.3
538	"	"		90.09	5.4	419.3
539				91.37	9.8	552.3
540	"	"		95.39	6.6	452.3
541	"			98.71	11.7	547.4
542	"	"		99.02	7.9	447.4
543	"			79.38	10.5	547.3
544	"	"		95.46	7.1	447.3

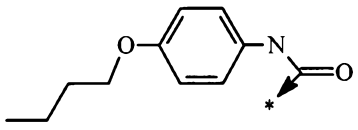
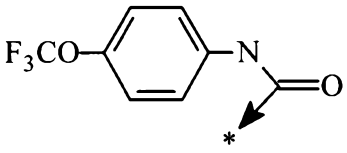
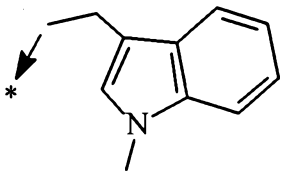
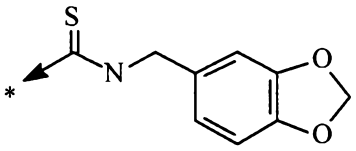
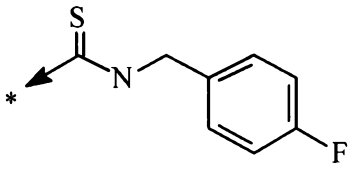
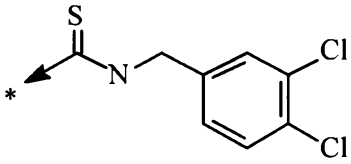
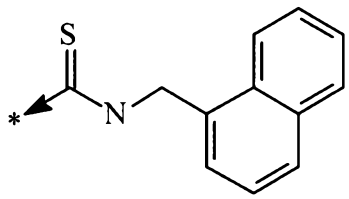
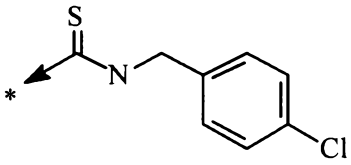
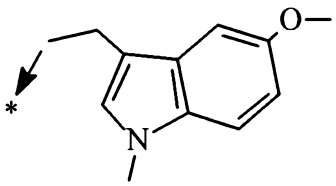
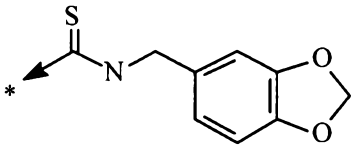
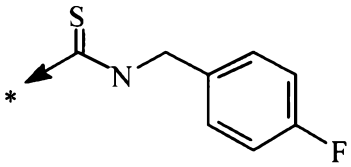
545	"			95.3	10.6	581.3
546	"	"		95.45	7.3	481.3
547	"			80.92	9.8	587.3
548	"	"		92.06	6.5	487.3
549				63	7.7	529.4
550	"	"		79	7.1	495.4
551	"			70	6.7	529.3
552	"	"		77	6.3	495.3
553	"			61	6.9	563.3
554	"	"		69	6.5	529.3
555	"			69	6.1	569.3

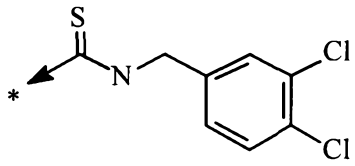
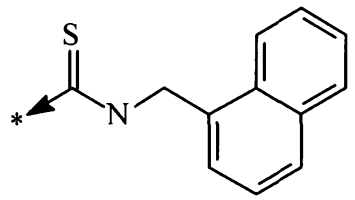
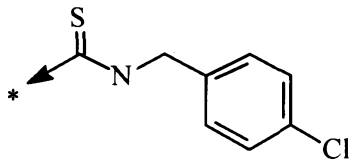
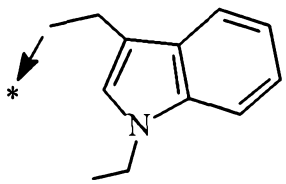
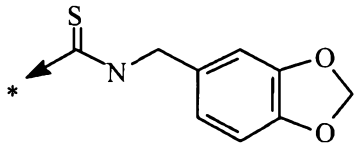
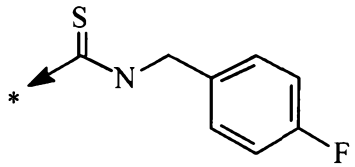
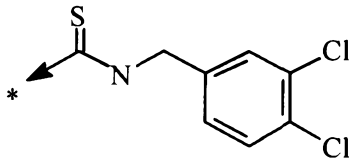
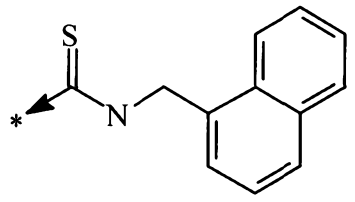
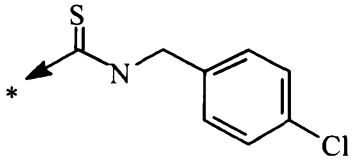
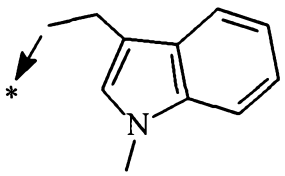
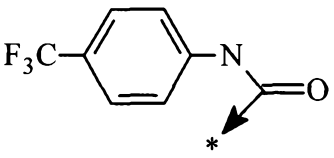
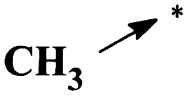
556	"	"		76	5.8	535.3
557				79	5.9	555.3
558	"	"		88	5.6	521.3
559	"			90.81	7.4	550.4
560	"	"		95.6	6.9	516.4
561	"			80.85	6.4	550.3
562	"	"		85.8	6.0	516.3
563	"			92.92	6.6	584.3
564	"	"		97.26	6.3	550.3
565	"			82.91	5.8	590.3

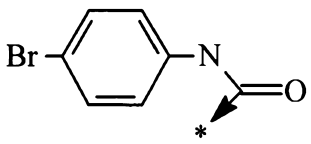
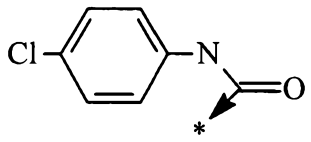
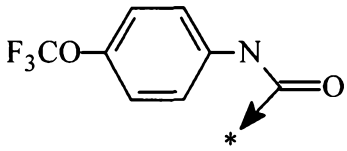
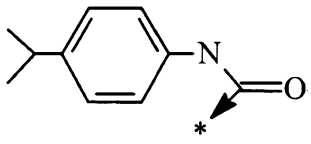
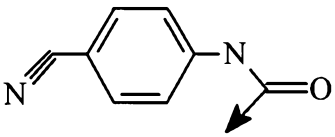
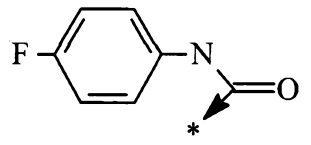
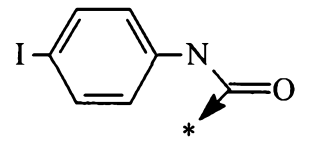
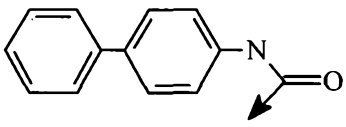
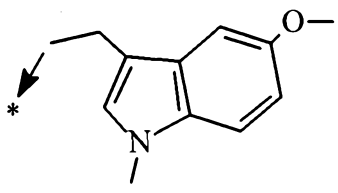
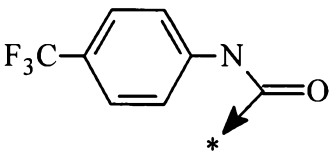
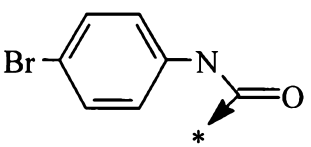
566	"	"		87.77	5.5	556.3
567				86	6.0	517.3
568	"	"		83.41	5.7	483.3
569	"			95	7.6	512.3
570	"	"		94.08	7.1	478.4
571	"			87.39	6.5	512.3
572	"	"		90.06	6.1	478.3
573	"			85.61	6.8	546.2
574	"	"		83.51	6.4	512.3
575	"			78.63	5.9	552.3

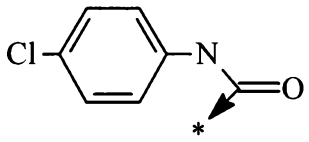
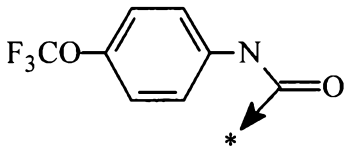
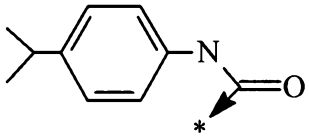
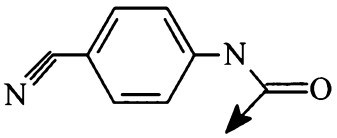
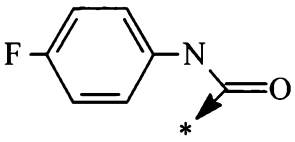
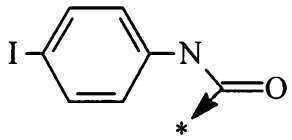
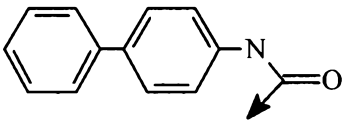
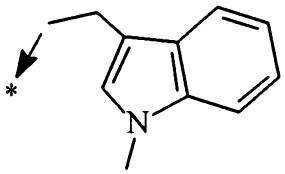
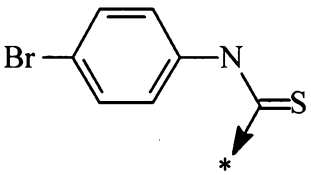
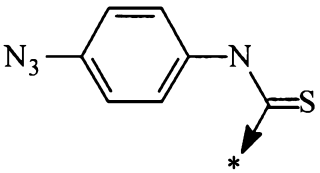
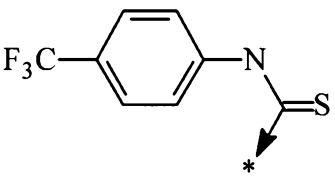
576	"	"		79.58	5.6	518.3
577				84	7.1	585.3
578	"	"		91	6.7	551.3
579	"			89.59	8.6	580.4
580	"	"		97.13	7.9	546.4
581	"			83	7.6	580.3
582	"	"		92.05	7.1	546.3
583	"			86	7.8	614.3
584	"	"		95.49	7.3	580.3

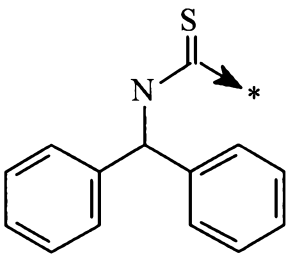
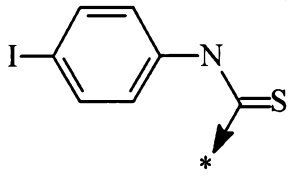
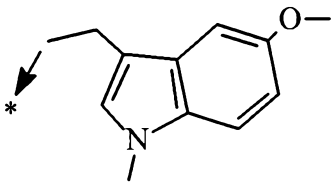
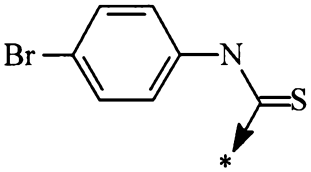
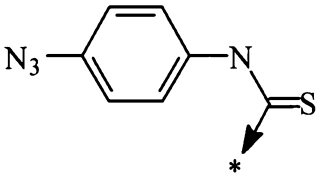
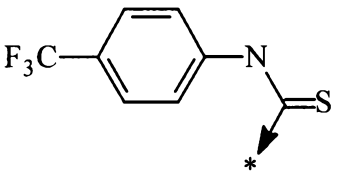
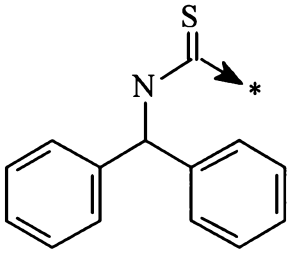
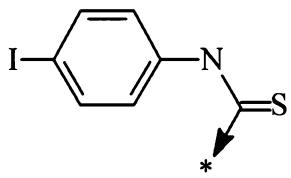
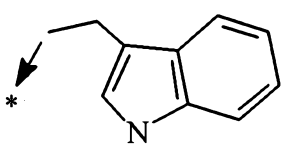
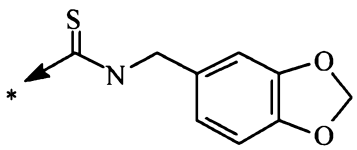
585	"			77	7.0	620.3
586	"	"		91.1	6.6	586.4
587				95	4.6	435
588	"		"	90	4.4	391.3
589	"		"	88	5.1	435.3
590	"		"	92	4.9	447.3
591	"		"	20.32	5.1	399.4
592			"	85	5.3	486.3
593	"		"	97	5.1	442.3

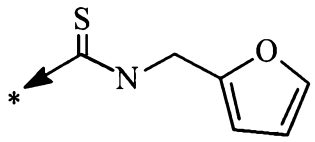
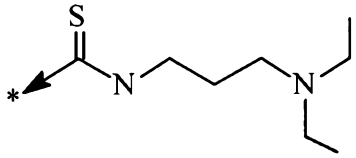
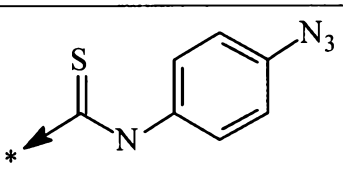
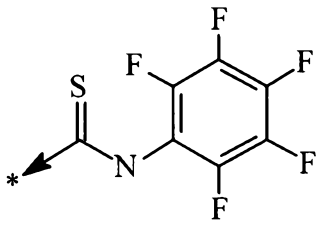
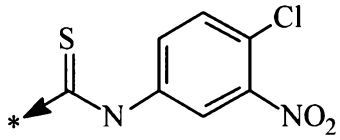
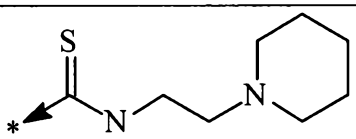
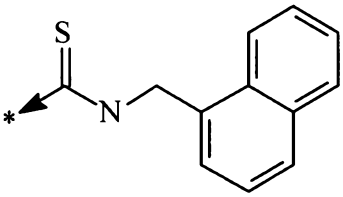
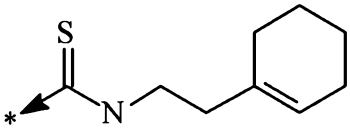
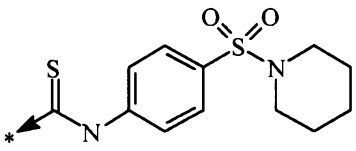
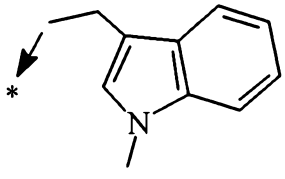
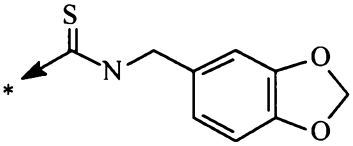
594	"		"	92	5.7	486.4
595	"		"	79	5.5	498.3
596			"	93.4	4.68	451.29
597	"		"	94.9	4.86	425.27
598	"		"	97.9	5.37	475.22
599	"		"	97.1	5.20	457.32
600	"		"	95.1	5.10	441.24
601			"	91.1	4.61	481.29
602	"		"	97.5	4.78	455.29

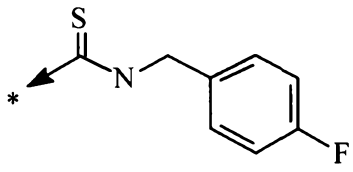
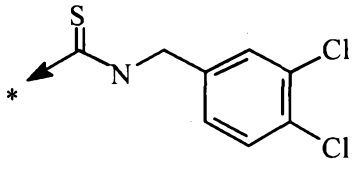
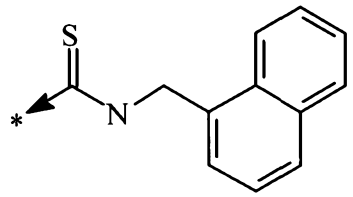
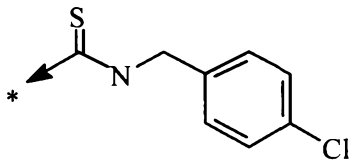
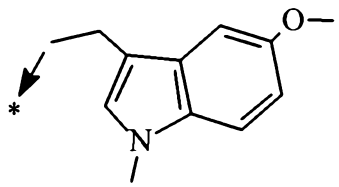
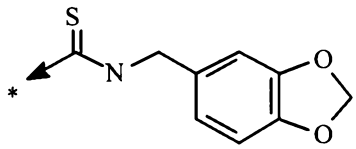
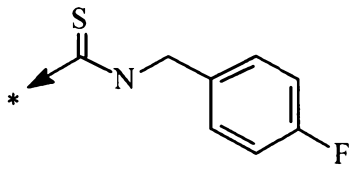
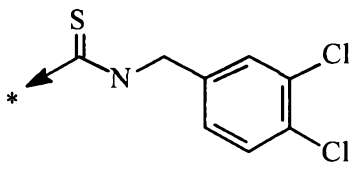
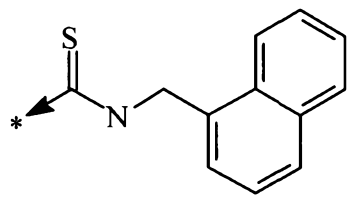
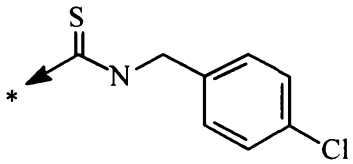
603	"		"	98.0	5.28	505.22
604	"		"	95.4	5.12	487.33
605	"		"	94.0	5.03	471.27
606			"	89.8	4.86	465.29
607	"		"	98.2	5.03	439.29
608	"		"	97.6	5.53	489.24
609	"		"	93.3	5.36	471.34
610	"		"	91.4	5.27	455.26
611				94	4.9	459.3

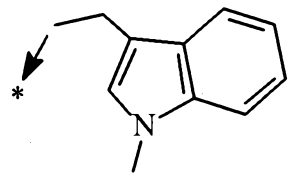
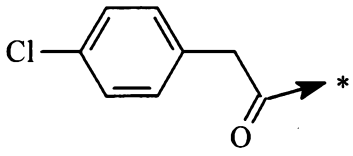
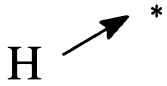
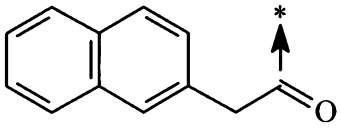
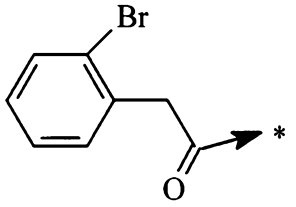
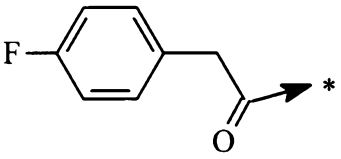
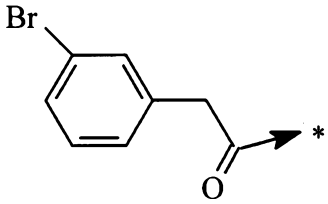
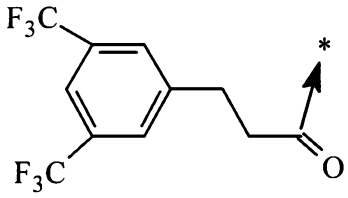
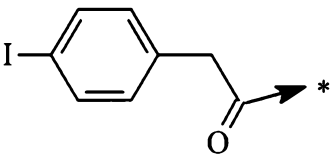
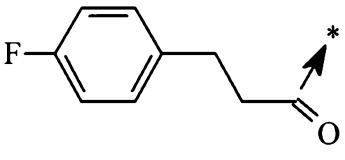
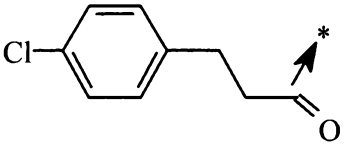
612	"		"	92.95	4.8	469.2
613	"		"	91.61	4.7	425.3
614	"		"	92	5.0	475.3
615	"		"	85.2	5.1	433.4
616	"		"	83	4.2	416.3
617	"		"	94.11	4.4	409.3
618	"		"	93.85	5.0	517.2
619	"		"	92.74	5.1	467.4
620			"	91	4.8	489.3
621	"		"	91.9	4.7	499.3

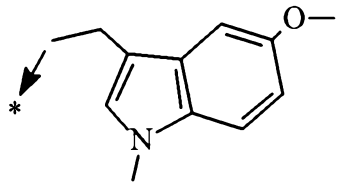
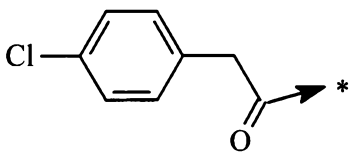
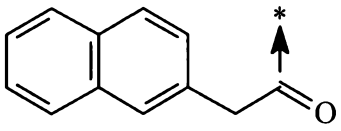
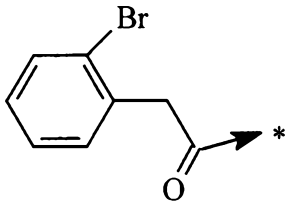
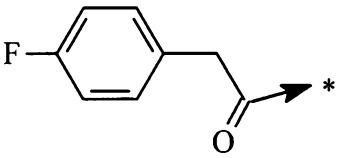
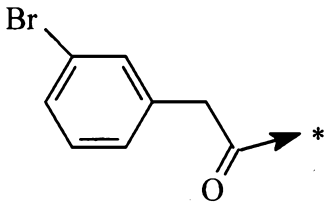
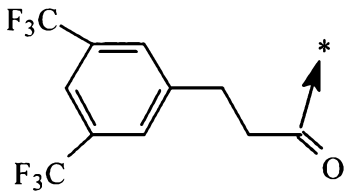
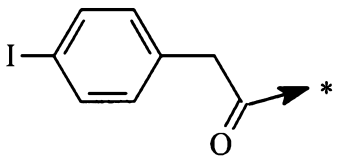
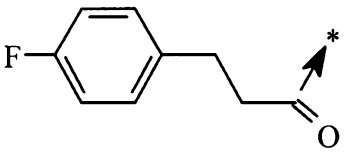
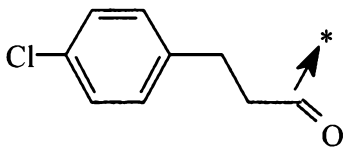
622	"		"	89.71	4.6	455.3
623	"		"	90	4.9	505.3
624	"		"	83.96	5.0	463.4
625	"		"	87	4.1	446.3
626	"		"	93.1	4.3	439.3
627	"		"	93.21	4.8	547.2
628	"		"	90.67	5.0	497.4
629			"	79.6	4.9	485.2
630	"		"	72.8	4.8	448.3
631	"		"	78.7	5.1	475.3

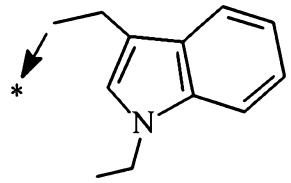
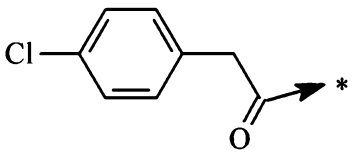
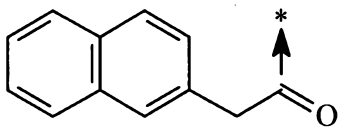
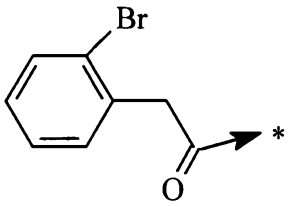
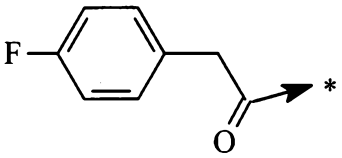
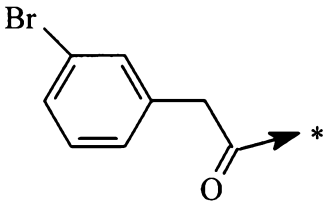
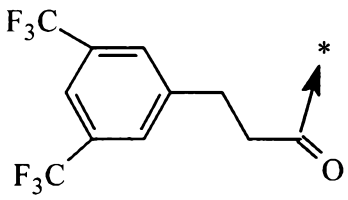
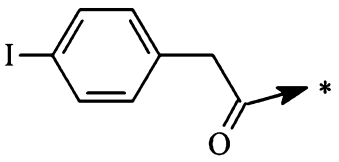
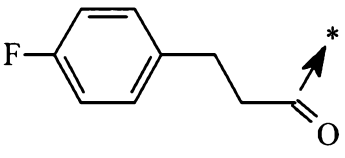
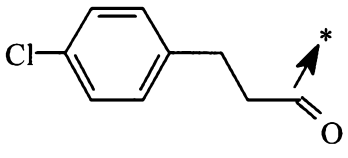
632	"		"	97.3	5.4	511.4
633	"		"	51.5	5.1	533.2
634			"	76.1	4.9	515.3
635	"		"	74.2	4.7	478.3
636	"		"	76.5	5.0	505.3
637	"		"	97.7	5.3	541.4
638	"		"	71.4	5.0	563.2
639			"	82.54	4.4	451.3

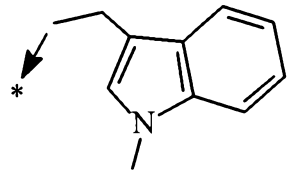
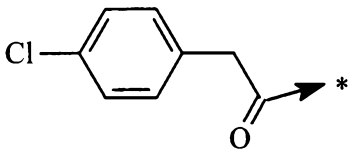
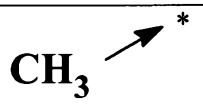
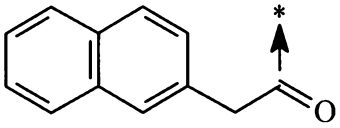
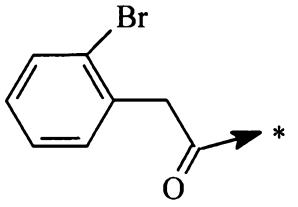
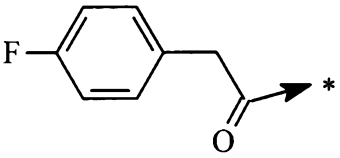
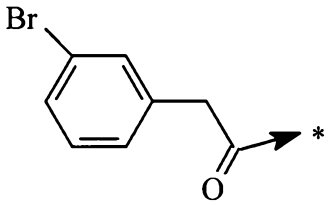
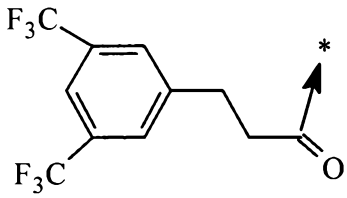
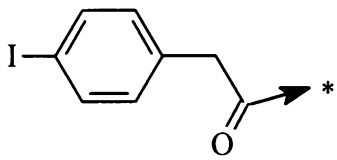
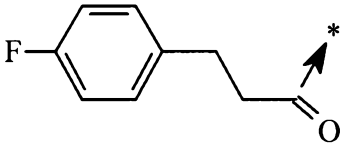
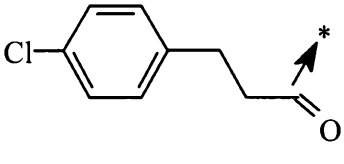
640	"		"	93.42	4.2	397.3
641	"		"	98.93	2.9	430.4
642	"		"	81.46	4.5	434.3
643	"		"	96.41	4.9	483.3
644	"		"	91.55	4.7	472.3
645	"		"	97.96	2.9	428.4
646	"		"	96.9	5.0	425.3
647	"		"	95.8	4.9	457.3
648	"		"	91.41	4.6	540.3
649			"	88.0	4.75	465.3

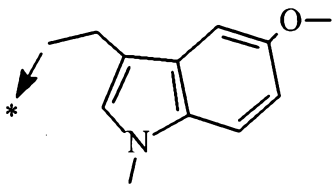
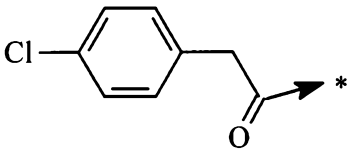
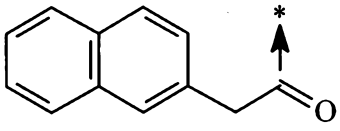
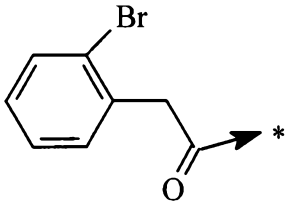
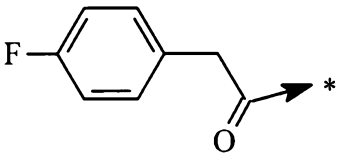
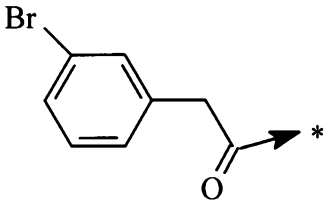
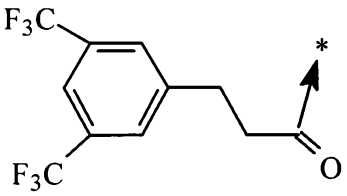
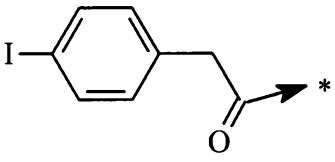
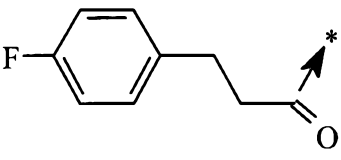
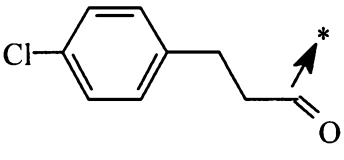
650	"		"	99.0	4.89	439.3
651	"		"	98.5	5.42	489.2
652	"		"	93.3	5.24	471.3
653	"		"	87.6	5.14	455.3
654			"	88.3	4.66	495.3
655	"		"	98.1	4.82	469.3
656	"		"	98.4	5.34	519.2
657	"		"	95.4	5.16	501.3
658	"		"	89.8	5.08	485.3

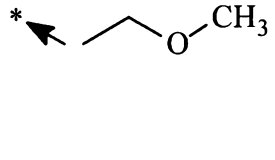
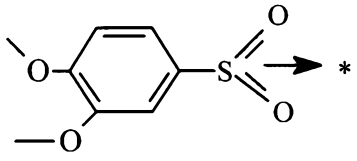
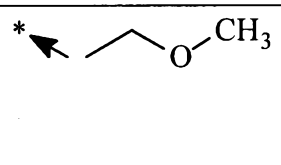
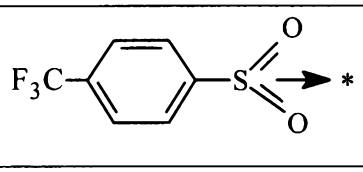
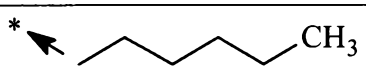
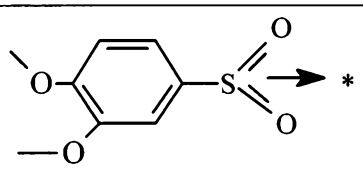
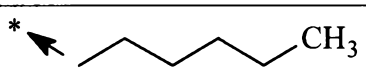
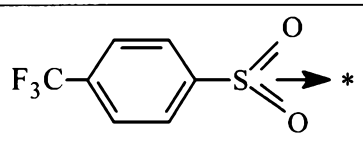
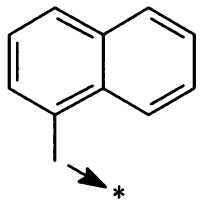
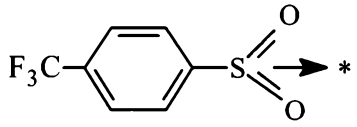
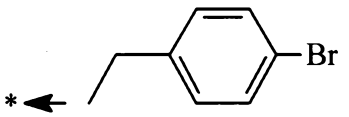
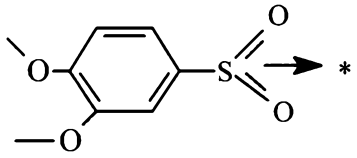
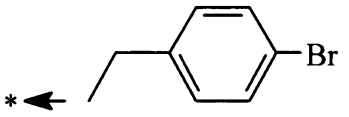
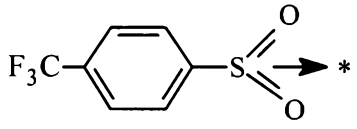
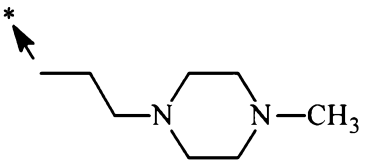
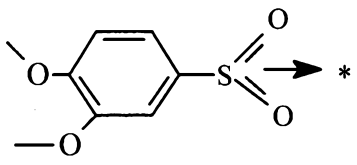
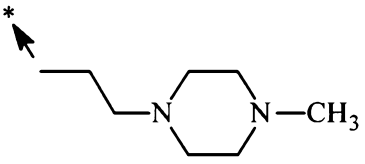
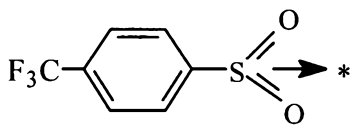
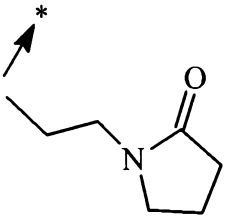
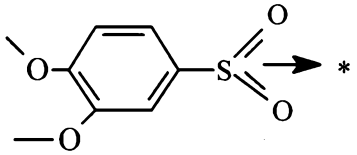
659				80.76	4.84	410.2
660	"		"	61.69	4.97	426.2
661	"		"	90.93	4.79	454.1
662	"		"	91.55	4.58	394.2
663	"		"	91.99	4.88	454.1
664	"		"	92.79	5.55	526.2
665	"		"	93.78	5.02	502.1
666	"		"	96.3	4.75	408.2
667	"		"	81.2	5.02	408.2

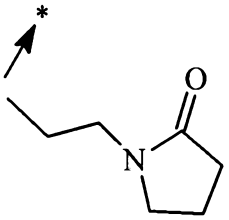
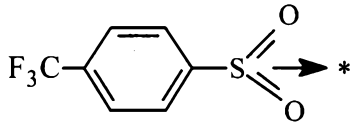
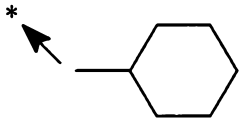
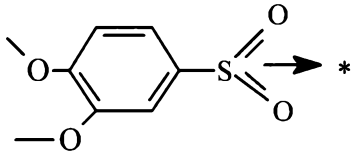
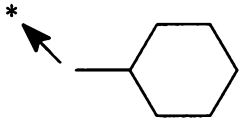
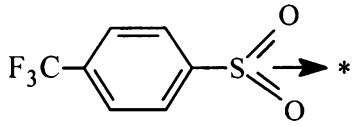
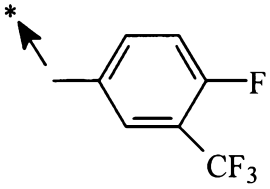
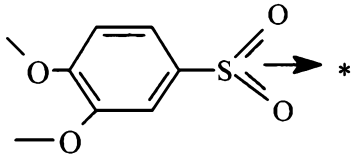
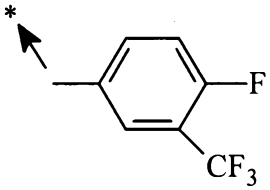
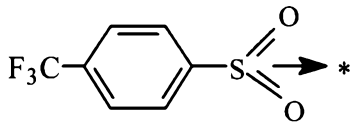
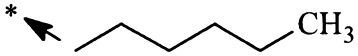
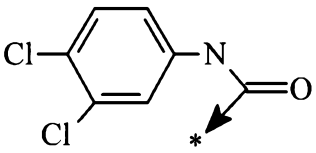
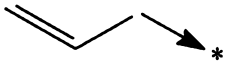
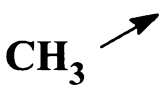
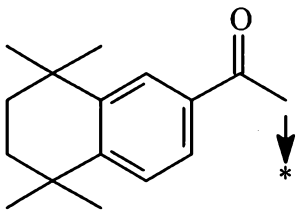
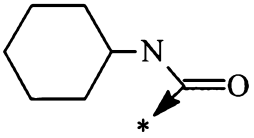
668			"	90.79	4.74	440.2
669	"		"	78.93	4.88	456.3
670	"		"	91.87	4.69	484.2
671	"		"	91.19	4.51	424.2
672	"		"	95.27	4.79	484.2
673	"		"	89.5	5.46	542.2
674	"		"	90.77	4.92	532.1
675	"		"	95.1	4.66	438.2
676	"		"	88.7	4.92	524.2

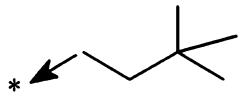
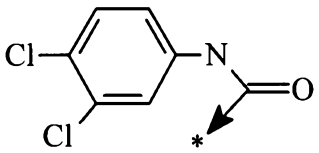
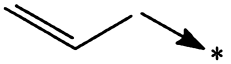
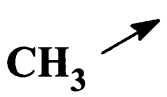
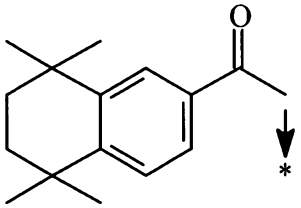
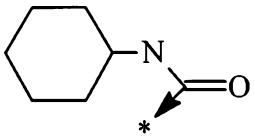
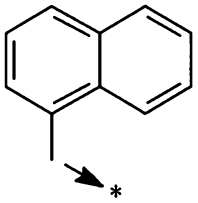
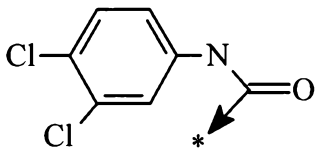
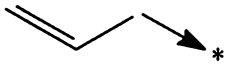
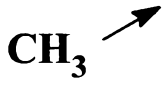
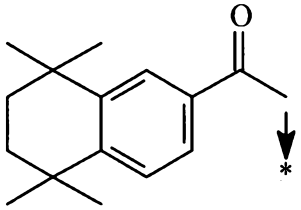
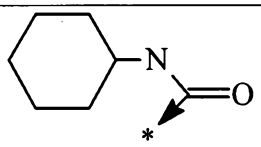
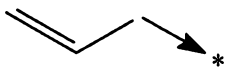
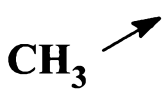
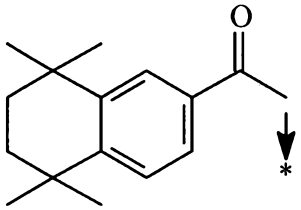
677			"	81.65	4.99	424.2
678	"		"	70.32	5.11	440.3
679	"		"	90.06	4.96	468.2
680	"		"	94.11	4.74	408.2
681	"		"	93.96	5.04	468.2
682	"		"	93.3	5.66	540.2
683	"		"	94.79	5.16	516.1
684	"		"	96.5	4.9	422.3
685	"		"	88.2	5.19	438.2

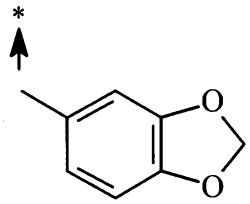
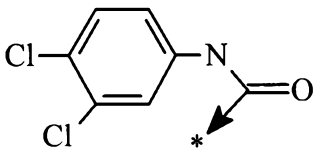
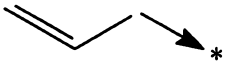
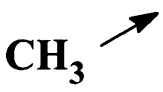
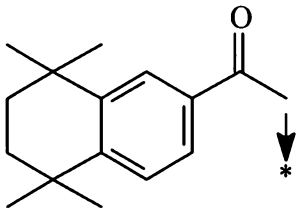
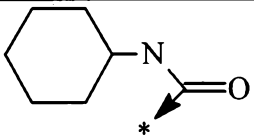
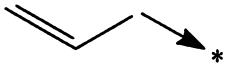
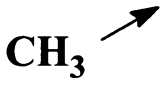
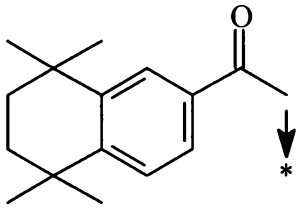
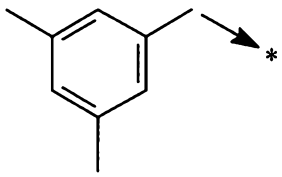
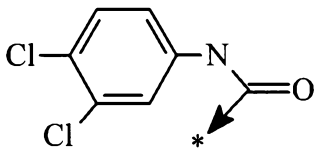
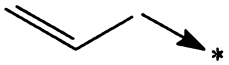
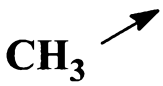
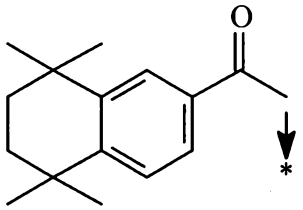
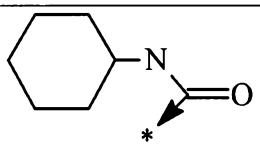
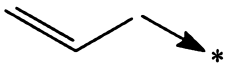
686				87.93	4.86	424.2
687	"		"	84.74	5	440.2
688	"		"	95.34	4.82	468.2
689	"		"	89.78	4.6	408.2
690	"		"	95.16	4.9	468.1633
691	"		"	95.6	5.56	540.2
692	"		"	95.24	5.05	516.3
693	"		"	96.6	4.8	422.2
694	"		"	90.4	5.04	438.2

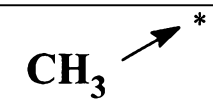
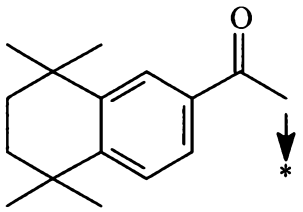
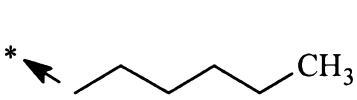
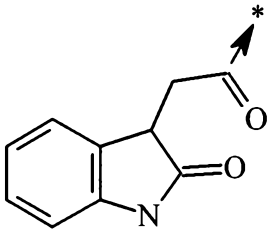
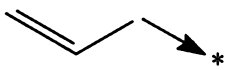
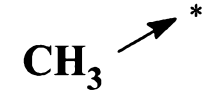
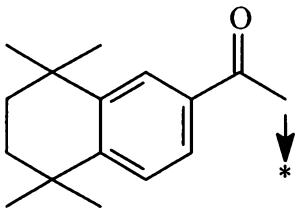
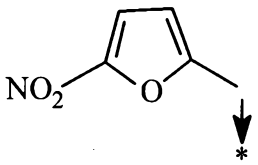
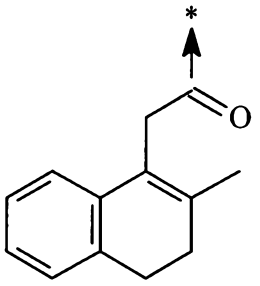
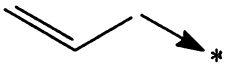
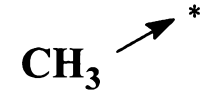
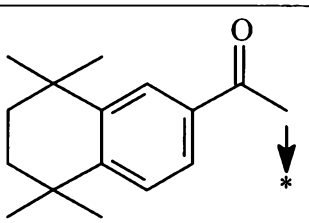
695			"	93.12	4.78	454.2
696	"		"	86.11	4.92	470.3
697	"		"	94.89	4.73	498.2
698	"		"	94.1	4.54	438.3
699	"		"	95.66	4.81	498.2
700	"		"	94.8	5.48	570.2
701	"		"	93.63	4.96	546.1
702	"		"	96.7	4.7	452.3
703	"		"	85.6	4.96	468.2

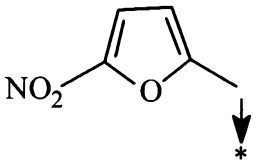
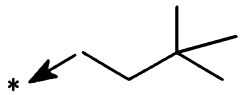
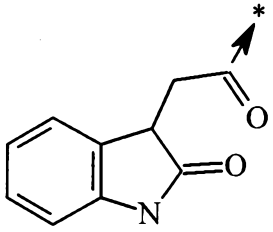
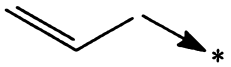
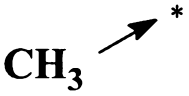
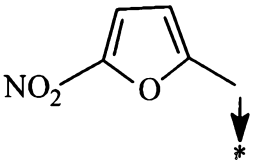
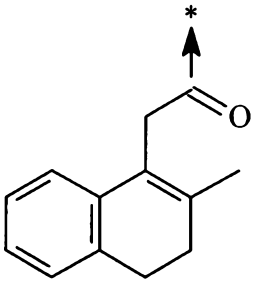
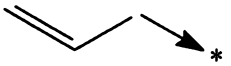
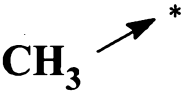
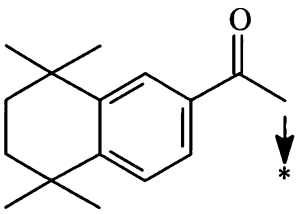
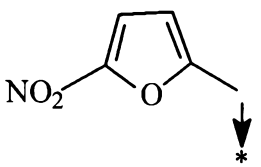
704				78.36	3.14	359.1
705			"	47.4	3.9	367.1
706			"	69.72	4.28	385.2
707			"	34.86	4.96	393.2
708			"	37.54	4.91	449.2
709			"	81.57	4.46	483.1
710			"	55.98	5.12	491.1
711			"	73.74	3.09	441.2
712			"	40.19	2.85	449.2
713			"	90.07	3.18	426.2

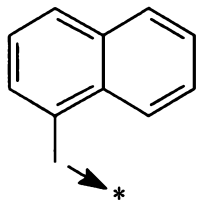
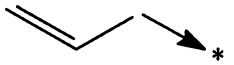
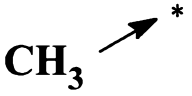
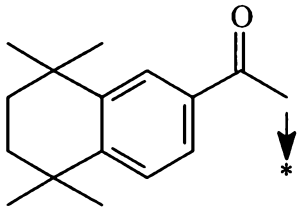
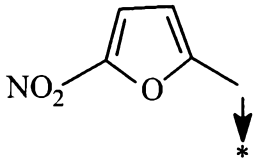
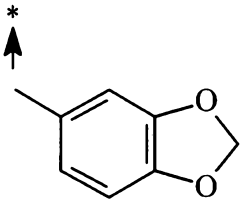
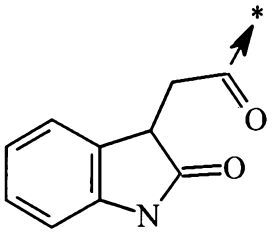
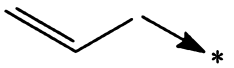
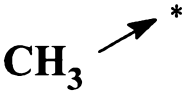
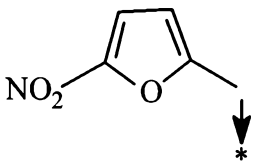
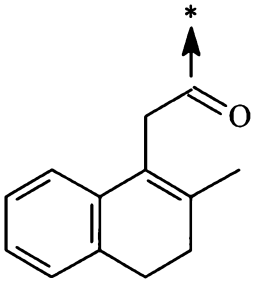
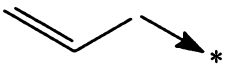
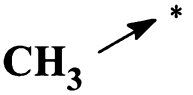
714			"	74.98	3.84	434.2
715			"	78.14	4.24	397.2
716			"	39.87	4.92	405.2
717			"	57.34	4.45	477.2
718			"	37.75	5.01	485.1
719				70.3	5.2	412.1
720	"	"		70.7	5.0	386.1
721	"	"		61.9	6.3	600.3
722	"		"	49.3	6.1	538.4

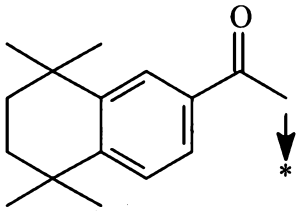
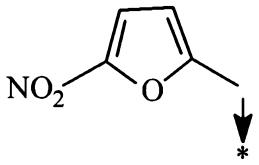
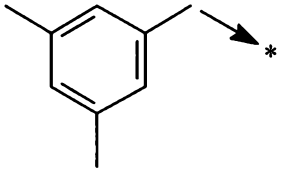
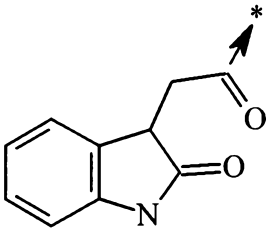
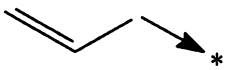
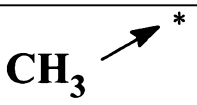
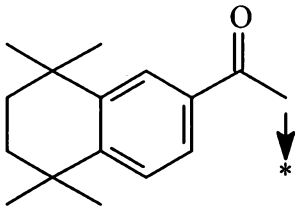
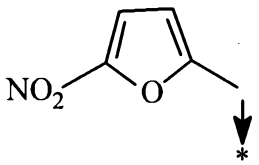
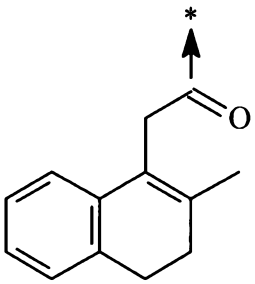
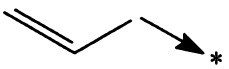
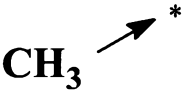
723				65.0	5.1	412.2
724	"	"		44.3	4.9	386.2
725	"	"		49.2	6.2	600.3
726	"		"	37.5	6.0	538.4
727				87.1	5.1	468.1
728	"	"		84.4	4.9	442.1
729	"	"		82.3	6.2	656.3
730	"			93.8	4.7	406.3
731	"	"		80.7	4.6	380.3
732	"	"		84.1	5.9	594.3

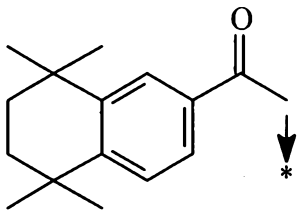
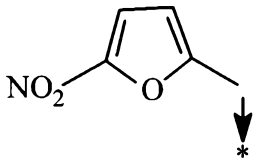
733				67.9	4.7	462.1
734	"	"		66.9	4.6	436.1
735	"	"		56.8	5.9	650.2
736	"			88.1	4.3	400.3
737	"	"		82.8	4.1	374.3
738	"	"		51.4	5.6	588.3
739				77.7	5.1	446.2
740	"	"		76.1	4.9	420.2
741	"	"		67.1	6.2	634.3
742	"			88.9	4.7	384.3

743	"	"		79.3	4.5	358.3
744	"	"		65.1	5.9	572.4
745				80.0	4.0	398.3
746	"	"		76.9	3.8	372.3
747	"	"		42.7	5.8	586.4
748	"	"		64.6	4.4	483.3
749	"			87.4	5.3	409.3
750	"	"		71.0	5.1	383.3
751	"	"		59.8	6.7	597.4

752	"	"		84.4	5.6	494.3
753				80.1	3.9	398.3
754	"	"		63.1	3.7	372.3
755	"	"		64.4	4.3	483.3
756	"			84.6	5.3	409.3
757	"	"		59.6	5.0	383.3
758	"	"		52.9	6.6	597.4
759	"	"		81.6	5.5	494.3

760		"		75.3	5.3	465.3
761	"	"		60.3	5.1	439.3
762	"	"		61.8	6.6	653.4
763	"	"		74.4	5.6	550.3
764				74.5	3.6	448.2
765	"	"		51.3	3.4	422.2
766	"	"		58.8	3.9	533.2
767	"			86.2	4.8	459.3
768	"	"		63.2	4.6	433.3

769	"	"		60.1	6.2	647.4
770	"	"		83.5	5.1	544.2
771				68.1	4.1	432.3
772	"	"		63.8	3.9	406.2
773	"	"		41.1	5.8	620.4
774	"	"		62.8	4.4	517.2
775	"			85.5	5.4	443.3
776	"	"		62.5	5.2	417.3

777	"	"		66.0	6.7	631.4
778	"	"		87.7	5.6	528.3

Pharmacological study

The compounds of the present invention were tested as regards their affinity for different sub-types of somatostatin receptors according to the procedures described below.

Study of the affinity for the sub-types of human somatostatin receptors:

The affinity of a compound of the invention for sub-types of human somatostatin receptors 1 to 5 (sst_1, sst_2, sst_3, sst_4 and sst_5, respectively) is determined by measurement of the inhibition of the bond of [^{125}I-Tyr^{11}]SRIF-14 to transfected CHO-K1 cells.

The gene of the sst_1 receptor of human somatostatin has been cloned in the form of a genomic fragment. A segment *Pst*I-X*mn*I of 1.5 Kb containing 100 bp of the non transcribed 5' region, 1.17 Kb of the coding region in totality, and 230 bp of the non transcribed 3' region is modified by the addition of the linker Bg1II. The resulting DNA fragment is subcloned in the *BamH*I site of a pCMV-81 in order to produce the expression plasmid in mammals (provided by Dr. Graeme Bell, Univ. Chicago). A cloned cell line expressing in a stable fashion the sst_1 receptor is obtained by transfection in CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. Cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The gene of the sst_2 receptor of human somatostatin, isolated in the form of a genomic fragment of DNA of 1.7 Kb *Bam*HI-*Hind*III and subcloned in a plasmid vector pGEM3Z (Promega), was provided by Dr. G. Bell (Univ. of Chicago). The expression vector of the mammalian cells is constructed by inserting the *Bam*H1-*Hind*II fragment of 1.7 Kb in endonuclease restriction sites compatible with the plasmid pCMV5. A cloned cell line is obtained by transfection in CHO-K1 cells using the calcium phosphate co-precipitation method. The plasmid pRSV-neo is included as selection marker.

The sst_3 receptor is isolated as a genomic fragment, and the complete coding sequence is contained in a *Bam*HI/*Hind*III fragment of 2.4 Kb. The expression plasmid in mammals, pCMV-h3, is constructed by insertion of the *Nco*I-*Hind*III fragment of 2.0 Kb in the EcoR1 site of the vector pCMV after modification of the terminations and addition of EcoR1 linkers. A cloned cell line expressing in a stable

fashion the sst_3 receptor is obtained by transfection in CHO-K1 cells (ATCC) by the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. Cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The expression plasmid of the human sst_4 receptor, pCMV-HX, was provided by Dr. Graeme Bell (Univ. Chicago). This vector contains the genomic fragment coding for the human sst_4 receptor of 1.4 Kb *Nhe*I-*Nhe*I, 456 bp of the non transcribed 5' region, and 200 bp of the non transcribed 3' region, cloned in the *Xba*I/*Eco*R1 sites of PCMV-HX. A cloned cell line expressing in a stable fashion the sst_4 receptor is obtained by transfection in CHO-K1 (ATCC) cells by the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. The cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The gene corresponding to the human sst_5 receptor, obtained by the PCR method using a genomic λ clone as probe, was provided by Dr. Graeme Bell (Univ. Chicago). The resulting PCR fragment of 1.2 Kb contains 21 base pairs of the non transcribed 5' region, the coding region in totality, and 55 bp of the non transcribed 3' region. The clone is inserted in an EcoR1 site of the plasmid pBSSK(+). The insert is recovered in the form of a *Hind*III-*Xba*I fragment of 1.2 Kb for subcloning in an expression vector in mammals, pCVM5. A cloned cell lines expressing in a stable fashion the sst_5 receptor is obtained by transfection in CHO-K1 cells (ATCC) by the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. The cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The CHO-K1 cells which express in a stable fashion one of the human sst receptors are cultured in an RPMI 1640 medium containing 10% of foetal calf serum and 0.4 mg/ml of geneticin. The cells are collected with EDTA at 0.5 mM and centrifuged at 500 g for approximately 5 minutes at approximately 4°C. The pellet is resuspended in 50 mM Tris buffer medium at pH 7.4 and centrifuged twice at 500 g for approximately 5 minutes at approximately 4°C. The cells are lysed by sonication then centrifuged at 39000 g for approximately 10 minutes at 4°C. The pellet is resuspended in the same buffer and centrifuged at 50000 g for approximately 10 minutes at approximately 4°C and the cell membranes in the pellet obtained are stored at –80°C.

The competitive inhibition tests of the bond with [^{125}I-Tyr^{11}]SRIF-14 are carried out in duplicate in 96-well polypropylene plates. The cell membranes (10 µg protein/well) are incubated with [^{125}I-Tyr^{11}]SRIF-14 (0.05 nM) for approximately 60 min. at approximately 37 °C in a 50 mM HEPES buffer (pH 7.4) containing BSA 0.2 %, $MgCl_2$ 5 mM, Trasylol 200 KIU/ml, bacitricin 0.02 mg/ml and phenylmethylsulphonyl fluoride 0.02 mg/ml.

The bound [^{125}I-Tyr^{11}]SRIF-14 is separated from the free [^{125}I-Tyr^{11}]SRIF-14 by immediate filtration through GF/C glass fibre filter plates (Unifilter, Packard) pre-impregnated with 0.1 % of polyethylenimine (P.E.I.), using a Filtermate 196 (Packard). The filters are washed with 50 mM HEPES buffer at approximately 0-4 °C for approximately 4 seconds and their radioactivity is determined using a counter (Packard Top Count).

The specific bond is obtained by subtracting the non-specific bond (determined in the presence of 0.1 µM of SRIF-14) from the total bond. The data relative to the bond are analyzed by computer-aided non-linear regression analysis (MDL) and the values of the inhibition constants (Ki) are determined.

Determination of the agonist or antagonist character of a compound of the present invention is carried out using the test described below.

Functional test: Inhibition of production of intracellular cAMP:

CHO-K1 cells expressing the sub-types of human somatostatin receptors (SRIF-14) are cultured in 24-well plates in an RPMI 1640 medium with 10% of foetal calf serum and 0.4 mg/ml of geneticin. The medium is changed the day preceding the experiment.

The cells at a rate of 10^5 cells/well are washed twice with 0.5 ml of new RPMI medium comprising 0.2 % BSA completed by 0.5 mM of 3-isobutyl-1-methylxanthine (IBMX) and incubated for approximately 5 min at approximately 37 °C.

- the production of cyclic AMP is stimulated by the addition of 1 mM of forskolin (FSK) for 15-30 minutes at approximately 37 °C.

- the inhibitory effect of the somatostatin of an agonist compound is measured by the simultaneous addition of FSK (1µM) , SRIF-14 (10^{-12} M to 10^{-6} M) and of the compound to be tested (10^{-10} M to 10^{-5} M).

• the antagonist effect of a compound is measured by the simultaneous addition of FSK (1μM), SRIF-14 (1 to 10 nM) and of the compound to be tested (10^{-10} M to 10^{-5} M).

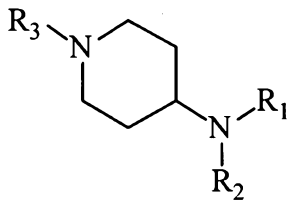
The reaction medium is eliminated and 200 ml of 0.1 N HCl is added. The quantity of cAMP is measured by a radioimmunological test (FlashPlate SMP001A kit, New England Nuclear).

Results:

The tests carried out according to the protocols described above have demonstrated that the products of general formula (I) defined in the present application have a good affinity for at least one of the sub-types of somatostatin receptors, the inhibition constant K_i being lower than micromolar for certain exemplified compounds.

Claims

1. Compounds of general formula



I

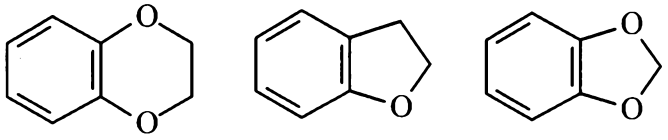
in racemic, enantiomeric form or all combinations of these forms, in which:

R_1 represents a linear or branched $(C_1\text{-}C_{16})$alkyl, alkenyl, alkynyl, $\text{-}(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $\text{–}(CH_2)_m\text{-}Z_{12}$ radical in which

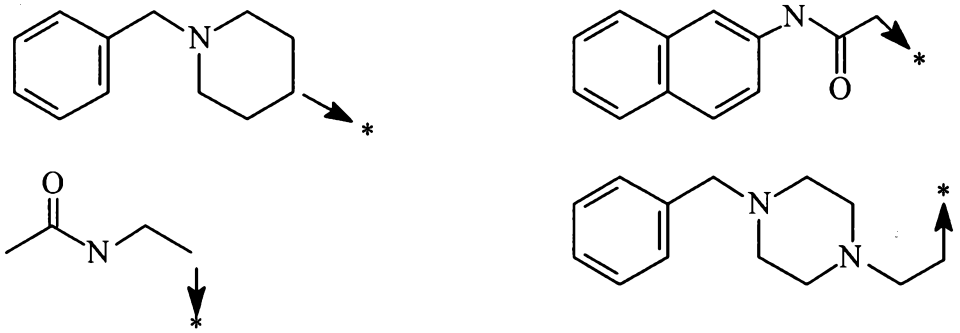
Z_{11} represents a $(C_1\text{-}C_6)$alkyl or aryl optionally substituted,

Z_{12} represents cyano, cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, optionally substituted $(C_3\text{-}C_7)$ heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl,

or Z_{12} represents a radical of formula

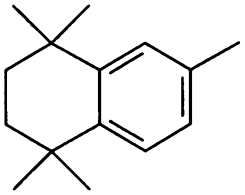


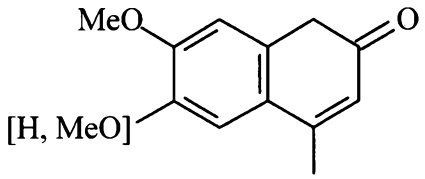
or R_1 represents a radical of formula



R_2 represents a radical of formula $\text{–}C(Y)NHX_1$, $\text{-}C(O)X_2$ or SO_2X_3;

R_3 represents the hydrogen atom, an optionally substituted alkyl, alkenyl, alkynyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl radical, or a radical of formula $\text{–}C(Y)\text{-}NHX_1$, $\text{-}(CH_2)_n\text{-}C(O)X_2$, SO_2X_3 or



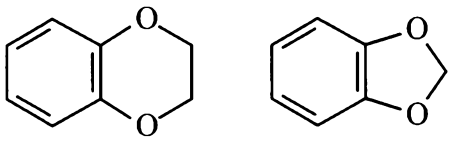


X_1 represents a linear or branched $(C_1\text{-}C_{15})$alkyl, alkenyl, alkynyl, $-(CH_2)_m\text{-}Y\text{-}Z_{21}$ or $-(CH_2)_pZ_{22}$ radical in which

Z_{21} represents a $(C_1\text{-}C_6)$alkyl

Z_{22} represents cyclohexenyl, indanyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl or heteroaryl optionally substituted,

or Z_{22} represents a radical of formula

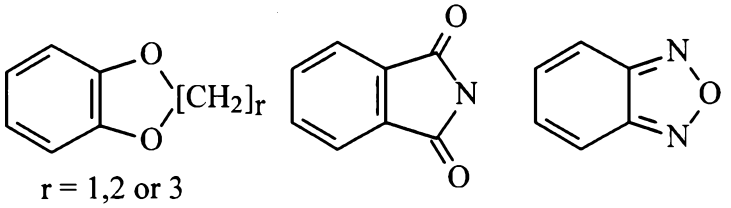


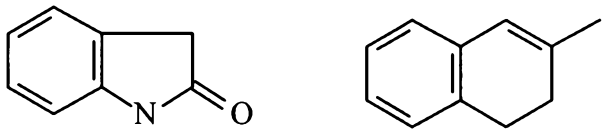
X_2 represents a linear or branched $(C_1\text{-}C_{10})$alkyl radical, an alkenyl radical optionally substituted by a phenyl radical (the phenyl radical being itself optionally substituted), an alkynyl radical, or a radical of formula $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $-(CH_2)_p\text{-}U\text{-}Z_{24}$ in which

Z_{23} represents a $(C_1\text{-}C_6)$alkyl or aryl optionally substituted;

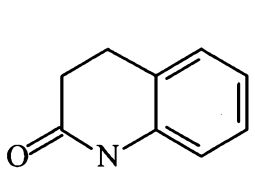
Z_{24} represents alkyl, cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl optionally substituted, $(C_3\text{-}C_7)$heterocycloalkyl, cyano, amino, mono or di-alkylamino, or aryl or heteroaryl optionally substituted,

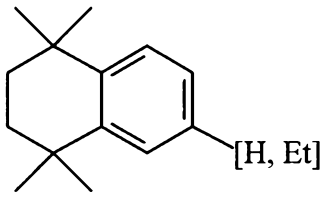
or Z_{24} represents a radical of formula

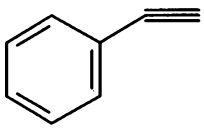


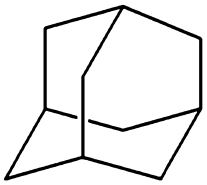


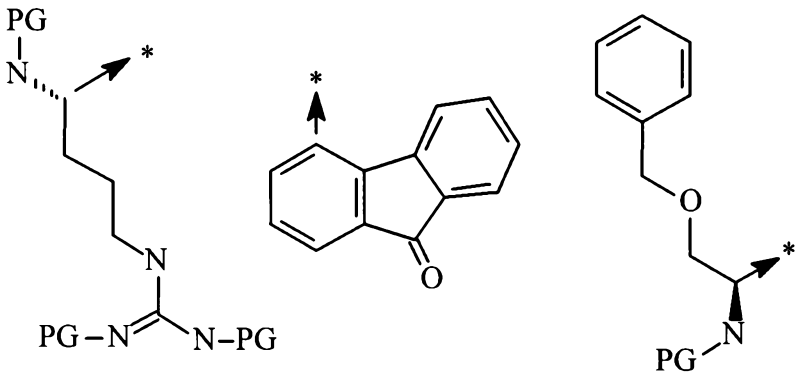
or X_2 represents a radical represented below:











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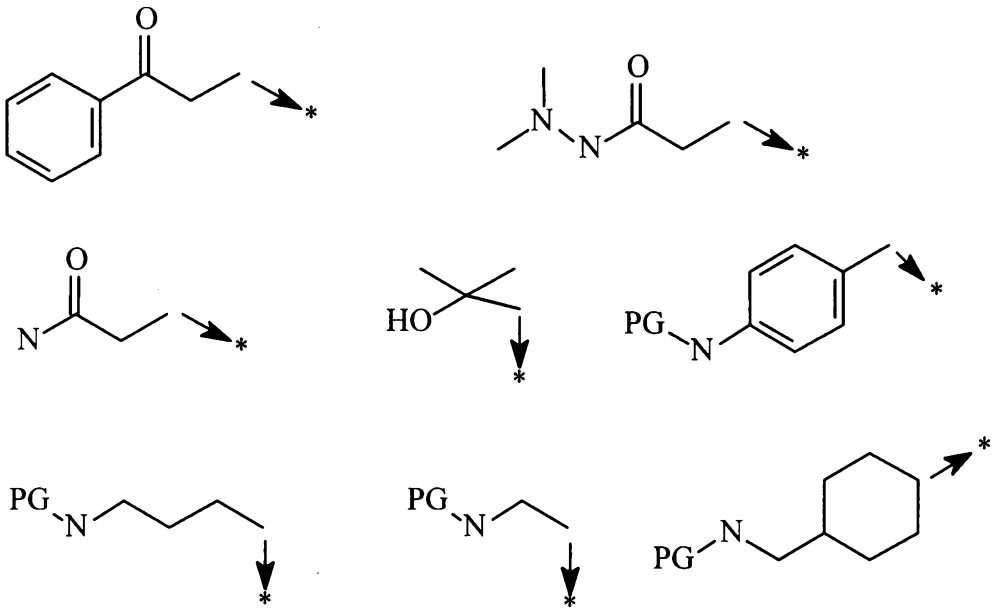
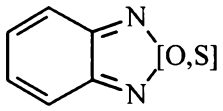


where the protective group (PG) represents H or *tert*-butyloxycarbonyl;

X_3 represents a linear or branched (C_1-C_{10})alkyl radical, an alkenyl radical optionally substituted by a phenyl radical (the phenyl radical being itself optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ in which

Z_{25} represents aryl or heteroaryl optionally substituted,

or X_3 represents a radical of formula



optionally substituted by one or more halo radicals

identical or different;

Y represents an oxygen or sulphur atom;

W represents an oxygen, sulphur or SO_2 atom;

U represents a covalent bond or the oxygen atom;

n is an integer from 0 to 4;

m is an integer from 1 to 6;

p is an integer from 0 to 6;

q is an integer from 0 to 2,

or their addition salts with pharmaceutically acceptable mineral or organic acids, except for the compounds of general formula I in which R_1 represents the alkyl, alkenyl or benzyl radical, R_2 represents optionally substituted benzyloxy and R_3 represents aralkyl.

2. Compounds of general formula I as defined in claim 1, characterized in that

i) the substituent or substituents which can be carried by the aryl radicals represented by Z_{11} and Z_{12} and heteroaryl represented by Z_{12} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phenyl, phenoxy, aminosulphonyl radicals;

ii) the substituent or substituents which can be carried by the heterocycloalkyl radical represented by Z_{12} are chosen independently from the oxy and alkyl radicals;

iii) the substituent or substituents which can be carried by the aryl and heteroaryl radicals represented by Z_{22} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkenyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido,

aminosulphonyl, piperidinosulphonyl, mono- or di-alkylamino, -C(O)-O-alkyl, -C(O)-alkyl, or phenyl, phenoxy, phenylthio, benzyloxy radicals, the phenyl radical being able to be substituted;

iv) the substituent or substituents which can be carried by the aryl radicals represented by Z_{23} and Z_{24}, cycloalkyl and heteroaryl represented by Z_{24} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, $OCHF_2$, SCF_3, nitro, cyano, azido, hydroxy, -C(O)O-alkyl, -O-C(O)-alkyl, -NH-C(O)-alkyl, alkylsulphonyl, mono- or di-alkylamino, amino, aminoalkyl, pyrrolyl, pyrrolydinyl or the radicals phenyl, phenoxy, phenylthio, benzyl, benzyloxy radicals the aryl radical of which is optionally substituted by one or more alkyl, CF_3 or halo radicals;

v) the substituent or substituents which can be carried by the aryl and heteroaryl radicals represented by Z_{25} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, nitro, cyano, -NH-C(O)-alkyl, alkylsulphonyl, amino, mono- and di-alkylamino, phenyl, pyridino radicals;

vi) the substituent which can be carried by the alkyl radical represented by R_3 is the cyano radical.

vii) the substituent or substituents which can be carried by the aralkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, nitro, cyano, -C(O)O-alkyl, alkylsulphonyl, thiadiazolyl radicals, or the phenyl and phenoxy radicals the phenyl radical of which is optionally substituted by one or more halo radicals.

viii) the substituent or substituents which can be carried by the heteroarylalkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo or nitro radicals.

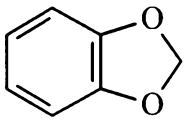
3. Compounds of general formula I as defined in one of claims 1 to 2, characterized in that

R_1 represents a linear or branched $(C_1\text{-}C_6)$alkyl radical, the $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $-(CH_2)_m\text{-}Z_{12}$ radical in which

Z_{11} represents a $(C_1\text{-}C_6)$alkyl,

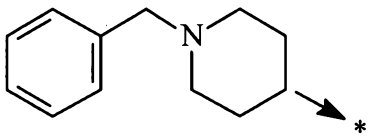
Z_{12} represents *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl optionally substituted, or aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy radicals,

or Z_{12} represents



Y represents the oxygen atom,

or R_1 represents a radical of formula

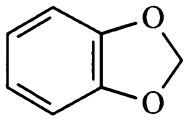


R_2 represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{15})$alkyl radical, or $-(CH_2)_pZ_{22}$ in which

Z_{22} represents cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl or heteroaryl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, –C(O)-O-alkyl, -C(O)-alkyl, or phenyl radicals,

or Z_{22} represents a radical of formula



X_2 represents a linear or branched $(C_1\text{-}C_{10})$alkyl , alkynyl, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $-(CH_2)_p\text{-}U\text{-}Z_{24}$ radical in which

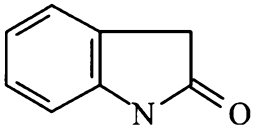
W represents SO_2,

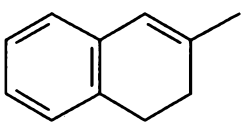
U represents a covalent bond,

Z_{23} represents an aryl radical;

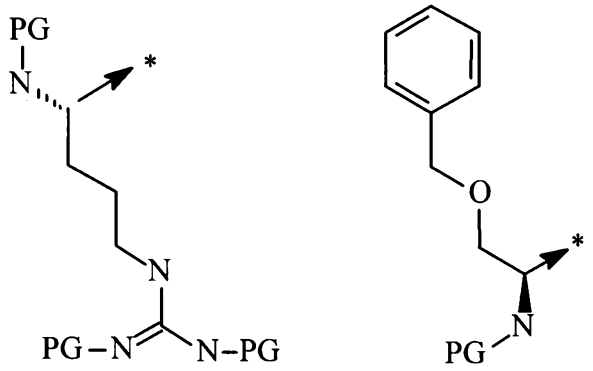
Z_{24} represents cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl optionally substituted by an aminoalkyl, or aryl or heteroaryl radical optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyl, mono- or di-alkylamino, amino

or Z_{24} represents a radical of formula





or X_2 represents



X_3 represents a–$(CH_2)_pZ_{25}$ radical in which Z_{25} represents an aryl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3,

R_3 represents the hydrogen atom, an alkyl, alkenyl, heteroarylalkyl radical optionally substituted or a radical of formula –C(Y)-NHX_1, -$C(O)X_2$ or SO_2X_3 in which

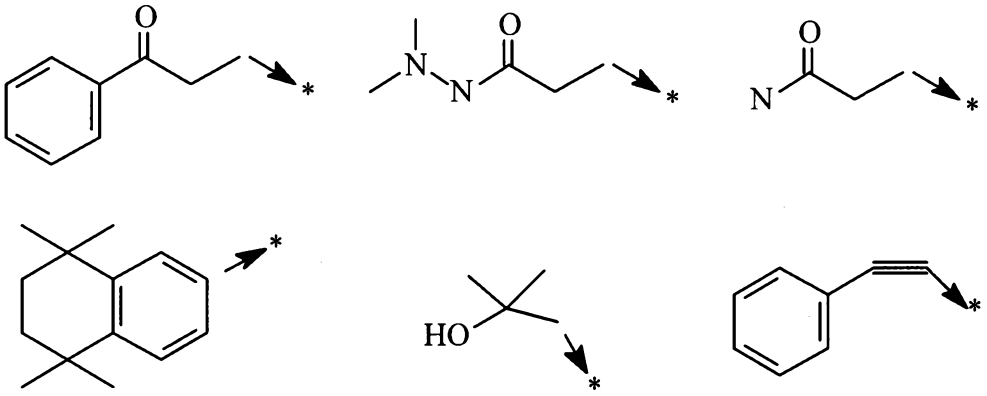
X_1 represents a–$(CH_2)_pZ_{22}$ radical in which

Z_{22} represents an aryl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals;

X_2 represents the vinyl radical substituted by a phenyl, the phenyl radical being itself optionally substituted by one or more halo, or –$(CH_2)_p$-U-Z_{24} radicals in which

Z_{24} represents alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, *bis*-phenyl, amino, mono or di-alkylamino, or aryl or heteroaryl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, hydroxy, CF_3, nitro, amino, mono- and di-alkylamino, pyrrolyl,

or X_2 represents a radical of formula



X_3 represents a linear or branched $(C_1\text{-}C_{10})$alkyl radical, the vinyl radical substituted by a radical (the phenyl radical being itself optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ in which

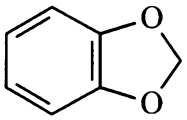
Z_{25} represents aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals.

4. Compounds of formula I as defined in one of claims 1 to 3, characterized in that R_1 represents a linear or branched $(C_1\text{-}C_6)$alkyl radical, the $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $-(CH_2)_m\text{-}Z_{12}$ radical in which

Z_{11} represents a $(C_1\text{-}C_6)$alkyl,

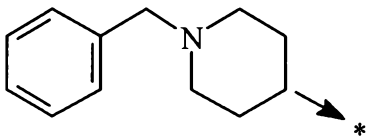
Z_{12} represents naphthyl, morpholino, *bis*-phenyl, pyrrolidinyl substituted by the oxy radical, or the phenyl, piperazinyl, pyridinyl and indolyl radicals which are optionally substituted by one or more substituents chosen independently from the bromo, fluoro, chloro, alkyl, alkoxy, $-CF_3$, $-OCF_3$ radicals;

or Z_{12} represents



Y represents the oxygen atom,

or R_1 represents a radical of formula:



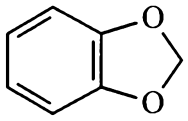
5. Compounds of formula I as defined in one of claims 1 to 4, characterized in that R_2 represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{10})$alkyl, or $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents cyclohexyl, cyclohexenyl, *bis*-phenyl, morpholino, piperidino, mono- or di-alkylamino, -C(O)-O-alkyl, or phenyl, naphthyl or furyl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy,

alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, –C(O)-O-alkyl, -C(O)-alkyl or phenyl radicals,

or Z_{22} represents a radical of formula



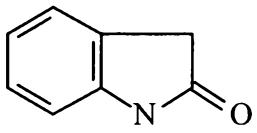
X_2 represents an alkyl, alkynyl, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ or $-(CH_2)_pZ_{24}$ radical in which

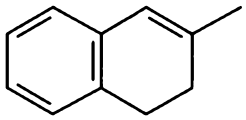
W represents SO_2;

Z_{23} represents the phenyl radical;

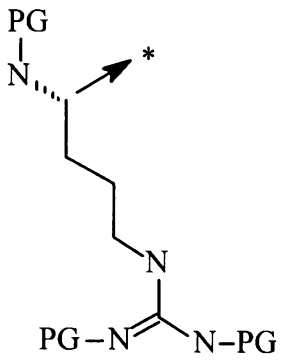
Z_{24} represents cyclohexenyl, *bis*-phenyl, cyclohexyl optionally substituted by an aminoalkyl, or phenyl, naphthyl, benzothienyl, thienyl or indolyl radical optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyl, -NH-C(O)-alkyl, mono- or di-alkylamino, amino, or

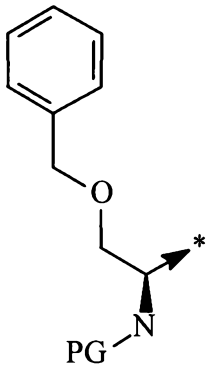
Z_{24} represents a radical of formula





or X_2 represents





X_3 represents a $-(CH_2)_pZ_{25}$ radical in which Z_{25} represents the phenyl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3.

6. Compounds of formula I as defined in one of claims 1 to 5, characterized in that R_3 represents the hydrogen atom, an alkyl, alkenyl or furyl-methyl radical substituted

by one or more nitro radicals, or a radical of formula $-C(Y)-NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

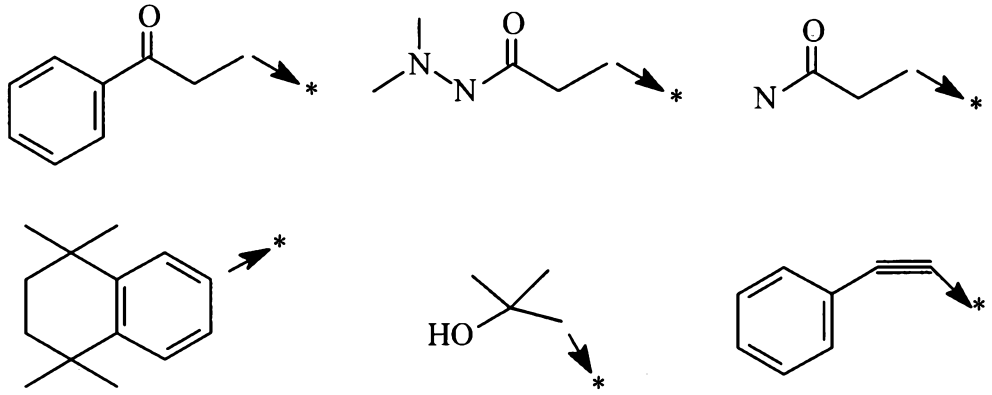
X_1 represents a $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents the phenyl or naphthyl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals,

X_2 represents the vinyl radical substituted by a phenyl radical itself optionally substituted by one or more halo, or $-(CH_2)_p-U-Z_{24}$ radicals in which

Z_{24} represents alkyl, cyclohexyl, tetrahydrofuryl, *bis*-phenyl, amino, mono- or di-alkylamino, or phenyl, indolyl, thienyl, pyridinyl, benzothienyl and furyl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, amino, mono- and di-alkylamino, nitro, hydroxy, pyrrolyl

or X_2 represents a radical of formula



X_3 represents a linear or branched (C_1-C_{10})alkyl radical, the vinyl radical substituted by a phenyl, CF_3, or $-(CH_2)_pZ_{25}$ radical in which

Z_{25} represents a phenyl, naphthyl, thienyl, pyrazolyl or thiazolyl radical optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals.

7. Compounds of formula I as defined in one of claims 1 to 6, characterized in that R_1 represents the $-(CH_2)_mZ_{12}$ radical in which m = 2 and Z_{12} represents *bis*-phenyl or the indolyl radical substituted by one or more substituents chosen independently from the alkyl and alkoxy radicals.

8. Compounds of formula I as defined in one of claims 1 to 7, characterized in that R_2 represents the radicals of formula $-C(Y)NHX_1$ and $-C(O)X_2$ in which

Y represents S;

X_1 represents a phenyl radical optionally substituted by one or more azido radicals,

X_2 represents $-(CH_2)_pZ_{24}$ in which

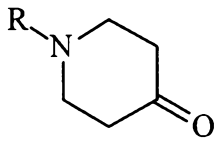
p is equal to 1, 2 or 3,

Z_{24} represents cyclohexyl, or phenyl or benzothienyl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo or $-CF_3$.

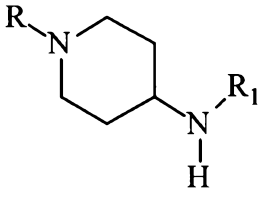
9. Compounds of formula I as defined in one of claims 1 to 8, characterized in that R_3 represents the hydrogen atom or the methyl radical.

10. Process for the preparation, in liquid phase, of compounds of formula I as defined in claim 1, characterized in that it comprises

the reducing amination of the following N-substituted piperidone



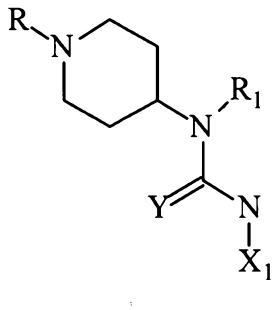
in which R represents the methyl or Boc radical, in the presence of an amine of formula R_1NH_2 in which R_1 has the meaning indicated in claim 1, in order to obtain the compound of formula 1



(1)

which compound of formula (1) is reacted with

A) either a compound of formula $X_1NC(Y)$ in which X_1 and Y have the meaning indicated in claim 1, in order to obtain a compound of formula (2)

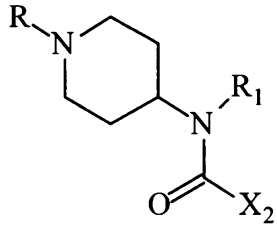


(2)

which compound of formula (2) represents the corresponding compound of formula (I) in which R_3 represents Me or Boc and which, when R_3 represents Boc, can be subjected to an acid treatment in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

which compound of formula (I) thus obtained can be reacted with a compound of formula $X_1NC(Y)$, X_2CO_2H or X_3SO_2Cl in which X_1, Y, X_2 and X_3 have the meaning indicated in claim 1, in order to obtain the corresponding compound of formula I in which R_2 represents a radical of formula $-C(Y)NHX_1$ and R_3 the $-C(Y)-NHX_1$, $-C(O)X_2$ or SO_2X_3 radical respectively;

B) or a compound of formula X_2CO_2H in which X_2 has the meaning indicated in claim 1, in order to obtain a compound of formula (3)



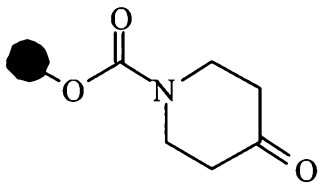
(3)

which compound of formula (3) represents the corresponding compound of formula (I) in which R_3 represents Me or Boc and which, when R_3 represents Boc, can be subjected to an acid treatment in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

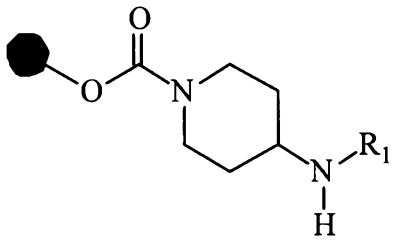
which compound of formula (I) thus obtained can be reacted with a compound of formula $X_1NC(Y)$, X_2CO_2H or X_3SO_2Cl in which X_1, Y, X_2 and X_3 have the meaning indicated above, in order to obtain the corresponding compound of formula I in which R_2 represents a radical of formula $-C(O)X_2$ and R_3 the $-C(Y)-NHX_1$, $-C(O)X_2$ or SO_2X_3 radical respectively.

11. Process for the preparation, in solid phase, of compounds of formula I as defined in claim 1, characterized in that it comprises

the reducing amination of the ketonic resin



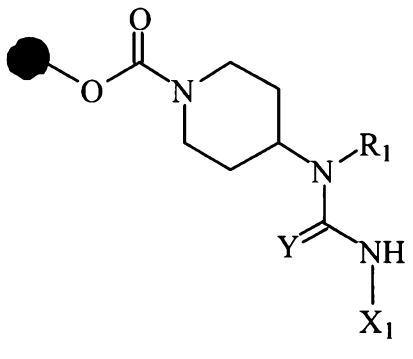
in the presence of an amine of formula R_1NH_2 in which R_1 has the meaning indicated in claim 1, in order to obtain the compound of formula (4)



(4)

which compound of formula (4) is reacted with

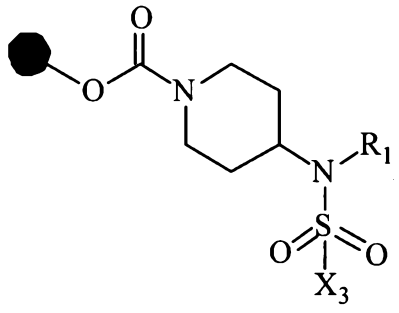
A) either a compound of formula $X_1NC(Y)$ in which X_1 and Y have the meaning indicated in claim 1, in order to obtain a compound of formula (5)



(5)

followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

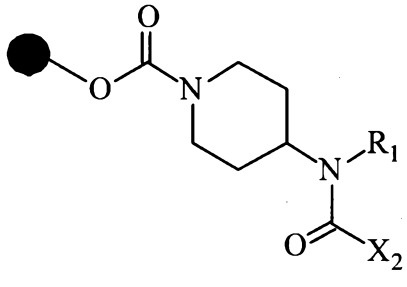
B) or a compound of formula X_3SO_2Cl in which X_3 has the meaning indicated in claim 1, in order to obtain a compound of formula (6)



(6)

followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom,

C) or a compound of formula X_2CO_2Cl in which X_2 has the meaning indicated above, in order to obtain a compound of formula (7)



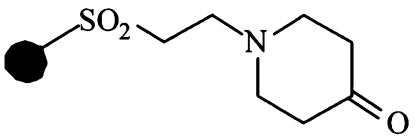
(7)

followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom;

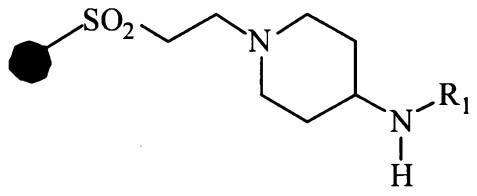
D) or a compound of formula X_2CO_2H in which X_2 has the meaning indicated in claim 1, in order to obtain a compound of formula (7) as defined above, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I) in which R_3 represents the hydrogen atom.

12. Process for the preparation, in solid phase, of compounds of formula I as defined in claim 1, characterized in that it comprises

the reducing amination of the ketonic resin



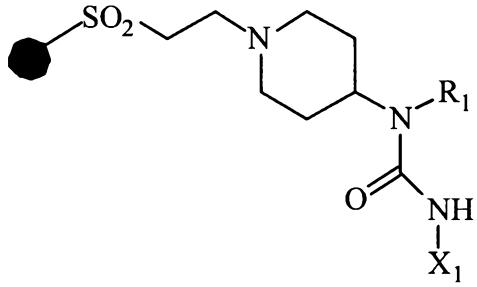
in the presence of an amine of formula R_1NH_2 in which R_1 has the meaning indicated in claim 1, in order to obtain the compound of formula (8)



(8)

which compound of formula (8) is reacted with

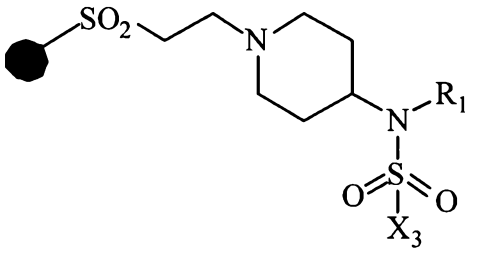
A) either a compound of formula $X_1NC(O)$ in which X_1 has the meaning indicated above, in order to obtain a compound of formula (9)



(9)

which compound (9) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined in claim 1 and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I);

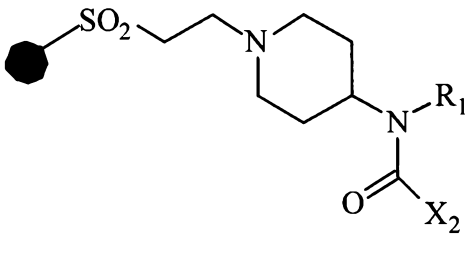
B) or a compound of formula X_3SO_2Cl in which X_3 has the meaning indicated in claim 1, in order to obtain a compound of formula (10)



(10)

which compound (10) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined in claim 1 and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I);

C) or a compound of formula X_2CO_2Cl in which X_2 has the meaning indicated above, in order to obtain a compound of formula (11)



(11)

which compound (11) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined in claim 1 and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I);

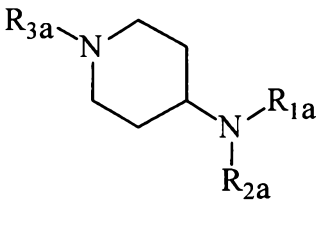
D) or a compound of formula X_2CO_2H in which X_2 has the meaning indicated in claim 1, in order to obtain a compound of formula (11) as defined above,

which compound (11) thus formed is reacted with a compound of formula R_3X in which R_3 is as defined in claim 1 and X represents Br or I, followed by cleavage of the resin in order to obtain the corresponding compound of formula (I).

13. As medicaments, the products of formula I as defined in one of claims 1 to 9, as well as the addition salts with pharmaceutically acceptable mineral or organic acids of said products of formula I.

14. Pharmaceutical compositions containing, as active ingredient, at least one of the medicaments as defined in claim 13, in combination with a pharmaceutically acceptable support.

15. Use of a compound of general formula I_a



I_a

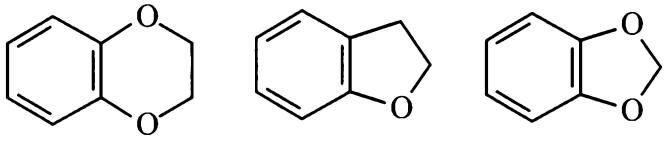
in racemic, enantiomeric form or any combination of these forms, in which:

R_{1a} represents a linear or branched (C_1-C_{16})alkyl, alkenyl, alkynyl, -$(CH_2)_m$-Y-Z_{11} or –$(CH_2)_m$-Z_{12} radical in which

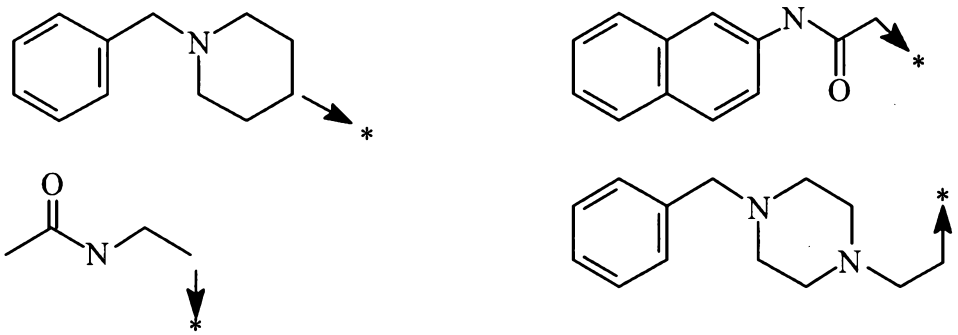
Z_{11} represents a (C_1-C_6)alkyl or aryl optionally substituted,

Z_{12} represents cyano, cyclohexenyl, *bis*-phenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl optionally substituted, aryl optionally substituted or heteroaryl optionally substituted,

or Z_{12} represents a radical of formula

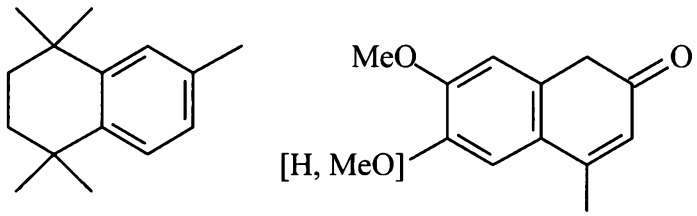


or R_{1a} represents a radical of formula



R_{2a} represents a radical of formula –C(Y)NHX_1, -C(O)X_2 or SO_2X_3;

R_{3a} represents the hydrogen atom, an alkyl optionally substituted, alkenyl, alkynyl, aralkyl optionally substituted, heteroarylalkyl optionally substituted radical, or a radical of formula –C(Y)-NHX_1, -$(CH_2)_n$-C(O)X_2, SO_2X_3 or

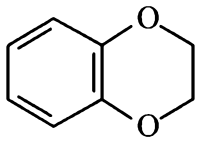
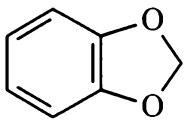


X_1 represents a linear or branched (C_1-C_{15})alkyl, alkenyl, alkynyl, -$(CH_2)_m$-Y-Z_{21} or –$(CH_2)_p$$Z_{22}$ radical in which

Z_{21} represents a (C_1-C_6)alkyl

Z_{22} represents cyclohexenyl, indanyl, *bis*-phenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl or heteroaryl optionally substituted,

or Z_{22} represents a radical of formula

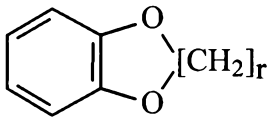



X_2 represents a linear or branched $(C_1\text{-}C_{10})$alkyl, alkenyl optionally substituted by a phenyl radical (the phenyl radical itself being optionally substituted), alkynyl radical, or a radical of formula $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $-(CH_2)_p\text{-}U\text{-}Z_{24}$ in which

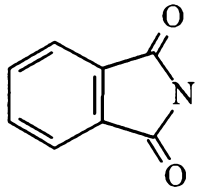
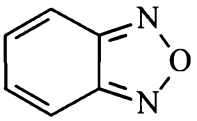
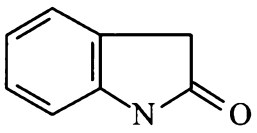
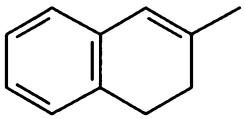
Z_{23} represents a $(C_1\text{-}C_6)$alkyl or aryl optionally substituted;

Z_{24} represents alkyl, cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl optionally substituted, $(C_3\text{-}C_7)$heterocycloalkyl, cyano, amino, mono- or di-alkylamino, or aryl or heteroaryl optionally substituted,

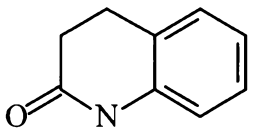
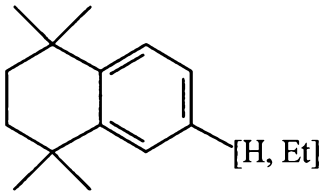
or Z_{24} represents a radical of formula

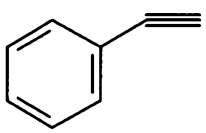
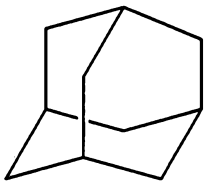


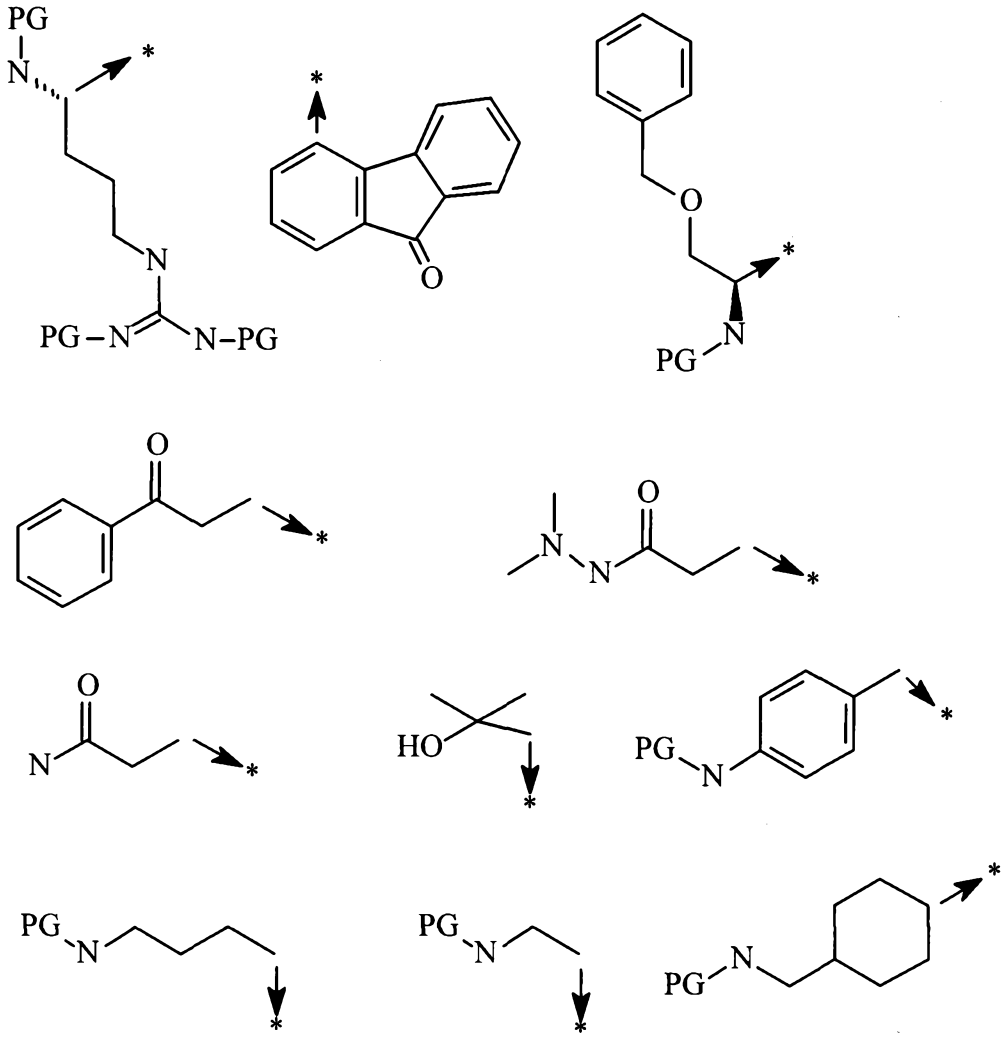
r = 1,2 or 3

or X_2 represents a radical shown below:

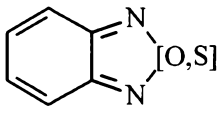


where the protective group (PG) represents H or *tert*-butyloxycarbonyl;

X_3 represents a linear or branched (C_1-C_{10})alkyl, alkenyl optionally substituted by a phenyl radical (the phenyl radical itself being optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ radical in which

Z_{25} represents aryl or heteroaryl optionally substituted,

or X_3 represents a radical of formula

 optionally substituted by one or more identical or different halo radicals;

Y represents an oxygen or sulphur atom;

W represents an oxygen, sulphur or SO_2 atom;

U represents a covalent bond or the oxygen atom;

n is an integer from 0 to 4;

m is an integer from 1 to 6;

p is an integer from 0 to 6;

q is an integer from 0 to 2,

or their addition salts with pharmaceutically acceptable mineral or organic acids, for the preparation of a medicament intended to treat pathological states or diseases in which one or more somatostatin receptors is (are) involved.

16. Use of products of general formula I_a according to claim 15, characterized in that

i) the substituent(s) which can be carried by the aryl radicals represented by Z_{11} and Z_{12} and heteroaryl represented by Z_{12} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phenyl, phenoxy, aminosulphonyl radicals;

ii) the substituent(s) which can be carried by the heterocycloalkyl radical represented by Z_{12} are chosen independently from the oxy and alkyl radicals;

iii) the substituent(s) which can be carried by the aryl and heteroaryl radicals represented by Z_{22} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkenyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, aminosulphonyl, piperidinosulphonyl, mono- or di-alkylamino, -C(O)-O-alkyl, -C(O)-alkyl radicals, or phenyl, phenoxy, phenylthio, benzyloxy, the phenyl radical being able to be substituted;

iv) the substituent(s) which can be carried by the aryl radicals represented by Z_{23} and Z_{24}, cycloalkyl and heteroaryl represented by Z_{24} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, $OCHF_2$, SCF_3, nitro, cyano, azido, hydroxy, -C(O)O-alkyl, -O-C(O)-alkyl, -NH-C(O)-alkyl, alkylsulphonyl, mono- or di-alkylamino, amino, aminoalkyl, pyrrolyl, pyrrolydinyl radicals or the phenyl, phenoxy, phenylthio, benzyl, benzyloxy radicals the aryl radical of which is optionally substituted by one or more alkyl, CF_3 or halo radicals;

v) the substituent(s) which can be carried by the aryl and heteroaryl radicals represented by Z_{25} are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, nitro, cyano, -NH-C(O)-alkyl, alkylsulphonyl, amino, mono- and di-alkylamino, phenyl, pyridino radicals;

vi) the substituent which can be carried by the alkyl radical represented by R_3 is the cyano radical.

vii) the substituent(s) which can be carried by the aralkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, nitro, cyano, -C(O)O-alkyl, alkylsulphonyl, thiadiazolyl radicals, or the phenyl and phenoxy radicals the phenyl radical of which is optionally substituted by one or more halo radicals.

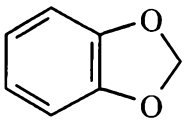
viii) the substituent(s) which can be carried by the heteroarylalkyl radical represented by R_3 are chosen independently from the fluoro, chloro, bromo or nitro radicals.

17. Use of products of general formula I_a according to one of claims 15 to 16, characterized in that R_{1a} represents a linear or branched $(C_1\text{-}C_6)$alkyl radical, the $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $-(CH_2)_m\text{-}Z_{12}$ radical in which

Z_{11} represents a $(C_1\text{-}C_6)$alkyl,

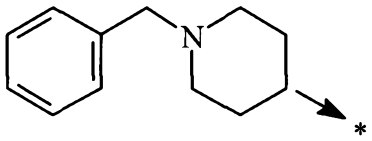
Z_{12} represents *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl optionally substituted, or aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy radicals,

or Z_{12} represents



Y represents the oxygen atom,

or R_{1a} represents a radical of formula



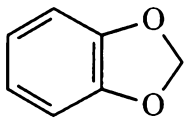
18. Use of products of general formula I_a according to one of claims 15 to 17, characterized in that R_{2a} represents a radical of formula $-C(Y)NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{15})$alkyl, or $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, mono- or di-alkylamino, -C(O)-O-alkyl, or aryl

or heteroaryl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, –C(O)-O-alkyl, -C(O)-alkyl, or phenyl radicals,

or Z_{22} represents a radical of formula



X_2 represents a linear or branched $(C_1\text{-}C_{10})$alkyl, alkynyl, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ or $-(CH_2)_p\text{-}U\text{-}Z_{24}$ radical in which

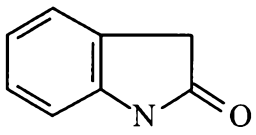
W represents SO_2,

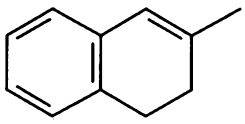
U represents a covalent bond,

Z_{23} represents an aryl radical;

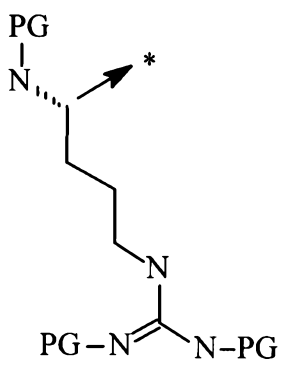
Z_{24} represents cyclohexenyl, *bis*-phenyl, $(C_3\text{-}C_7)$cycloalkyl optionally substituted by an aminoalkyl radical, or aryl or heteroaryl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyl, mono- or di-alkylamino, amino

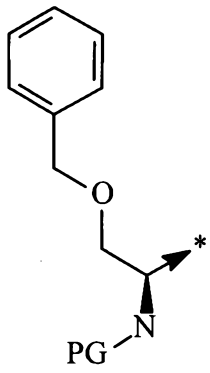
or Z_{24} represents a radical of formula





or X_2 represents





X_3 represents a $-(CH_2)_pZ_{25}$ radical in which Z_{25} represents an aryl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3.

19. Use of products of general formula I_a according to one of claims 15 to 18, characterized in that R_{3a} represents the hydrogen atom, an alkyl, alkenyl, heteroarylalkyl radical optionally substituted or a radical of formula -C(Y)-NHX_1, -$C(O)X_2$ or SO_2X_3 in which

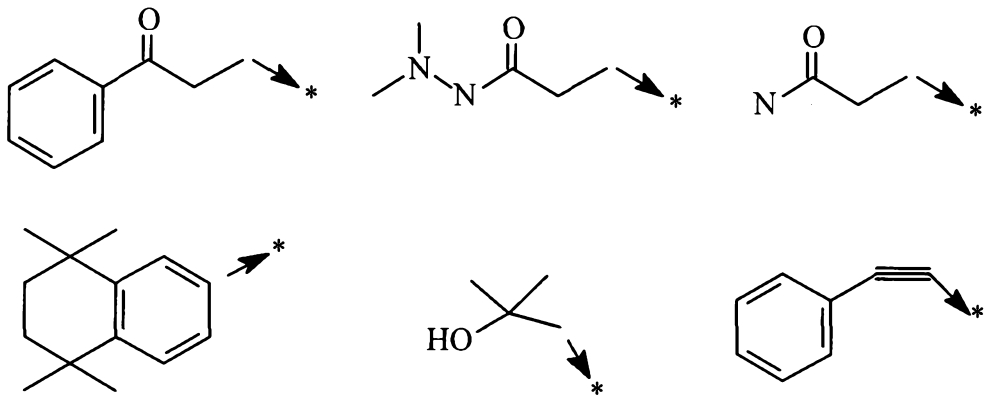
X_1 represents a $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents an aryl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals;

X_2 represents the vinyl radical substituted by a phenyl, the phenyl radical itself being optionally substituted by one or more halo radicals, or $-(CH_2)_p$-U-Z_{24} in which

Z_{24} represents alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, *bis*-phenyl, amino, mono- or di-alkylamino, or aryl or heteroaryl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, hydroxy, CF_3, nitro, amino, mono- and di-alkylamino, pyrrolyl,

or X_2 represents a radical of formula



X_3 represents a linear or branched (C_1-C_{10})alkyl radical, the vinyl radical substituted by a radical (the phenyl radical itself being optionally substituted), CF_3, or $-(CH_2)_pZ_{25}$ in which

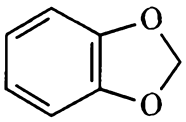
Z_{25} represents aryl or heteroaryl optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals.

20. Use of products of general formula I_a according to one of claims 15 to 19, characterized in that R_{1a} represents a linear or branched $(C_1\text{-}C_6)$alkyl radical, the $\text{-}(CH_2)_m\text{-}Y\text{-}Z_{11}$ or $\text{–}(CH_2)_m\text{-}Z_{12}$ radical in which

Z_{11} represents a $(C_1\text{-}C_6)$alkyl,

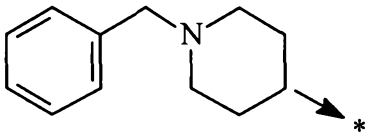
Z_{12} represents naphthyl, morpholino, *bis*-phenyl, pyrrolidinyl substituted by the oxy radical, or the phenyl, piperazinyl, pyridinyl and indolyl radicals which are optionally substituted by one or more substituents chosen independently from the bromo, fluoro, chloro, alkyl, alkoxy, $\text{-}CF_3$, $\text{-}OCF_3$ radicals;

or Z_{12} represents



Y represents the oxygen atom,

or R_{1a} represents a radical of the following formula:

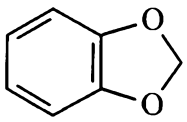


21. Use of products of general formula I_a according to one of claims 15 to 20, characterized in that R_{2a} represents a radical of formula $\text{–}C(Y)NHX_1$, $\text{-}C(O)X_2$ or SO_2X_3 in which

X_1 represents a linear or branched $(C_1\text{-}C_{10})$alkyl, or $\text{–}(CH_2)_pZ_{22}$ radical in which

Z_{22} represents cyclohexyl, cyclohexenyl, *bis*-phenyl, morpholino, piperidino, mono- or di-alkylamino, $\text{-}C(O)\text{-}O\text{-}$alkyl, or phenyl, naphthyl or furyl optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, piperidinosulphonyl, $\text{–}C(O)\text{-}O\text{-}$alkyl, $\text{-}C(O)$-alkyl or phenyl radicals,

or Z_{22} represents a radical of formula



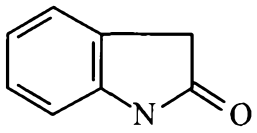
X_2 represents an alkyl, alkynyl, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ or $-(CH_2)_pZ_{24}$ radical in which

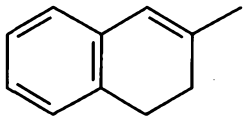
W represents SO_2;

Z_{23} represents the phenyl radical;

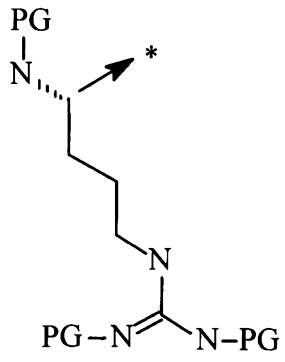
Z_{24} represents cyclohexenyl, *bis*-phenyl, cyclohexyl optionally substituted by an aminoalkyl radical, or phenyl, naphthyl, benzothienyl, thienyl or indolyl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo, alkyl, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyl, -NH-C(O)-alkyl, mono- or di-alkylamino, amino, or

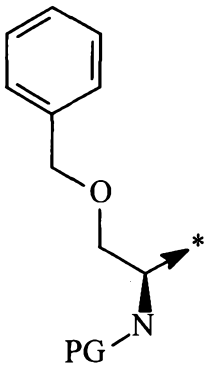
Z_{24} represents a radical of formula





or X_2 represents





X_3 represents a $-(CH_2)_pZ_{25}$ radical in which Z_{25} represents the phenyl radical optionally substituted by one or more identical or different radicals chosen from alkoxy and CF_3.

22. Use of products of general formula I_a according to one of claims 15 to 21, characterized in that R_{3a} represents the hydrogen atom, an alkyl, alkenyl or furyl-methyl radical substituted by one or more nitro radicals, or a radical of formula $-C(Y)-NHX_1$, $-C(O)X_2$ or SO_2X_3 in which

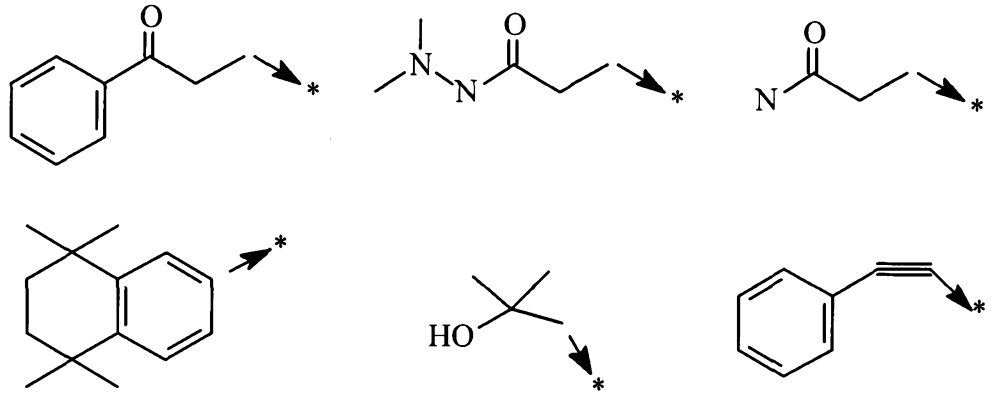
X_1 represents a $-(CH_2)_pZ_{22}$ radical in which

Z_{22} represents the phenyl or naphthyl radical optionally substituted by one or more radicals chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, phenoxy radicals,

X_2 represents the vinyl radical substituted by a phenyl radical itself optionally substituted by one or more halo, or $-(CH_2)_p$-U-Z_{24} radicals in which

Z_{24} represents alkyl, cyclohexyl, tetrahydrofuryl, *bis*-phenyl, amino, mono- or di-alkylamino, or phenyl, indolyl, thienyl, pyridinyl, benzothienyl and furyl optionally substituted by one or more radicals chosen from alkoxy, bromo, chloro, fluoro, amino, mono- and di-alkylamino, nitro, hydroxy, pyrrolyl

or X_2 represents a radical of formula



X_3 represents a linear or branched $(C_1$-$C_{10})$alkyl radical, the vinyl radical substituted by a phenyl, CF_3, or $-(CH_2)_pZ_{25}$ radical in which

Z_{25} represents a phenyl, naphthyl, thienyl, pyrazolyl or thiazolyl radical optionally substituted by one or more substituents chosen independently from the fluoro, chloro, bromo, iodo, alkyl, alkoxy, CF_3, nitro, -NH-C(O)-alkyl, mono- and di-alkylamino radicals;

23. Use of products of general formula I_a according to one of claims 15 to 22, characterized in that R_{1a} represents the $-(CH_2)_mZ_{12}$ radical in which m = 2 and Z_{12} represents *bis*-phenyl or the indolyl radical substituted by one or more substituents chosen independently from the alkyl and alkoxy radicals.

24. Use of products of general formula I_a according to one of claims 15 to 23, characterized in that R_{2a} represents radicals of formula $-C(Y)NHX_1$ and $-C(O)X_2$ in which

Y represents S;

X_1 represents a phenyl radical optionally substituted by one or more azido radicals,

X_2 represents $-(CH_2)_pZ_{24}$ in which

p is equal to 1, 2 or 3,

Z_{24} represents cyclohexyl, or phenyl or benzothienyl optionally substituted by one or more radicals chosen from fluoro, chloro, bromo, iodo or $-CF_3$.

25. Use of products of general formula I_a according to one of claims 15 to 24, characterized in that R_{3a} represents the hydrogen atom or the methyl radical.

26. Use according to one of claims 15 to 25 for the preparation of a medicament intended to treat acromegalia, hypophyseal adenomas and endocrine gastroenteropancreatic tumors including carcinoid syndrome.