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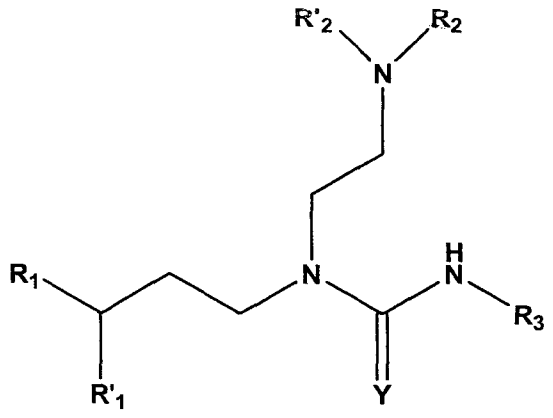
(54) Title: UREA DERIVATIVES USEFUL AS CALCIUM RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention provides compounds of formula (I): in which Y is oxygen or sulphur; R_1 and R'_1 are optionally substituted aryl, heteroaryl or a fused ring structure, R_2 and R'_2 are each H, or optionally substituted alkyl, alkylaminoalkyl or dialkylaminoalkyl, or R_2 and R'_2 and their N form a saturated or unsaturated optionally substituted heterocycle, R_3 represents a group of formula $-(CH_2)P-Ar-Rn$, wherein p is 0 or 1 and, when p is 1, is optionally substituted, Ar is aryl or heteroaryl, and each R is H, halogen; hydroxyl; trifiuoromethyl; linear and branched alkyl, alkenyl, alkynyl, and alkoxyl groups, all optionally further substituted by one or more of hydroxy groups, halogen atoms, alkoxy groups, amino groups, and alkylthio groups; linear and branched alkoxyl groups; linear and branched thioalkyl groups; aryl groups; aralkyl groups; aralkoxy groups; aryloxy groups; perfluoroalkyl; -CN; $-NR_4R_5$, $-C(=X)NR_4R_5$,$-O-C(=X)NR_4R_5$, $-SO_2NR_4R_5$, - Alk-NR_4R_5, $-NZC(=X)(NH)_qR_6$, -Alk-$NZC(=X)(NH)_qR_6$, $-C(=X)R_6$, -Alk-$C(=X)(NH)_qR_6$, $-NHSO_2R_7$, $-SO_2R_7$, $-SOR_7$, $-SR_7$, or is a saturated or unsaturated heterocyclyl group, and salts and esters thereof, are useful in the treatment of conditions susceptible to modulating ion channels, to a process for their preparation, their application by way of medicaments, and to pharmaceutical compositions containing them.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

UREA DERIVATIVES USEFUL AS CALCIUM RECEPTOR MODULATORS

The present invention relates to urea derivatives useful in the physiological modulation of the activity of inorganic ions, particularly through their effect on inorganic ion receptors and especially on membrane calcium receptors capable of binding extracellular calcium; to processes for the preparation thereof; to their use as medicaments; to pharmaceutical compositions containing them; and to the their uses.

Extracellular calcium concentration is precisely regulated in the organism and one of the key elements of this regulation is the calcium receptor known as the Ca sensing receptor or CaSR. A receptor of this type at the surface of specific cells can detect the presence of calcium. Specific cells of the organism respond not only to chemical signals, but also to ions such as extracellular calcium ions (Ca^{++}): changes in the concentration of these extracellular Ca^{++} ions can modify the functional responses of these cells. These cells include parathyroid cells which secrete the parathyroid hormone known as PTH. Parathyroid cells thus have at their surface the calcium receptor (CaSR), which detects changes in extracellular calcium concentration, and initiates the functional response of this cell, which is a modulation of the secretion of the parathyroid hormone (PTH). PTH, by acting in particular on the bone cells or on the renal cells, increases the calcium level in the blood. This increase then acts as a negative control on PTH secretion. The reciprocal relationship between calcium concentration and PTH level is an essential mechanism for calcium homeostasis maintenance.

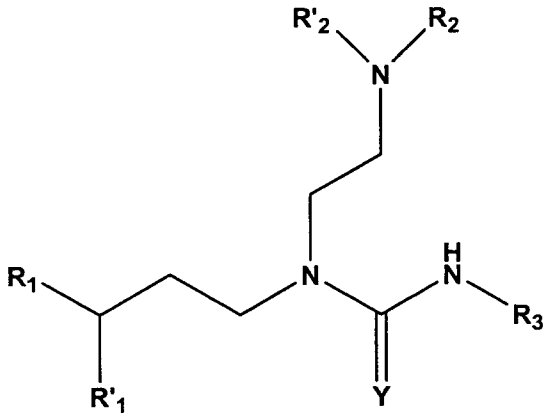
The cloning of the calcium receptor by Brown in 1993 consequently demonstrated two possible signalling pathways for this G protein coupled receptor: one pathway by activation of the Gi protein (sensitive to the pertussis toxin) which stimulates phospholipase C and inhibits adenylate cyclase; the other pathway by activating the Gq protein responsible for mobilising intracellular calcium. These two signalling pathways, either independently of one another or together, can be activated so as to trigger the associated biological effect.

On its extracellular portion, the calcium receptor is a low affinity receptor which is stimulated by millimolar concentrations of agonists, in particular the calcium ion Ca^{2+}. In addition, this receptor can also be activated by some divalent metals (magnesium) or trivalent metals (gadolinium, lanthanum, etc.) or else by polycationic compounds such as neomycin or spermin.

Novel compounds acting on the transmembrane portion of the receptor have been identified by Edward F. Nemeth *et al* (company NPS, US-A-6,211,244, EP-A-787 122, WO-A-6031003) and allow the calcium receptor to be modulated allosterically. The action of first generation and second generation compounds on the pharmacological regulation of parathyroid hormone (PTH) secretion is described, for example, by E. F. Nemeth in Current Pharmaceutical Design, 2002, 8, 2077-2087. In particular, the compound AMG073 (cinacalcet, Sensipar®, Mimpara ®) acts as an agonist of the calcium receptor and was sold in the United States in 2004 for the treatment of secondary hyperparathyroidism (Idrugs, 2003, 6, 587-592 J. Iqbal, M. Zaidi, A. E. Schneider).

In the present invention, the compounds can have, in particular, an effect on PTH secretion which, without being bound by theory, is likely to result from the activation of the beta-gamma subunits of the G proteins, whether they are specifically Gi (similarly to the trivalent cation) or simultaneously Gi and Gq.

Thus, in a first aspect, the present invention provides a compound of formula (I):

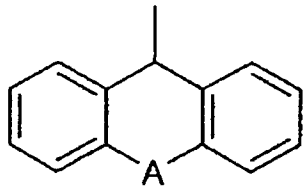


(I)

wherein:

Y is oxygen or sulphur;

R_1 and R'_1 are the same or different, and each represents an aryl group, a heteroaryl group, or R_1 and R'_1, together with the carbon atom to which they are linked, form a fused ring structure of formula:



in which A represents a single bond, a methylene group, a dimethylene group, oxygen, nitrogen or sulphur, said sulphur optionally being in the sulphoxide or sulphone forms,

wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group ***c***

wherein the group ***c*** consists of: halogen atoms, hydroxyl, carboxyl, linear and branched alkyl, hydroxyalkyl, haloalkyl, thioalkyl, alkenyl, and alkynyl groups; linear and branched alkoxyl groups; linear and branched alkylthio groups; hydroxycarbonylalkyl; alkylcarbonyl; alkoxycarbonylalkyl; alkoxycarbonyl; trifluoromethyl; trifluoromethoxyl; -CN; $-NO_2$; alkylsulphonyl groups optionally in the sulphoxide or sulphone forms; wherein any alkyl component has from 1 to 6 carbon atoms, and any alkenyl or alkynyl components have from 2 to 6 carbon atoms,

and wherein, when there is more than one substituent, then each said substituent is the same or different,

R_2 and R'_2, which may be the same or different, each represents: a hydrogen atom ; a linear or branched alkyl group containing from 1 to 6 carbon atoms and optionally substituted by at least one halogen atom, hydroxy or alkoxy group containing from 1 to 6 carbon atoms; an alkylaminoalkyl or dialkylaminoalkyl group wherein each alkyl group contains from 1 to 6 carbon atoms,

or R_2 and R'_2, together with the nitrogen atom to which they are linked, form a saturated or unsaturated heterocycle containing 0, 1 or 2 additional heteroatoms and having 5, 6, or 7 ring atoms, said heterocycle being optionally substituted by at least one substituent selected from the group ***c*** defined above,

and wherein, when there is more than one substituent, said substituent is the same or different,

R_3 represents a group of formula $-(CH_2)_p$-Ar-R_n,

in which p is 0 or 1 and, when p is 1, $(CH_2)_p$ may be substituted by methyl, chlorine, fluorine, hydroxy, or trimethyl, Ar represents an aryl or heteroaryl group, n is equal to the number of positions that can be substituted on Ar, and wherein each R, which may be the same or different, represents a hydrogen atom or a substituent selected from the group consisting of:

group ***a***, in which group ***a*** consists of: halogen atoms; hydroxyl; trifluoromethyl; linear and branched alkyl, alkenyl, alkynyl, and alkoxyl groups, all optionally further substituted by one or more of hydroxy groups, halogen atoms, alkoxy groups, amino groups, and alkylthio groups; linear and branched alkoxyl groups; linear and branched thioalkyl groups; aryl groups; aralkyl groups; aralkoxy groups; aryloxy groups; perfluoroalkyl; perfluoroalkoxy; -CN;

the groups $-NR_4R_5$, $-C(=X)NR_4R_5$, $-O-C(=X)NR_4R_5$, $-SO_2NR_4R_5$, or $-Alk-NR_4R_5$,

in which X is oxygen or sulphur,

Alk is an alkyl group, and

R_4 and R_5 are the same or different and are H, alkyl, aralkyl, aryl, heteroaryl or heteroaralkyl and are optionally further substituted by one or more substituents selected from trifluoromethyl, halogen atoms and hydroxyl groups;

the groups $-NZC(=X)(NH)_qR_6$, $-Alk-NZC(=X)(NH)_qR_6$, $-C(=X)R_6$, or $-Alk-C(=X)(NH)_qR_6$,

in which Z is H or $C(=X)R_6$ wherein each X and each R_6 is the same or different,

q is 0 or 1 and, when q is 1, $(NH)_q$ is optionally substituted with a methyl, ethyl, or trifluoromethyl group,

X is oxygen or sulphur,

Alk is an alkyl group, and

R_6 is H, OH, alkyl, aralkyl, aryl, heteroaryl or heteroaralkyl and is optionally further substituted by one or more substituents selected from trifluoromethyl, halogen atoms and hydroxyl groups or,

when C(=X) is CO, then $C(=X)R_6$ may form an ester or thioester grouping;

the groups $-NHSO_2R_7$, $-SO_2R_7$, $-SOR_7$, or $-SR_7$,

in which R_7 is OH or amino, or R_7 is alkyl, aralkyl, alkylamino, aralkylamino, aryl, heteroaryl or heteroaralkyl, optionally further substituted by one or more

substituents selected from trifluoromethyl, halogen atoms and hydroxyl groups;

and saturated or unsaturated heterocyclyl groups, said heterocyclyl groups being mono- or bi- cyclic and being optionally substituted by one or more substituents, which may be the same or different, selected from the group ***b***,

wherein the group ***b*** consists of: halogen atoms; hydroxyl; carboxyl; aldehyde groups; linear and branched alkyl, alkenyl, alkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, haloalkyl, haloalkenyl, and haloalkynyl groups; linear and branched alkoxyl groups; linear and branched thioalkyl groups; alkoxycarbonyl; hydroxycarbonylalkyl; alkoxycarbonylalkyl; perfluoroalkyl; perfluoroalkoxy; -CN; acyl; amino, alkylamino, dialkylamino, acylamino, and diacylamino groups; alkyl groups substituted with an amino, alkylamino, dialkylamino, acylamino, or diacylamino group; $CONH_2$; alkylamido groups; alkylthio and the oxidised sulphoxide and sulphone forms thereof; sulphonyl, alkylsulphonyl groups; and sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups,

wherein, in groups ***a*** and ***b***, any alkyl components contain from 1 to 6 carbon atoms, and any alkenyl or alkynyl components contain from 2 to 6 carbon atoms, and are optionally substituted by at least one halogen atom or hydroxy group, and wherein any aryl component is optionally a heteroaryl group,

and when n is at least two, then two adjacent groups R may form a 5, 6, or 7 membered fused carbocyclic or heterocyclic ring with Ar, said fused ring being optionally further substituted with an oxo group or a substituent selected from group ***b*** as defined above,

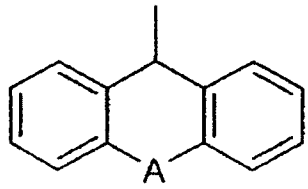
provided that, when p is 0, Ar is not thiazolyl or oxazolyl, either unfused or fused with a monocyclic aryl or a monocyclic heteroaryl in which the or any heteroatom is nitrogen,

and salts and esters thereof.

It will be appreciated that compounds of formula (I) may be in any racemic, enantiomeric or diastereoisomeric isomeric form. Salts include addition salts with inorganic

and organic acids or bases. Esters are as described below. Salts and esters are preferably pharmaceutically acceptable.

Preferred compounds are those wherein R_1 and R'_1 are the same or different, and each represents a monocyclic aryl group, a monocyclic heteroaryl group, or R_1 and R'_1, together with the carbon atom to which they are linked, form a fused ring structure of formula:



in which A is as defined,

wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group ***c*** as defined above.

More preferably, R_1 and R'_1 each represent a phenyl, pyridinyl, or thienyl radical, or R_1 and R'_1 represents a fused ring structure as defined, wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted as defined. More preferably, each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group ***c'***: fluorine and chlorine atoms, hydroxyl, linear and branched alkyl, alkylthio, hydroxyalkyl, and fluoroalkyl groups; linear and branched alkoxyl groups; trifluoromethyl; trifluoromethoxyl; -CN; alkylcarbonyl groups; alkylsulphonyl groups, and any alkyl component has from 1 to 4 carbon atoms,

and wherein, when there is more than one substituent, then each said substituent is the same or different.

Particularly preferably, each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group consisting of: fluorine and chlorine atoms, hydroxy groups, linear or branched alkoxy groups containing from 1 to 5 carbon atoms, linear or branched alkyl groups containing from 1 to 5 carbon atoms, trifluoromethyl and trifluoromethoxy groups, and -CN groups,

and wherein, when there is more than one substituent, then each said substituent is the same or different.

R_2 and R'_2, which may be the same or different, each preferably represents a methyl or ethyl group, or, together with the nitrogen atom to which they are linked, form a morpholinyl,

thiomorpholinyl, piperidinyl, piperazinyl, or homopiperazinyl group optionally substituted at least one substituent selected from the group consisting of: chlorine atoms, hydroxyl groups, trifluoromethyl groups, hydroxyl groups, alkoxy groups, hydroxyalkyl groups, and alkyl groups.

More preferably, R_2 and R'_2, together with the nitrogen atom to which they are linked, form a morpholinyl group optionally substituted by at least one substituent selected from the group consisting of: trifluoromethyl groups and alkyl groups. Any such optional substituent is preferably at least one methyl group.

Preferably R_2 and R'_2, together with the nitrogen atom to which they are linked, form a morpholinyl group or thiomorpholinyl group.

Preferably, Ar is an aryl or heteroaryl group selected from the group consisting of: phenyl, naphthyl, monocyclic heteroaryls, and bicyclic heteroaryls. More preferably, Ar is selected from the group consisting of: phenyl, naphthyl, thienyl, thiazolyl, isothiazolyl, furanyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, indolyl, pyrrolyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyridazinyl groups. It is particularly preferred that Ar is a phenyl group.

Preferred compounds of the invention are those wherein each R is selected from hydrogen and substituents ***a'***: fluorine atoms; chlorine atoms; hydroxyl groups; carboxyl groups; aldehyde groups; linear and branched alkyl, hydroxyalkyl, and fluoroalkyl groups; linear and branched alkoxyl groups; linear and branched thioalkyl groups; alkoxycarbonyl groups; benzylcarbonyl groups; hydroxycarbonylalkyl groups; alkoxycarbonylalkyl groups; trifluoromethyl groups; trifluoromethoxy groups; -CN groups; amino, alkylamino, dialkylamino, acylamino, and diacylamino groups; alkoxycarbonylamino, alkylcarbonylamino groups; alkylaminocarbonyloxy groups; alkyl groups substituted with an amino, alkylamino, dialkylamino, acylamino, or diacylamino group; $CONH_2$; alkylamido groups; alkylthio; alkylsulphoxide; sulphonyl, and alkylsulphonyl groups; sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups; trifluoromethylsulphoxide; trifluoromethylsulphonyl groups; trifluoromethylsulphonamide, and di(trifluoromethylsulphonyl)amino groups; alkylcarbonylalkyl; and saturated monocyclic heterocyclyl groups, said heterocyclyl groups being optionally substituted by one or more substituents, which may be the same or different, selected from the group ***b*** as defined above.

More preferably, each R is selected from hydrogen and substituents ***a''***: chlorine atoms; hydroxyl groups; carboxyl groups; linear and branched alkyl, hydroxyalkyl; linear and

branched alkoxyl groups; alkoxycarbonyl groups; hydroxycarbonylalkyl groups; alkoxycarbonylalkyl groups; trifluoromethyl groups; trifluoromethoxy groups; -CN groups; amino, alkylamino, and dialkylamino groups; alkoxycarbonylamino, alkylcarbonylamino groups; alkylaminocarbonyloxy groups; alkyl groups substituted with an amino, alkylamino, or dialkylamino group; $CONH_2$; alkylcarbonylalkyl; alkylthio; sulphonyl and alkylsulphonyl groups; sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups; trifluoromethylsulphoxide; trifluoromethylsulphonyl groups; trifluoromethylsulphonamide, and di(trifluoromethylsulphonyl)amino groups; pyrrolidinyl, piperidinyl piperazinyl, morpholinyl, and thiomorpholinyl groups optionally substituted by one or more substituents, which may be the same or different, selected from the group ***b*** as defined above.

More preferably, any pyrrolidinyl, piperidinyl piperazinyl, morpholinyl, and thiomorpholinyl groups of substituents ***b*** are selected from substituents ***b'*** consisting of: chlorine atoms; hydroxyl groups; linear and branched alkyl, hydroxyalkyl, and alkoxyl groups; trifluoromethyl groups; trifluoromethoxy groups; -CN groups; amino, alkylamino, and dialkylamino groups; sulphonyl, alkylsulphonyl groups; and sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups. Particularly preferably, any such pyrrolidinyl, piperidinyl piperazinyl, morpholinyl, and thiomorpholinyl groups are unsubstituted.

In general, it is preferred that any alkyl, alkenyl or alkynyl component has no more than 4 carbon atoms.

Any alkylsulphonyl substituent is preferably a trifluoromethyl or methylsulphonyl substituent, and more preferably a methylsulphonyl substituent, such as a methylsulphonylamino, or methylsulphonamide substituent.

In the compounds of the present invention, Y may be oxygen or sulphur, and is preferably oxygen, such that preferred compounds are urea derivatives.

The substituents R_1 and R'_1 are the same or different, and there is no particular preference for whether they are the same or different, although more preferred groups are as defined above. There is no particular preference for the nature of the aryl group or heteroaryl group, although it is generally preferred that they be monocyclic and 5- or 6- membered.

In the compounds of the present invention, where a sulphur atom is present, other than when present as part of a >C=S group, then it may be present in the sulphoxide (SO) or sulphone (SO_2) forms, where desired.

In general, carboxyl groups are in the form –COOH, and branched alkyl may take the form of singly or multiply branched alkyl, such as t-butyl or 4-methylpentyl, for example. Alkyl groups preferably contain from 1 to 6 carbons, and more preferably from 1 to 4 carbon atoms. Methyl and ethyl are particularly preferred as substituents. Similar considerations apply to hydroxyalkyl, haloalkyl, alkylthio, alkenyl, and alkynyl groups. Hydroxyalkyl may be substituted by one or more hydroxyl groups, but preferably one. Thioalkyl groups typically take the form HS-Alk-, where Alk indicates an alkyl group. Hydroxycarbonylalkyl typically take the form HOOC-Alk-. Alkylcarbonyl groups take the form Alk-CO-, while alkoxycarbonylalkyl groups take the form AlkOCOAlk-. Alkoxycarbonyl groups take the form AlkOCO-. Alkylthio groups take the form Alk-S- and are optionally in the sulphoxide (Alk-SO-) or sulphone (Alk-SO_2-) forms. Any alkyl component preferably has from 1 to 6 carbon atoms, so that alkoxycarbonylalkyl may be hexyl-5-pentanoate or methylmethanoate for example. Alkenyl and alkynyl components have from 2 to 6 carbon atoms, and take the form of an alkyl group possessing at least one double or triple bond between adjacent carbons. It is preferred that there is only one such unsaturated bond per alkenyl or alkynyl substituent.

Where multiple substituents are selected from a common group, such as substituents ***a, b*** or ***c***, then each substituent is the same or different.

R_2 and R'_2, when representing alkyl, are preferably methyl or ethyl, and it is further preferred that these are unsubstituted or substituted with one or more fluorine atoms. Similar considerations apply when R_2 and R'_2 represent alkylamino or dialkylamino groups.

When R_2 and R'_2 form a heterocycle, it is preferred that this is saturated and contains 5 or 6 ring atoms, said heterocycle being optionally substituted by at least one substituent selected from the group ***c*** as defined.

When R_2 and R'_2 represent an unsaturated heterocycle, the additional heteroatoms, if any, may typically be selected from oxygen, sulphur and nitrogen. Exemplary unsaturated heterocycles include, imidazole, pyrazole, indazole, benzimidazole, purine, aza-benzimidazole, triazole, pyrrole, indole, isoindazole, and azaindole.

More generally, it is preferred that, when R_2 and R'_2, together with the nitrogen atom to which they are linked, form a heterocycle, then the heterocycle is saturated. Preferred saturated heterocycles are morpholinyl, thiomorpholinyl, piperazinyl, homopiperazinyl, and piperidinyl groups, preferably morpholinyl and thiomorpholinyl, and particularly

morpholinyl.

There is no particular restriction on the nature of the aryl or heteroaryl group represented by Ar, but it is generally preferred that such a group is monocyclic or bicyclic, preferably containing 5, 6, 9 or 10 ring atoms.

In R_n, n is equal to the number of ring atoms on the aryl or hetroaryl group that are available for substitution, which will exclude the linking atom. Thus, n is equal to 5 for phenyl. It is generally preferred at least two groups R represent H or Cl, preferably H.

In R_3, $(CH_2)_p$ is preferably be a straight bond or is methyl or methyl substituted with another methyl, but is preferably a straight bond.

The moiety C(=X) may be present in R as part of acyl, ester, or amide group, for example. X may be sulphur or oxygen, but is preferably oxygen. More preferably, where there is more than one moiety C(=X), then each occurrence is carbonyl.

When a group R comprises Alk, then it is preferred that Alk is methylene or ethylene.

When a group R comprises the moiety NR_4R_5, then it is preferred that each of R_4 and R_5 is separately selected from hydrogen, methyl, ethyl, hydroxymethyl and hydroxyethyl, preferably hydrogen or methyl.

When a group R comprises the moiety -NZC(=X), then Z is preferably H. Where there is more than one occurrence, then it is preferred that every occurrence is H.

When a group R comprises the group R_6, then R_6 is preferably hydrogen, hydroxy, alkyl, or trifluoromethyl.

When a group R represents a group $-NZC(=X)(NH)_qR_6$, $-Alk-NZC(=X)(NH)_qR_6$, $-C(=X)(NH)_qR_6$, or $-Alk-C(=X)(NH)_qR_6$, then q is 0 or 1, preferably 0. When q is 1, then preferred meanings for $(NH)_qR_6$ are amino, methylamino and dimethylamino, preferably amino.

When a group R represents a group $-NZC(=X)(NH)_qR_6$, $-Alk-NZC(=X)(NH)_qR_6$, $-C(=X)(NH)_qR_6$, or $-Alk-C(=X)(NH)_qR_6$, then a preferred meaning of $-C(=X)(NH)_qR_6$ is a carboxylic ester moiety, where q is 0 and R_6 preferably represents an alkoxy, akenyloxy, alkynyloxy, aryloxy or aralkyloxy group, more preferably alkoxy, and is optionally further substituted by one or more substituents selected from trifluoromethyl, halogen atoms and hydroxyl groups, particularly preferably chlorine, fluorine, hydroxy, and/or phenyl.

When at least one R represents a group $-NHSO_2R_7$, $-SO_2R_7$, $-SOR_7$, or $-SR_7$, then R_7 is preferably OH, amino, alkyl, hydroxyalkyl, or trifluoromethyl.

One preferred group of compounds of the invention is where at least one R represents an aryl, aralkyl, heteroaryl, or heteroaralkyl group. Preferably only one R represents such a group, and the group id preferably selected from aryl and heteroaryl groups. Preferred aryl and heteroaryl groups include oxazolyl, methyltetrazolyl, isoxazolyl, furanyl, isoxazolyl, benzimidazolyl, and thiophene.

In general, it is preferred that no more than two substituents R are selected from said substituents ***a***.

In the group ***a***, and elsewhere, hydroxyalkenyl and hydroxyalkynyl groups are as defined above for alkenyl and alkynyl, and have one or more hydroxyl groups present, preferably one. Similarly, haloalkyl, haloalkenyl, and haloalkynyl groups have one or more halogen atoms present thereon, preferably selected from iodine, bromine, chlorine and fluorine, preferably chlorine or fluorine. Perhalo substituents are preferably perfluoro substituents, preferably trifluoromethyl. Where an alkyl group is specified herein, then this may include haloalkyl, particularly fluoroalkyl, and especially trifluoromethyl groups, although unsubstituted alkyl are genrally preferred over halo-substituted alkyls. The most preferred haloalkyl group is trifluoromethyl. Linear and branched alkoxyl groups and linear and branched thioalkyl groups are as defined above for linear and branched alkyl groups. Aralkoxy groups take the form Ar-AlkO-, while aryloxy groups take the form ArO-, where Ar is an aryl or heteroaryl group. It will be understood that similar considerations apply to aralkoxycarbonyl and aryloxycarbonyl, and other groups specifying aralkoxy and aryloxy.

Acyl groups are those consisting of a carboxylic acid residue linked *via* the -CO- moiety. Alkyl-, aralkyl-, and aryl- amido groups have the appropriate groups linked *via* the nitrogen, such as Alk-CONH-. Amido takes the form of -CONH-, so that alkylamido takes the form alkyl-CONH-, for example, while aralkylamido takes the form aryl-alkyl-CONH-.

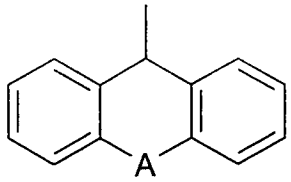
Sulphonamide, alkylsulphonamide, di(alkylsulphonyl)amino, aralkylsulphonamide, di(aralkylsulphonyl)amino, arylsulphonamide, and di(arylsulphonyl)amino are of the form sulphonyl or disulphonyl substituted on nitrogen, such as Alk-SO_2-NH-.

Alkoxycarbonylamino groups take the form Alk-O-CONH-, and aralkoxycarbonylamino, aryloxycarbonylamino, alkylcarbonylamino, aralkylcarbonylamino, and arylcarbonylamino groups should be construed accordingly. Alkylaminocarbonyloxy groups take the form Alk-NHCOO-, and aralkylaminocarbonyloxy and arylaminocarbonyloxy groups should be construed accordingly.

One group of compounds of formula (I) is defined as follows:

R_1 and R'_1, which may be the same or different, represent an aryl radical, a heteroaryl radical, an aryl or heteroaryl radical substituted by one or more halogen atoms, by one or more hydroxy groups, by one or more linear or branched alkyl, fluoroalkyl or alkoxy radicals containing from 1 to 6 carbon atoms, by one or more trifluoromethyl, trifluoromethoxy, -CN, $-NO_2$, acetyl, carboxyl, carboalkoxy, thioalkyl groups and the oxidised sulfoxide and sulfone forms thereof,

or R_1 and R'_1 form, with the carbon atom to which they are linked, a cycle of formula:



in which A represents a single bond, a $-CH_2-$group, an oxygen, sulfur or nitrogen atom optionally substituted by an alkyl or an acetyl,

R_2 and R'_2 form, with the nitrogen atom to which they are linked, a saturated heterocycle containing 4 or 5 carbon atoms which may optionally be substituted by one or more linear or branched alkyl radicals containing from 1 to 6 carbon atoms, said heterocycle optionally containing a further heteroatom, which may itself optionally be substituted by an R_5 radical, in which R_5 represents a hydrogen atom, a linear or branched alkyl radical containing from 1 to 6 carbon atoms, a carboalkoxy radical,

or R_2 and R'_2, which may be the same or different, represent a hydrogen atom, a linear or branched alkyl radical containing from 1 to 6 carbon atoms optionally substituted by a hydroxy or alkoxy radical containing from 1 to 6 carbon atoms,

R_3 represents an aryl radical, a heteroaryl, a substituted aryl radical or a heteroaryl substituted by one or more groups selected from a halogen atom, a hydroxy radical, an alkyl, fluoroalkyl, hydroxyalkyl or alkoxyalkyl radical, which may be linear or branched, containing from 1 to 6 carbon atoms, a linear or branched alkoxy group containing from 1 to 6 carbon atoms, a -CO-OR or -CO-NHR radical in which R represents a hydrogen atom or an alkyl, benzyl or aralkyl radical, optionally substituted by one or more fluorine atoms or hydroxy groups,

or R_3 represents an aryl radical or a heteroaryl substituted by:

- an aldehyde radical, a linear or branched -CHOH-alkyl or -CO-alkyl radical, containing from 1 to 6 carbon atoms, a trifluoromethyl or trifluoromethoxy radical, a -CN group, a thioalkyl radical and the oxidised, sulfoxide or sulfone forms thereof, linear or branched, containing from 1 to 6 carbon atoms, an $-SO_2-(CH_2)n-OH$ group in which n represents an integer of 1, 2 or 3, an $-SO_p-CF_3$ group, in which p represents an integer of 0, 1 or 2, or

- an amino, alkylamino, dialkylamino, -NH-CO-alkyl, -NHCOObenzyl, $-NHSO_2$alkyl, $-NHSO_2CF_3$ group, an amido, alkylamido, dialkylamido or hydroxyalkylamido group, a thioamido group or

- a phenyl group, optionally substituted by one or more halogen, alkyl, hydroxy, alkoxy, carboxy, carboalkoxy or amino groups and the NHCOalkyl, $NHSO_2$alkyl and NHCOOalkyl, NHCOObenzyl forms thereof,

- a heteroaryl group optionally substituted by one or more halogen, alkyl, hydroxy or alkoxy groups containing from 1 to 6 carbon atoms, amino groups and the NHCOalkyl, $NHSO_2$alkyl and NHCOOalkyl, carboxy or carboalkoxy forms thereof, said linear or branched alkyls or alkoxy containing from 1 to 6 carbon atoms,

or R_3 represents a heteroaryl, excluding the thiazolyl, oxazolyl, benzothiazolyl or benzoxazolyl groups, which may optionally be substituted,

or R_3 represents a $-CH_2$-aryl, $-CH_2$-heteroaryl, $-CH(CH_3)$-aryl or $-CH(CH_3)$-heteroaryl radical, aryls or heteroaryls being optionally substituted,

said products of formula (I) being in all possible racemic, enantiomeric and diastereoisomeric isomeric forms, as well as the addition salts with inorganic and organic acids or with inorganic and organic bases of said products of formula (I).

Exemplary meanings of the terms used in this group and elsewhere herein are as follows:

- the term aryl group designates unsaturated, monocyclic radicals or radicals consisting of condensed carbocyclic rings. Examples of an aryl radical include the phenyl, naphth-1-yl and naphth-2-yl, indane, indene or tetrahydronaphthyl or oxotetrahydronaphthyl radicals,

- the term substituted aryl denotes that the aryl group is substituted by one or more groups of the halogen, alkyl, fluoroalkyl, hydroxy, alkoxy, fluoroalkoxy, carboxy, carboalkoxy, nitrile, nitro or thioalkyl type and the oxidised sulfoxide and sulfone forms thereof, SCF_3 and other thiofluoroalkyl groups and the oxidised forms thereof, amino groups

and the NHCO-alkyl, $NHSO_2$-alkyl, NHCOO-alkyl, NHCOObenzyl derivatives thereof, by a substituted or unsubstituted aryl, by a substituted or unsubstituted heteroaryl, or by a heterocycle,

- the term heterocycle designates, for example, morpholinyl, thiomorpholinyl, piperazinyl, N-alkylpiperazinyl, piperidinyl, pyrrolidinyl, imidazolidinyl, 2,6-dimethyl morpholinyl, quinuclidinyl, homopiperazinyl radicals,

- the term halogen atom designates the chlorine, fluorine, bromine or iodine atom, or preferably the fluorine or chlorine atom,

- the term linear or branched alkyl radical containing from 1 to 6 carbon atoms designates, for example, the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tert-butyl, pentyl and isopentyl radicals as well as the linear or branched positional isomers thereof,

- the term fluoroalkyl designates a linear or branched alkyl in which one or more or all the hydrogen atoms are replaced by one or more fluorine atoms,

- the term linear or branched alkoxy radical containing from 1 to 6 carbon atoms designates, for example, the methoxy, ethoxy, propoxy, isopropoxy and butoxy radicals, linear, secondary or tertiary or pentoxy, as well as the linear or branched positional isomers thereof,

- the term linear or branched thioalkyl radical containing from 1 to 6 carbon atoms designates radicals such as, in particular, thiomethyl, thioethyl, thiopropyl, thioisopropyl, thiobutyl, thioisobutyl, thiosec-butyl and thiotert-butyl radicals, as well as the linear or branched positional isomers thereof,

- the term heteroaryl designates for example a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, pyrrolyl, furanyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, benzothiazolyl, pyrazolyl, isoxazolyl, pyridinazyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, benzofuranyl, benzimidazolyl, indazolyl, tetraquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, indolyl, carbazolyl, indolinyl, alpha- or beta-carbolinyl, thienyl, benzothienyl, benzoxazolyl, oxadiazole, 2,3 dihydroindolyl, isoindolyl, purinyl, naphthyridinyl, quinoxalinyl, carbazolyl, benzodioxinyl, 2,3 dihydrobenzodioxinyl, oxodihydro isobenzofuran or isobenzofuran radical,

- the term substituted heteroaryl means that the heteroaryl group is substituted by one or more groups of the halogen, alkyl, fluoroalkyl, alkoxy, fluoroalkoxy, carboxy, carboalkoxy,

nitrile, nitro or thioalkyl type and the oxidised sulfoxide and sulfone forms thereof, amino groups and the NHCO-alkyl, NHCO-fluoroalkyl, $NHSO_2$-alkyl, $NHSO_2$-fluoroalkyl, NHCOO-alkyl, NHCOO-benzyl, heterocycle, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl derivatives thereof.

Within this group, preferred products of formula (I) are those in which R_1, R'_1, R_2 and R'_2 have the meaning given above and R_3 represents a phenyl radical, a heteroaryl radical, a substituted phenyl radical, a heteroaryl radical substituted by one or more groups selected from a halogen atom, a hydroxy radical, a linear or branched alkyl, fluoroalkyl, hydroxyalkyl or alkoxyalkyl radical containing from 1 to 6 carbon atoms, a linear or branched alkoxy or alkoxycarbonyl group containing from 1 to 6 carbon atoms, a -CO-OR or -CO-NHR radical in which R represents a hydrogen atom or an alkylbenzyl or aralkyl radical optionally substituted by one or more fluorine atoms or hydroxy groups,
or R_3 represents an aryl or heteroaryl radical substituted by:

- an aldehyde radical, a linear or branched -CHOH-alkyl or -CO-alkyl radical, containing from 1 to 6 carbon atoms, a trifluoromethyl or trifluoromethoxy radical, a -CN group, a thioalkyl radical and the oxidised, sulfoxide or sulfone forms thereof, linear or branched, containing from 1 to 6 carbon atoms, an $-SO_2-(CH_2)n-OH$ group in which n represents an integer of 1, 2 or 3, an $-SO_p-CF_3$ group, in which p represents an integer of 0, 1 or 2,

- an amino, alkylamino, dialkylamino, -NH-CO-alkyl, -NHCOObenzyl, $-NHSO_2$alkyl or $-NHSO_2CF_3$ group, an amido, alkylamido, dialkylamido or hydroxyalkylamido group, a thioamido group,

- a phenyl group optionally substituted by a halogen, alkyl, hydroxy, alkoxy, carboxy, carboalkoxy or amino group and the NHCOalkyl, $NHSO_2$alkyl, NHCOOalkyl and NHCOObenzyl forms thereof,

- a heteroaryl group optionally substituted by a halogen, alkyl, hydroxy or alkoxy group containing from 1 to 6 carbon atoms, an amino group and the NH-COalkyl, $NHSO_2$alkyl and NHCOOalkyl forms thereof, carboxy or carboalkoxy groups, said linear or branched alkyls or alkoxy containing from 1 to 6 carbon atoms,

or R_3 represents a heteroaryl, excluding the thiazolyl, oxazolyl, benzothiazolyl or benzoxazolyl groups, which may optionally be substituted,

or R_3 represents a benzyl, chlorobenzyl, methylthienyl or ethyl-1-naphthyl radical,

and more particularly the products of formula (I), in which R_1, R'_1, R_2 and R'_2 have the meaning given above and R_3 represents a phenyl radical, a phenyl radical substituted by one or more groups selected from a halogen atom, a hydroxy radical, an alkyl, fluoroalkyl, hydroxyalkyl or alkoxyalkyl radical, linear or branched, containing from 1 to 6 carbon atoms, a linear or branched alkoxy or alkoxycarbonyl group containing from 1 to 6 carbon atoms, a -CO-OR or -CO-NHR radical in which R represents a hydrogen atom or an alkyl, benzyl or aralkyl radical optionally substituted by one or more fluorine atoms or hydroxy groups,

or R_3 represents a phenyl radical substituted by:

- an aldehyde radical, a linear or branched -CHOH-alkyl or -CO-alkyl radical, containing from 1 to 6 carbon atoms, a trifluoromethyl, trifluoromethoxy radical, a -CN group, a thioalkyl radical and the oxidised, sulfoxide or sulfone forms thereof, linear or branched, containing from 1 to 6 carbon atoms, an $-SO_2-(CH_2)n-OH$ group in which n represents an integer of 1, 2 or 3, an $-SO_p-CF_3$ group, in which p represents an integer of 0, 1 or 2,

- an amino, alkylamino, dialkylamino, -NH-CO-alkyl, -NHCOObenzyl, $-NHSO_2$alkyl, $-NHSO_2CF_3$ group, an amido, alkylamido, dialkylamido or hydroxyalkylamido group, a thioamido group,

- a phenyl group optionally substituted by a halogen, alkyl, hydroxy, alkoxy, carboxy, carboalkoxy or amino group and the NHCOalkyl, $NHSO_2$alkyl and NHCOOalkyl, NHCOObenzyl forms thereof,

- a heteroaryl group optionally substituted by a halogen, alkyl, hydroxy or alkoxy group containing from 1 to 6 carbon atoms, an amino group and the NHCOalkyl, $NHSO_2$alkyl and NHCOOalkyl, carboxy or carboalkoxy forms thereof, said linear or branched alkyls or alkoxy containing from 1 to 6 carbon atoms,

or R_3 represents a benzyl, chlorobenzyl, methylthienyl or ethyl-1-naphthyl radical,

or R_3 represents a benzodioxolyl, dihydrobenzodioxinyl, 3-oxo-1,3-dihydroisobenzofuraryl, 8-oxotetrahydronaphthalenyl, 2,3-dihydroindolyl, indazolyl, carbazolyl, isoquinolyl, quinolinyl, thiophenyl, pyridinyl, benzimidazolyl, pyrazolyl, pyrimidinyl, isoxazolyl or isothiazolyl radical, optionally substituted by one or more chlorine or fluorine atoms, a linear or branched alkyl, fluoroalkyl, alkoxy or carboalkoxy group containing from 1 to 3 carbon atoms or substituted by an optionally substituted phenyl or thiazolyl group. As with all other definitions, unless otherwise indicated or apparent from the

context, said products of formula (I) may be in all possible racemic, enantiomeric and diastereoisomeric isomeric forms, as well as the addition salts with inorganic and organic acids or with inorganic and organic bases of said products of formula (I).

Of the latter, the following are particularly preferred:

- the products of formula (I), as defined above, in which R_1 and R'_1 represent a phenyl radical, a pyridinyl radical, a thienyl radical, a substituted phenyl, substituted pyridinyl or substituted thienyl radical, substituted by one or more fluorine or chlorine atoms, by one or more hydroxy groups, by one or more alkoxy groups, linear or branched, containing from 1 to 6 carbon atoms, by one or more linear or branched alkyl groups containing from 1 to 6 carbon atoms, by one or more trifluoromethyl or trifluoromethoxy groups, by a -CN group,

and, more particularly, products of formula (I) as defined in above, in which R_1 and R'_1 represent a phenyl radical,

- the products of formula (I) as defined above, in which R_2 and R'_2 form, with the nitrogen atom to which they are linked, a morpholinyl, dimethylmorpholinyl, piperidinyl, thiomorpholinyl or N-alkyl piperazinyl radical or R_2 and R'_2 represent a methyl or ethyl radical.

More preferred are products of formula (I), as defined above, in which:

R_3 represents a phenyl radical, a phenyl radical substituted by one or more groups selected from a fluorine, chlorine, bromine or iodine atom, a hydroxy radical, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, methoxy, ethoxy, propoxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tertbutoxycarbonyl or pentafluoropentoxycarbonyl radical, a piperidinylmethyl group, an aldehyde radical, $-CH_2OH$, $-CHOH-CH_3$, -CO-alkyl radical, linear or branched, containing from 1 to 6 carbon atoms, a trifluoromethyl or trifluoromethoxy radical, a -CN group, a thiomethyl, thioethyl or thioisopropyl radical and the oxidised, sulfoxide and sulfone forms thereof, an $-S(O)_2-(CH_2)n-OH$ group, in which n represents an integer of 1, 2 or 3, an $-S(O)_2-CF_3$ group, an $-S-CF_3$ group, an amino, methylamino, ethylamino, dimethylamino, diethylamino, -NH-CO-methyl, -NH-CO-ethyl, $-NHSO_2$-methyl, $-NHSO_2$-ethyl, -NHCOOmethyl, -NHCOOethyl, -NHCOObenzyl group, an amido, methylamido, dimethylamido or hydroxymethylamido or hydroxyethylamido group, a thioamide $-CS-NH_2$ group,

or R_3 represents a phenyl radical substituted by a phenyl group, a pyridinyl, morpholinyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, tetrazolyl or pyrazolyl group, said groups optionally being substituted by one or more chlorine or fluorine atoms, an alkyl, fluoroalkyl, alkoxy or carboalkoxy group, linear or branched, containing from 1 to 3 carbon atoms,

or R_3 represents a benzyl, chlorobenzyl, methylthienyl, ethyl-1-naphthyl radical,

or R_3 represents a benzodioxolyl, dihydrobenzodioxinyl, 3-oxo-1,3-dihydroisobenzofuraryl, 8-oxotetrahydronaphthalenyl, 2,3-dihydroindolyl, indazolyl, carbazolyl, isoquinolyl, quinolinyl, thiophenyl, pyridinyl, benzimidazolyl, pyrazolyl, pyrimidinyl, isoxazolyl or isothiazolyl radical, optionally substituted by one or more chlorine or fluorine atoms, an alkyl, fluoroalkyl, alkoxy, acetyl or carboalkoxy group linear or branched containing from 1 to 3 carbon atoms or by a phenyl group.

More preferred are products of formula (I), in which R_1 and R'_1 represent a phenyl group, R_2 and R'_2 form, with the nitrogen atom to which they are linked, a morpholinyl radical and

R_3 represents a phenyl group optionally substituted by one or more chlorine or fluorine atoms, by one or more radicals from a -CO-OR radical, in which R represents a hydrogen atom, an alkyl radical, a -CO-alkyl radical, said alkyl radicals, linear or branched, containing from 1 to 6 carbon atoms, a trifluoromethyl or trifluoromethoxy radical, a thioalkyl or alkylsulfone radical, an oxazolyl or methyltetrazolyl, furanyl or thienyl group.

Addition salts with inorganic or organic acids of the products of formula (I) can optionally be salts formed between a molecule of formula (I) and one, two or three acid molecules. These salts may be, for example, salts formed with hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric, phosphoric, propionic, acetic, trifluoroacetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic or ascorbic acids, alkylmonosulphonic acids such as, for example, methanesulphonic acid, ethanesulphonic acid, propanesulphonic acid, alkyldisulphonic acids such as, for example, methanedisulphonic acid, alpha-, beta-ethane disulphonic acid, arylmonosulphonic acids such as benzenesulphonic acid and aryl disulphonic acids.

Stereoisomerism can be defined broadly as isomerism of compounds having the same general formulae, but of which the different groups are disposed differently in space such as, in particular, in monosubstituted cyclohexanes of which the substituent can be in the axial or

equatorial position, and the various possible rotational configurations of ethane derivatives. However, there is another type of stereoisomerism due to the different spatial arrangements of substituents fixed either on double bonds or on rings, which is often called geometric isomerism or cis-trans isomerism. The term stereoisomers is used in its broadest sense in the present application and therefore relates to all of the above-mentioned compounds.

The products of which the names follow are particularly preferred compounds of the invention, as are medicaments containing them:

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

3-(4-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(3-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(2-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-fluoro-5-trifluoromethylphenyl)-1-(2-morpholin-4-yl)urea;

3-(3,4-dichlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(3,4-dimethoxyphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-methoxyphenyl)-1-(2-morpholin-4-ylethyl)urea;

4-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid ethyl ester;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(4–trifluoromethoxyphenyl)urea;

3-(3-Bromophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-trifluoromethylphenyl)urea;

3-(3,5-bis-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-bromo-6-trifluoromethyl-phenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-bromophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

4-methoxy-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

4-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

3-(3-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester;

3-(2-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(3-acetylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-methylsulphanylphenyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3–trifluoromethoxyphenyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3–ethylsulphonyl-6-methoxyphenyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(2-hydroxyethanesulfonyl)phenyl]-1-(2-morpholin-4-yl-ethyl)urea;
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-2-methylbenzoic acid methyl ester;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-trifluoromethanesulfonyl-phenyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-propionylphenyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-trifluoromethylsulfanyl-phenyl)urea;
1-(3,3-diphenylpropyl)-3-(3-methanesulfonylphenyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-ethylsulfanylphenyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-isopropylsulfanylphenyl)-1-(2-morpholin-4-ylethyl)urea;
3-(4-chloro-3-methylsulfanylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)urea;
3-(3,5-dichlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-iodophenyl)-1-(2-morpholin-4-ylethyl)urea;
3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(3-dimethylaminophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester hydrochloride;
3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea hydrochloride;
1-(3,3-diphenylpropyl)-3-(3-methanesulphinylphenyl)-1-(2-morpholin-4-ylethyl)urea;
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid;
2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid;
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester;
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester hydrochloride;
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid 2-hydroxy ester.;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester hydrochloride;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid benzyl ester;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzamide;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-N-(2-hydroxy-ethyl)-benzamide;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiobenzamide;

1-(3,3-diphenylpropyl)-3-[3-(4-methylthiazol-2-yl)-phenyl]-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-hydroxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-chloro-3-hydroxymethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-formylphenyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-chloro-3-formylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-[4-chloro-3-(1-hydroxyethyl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-methoxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-piperidin-1-ylmethyl-phenyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea hydrochloride;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-yl-4-chlorophenyl)urea;

3-[4-Chloro-3-(1-methyl-1H-tetrazol-5-yl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-[4-Chloro-3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-Biphenyl-4-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

Biphenyl-3-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-pyridin-3-ylphenyl)urea;

(1-(3,3-diphenylpropyl)-3-(3-furan-3-ylphenyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea hydrochloride;

3-[3-(5-chlorothiophen-2-yl)-phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-thiophen-3-ylphenyl)urea;
1-(3,3-diphenylpropyl)-3-(2'-methoxybiphenyl-3-yl)-1-(2-morpholin-4-ylethyl)urea;
3-(2',4'-dichlorobiphenyl-3-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(3-methylisoxazol-5-yl)-phenyl]-1-(2-morpholin-4-ylethyl)urea;
3-[3-(1H-benzimidazole-2-yl)-phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(3-Benzothiazol-2-ylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-[3-(2H-tetrazol-5-yl)phenyl]urea hydrochloride;
1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(1-methyl-1H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(1-methyl-1H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
3-benzo[1,3]dioxol-5-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxo-1,3-dihydroisobenzofuran-5-yl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(8-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)urea;
3-(1-acetyl-2,3-dihydro-1H-indol-6-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(1H-indazol-6-yl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(9-ethyl-9H-carbazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-isoquinolin-7-yl-1-(2-morpholin-4-ylethyl)urea;
3-(2-chloro-benzyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-thiophen-2-ylmethylurea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(1-naphthalen-1-ylethyl)urea;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiophene-2-carboxylic acid methyl ester;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-pyridin-3-ylurea;

1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;

3-(1-benzyl-1H-benzimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(2-methyl-5-phenyl-2,5-dihydro-1H-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;

3-(4,6-dimethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(4-methoxy-6-methylpyrimidin-2-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-pyrazin-2-ylurea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(4-thiazol-2-ylpyrimidin-2-yl)urea;

1-(3,3-diphenylpropyl)-3-(5-methylisoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-methyl-5-phenylisoxazol-4-yl)-1-(2-morpholin-4-ylethyl)urea;

3-[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(5-methyl-3-phenylisoxazol-4-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-phenyl-2H-pyrazol-3-yl)urea;

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-phenyl-[1,2,4]thiadiazol-5-yl)urea;

5-[3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-3-propyl-isoxazole-4-carboxylic acid ethyl ester;

3-(3,4-dimethyl-isoxazol-5-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea.;

3-[3-[2-(9H-fluoren-9-yl)-ethyl]-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

3-[3-[2-(9H-fluoren-9-yl)ethyl]-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)-1-(3-phenyl-3-thiophen-2-ylpropyl)urea;

1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)-1-(3-phenyl-3-thiophen-2-yl-propyl)urea dihydrochloride;

3-[3-(2-morpholin-4-ylethyl)-3-(3-phenyl-3-thiophen-2-ylpropyl)ureido]benzoic acid methyl ester;

1-(3,3-di-thiophen-2-ylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;

3-[3-(3,3-dithiophen-2-yl-propyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

1-(3,3-dithiophen-2-ylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea dihydrochloride;

1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-thiomorpholin-4-ylethyl)urea;

1-[2-(2,6-dimethylmorpholin-4-yl)-ethyl]-1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]urea;

3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-Diphenylpropyl)-3-(1-methyl-1H-benzoimidazol-2-yl)-1-(2-morpholin-4-ylethyl)-urea;

3-(1H-Benzoimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)-3-(5-phenylsulfanyl-1H-benzoimidazol-2-yl)-urea;

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)urea;

1-(3,3-Diphenylpropyl)-3-(5-methyl-2-phenyl-2H-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-phenyl[1,3,4] thiadiazol-2-yl)-urea;

3-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-yl-ethyl)ureido]-5-phenylthiophene-2-carboxylic acid methyl ester;

3-[2-(4-Chlorophenylsulfanyl)-6-methoxypyridin-3-yl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)urea;

2-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid ethyl ester;

6-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]nicotinic acid methyl ester;

3-(3-Chloro-5-trifluoromethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-urea;

3-(6-Chloro-2-methylsulfanylpyrimidin-4-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-urea;

2-(4-Chlorobenzyl)-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)-ureido]oxazole-4-carboxylic acid ethyl ester;
1-(3,3-Diphenylpropyl)-3-(4-methoxybenzo[d]isoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-Diphenylpropyl)-3-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;
6-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]nicotinamide; and
1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(1,4,6-trimethyl-1H-pyrazolo[3,4-b]pyridin-3-yl)urea hydrochloride.

Preferred compounds are:
3-[3-(3,3diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester and the hydrochloride thereof,
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester and the hydrochloride thereof,
2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester and the hydrochloride thereof,
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-(3-ethylcarbonylphenyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-(3-methylsulphanylphenyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)-1-(3-phenyl-3-thiophen-2-ylpropyl)urea,

3-[3-(2-morpholin-4-ylethyl)-3-(3-phenyl-3-thiophen-2-ylpropyl)ureido]benzoic acid methyl ester,

1-(3,3-diphenylpropyl)-3-(4-methoxy-6-methylpyrimidin-2-yl)-1-(2-morpholin-4-ylethyl)urea,

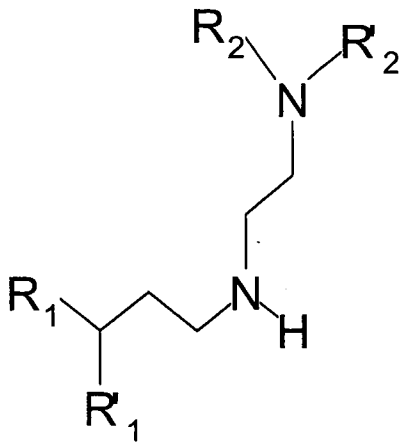
3-(4,6-dimethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(morpholin-4-ylethyl)urea,

1-(3,3-diphenylpropyl)-3-(5-methylisoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea.

The present invention relates, in particular, to the products of formula (I) as defined above, corresponding to the product formulae of examples 1 to 144 described hereinafter in the experimental section.

In the following processes, and elsewhere herein wherein referred to, R_1, R_1', R_2, R_2', and R_3 are synonymous with R^1, $R^{1'}$, R^2, $R^{2'}$, and R^3, respectively.

The present invention further relates to a process for preparing products of formula (I), as defined above, and the salts and/or isomers thereof, the process being characterised in that a compound of formula (II):



(II)

in which R_1, R'_1, R_2 and R'_2 are as defined,

is reacted with an isocyanate of formula (A):

$$R_3\text{-}N{=}C{=}O \qquad (A)$$

in which R_3 is as defined,

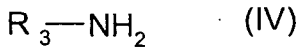
thereby to obtain the desired product of formula (I), which may optionally be converted into another product of formula (I) and, if desired, may further be salified to obtain a salt thereof, and/or the product obtained may optionally be subjected to a resolution reaction to resolve the racemic forms in order to obtain the required isomeric forms.

Under the preferred conditions for carrying out this process of the invention:

- the product of formula (II) is reacted with the product of formula (A) within an anhydrous organic solvent such as dichloromethane, and/or

- the isocyanate of formula (A) may be generated *in situ* from the carboxylic acid R_3COOH of formula (A') by the action of diphenylphosphoryl azide (DPPA) within an anhydrous solvent such as toluene and a base such as triethylamine.

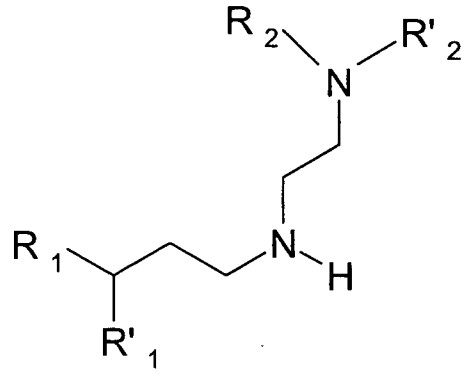
According to a variation of the process for preparing products of formula (I), as defined above, these products may be prepared by a process which is characterised in that a compound of formula (IV):



$$R_3—NH_2 \qquad (IV)$$

in which R_3 is as defined, is subjected

- either to the action of triphosgene to obtain an activated intermediate which is reacted with a compound of formula (II):



(II)

in which R_1, R'_1, R_2 and R'_2 are as defined,

-or to the action of carbonyl diimidazole, then to a compound of formula (II) above,

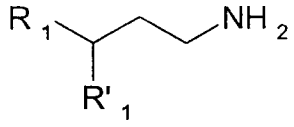
to obtain the desired product of formula (I), in which R_1, R'_1, R_2, R'_2 and R_3 are as defined, which can optionally be further salified in order to obtain the salt thereof and/or, if desired, subjected to a resolution reaction to resolve the racemic forms in order to obtain the required isomeric forms thereof.

Under the preferred conditions for carrying out the invention, this process is characterised in that:

- the compound of formula (IV) is reacted with triphosgene within an anhydrous organic solvent such as dichloromethane in the presence of an amine such as triethylamine or diisopropylethylamine in order to obtain as an intermediate a carbamoyl chloride which is reacted with a compound of formula (II) within an anhydrous organic solvent such as dichloromethane,

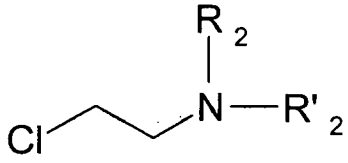
- the compound of formula (IV) is reacted with carbonyl diimidazole within an anhydrous organic solvent such as dichloromethane.

According to the invention, the compounds of formula (II) may be prepared by a process which is characterised in that a compound of formula (V):



(V)

in which R_1 and R'_1 are as defined, is subjected to the action of a compound of formula (VI):



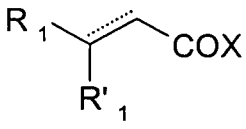
(VI)

in which R_2 and R'_2 are as defined, to obtain the desired compound of formula (II) in which R_1, R'_1, R_2 and R'_2 are as defined.

Under the preferred conditions for carrying out the invention, this process for preparing products of formula (II) is characterised in that:

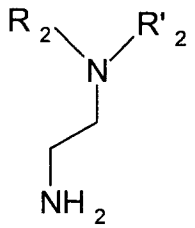
- the compound of formula (V) is reacted with the product of formula (VI) under reflux of the mixture in the presence of acetonitrile, triethylamine and potassium carbonate.

The compounds of formula (II) can also be prepared by a process which is characterised in that a compound of formula (VII):



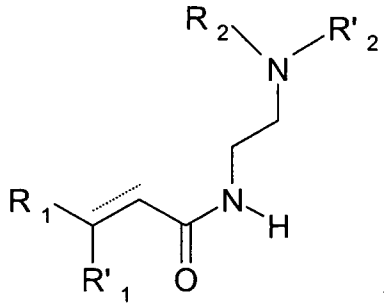
(VII)

in which R_1 and R'_1 are as defined and X represents a hydroxy radical or a chlorine atom, is subjected to the action of a compound of formula (VIII):



(VIII)

in which R_2 and R'_2 are as defined, in the presence of an inert organic solvent to obtain a product of formula (IX):



(IX)

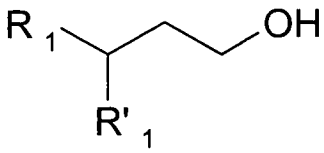
in which R_1, R'_1, R_2 and R'_2 are as defined, whereafter the product of formula (IX) thus obtained is reduced in order to obtain the desired product of formula (II) in which R_1, R'_1, R_2 and R'_2 are as defined.

Under the preferred conditions for carrying out the invention, this process for preparing products of formula (II) is characterised in that:

- the compound of formula (VII) is reacted with the compound of formula (VIII) within an anhydrous organic solvent such as dichloromethane; and/or

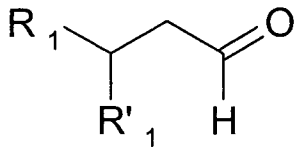
- the product of formula (IX) is reduced using $LiAlH_4$ and optionally in the presence of $AlCl_3$ within an anhydrous organic solvent such as tetrahydrofuran or diethyl ether.

According to a variation, the products of formula (II), as defined above, may also be prepared by a preparation process, characterised in that a compound of formula (X):



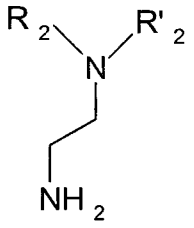
(X)

in which R_1 and R'_1 are as defined, is subjected to oxidation in order to obtain a compound of formula (XI):



(XI)

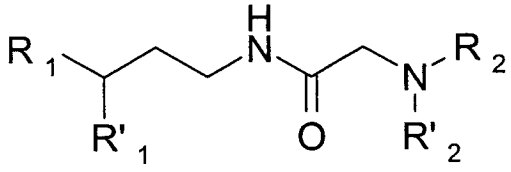
in which R_1 and R'_1 are as defined, then to the action of a compound of formula (VIII), for a stage of reductive amination in the presence of a reducing agent such as $NaBH_3CN$:



(VIII)

in which R_2 and R'_2 are as defined, in the presence of an inert organic solvent, in order to obtain the desired product of formula (II) in which R_1, R'_1, R_2 and R'_2 are as defined.

Finally the products of formula (II) may be prepared by a process characterised in that an amine of formula (V) is subjected to acylation with chloroacetyl chloride, followed by reaction with the amine $NHR_2R'_2$ in order to obtain the amide of formula (XII):



(XII)

in which R_1, R'_1, R_2 and R'_2 are as defined, followed by reduction of the amide of formula (XII) in order to obtain the desired amine of formula (II) in which R_1, R'_1, R_2 and R'_2 are as defined.

Under the preferred conditions for carrying out the invention, this process for preparing products of formula (II) is characterised in that:

- the compound of formula (XII) if formed from the amine $R_2R'_2NH$ within an inert organic solvent such as DMF, and/or

- the product of formula (XII) is reduced using $LiAlH_4$ and optionally in the presence of $AlCl_3$ within an anhydrous organic solvent such as tetrahydrofuran or diethyl ether.

To prepare a product of formula (I) in which R^3 represents an aryl substituted by an alkylsulphone, a product of formula (I) in which R^3 represents an aryl substituted by a thioalkyl will generally first be prepared, after which this product is then oxidised in order to obtain the desired product of formula (I).

This process is hereinafter called method "G".

To prepare a product of formula (I) in which R^3 represents an aryl substituted by a -COOH radical, an ester of said product of formula (I) is first prepared in which this carboxy group is protected (product of formula (I) in which R^3 represents an aryl substituted by a -COOR group in which R represents an alkyl or aralkyl radical), then this ester is saponified in order to obtain the corresponding acid of formula (I) which may optionally be salified.

This process is hereinafter called method "H".

The products of formula (I) in which R^3 represents an aryl substituted by an alkoxycarbonyl radical may be prepared:

- either by employing the above-described general process,
- or by esterification of the corresponding benzoic acid (product of general formula (I) in which R^3 represents a benzoic acid radical), by means of an iodised derivative of formula R_A-I in which R_A represents an alkyl or hydroxyalkyl radical and I represents an iodine atom.

This process is hereinafter called method "I".

The products of formula (I) in which R^3 represents an aryl substituted by a group -CO-R_4 in which R_4 represents an amino, alkylamino, dialkylamino group, may be prepared by reaction of a corresponding benzoic acid derivative (product of general formula (I) in which R^3 represents a benzoic acid residue) with an amine of formula: H-R_4, by methods known to those skilled in the art.

This process is hereinafter called method "J".

The products of formula (I) in which R^3 represents an aryl substituted by a thioamide group may be prepared by starting from the product of general formula (I) in which R^3 represents an aryl substituted by a nitrile group by reaction of diethyl dithiophosphate. This process is hereinafter called method "K".

The products of formula (I) in which R^3 represents an aryl substituted by a thiazolyl group may be prepared by action of a halogenated alpha-ketone on a product of general formula (I) in which R^3 represents an aryl substituted by a thioamide group.

The products of formula (I) in which R^3 represents an aryl substituted by an oxazolyl group may be prepared by reaction of tosylmethyl isocyanide with a product of general formula (I) in which R^3 represents an aryl substituted by an aldehyde group.

The products of formula (I) in which R^3 represents an aryl substituted by a substituted or unsubstituted benzimidazole group may be prepared by reaction of substituted or unsubstituted 1,2-phenylenediamine with a product of general formula (I) in which R^3 represents an aryl substituted by an ester group.

Similarly, starting from the same product of general formula (I), the compounds with R^3 representing an aryl substituted by a substituted or unsubstituted benzothiazole group may be prepared by reaction with substituted or unsubstituted 2-aminothiophenol.

The products of formula (I) in which R^3 represents an aryl substituted by a primary alcohol, aldehyde group may be prepared by reducing the corresponding ester (product of general formula (I) in which R^3 represents an aryl substituted by an ester).

The products of formula (I) in which R^3 represents an aryl substituted by a secondary or tertiary CH_2-alkoxy or CH_2-amine group may be prepared by starting from the product of general formula (I) in which R^3 represents an aryl substituted by a primary alcohol group CH_2OH. These products are prepared by direct action of an alkyl halide on the hydroxy function or by indirect action of an alcohol or a primary or secondary amine after prior activation of this hydroxy group *via* a mesylate or halide.

This process is hereinafter called method "L".

The products of formula (I) in which R^3 represents an aryl substituted by a phenyl group, an aryl group substituted by an aryl or heteroaryl, optionally substituted, may be prepared by a Suzuki coupling reaction by means of a boric acid derivative of formula Ar-B-$(OH)_2$ in which argon represents the residue of a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl, starting from a product of general formula (I) in which R^3 represents an aryl group substituted by a bromine atom.

This process is hereinafter called methods "M" and "N", depending on the technology employed.

Finally, according to a variation of the preparation process, the products of formula (I) in which R^3 represents a phenyl group substituted by a tetrazole or alkyltetrazole radical, may be obtained by starting from the corresponding nitrile (product of general formula (I) in which R^3 represents an aryl substituted by a nitrile group) by reaction with a tributyl tin azide

in order to obtain products of formula (I) in which R^3 represents a phenyl group substituted by a tetrazole radical, followed by a reaction with an alkyl halide in order to obtain the product of formula (I) in which R^3 represents a phenyl group substituted by an alkyltetrazole radical.

The above-described products may, if desired, be subjected to salification reactions, for example using an inorganic or organic acid or an inorganic or organic base, by conventional methods known to the person skilled in the art.

The possible optically active forms of the above-described products may be prepared by resolving the racemic forms by conventional methods known to the person skilled in the art.

The above reactions are further illustrated in the accompanying, non-limiting Examples.

The products of formula (I) as defined above and their addition salts with acids or bases have beneficial pharmacological properties.

The products of the present invention can thus act on an inorganic ion, especially calcium, receptor and thus modulate one or more activities of the receptor.

Products of the present application which act on calcium receptors may thus be used, in particular, for the treatment or prevention of diseases or disorders linked with abnormal physiological behaviour of inorganic ion receptors and, in particular, of calcium receptors such as membrane calcium receptors capable of binding extracellular calcium (Ca sensing receptor CaSR).

It will be appreciated that mention of calcium receptors and CaSR herein includes reference to other inorganic ion receptors unless otherwise indicated or apparent from the context. It will be noted that the preferred target receptor of the present invention is the calcium receptor, and especially CaSR.

The products of the present invention as defined above are capable of modulating the activity of the calcium receptor. The products of the present invention can thus act as agonists or antagonists of the calcium receptor.

While the compounds of the invention are believed to exert their effects by interacting with the calcium sensing receptor (CaSR), the mechanism of action by which the compounds act is not a limiting embodiment of the invention. For example, compounds of the invention may interact with calcium sensing receptors other than CaSR.

Thus, the products of the present invention are of particular use in regulating the serum levels of PTH and extracellular Ca^{++}. Preferred products of the present invention possess agonistic properties toward the calcium receptor and can therefore be used, in particular, to participate in a reduction of the serum levels in the parathyroid hormone known as PTH: these products could thus be useful, in particular, for the treatment of diseases such as hyperparathyroidism. Similarly, abnormalities in calcium homeostasis can be treated with these compounds, in particular hypercalcaemia. Still in the region of the parathyroid, the compounds of formula (I) as defined can treat hyperplasia and parathyroid adenoma.

Another preferred class of products of formula (I) as defined above has properties which enable them to reduce bone resorption which depends directly on the fluctuation of circulating PTH levels: these products could be useful, in particular, for the treatment of diseases such as osteoporosis, osteopaenia Paget's disease and the reconstruction of fractures. They can also be used in the treatment and prophylaxis of polyarthritis and osteoarthritis.

It will be appreciated that reference to treatment herein includes reference to all applicable forms of treatment and prophylaxis.

With regard to digestion, the products of the present invention may also be used for the treatment of motor disorders (such as diarrhoea or constipation), functional digestive disorders, ulcerous diseases, sarcoidosis, familial adenomatous polyposis, polyps of the intestine and colon, cancer of the colon and intestinal malabsorption.

The presence of the calcium receptor in various cells of the nervous system (in particular the pituitary gland and hypothalamus) indicates that the products of the present invention can thus be used for the treatment or prevention of diseases or disorders such as, in particular: inappropriate antidiuretic hormone secretion (ADH syndrome), convulsions, stroke, cranial traumatism, diseases of the spinal marrow, neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease and Huntington's chorea), dementia, migraine, cerebral hypoxia, abnormalities in growth hormone secretion, psychiatric diseases (such as depression, anxiety, obsessive behaviour disorder, schizophrenia, post-traumatic stress, and neuroleptic malignant syndrome).

The products of formula (I) of the present invention may also possess therapeutic properties in regard of the following: thrombopaenia, platelet hypo- or hyper-coagulability, arterial hypertension, cardiac insufficiency, prevention or attenuation of renal toxicity of

aminosides, renal lithiasis, pancreas insufficiency, diabetes, psoriasis, breast adenoma and cancer, cirrhosis, biliary lithiasis, and obesity.

The present invention further provides medicaments comprising compounds of formula (I), in any and all possible racemic, enantiomeric and diastereoisomeric isomeric forms, as well as the pharmaceutically acceptable addition salts thereof with inorganic and organic acids or inorganic or organic bases.

It is especially preferred that the compounds of formula (I) as defined above are used in the treatment and prophylaxis of diseases needing control of PTH hormone levels in the plasma.

It is especially preferred that the compounds of formula (I) as defined above are used in the treatment and prophylaxis of hypercalcaemia or hyperparathyroidism. Such products are particularly useful for the treatment or prevention of hyperparathyroidism.

In a preferred aspect the present invention provides medicaments comprising a compound of formula (I), and/or an addition salt thereof.

Preferred compounds are those listed above and as described in the accompanying Examples, especially when present as the active ingredient of a medicament.

The invention also relates to pharmaceutical compositions containing at least one of the medicaments defined above as the active ingredient.

The invention further relates to the use of the compounds of formula (I) as defined above and/or their pharmaceutically acceptable salts:

- for the manufacture of medicaments for the treatment or prevention of diseases or disorders linked to abnormal physiological behaviour of inorganic ion receptors and in particular of the calcium receptor, characterised in that the calcium receptor is expressed in at least one of the parathyroid, the thyroid, the bone cells, the renal cells, the lung, the brain, the pituitary gland, the hypothalamus, the gastrointestinal cells, the pancreas cells, the skin cells, the cells of the central or peripheral nervous system and the smooth muscle cells,

- for the manufacture of medicaments for the prevention or treatment of cancers, in particular of the parathyroid and/or the digestive tract,

- for the manufacture of medicaments for the prevention or treatment of neurodegenerative diseases,

- for the manufacture of medicaments for the prevention or treatment of bone and articular metabolism diseases, in particular osteoporosis, osteopaenia and Paget's disease, rheumatoid arthritis and/or osteoarthritis,

- for the manufacture of medicaments for the prevention or treatment of abnormal calcium homeostasis,

- for the manufacture of medicaments for the prevention or treatment of hyperplasia and/or parathyroid adenoma,

- for the manufacture of medicaments for the prevention or treatment of intestinal malabsorption,

- for the manufacture of medicaments for the prevention or treatment of biliary lithiasis and/or renal lithiasis,

- for the manufacture of medicaments for the prevention or treatment of hyperparathyroidism, characterised in that secondary hyperparathyroidism is observed in the event of renal insufficiency,

- for the manufacture of medicaments for the prevention or treatment of ionised serum calcium level reduction during the treatment of hypercalcaemia,

- for the manufacture of medicaments for the prevention or treatment of cardiovascular diseases.

In one aspect, the invention provides a method of inhibiting, decreasing or preventing vascular calcification in an individual. The method comprises administering to the individual a therapeutically effective amount of the calcimimetic compound of the invention. In one aspect, administration of the compound of the invention retards or reverses the formation, growth or deposition of extracellular matrix hydroxyapatite crystal deposits. In another aspect of the invention, administration of the compound of the invention prevents the formation, growth or deposition of extracellular matrix hydroxyapatite crystal deposits.

In one aspect, the compounds of the invention may be used to prevent or treat atherosclerotic calcification and medial calcification and other conditions characterized by vascular calcification. In one aspect, vascular calcification may be associated with chronic renal insufficiency or end-stage renal disease. In another aspect, vascular calcification may be associated with pre- or post-dialysis or uremia. In a further aspect, vascular calcification may be associated with diabetes mellitus I or II. In yet another aspect, vascular calcification may be associated with a cardiovascular disorder.

In one aspect, administration of an effective amount of the compounds of the invention can reduce serum PTH without causing aortic calcification. In another aspect, administration of the compounds of the invention can reduce serum creatinine level or can prevent increase of serum creatinine level. In another aspect, administration of the compounds of the invention can attenuates parathyroid (PT) hyperplasia.

The compounds of the invention may be administered alone or in combination with other drugs for treating vascular calcification, such as vitamin D sterols and/or RENAGEL®. Vitamin D sterols can include calcitriol, alfacalcidol, doxercalciferol, maxacalcitol or paricalcitol. In one aspect, the compounds of the invention can be administered before or after administration of vitamin D sterols. In another aspect, the compounds of the invention can be co-administered with vitamin D sterols. The methods of the invention can be practised to attenuate the mineralising effect of calcitriol on vascular tissue. In one aspect, the methods of the invention can be used to reverse the effect of calcitriol of increasing the serum levels of calcium, phosphorus and Ca x P product thereby preventing or inhibiting vascular calcification. In another aspect, the compounds of the invention of the invention can be used to stabilise or decrease serum creatinine levels. In one aspect, in addition to creatinine level increase due to a disease, a further increase in creatinine level can be due to treatment with vitamin D sterols such as calcitriol. In addition, the compounds of the invention may be administered in conjunction with surgical and non-surgical treatments. In one aspect, the methods of the invention can be practised in injunction with dialysis.

In one aspect, the compounds of the invention can be used for treating abnormal intestinal motility disorders such as diarrhoea. The methods of the invention comprise administering to the individual a therapeutically effective amount of the compounds of Formula I.

As used herein, the term "diarrhoea" refers to a condition of three or more unformed stools in a 24-hour period of volume more than 200 g per day. In one aspect, diarrhoea can be osmotic, *i.e.*, resulting if the osmotic pressure of intestinal contents is higher than that of the serum. This condition may result from malabsorption of fat (*e.g.*, in celiac disease) or of lactose (*e.g.*, in intestinal lactase deficiency), or it can happen due to the use of certain laxatives (*e.g.*, lactulose, magnesium hydroxide) or artificial sweeteners (*e.g.*, sorbitol, mannitol). In another aspect, diarrhoea can be secretory, *i.e.*, occurring when there is a net secretion of water into the lumen. This may occur with bacterial toxins (such as those

produced, *e.g.*, by E.coli and Vibrio cholerae), or with hormones, such as vasoactive intestinal polypeptide, which is produced by rare islet cell tumors (pancreatic cholera). Both osmotic and secretory diarrhoeas result from abnormalities in the small intestine such that the flow of water through the ileocecal area overcomes the absorptive capacity of the colon.

In a further aspect, diarrhoea can be exudative diarrhoea, *i.e.*, resulting from direct damage to the small or large intestinal mucosa. This type of diarrhoea can be caused by infectious or inflammatory disorders of the gut. In one aspect, exudative diarrhoea can be associated with chemotherapy, radiation treatment, inflammation or toxic traumatic injury. In another aspect, exudative diarrhoea can be associated with a gastrointestinal or abdominal surgery.

In another aspect, diarrhoea can be due to acceleration of intestinal transit (rapid transit diarrhoea). Such condition may occur because the rapid flow-through impairs the ability of the gut to absorb water.

In one aspect, the invention provides the compounds and compositions for treating abnormal gastric fluid secretion / absorption disorders in conjunction with treating underlying causes of, for example, diarrhoea or with other treatment methods. In one aspect, calcimimetics can be administered to a subject before, after or concurrently with oral rehydration therapy. For example, oral rehydration therapy may contain the following ingredients: sodium, potassium, chloride, bicarbonate, citrate and glucose. In another aspect, the compounds of the invention can be administered to a subject before, after or concurrently with an antimotility agent, such as loperamide (Imodium), diphenoxylate, or bismuth subsalicylate (Pepto-Bismol). In another aspect, calcimimetics can be administered with antibiotics (*e.g.*, trimethoprim-sulfamethoxazole (Bactrim DS), ciprofloxacin (Cipro), norfloxacin (Noroxin), ofloxacin (Floxin), doxycycline (Vibramycin), erythromycin). In one aspect, the compounds of the invention can be administered together with calcium or polyamines such as spermine, spermidine, putrescine, and ornithine metabolites or amino acids such of L-tryptophan, L-phenylalanine. In another aspect, the compounds of the invention can be administered together with sodium and glucose. In addition, the compounds of the invention may be administered in conjunction with surgical and non-surgical treatments.

The invention further provides methods for modulating intestinal fluid secretion and absorption. In one aspect, the purpose can be to increase fluid absorption and/or decrease

fluid secretion in a subject and thus the methods of the invention can comprise administering an effective amount of a pharmaceutical composition comprising a compound of the invention.

The invention provides methods of modulation the absorption or secretion of a drug, poison or nutrient in the intestinal tract of a subject, comprising administering an effective amount of a pharmaceutical composition comprising a compound of the invention together with a pharmaceutically acceptable carrier to the subject. In one aspect, the invention provides methods of treatment of a malassimilation or a malabsorption of a subject, comprising administering an effective amount of a pharmaceutical composition comprising a compound of Formula I together with a pharmaceutically acceptable carrier to the subject.

As used herein, the term "malassimilation" encompasses impaired processes of food digestions and absorption occurring in one of two ways (1) through intraluminal disorders (maldigestion of food) and (2) through intramural disorders (malabsorption of food).

Methods of the invention comprising administering a pharmaceutical composition of the invention can also be practised to treat malnutrition in a subject. For example, a subject can be malnourished if the subject is grossly underweight (weight for height is below 80% of the standard), grossly overweight (weight for height above 120% of the standard), if the subject unintentionally lost 10% or more of body weight, has a gastrointestinal tract surgery, experienced nutrient losses (*e.g.*, from diarrhoea, dialysis, vomiting), has increased metabolic needs (*e.g.*, due to pregnancy, lactation, increased physical activity, fever, injury), is an alcoholic or chronic drug user (antibiotics, antidepressants, diuretics), has medical conditions which interfere with nutrient intake, absorption, metabolism, or utilisation, has poor dentition (particularly in the elderly subjects), or has mouth sores due to herpes, HIV or chemotherapy. In another aspect, the subject can be malnourished due to dietary risk factors (*e.g.*, loss of appetite, inadequate food or nutrient intake, lack of variety of foods, fad, weight-loss diets, inadequate fibre, excessive fat, sodium, sugar, excess alcohol, eats too few fruits, vegetables) or due to social risk factors (*e.g.*, chronic ill health, poverty, inadequate money to buy food, low socioeconomic status, immobility or inability to purchase, store, or cook food, social isolation, eats alone most of the time, substance abuser, conditions which limit subject's ability to eat). Further, the methods of the invention can be practised when a subject has limited access to nutrients such as during survival following environmental disasters, survival at sea, marooning and deep-sea living or space travel.

The products of formula (I) and their pharmaceutically acceptable salts may be administered to animals, preferably to mammals and, in particular, to humans, as therapeutic or prophylactic medicaments.

They may be administered as they are or in a mixture with one or more compounds of formula (I) or else in the form of a pharmaceutical composition containing as the active compound an effective dose of at least one product of formula (I) and/or their pharmaceutically acceptable salts and common pharmaceutically inert excipients and/or additives.

These pharmaceutical compositions can be administered buccally, enterally or parenterally or topically to the skin and mucous membranes or by intravenous or intramuscular injection.

The medicaments may therefore be administered orally, for example in the form of pills, tablets, coated tablets, gel-coated tablets, granules, hard and soft capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures.

The medicaments may however be effectively administered rectally, for example in the form of suppositories, or as pessaries, or parenterally, for example in the form of injectable solutions or infusions, microcapsules or implants, percutaneously, for example in the form of an ointment, solutions, pigments or colorants, transdermally (patches) or by other methods, for example in the form of an aerosol or nasal spray.

The medicaments according to the present invention may therefore be formulated as pharmaceutical compositions containing one or more products of formula (I) as defined above.

Pharmaceutical compositions of this type can therefore constitute the form in which the products of formula (I) as defined above are used in the therapeutic application thereof.

The pharmaceutical compositions according to the invention are prepared by conventional methods, pharmaceutically inert organic or inorganic excipients being added to the compounds of formula (I) and/or their pharmaceutically acceptable salts.

These compositions may therefore be solid or liquid and may have any pharmaceutical forms commonly employed in human medicine, for example, simple tablets or dragees, pills, tablets, hard capsules, droplets, granules, injectable preparations, ointments, creams or gels; they are prepared by conventional methods.

Excipients such as lactose, cornstarch or derivatives thereof, talc, stearic acid or the salts thereof, for example, may be used for producing pills, tablets, coated tablets and hard gelatin capsules.

Suitable vehicles for soft gelatin capsules or suppositories include, for example, fats, semi-solid or liquid polyol waxes and natural or modified oils, etc. Appropriate vehicles for the preparation of solutions, for example injectable solutions, emulsions or syrups include, for example, water, alcohols, glycerol, polyols, sucrose, invert sugars, glucose, vegetable oils, etc. Suitable vehicles for microcapsules or implants include, for example, glyoxylic and lactic acid copolymers. The pharmaceutical preparations normally contain from 0.5 % to 90 % by weight of products of formula (I) and/or the physiologically acceptable salts thereof.

The active principle may be incorporated in excipients which are normally used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fats of animal or vegetable origin, paraffin derivatives, glycols, various wetting agents, dispersants or emulsifiers and preservatives.

In addition to the active principles and excipients, the pharmaceutical compositions may contain additives such as, for example, diluents, disintegrating agents, binders, lubricants, wetting agents, stabilisers, emulsifiers, preservatives, sweeteners, colorants, flavourings or aromatising agents, thickeners, buffers and also solvents or solubilisers or retarding agents and also salts to modify osmotic pressure, coating agents or antioxidants.

They can also contain two or more products of formula (I) and/or their pharmaceutically acceptable salts as defined above. Moreover, in addition to at least one or more products of formula (I) and/or their pharmaceutically acceptable salts, they can contain at least one or more other active principle which can be used therapeutically or prophylactically.

Pharmaceutical compositions of this type contain as active compound an effective dose of at least one product of formula (I) and/or its pharmaceutically acceptable salts as well as one or more pharmaceutically acceptable excipients and/or vehicles and optionally one or more conventional additives.

The present invention thus extends to pharmaceutical compositions containing at least one of the medicaments as defined above as the active ingredient.

When using the products of formula (I), the doses can vary within wide limits and will be determined by the skilled physician, taking into account such factors as the age, weight

and sex of the patient. Other factors to be taken into consideration include the compound employed, the nature and severity of the disease to be treated, whether the condition is serious or chronic, and whether a prophylactic treatment is being employed.

The pharmaceutical compositions normally contain from 0.2 to 500 mg, preferably from 1 to 200 g of compound of formula (I) and/or their pharmaceutically acceptable salts.

In the case of oral administration, the daily dose varies generally from 0.05 to 10 mg/kg and preferably from 0.1 to 8 mg/kg, in particular from 0.1 to 6 mg/kg. For an adult, for example, a daily dose varying from 5 to 500 mg could be considered.

In the case of intravenous administration, the daily dose varies approximately from 0.05 to 6 mg/kg and preferably from 0.1 to 5 mg/kg.

The daily dose may be divided into a plurality of portions, for example 2, 3 or 4 portions, in particular if a large amount of active ingredient is to be administered. It may possibly be necessary to administer the various doses in an increasing or decreasing manner, depending on the behaviour in an individual case. These doses may be applied multiple times per day, once a day, once every other day, or any other regimen deemed appropriate by the skilled physician. Apart from the use of the products of formula (I) as defined above as medicaments, their use as a vehicle or support for active compounds for transporting these active compounds specifically toward a site of action can also be envisaged (Drug targeting, see Targeted Drug Delivery, R.C. Juliano, Handbook of Experimental Pharmacology, Vol. 100, Ed. Born, G.V.R. *et al*, Springer Verlag). The active compounds which may be transported are, in particular, those used for the treatment or prevention of the above-mentioned diseases.

The pharmaceutical compositions according to the present invention thus containing compounds of formula (I) and/or their pharmaceutically acceptable salts can thus be used, in particular, for the treatment or prevention of diseases necessitating the administration of products which are agonists or antagonists of inorganic ion receptors such as, in particular, calcium receptors.

The present invention accordingly relates, in particular, to the use of the products of formula (I) as defined above and/or their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment or prevention of diseases or disorders linked to abnormal physiological behaviour of inorganic ion receptors and in particular of calcium receptors.

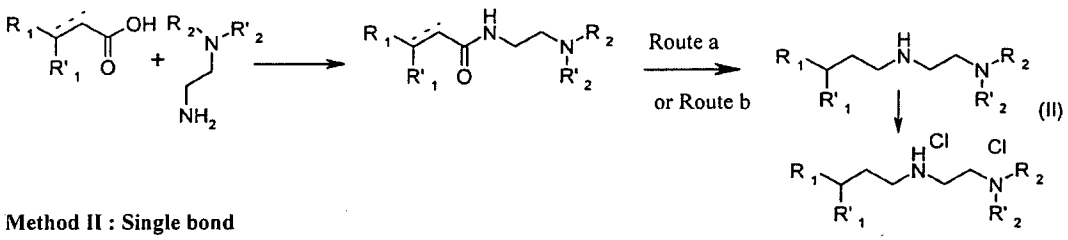
The pharmaceutical compositions according to the present invention can thus be used as medicaments for the above-mentioned therapeutic applications.

The experimental section hereinafter gives examples of preparation of products of formula (I). These examples illustrate the invention without limiting it in any way.

As mentioned hereinafter, the products of formula (I) may be obtained by starting from compounds of formula (II). These compounds of formula (II) may be obtained as described above, and as shown in the three methods of synthesis described below:

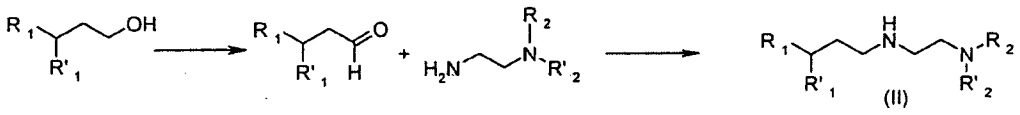
Method I:

Method II:

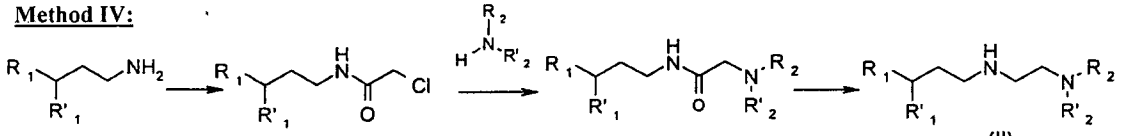


Method II : Single bond
Method IIb : Double bond

Method III:



Method IV:



The preparation of 3,3-diphenyl-propyl)(2-morpholin-4-yl-ethyl)-amine of formula (II) by methods I, II and III will be described hereinafter by way of example:

Method I: Alkylation

Preparation of 3,3-(diphenylpropyl)(2-morpholin-4-yl-ethyl)amine:

35 g (165.6 mmol) of *gem*-diphenylpropylamine, 700 mL of acetonitrile, 6.2 g (33.1 mmol) of *N*-(2-chloroethyl) morpholine in hydrochloride form, 4.62 ml (33.1 mmol) of triethylamine and 9.16 g (66.24 mmol) of potassium carbonate are introduced in succession into a flask placed under argon and topped by a condenser. The reaction medium is heated under reflux for 5 days. The acetonitrile is eliminated on a rotary evaporator and the mixture is taken up with water and dichloromethane. The aqueous phase is extracted with dichloromethane, then the organic phases are combined, washed with a saturated NaCl solution and dried over $MgSO_4$. After evaporation, a mixture of the desired product and *gem*-diphenylpropylamine introduced in a large excess is obtained.

Purification of the crude reaction product by flash chromatography over silica gel (elution gradient: heptane 100 %, CH_2Cl_2 100 % then CH_2Cl_2/MeOH/NH_4OH 98/2/0.1 to 90/10/0.1) leads to 7.18 g of secondary amine (yield = 67 %).

Method II: Peptide coupling and reduction

Preparation of *N*-(2-morpholin-4-ylethyl)-3,3-diphenylpropionamide:

25 g (0.11 mmol, 1 eq.) of 3,3-diphenyl propanoic acid are dissolved in 75 mL of CH_2Cl_2 under argon. 16.42 g (0.12 mmol, 1.1 eq.) of HOBt and 23.30 g (0.12 mmol, 1.1 eq.) of EDC, HCl are added. The solution is stirred for 45 min. at room temperature then 16 mL (0.12 mmol, 1.1 eq.) of 4-(2-aminoethyl)morpholine are added dropwise. The solution is stirred for 1 hour 30 min. at room temperature and the colour of the mixture changes from yellow to orange.

Some 0.1 M HCl is added to the mixture. The organic phase is washed twice with 0.1 M HCl, three times with a saturated sodium bicarbonate solution and once with brine. It is then dried over $MgSO_4$, filtered and concentrated. The solid obtained is recrystallised in 40 mL of AcOEt. 32.43 g of a white powder are recovered (yield = 87 %).

Preparation of 3,3-(diphenylpropyl)(2-morpholin-4-ylethyl)amine:

Route a: Reduction by $LiAlH_4$

10 g (29.55 mmol, 1 eq.) of *N*-(2-morpholin-4-ylethyl)-3,3-diphenylpropionamide are dissolved in a 4/1 mixture of diethyl ether and THF under argon. 65 mL (35.45 mmol, 2.2 eq.) of 1 M $LiAlH_4$ in THF are added dropwise and the mixture is heated under reflux (50 °C) for 21 hours. 4.9 mL of water, 2.5 mL of 15 % aqueous NaOH then a further 12.3 mL of

water are added to the reaction mixture. After stirring for 15 min, the aqueous phase is extracted with CH_2Cl_2. The organic phase is subsequently washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture obtained is filtered over silica (eluent: 9/1/0.1 CH_2Cl_2/MeOH/NH_4OH) and an amorphous paste is recovered (9.6 g, yield = 100 %).

Route b: Reduction by $LiAlH_4/AlCl_3$

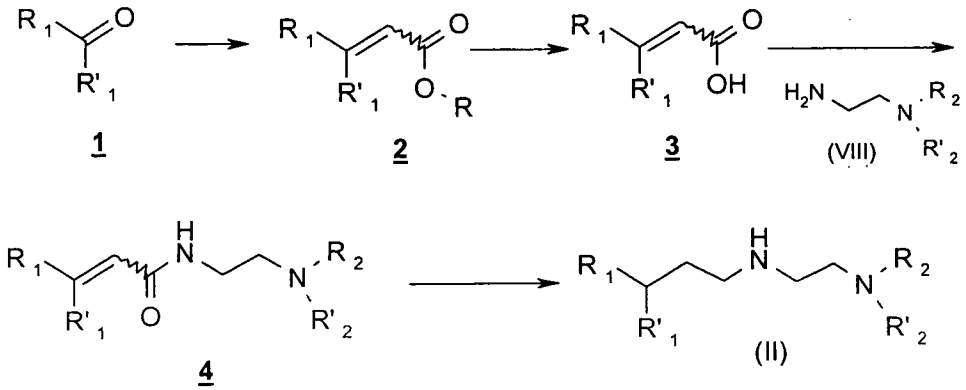
27.6 g (0.21 mol, 0.5 eq.) of $AlCl_3$ are added batchwise to a solution of 140 g (0.42 mol, 1.0 eq.) of *N*-(2-morpholin-4-ylethyl)-3,3-diphenylpropionamide in 3.5 L of THF (slightly exothermic addition) under an inert atmosphere and at 0 °C in a 5 L flask. Once the medium has become homogeneous, still at 0 °C, 23.6 g (0.62 mol, 1.5 eq.) of $LiAlH_4$ are added in small batches so that the temperature does not exceed 5 °C (initially a markedly exothermic addition). The temperature of the reaction medium is then raised progressively under reflux of the THF and heating is continued for 1 hour.

The mixture is then cooled to 0 °C and 1 L of water is added carefully (initially dropwise). It is important to observe the prescribed dilutions because the medium thickens markedly during this hydrolysis. The resultant suspension is filtered, and the salts are rinsed with 2 L of ethyl acetate. All of the filtrates are placed in a 10 L reactor and decanted. The aqueous phase is extracted again with 2 L of ethyl acetate and the organic fractions are collected, washed with 2 L of a saturated aqueous solution of NaCl and concentrated under reduced pressure. The oil thus obtained is taken up in 1 L of ethyl acetate, dried over sodium sulphate, filtered and concentrated until dry under reduced pressure to lead to the obtaining of 130 g of a yellow oil.

Purification is carried out during salification, as follows: 500 mL (1 mol, 2.5 eq.) of a 2.5 M solution of hydrochloric acid are added to the foregoing oil and the mixture is concentrated under reduced pressure. 500 mL of ethanol are added and the mixture is concentrated again. This last procedure is carried out 3 more times and the salt crystallises during this treatment. The last time the ethanol is concentrated to a total mass of 480 g (corresponding to 2 parts of ethanol) and the suspension obtained is cooled to 0 °C, then filtered and washed with 150 mL of cold ethanol. After drying under a vacuum created by a vane pump, 122 g (72 %) of (3,3-diphenylpropyl)(2-morpholin-4-ylethyl)amine dihydrochloride are obtained in the form of a white crystalline solid.

Method IIa: Peptide coupling and reduction

The unsaturated acid analogues **3** can be synthesised in accordance with the following reaction scheme:



Preparation of unsaturated acids, **3**

1 eq. of acetophenone derivative **1** is dissolved in dry THF in a flask equipped with a condenser, under argon. 1.3 eq. of triethylphosphonoacetate are introduced and 1.3 eq. of 60 % NaH in oil are added batchwise to the solution. The mixture is heated under reflux for 3 hours at 70-80 °C. 1 eq. of triethylphosphonoacetate and 1 eq. of 60 % NaH in oil are added to the medium. The mixture is stirred for 2 hours at 70-80 °C. Water is added, then the THF is concentrated. The basic aqueous phase is extracted with AcOEt and the organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product obtained is subjected to chromatography over silica gel to give the conjugate ester **2** in the form of crystals (yield approximately 70 %).

1 eq. of **2** is dissolved in EtOH, 2 eq. of 1 N sodium hydroxide are added and the mixture is stirred for 45 min. at 60 °C. The reagent dissolves completely while hot. The ethanol is concentrated, the residue is taken up in the water and AcOEt is added.. The aqueous phase is acidified to pH 3, then extracted with AcOEt. The organic phase is washed with brine, dried, filtered and concentrated to give the conjugate acid **3** quantitatively.

Preparation of unsaturated amide derivatives, **4**

1 eq. of propanoic acid analogue **3** is dissolved in a 9/1 mixture of DCM/DMF under Ar, 1.1 eq. of HOBt and 1.1 eq. of EDC, HCl are then introduced in succession. The mixture is stirred for 30 min. at room temperature and 1.1 eq. of aminoethylamine of formula (VIII) are added. The mixture is stirred for 5 hours at room temperature. 0.7 eq. of amino-ethylamine of formula (VIII) and 0.7 eq. of EDC, HCl are added. The mixture is stirred for

one night at room temperature. Dichloromethane is added, the organic phase is washed with a 0.1 N HCl solution, with a saturated $NaHCO_3$ solution then finally with brine. It is dried over $MgSO_4$, filtered and concentrated. The crude product obtained is subjected to chromatography over silica gel and may be recrystallised. The yields are approximately 75 %.

Reduction by $LiAlH_4/AlCl_3$ (synthesis of the amine of formula (II))

1 eq. of the unsaturated amide analogue **4** is dissolved in THF in a 250 mL flask placed in an argon atmosphere. After cooling the solution to 0 °C, 0.5 eq. of $AlCl_3$ is added batchwise. Once the medium has become homogeneous, 2.5 eq. of $LiAlH_4$ in a 1 M solution in THF are added slowly. The mixture is kept at 0 °C during the addition, is then heated under reflux (60 °C) for 1 hour and cooled to 0 °C. 7 mL of water are then added very slowly to the solution to avoid a violent reaction. The salts are filtered and rinsed with ethyl acetate. The filtrate is recovered, water is added and the aqueous phase is extracted with ethyl acetate. The organic phase is washed once with water then once with brine, is subsequently dried over $MgSO_4$, filtered and concentrated. The paste obtained is subjected to chromatography over silica gel in order to obtain the amine of formula (II) in a yield of approximately 80 %.

Method III: Oxidation in aldehyde and reductive amination

Preparation of 3,3-diphenylpropionaldehyde:

4.69 mL (23.55 mmol, 1 eq.) of 3,3-diphenylpropanol are dissolved in 100 mL of CH_2Cl_2 under argon. 10.5 g (24.73 mmol, 1.05 eq.) of Dess Martin Periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one) are added to the mixture and the solution is stirred for 1 hour 30 min. at 0 °C. 100 mL of 2 M sodium hydroxide and 100 mL of CH_2Cl_2 are then added. The organic phase is washed with 2 M sodium hydroxide (twice), with water (twice), dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica gel (eluent: 5/1 heptane/AcOEt). An oil which crystallises in the form of a white product is recovered (4.76 g, yield = 96 %).

Preparation of 3,3-(diphenylpropyl)(2-morpholin-4-ylethyl)amine:

200 mg (0.95 mmol, 1 eq.) of 3,3-diphenylpropionaldehyde are dissolved in 2 mL of EtOH and 187 µL (1.43 mmol, 1.5 eq.) of 4-(2-aminoethyl)morpholine are added to the medium under argon. Once 20 mg (0.09 mmol, 1 eq.) of 10 % Pd/C have been added, the reaction is placed under H_2, atmospheric pressure and the mixture is stirred for 16 hours at room temperature. The catalyst is removed by filtration over Celite®. A saturated sodium

bicarbonate solution is added and the aqueous phase is extracted with AcOEt. The organic phase is subsequently washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over alumina (eluent: 1/1 heptane/CH_2Cl_2) to give 251 mg of amine (yield = 81 %).

The preparation of 3,3-diphenylpropyl)(2-thiomorpholin-4-ylethyl)amine of formula (II) by method IV is described hereinafter by way of example:

Method IV: Alkylation and amide reduction

Preparation of *N*-chloromethyl-3,3-diphenylpropionamide

1 g (4.73 mmol, 1 eq.) of 3,3-diphenylpropylamine and 732 µL (5.21 mmol, 1.1 eq.) of triethylamine are diluted in 30 mL of DCM at 0 °C under argon. 300 µL (3.77 mmol, 0.8 eq.) of chloroacetyl chloride are added dropwise. White fumes form then gradually dissipate. The mixture is stirred for 45 min. at 0 °C, the solution becomes red. A dilute HCl solution is added then the aqueous phase is extracted with DCM. The organic phase is washed once with water then once with brine, dried over $MgSO_4$, filtered and concentrated. The product is obtained in the form of oil (m = 1.36 g, yield = 100 %).

Preparation of *N*-(3,3-diphenylpropyl)-2-thiomorpholin-4-ylacetamide

700 mg (2.43 mmol, 1 eq.) of *N*-chloromethyl-3,3-diphenylpropionamide, 508 µL (2.92 mmol, 1.2 eq.) of diisopropylethylamine, 245 µL (2.43 mmol, 1 eq.) of thiomorpholine and 5 mL of DMF are introduced into a sealed tube. The mixture is heated for 8 min. by microwave at 180 °C. A saturated sodium bicarbonate solution is added to the mixture and the aqueous phase is extracted with ethyl acetate. The organic phase is washed with brine, dried, filtered concentrated. The solid obtained is recrystallised in diethyl ether (m = 769 mg, yield = 89 %).

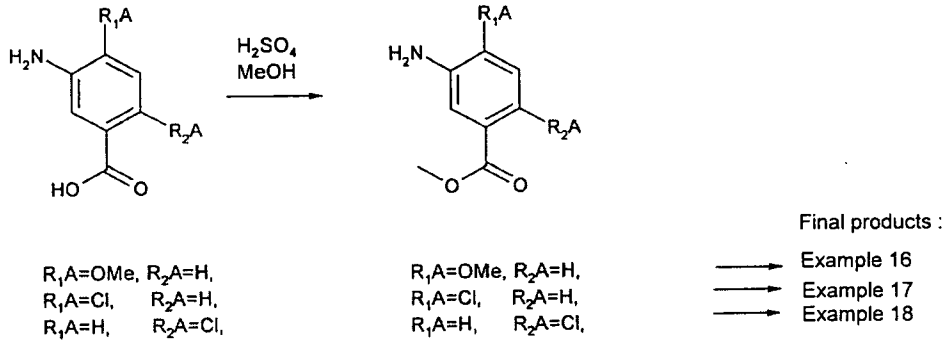
Preparation of (3,3-diphenylpropyl)(2-thiomorpholin-4-ylethyl)amine of formula (II)

Obtained from *N*-(3,3-diphenyl-propyl)-2-thiomorpholin-4-yl-acetamide by the above-described Method II, route b ($AlCl_3$+$LiAlH_4$).

The products of formula (IV) may be prepared by one of the following methods.

I: Route 1) - by modification of anilines:

a) by esterification starting from an acid



Preparation of 5-amino-2-chlorobenzoic acid methyl ester, R_1A =H, R_2A =Cl:

5-amino-2-chlorobenzoic acid (87 mg, 0.5 mmol) is dissolved in 5 mL of MeOH and 0.1 mL of concentrated H_2SO_4 in a 10 mL flask. The solution is heated under reflux for 16 hours. The solvent is evaporated and the residue is taken up in dichloromethane. Water is added and the aqueous phase is extracted with dichloromethane. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The product is obtained in solid form (m = 89 g, yield = 94 %).

5-amino-2-chloro-benzoic acid methyl ester

MS: 185.9^+ $(M+H)^+$

TLC: Rf: 0.26 (eluent: 4/1 dichloromethane/ethyl acetate)

3-amino-4-methoxy benzoic acid methyl ester

MS: 181.9^+ $(M+H)^+$

TLC: Rf: 0.58 (eluent: 4/1 dichloromethane/ethyl acetate)

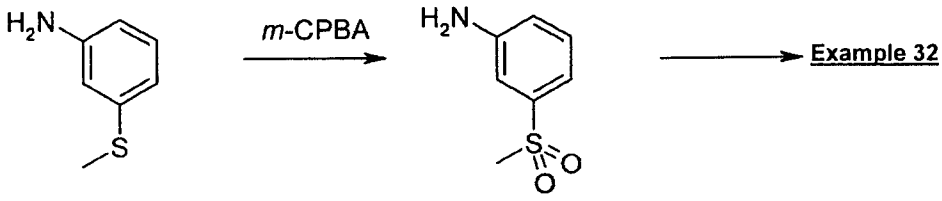
3-amino-4-chlorobenzoic acid methyl ester

MS: 185.9^+ $(M+H)^+$

TLC: Rf: 0.31 (eluent: 4/1 dichloromethane/ethyl acetate)

b) by oxidation of a thiomethyl group:

Preparation of 3-methanesulphonylphenylamine



150 mg (1.22 mmol, 1 eq.) of (3-methylmercapto)aniline are dissolved in 3 mL of chloroform. 420 mg (2.43 mmol, 2 eq.) of *meta*-chloroperbenzoic acid are added to this solution. The mixture is stirred for 1 hour 30 min. at 0 °C. A saturated $NaHCO_3$ solution is added and the aqueous phase is extracted with DCM. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by chromatography over silica gel (eluent: DCM/AcOEt 8/1 to 6/1) to give 30 mg of product (yield = 14 %).

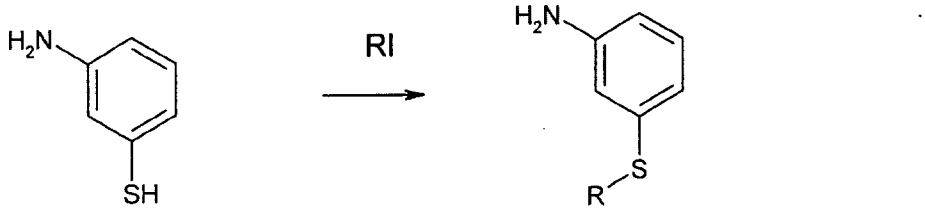
^{1}H NMR(400 MHz, $CDCl_3$): ppm 3.02 (s, 3H, CH3), 3.73-4.22 (m, 2H, NH2), 6.89 (d, 1H, aromatic H), 7.18-7.23 (m, 3H, aromatic H)

MS: 172.09$^+$ $(M+H)^+$, 213.13$^+$ $(M+H+CH_3CN)^+$

TLC: Rf = 0.31 (eluent: DCM/AcOEt 4/1)

c) by alkylation of a thiol:

Preparation of 3-ethylsulphanylphenylamine, **5** and of 3-isopropylsulphanylphenylamine, **6**:



300 mg (2.40 mmol, 1 eq.) of 3-aminothiophenol are dissolved in 3 mL of DMF. 96 mg (2.40 mmol, 1 eq.) of 60 % NaH in oil are added then, at 0°C, 192 µL (2.40 mmol, 1 eq.) of iodoethane are added for **5** and 239 µL (2.40 mmol, 1 eq.) of 2-iodopropane are added for **6**.

The solution is stirred at room temperature for 24 hours and water is added. The aqueous phase is extracted with ethyl acetate. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by chromatography over silica gel (eluent: heptane/AcOEt 6/1 and 4/1) (**5**: m = 220 mg, yield = 60 %, **6**: m = 140 mg, yield = 35 %).

3-ethylsulphanyl-phenylamine, **5**:

1H NMR(400 MHz, $CDCl_3$): ppm 1.33 (t, 3H, CH3), 2.94 (q, 2H, CH2), 3.50-3.75 (m, 2H, NH2), 6.52 (d, 1H, aromatic H), 6.68 (s, 1H, aromatic H), 6.75 (d, 1H, aromatic H), 7.09 (t, 1H, aromatic H).

TLC: Rf = 0.15 (eluent: heptane/AcOEt 4/1)

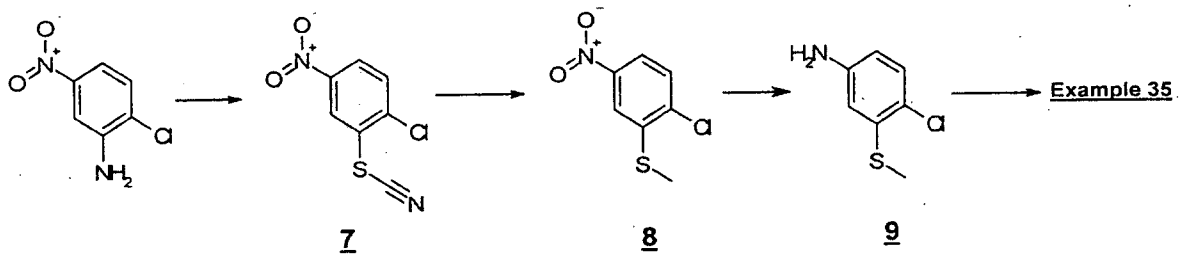
3-Isopropylsulphanyl-phenylamine, **6**:

^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.32 (d, 6H, CH3), 3.38 (sept, 1H, CH), 3.56-3.72 (m, 2H, NH2), 6.56 (d, 1H, aromatic H), 6.76 (s, 1H, aromatic H), 6.82 (d, 1H, aromatic H), 7.10 (t, 1H, aromatic H).

TLC: Rf = 0.19 (eluent: heptane/AcOEt 4/1)

II.: Route 2)- starting from substituted nitro-benzenes:

Preparation 1: Synthesis of 4-chloro-3-methylsulphanyl-phenylamine, **9**:



7 **8** **9**

a): Preparation of 1-chloro-4-nitro-2-thiocyanatobenzene, 7:

500 mg (2.90 mmol, 1 eq.) of 2-chloro-5-nitrophenylamine are dissolved in 5 mL of HCl 6 N. Once a homogeneous paste has been obtained, the mixture is cooled to 0 °C, and a solution of 224 mg (3.24 mmol, 1.12 eq.) of sodium nitrite in 0.5 mL of iced water is added in 15 min. The temperature is kept between 0 °C and -3 °C during addition. After addition, the mixture is stirred for a further 30 min. Then, this mixture is added to a solution containing 0.4 g (4.12 mmol, 1.42 eq.) of KSCN and 0.35 g (2.88 mmol, 1 eq.) of CuSCN in 1 mL of water. Addition takes 20 min. at 25 °C. The yellow solution becomes fuming red

and a precipitate is formed. The mixture is stirred for one night at room temperature. The precipitate is filtered and washed with dichloromethane (6x3 mL). The organic phase is recovered and washed twice with water, dried over $MgSO_2$, filtered then concentrated. The crude product obtained is recrystallised in absolute EtOH (m = 446 mg, yield = 72 %).

^{1}H NMR(400 MHz, $CDCl_3$): ppm 7.69 (d, 1H, aromatic H), 8.23 (d, 1H, aromatic H), 8.61 (s, 1H, aromatic H).

TLC: Rf: 0.26 (eluent: DCM/AcOEt 1/1)

b) Preparation of 1-chloro-2-methylsulphanyl-4-nitrobenzene, 8:

324 mg (1.51 mmol, 1 eq.) of **7** are dissolved in 15 mL of MeOH, and 170 mg (3.02 mmol, 2 eq.) of potassium carbonate are added. The mixture is heated under reflux for 20 min. then cooled to room temperature. 151 µL (2.42 mmol, 1.6 eq.) of methyl iodide are added. The mixture is stirred for 1 hour at room temperature, then 47 µL (0.75 mmol, 0.5 eq.) of methyl iodide are added. The solution is stirred for one night at room temperature. Once the water has been added, the insoluble matter formed is filtered then washed with water. The crude reaction product is subjected to chromatography over silica gel (eluent: 10/1 heptane/DCM) (m = 215 mg, yield = 70 %).

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.60 (s, 3H, SCH_3), 7.52 (d, 1H, aromatic H), 7.95 (d, 1H, aromatic H), 8.01 (s, 1H, aromatic H).

TLC: Rf: 0.43 (eluent: DCM/heptane 1/1)

Preparation of 4-chloro-3-methylsulphanylphenylamine, 9:

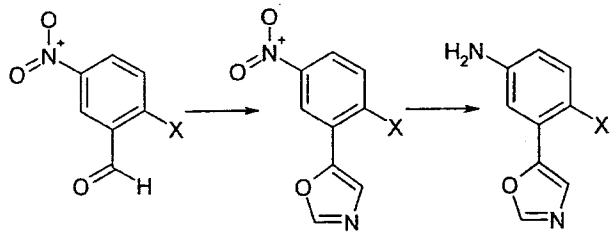
204 mg (1 mmol, 1 eq.) of **8** are dissolved in 2 mL of TFA. The solution is cooled to 0 °C and 123 mg (3.41 mmol, 3.4 eq.) of zinc powder are progressively added. The ice bath is removed and stirring is continued for 30 min. The mixture is rendered basic by adding an aqueous solution at 0 °C. The aqueous solution is extracted with DCM and the organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica gel (eluent: 1/1 heptane/DCM) (m = 150 mg, yield = 85 %).

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.45 (s, 3H, SCH_3), 3.60-3.80 (m, 2H, NH_2), 6.42 (d, 1H, aromatic H), 6.49 (s, 1H, aromatic H), 7.11 (d, 1H, aromatic H).

MS: 174.10^+ $(M+H)^+$, 215.13^+ $(M+H+CH_3CN)^+$

TLC: Rf = 0.21 (eluent: DCM/heptane 2/1)

Preparation 2: Preparation of 3-oxazol-5-ylphenylamine and 4-chloro-3-oxazol-5-yl-phenylamine for the synthesis of oxazole derivatives:



X = H
X = Cl

Method B → Example 67 → Example 69

Method F → Example 68 → Example 69

Preparation of 5-(3-nitrophenyl)oxazole

2.04 g (13.5 mmol, 1 eq.) of 3-nitrobenzaldehyde, 2.90 g (14.85 mmol, 1.1 eq.) of tosylmethyl isocyanide, 200 mL of MeOH and 200 mL of DME are introduced into a 1 L flask. 25 g of Amberlyst A26 OH- resin are added and the mixture is heated under reflux for 1 hour. The reaction medium is cooled to room temperature, then the resin is filtered over a frit and rinsed with methanol. After concentration to dryness, 2.56 g (yield = 100 %) of 5-(3-nitrophenyl)oxazole are obtained. The product is used without subsequent purification.

^{1}H NMR(400 MHz, $CDCl_3$): ppm 7.54 (s, 1H, aromatic H), 7.65 (t, 1H, aromatic H), 8.00 (d, 1H, aromatic H), 8.03 (s, 1H, $H_{oxazole}$), 8.22 (d, 1H, aromatic H), 8.53 (s, 1H, $H_{oxazole}$).

MS: 191^+ $(M+H)^+$

The product 5-(2-chloro-5-nitrophenyl)oxazole was prepared by the procedure described above.

^{1}H NMR(400 MHz, $CDCl_3$): ppm 7.69 (d, 1H, aromatic H), 7.95 (s, 1H, aromatic H), 8.08 (s, 1H, aromatic H), 8.15 (d, 1H, aromatic H), 8.74 (s, 1H, aromatic H).

MS: 225.19^+ $(M+H)^+$, 266.25^+ $(M+H+CH_3CN)^+$

TLC: Rf = 0.18 (eluent: heptane/AcOEt 4/1)

Preparation of 3-oxazol-5-ylphenylamine

1 g (5.26 mmol, 1 eq.) of 5-(3-nitrophenyl)oxazole and 10 mL of TFA are introduced into a 1 L flask. 1 g of zinc is carefully added in a plurality of batches. The mixture is stirred for 2 hours at room temperature then is poured over ice. Sodium hydroxide is slowly added

until the medium becomes basic, and the medium is extracted with diethyl ether. The organic phase is washed with a 1 M solution of HCl and the impurities are extracted with diethyl ether. The aqueous phase is again basified with sodium hydroxide and the product is extracted with diethyl ether. The organic phases are combined, dried over $MgSO_4$ and filtered. After concentration to dryness, 700 mg (yield = 83 %) of aniline 3-oxazol-5-yl-phenylamine are obtained, in the form of a beige solid. The product is used without subsequent purification.

^{1}H NMR(400 MHz, CD_3OD): ppm 6.74 (d, 1H, aromatic H), 7.05 (d, 1H, aromatic H), 7.09 (s, 1H, aromatic H), 7.18 (t, 1H, aromatic H), 7.41 (s, 1H, $H_{oxazole}$), 8.22 (s, 1H, $H_{oxazole}$).

MS: 161^+ $(M+H)^+$

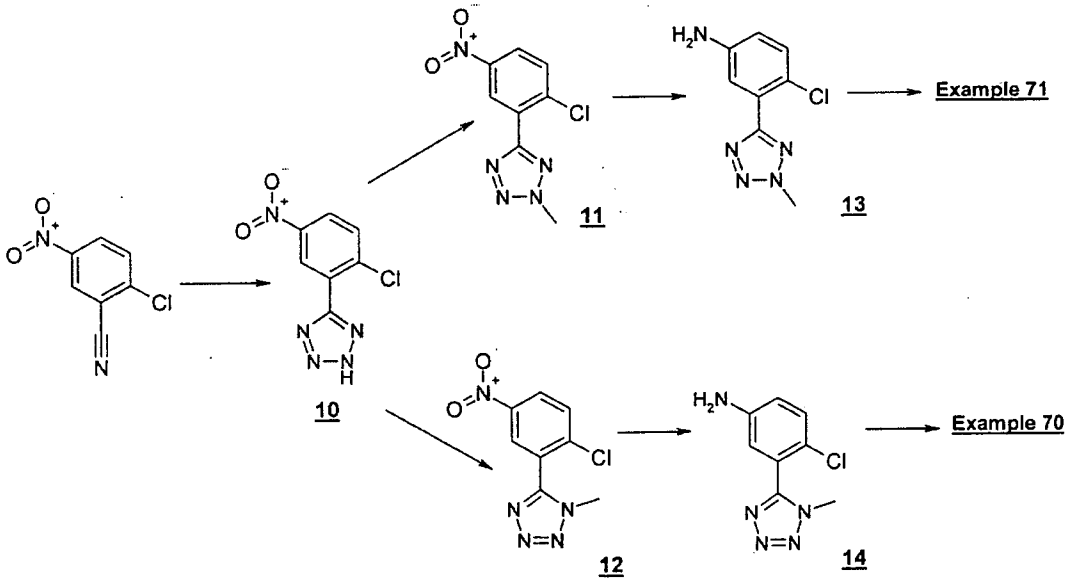
4-chloro-3-oxazol-5-ylphenylamine was prepared by the procedure described above.

^{1}H NMR(400 MHz, CD_3OD): ppm 6.73 (d, 1H, aromatic H), 7.17-7.26 (m, 2H, aromatic H), 7.72 (s, 1H, aromatic H), 8.29 (s, 1H, aromatic H).

MS: 195.14^+ $(M+H)^+$, 236.18^+ $(M+H+CH_3CN)^+$

TLC: Rf = 0.32 (eluent: heptane/AcOEt 1/1)

Preparation 3: Synthesis of 4-chloro-3-(2-methyl-2H-tetrazol-5-yl)phenylamine (isomer 1) and 4-chloro-3-(1-methyl-1H-tetrazol-5-yl)phenylamine (isomer 2), for the synthesis of methyltetrazole derivatives:



Preparation of 5-(2-chloro-5-nitrophenyl)-2H-tetrazole 10:

137 mg (0.750 mmol, 1 eq.) of 2-chloro-5-nitrobenzonitrile are dissolved in 8 mL of toluene, and 411 µl (1.5 mmol, 2 eq.) of tributyl tin azide are added to the reaction mixture. Then the mixture is heated under reflux of the toluene for one night. As the reaction is incomplete, 205 µl (0.75 mmol, 1 eq.) of azide are again added and the mixture is stirred under reflux for a further 5 hours. The mixture is then concentrated and 10 mL of HCl 2 N in Et_2O are added, the precipitate formed is filtered and washed with pentane and diethyl ether. 216 mg of product **10** are obtained (yield = 64 %).

^{1}H NMR(400 MHz, CD_3OD): ppm 7.94 (d, 1H, aromatic H), 8.43 (d, 1H, aromatic H), 8.78 (s, 1H, aromatic H)

MS: 224.12$^-$ $(M-H)^-$

TLC: Rf = 0.28 (eluent: DCM/MeOH 9/1)

Preparation of 5-(2-chloro-5-nitrophenyl)-2-methyltetrazole **11** and 5-(2-chloro-5-nitro-phenyl)-1-methyltetrazole **12:**

100 mg (0.382 mmol, 1 eq.) of 5-(2-chloro-5-nitrophenyl)-2H-tetrazole **10** are dissolved in 0.7 mL of CH_3CN and 0.2 mL of DMF. 29 µl (0.573 mmol, 1.5 eq.) of CH_3I and 63 mg (0.458 mmol, 1.2 eq.) of K_2CO_3 are added. The mixture is heated under reflux for 1 hour. The mixture is neutralised at room temperature with water and a saturated sodium bicarbonate solution. The aqueous phase is extracted with CH_2Cl_2, the organic phases collected are washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica gel (eluent: gradient 10/1 to 1/1 heptane/AcOEt) to give 150 mg of isomer **11** and 66 mg of isomer **12**(total yield= 76 %).

5-(2-chloro-5-nitrophenyl)-2-methyltetrazole (isomer 1), **11:**

^{1}H NMR(400 MHz, CDCl3): ppm 4.51 (s, 3H, CH3), 7.75 (d, 1H, aromatic H), 8.28 (d, 1H, aromatic H), 8.90 (s, 1H, aromatic H).

TLC: Rf = 0.55 (eluent: heptane/AcOEt 1/1)

5-(2-chloro-5-nitrophenyl)-1-methyltetrazole (isomer 2), **12:**

^{1}H NMR(400 MHz, $CDCl_3$): ppm 4.07 (s, 3H, CH3), 7.83 (d, 1H, aromatic H), 8.38-8.49 (m, 2H, aromatic H).

TLC: Rf = 0.35 (eluent: heptane/AcOEt 1/1)

The products **13** and **14** are obtained by reduction of the products **11** and **12** with zinc, in TFA (same procedure as for the synthesis of 4-chloro-3-methylsulphanyl-phenylamine, **9** from 1-chloro-2-methylsulphanyl-4-nitrobenzene, **8**).

4-chloro-3-(2-methyl-2H-tetrazol-5-yl)phenylamine (isomer 1), **13**

^{1}**H NMR**(400 MHz, $CDCl_3$): ppm 3.20-4.00 (m, 2H, NH2), 4.44 (s, 3H, CH3), 6.72 (d, 1H, aromatic H), 7.24-7.32 (m, 2H, aromatic H).

TLC: Rf = 0.29 (eluent: heptane/AcOEt 1/1)

4-chloro-3-(1-methyl-1H-tetrazol-5-yl)-phenylamine (isomer 2), **14**

^{1}**H NMR**(400 MHz, $CDCl_3$): ppm 3.30-3.90 (m, 2H, NH2), 4.01 (s, 3H, CH3), 6.79 (s, 1H, aromatic H), 6.85 (d, 1H, aromatic H), 7.30 (d, 1H, aromatic H).

TLC: Rf = 0.16 (eluent: heptane/AcOEt 1/1)

The products of Examples 70 and 71 are obtained from products **13** and **14** by employing method "B" below.

As mentioned hereinafter in the Examples, the products of formula (I) can be obtained in 5 different ways (hereinafter called Methods A), B), C), D) and E)):

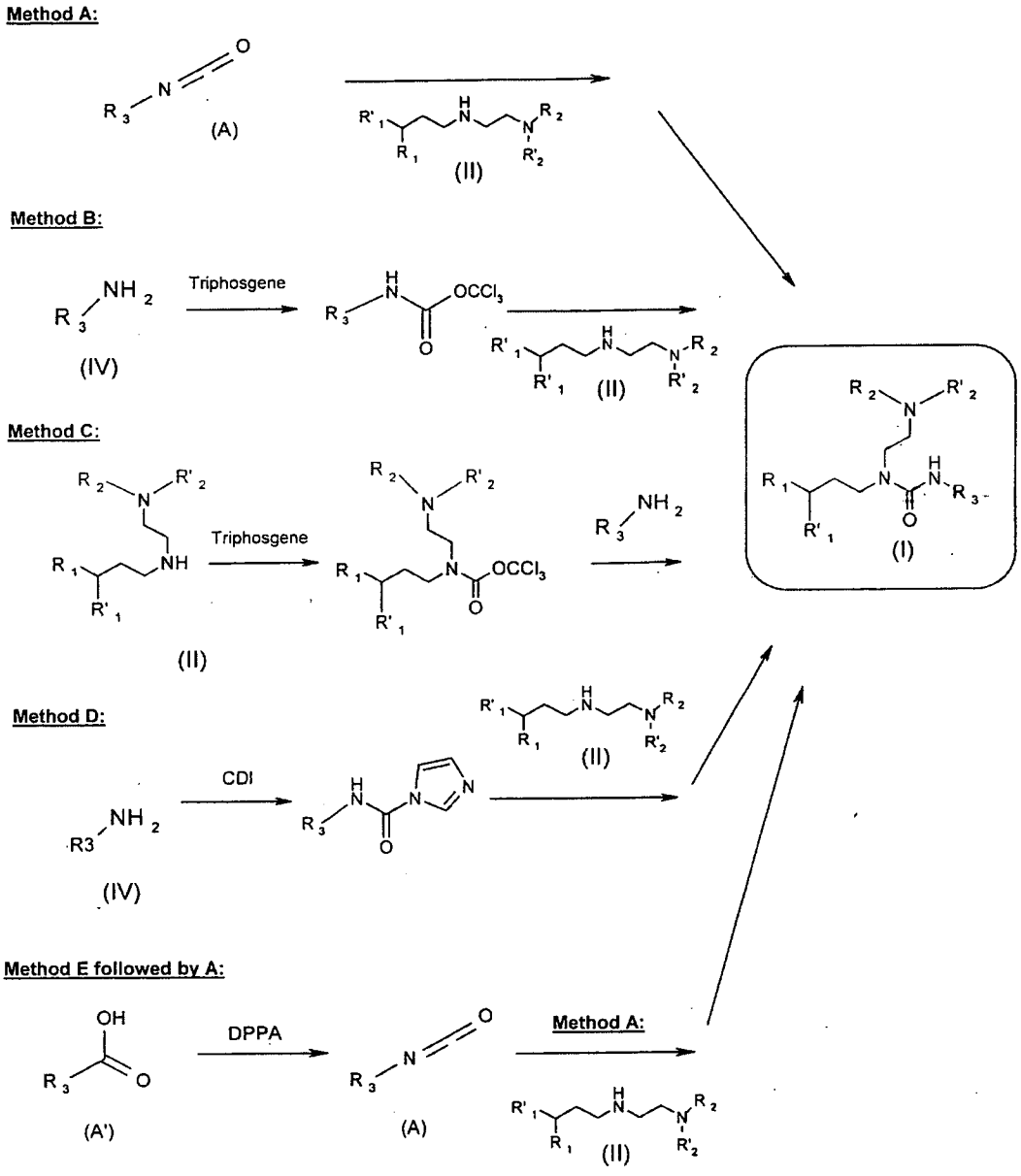
Method A). By action of an isocyanate of formula (A) on an amine of formula (II).

Method B). By action of triphosgene on a product of formula (IV) and addition of an amine of formula (II).

Method C). By action of triphosgene on an amine of formula (Ii) and addition of a product of formula (IV).

Method D). By action of carbonyl diimidazole (CDI) on a product of formula (IV) and addition of an amine of formula (II).

Method E). By action of diphenylphosphoryl azide (DPPA) on a product of formula (A') and addition of an amine of formula (II).



The methods are described by way of example with 3,3-(diphenylpropyl)(2-morpholin-4-yl-ethyl)amine as the amine of formula (II):

Method A). By action of an isocyanate on 3,3-diphenylpropyl-(2-morpholin-4-yl-ethyl)amine or other secondary amine.

1 eq. of 3,3-(diphenylpropyl)(2-morpholin-4-yl-ethyl)amine of formula (II) are dissolved in dichloromethane under an argon atmosphere in a 50 mL flask. 1.2 eq. of isocyanate of formula (A) are then added. The mixture is stirred for 2 hours at room temperature, then taken up in water. The aqueous phase is extracted with dichloromethane,

washed with brine, dried over $MgSO_4$, filtered and concentrated. The oil obtained is subjected to chromatography over silica gel in order to obtain the desired urea in yields of approximately 80 %.

Method B). By action of triphosgene on a product of formula (IV) and addition of 3,3-diphenylpropyl-(2-morpholin-4-yl-ethyl)amine or other secondary amine of formula (II).

0.6 eq. of triphosgene, 1 mL of CH_2Cl_2, 1 eq. of product of formula (IV) in 2 mL of CH_2Cl_2 and 1.2 eq. of diisopropylethylamine are introduced in succession into a flask placed under argon. The mixture is stirred for 1 hour at room temperature. 1.5 eq. of 3,3-diphenyl-propyl(2-morpholin-4-yl-ethyl)amine dissolved in 2 mL of CH_2Cl_2 are then added, and stirring is maintained for one night. The reaction medium is neutralised by a saturated solution of $NaHCO_3$ and dichloromethane. The organic phases are combined, then washed with a saturated NaCl solution. After drying over $MgSO_4$, filtration and concentration to dryness, the crude reaction product is purified by chromatography over silica gel, leading to the desired urea of formula (II) in yields of from 44 to 90 %.

Method C). By action of triphosgene on 3,3-diphenylpropyl(2-morpholin-4-ylethyl)-amine (or other secondary amine of formula (II) and addition of the product of formula (IV)).

The triphosgene (0.55 eq.) in solution in dichloromethane is introduced into a 10 mL flask under an argon atmosphere. 3,3-(Diphenylpropyl)(2-morpholin-4-ylethyl)amine (1 eq.) and DIEA (1.2 eq.) in solution in dichloromethane are introduced into a second 10 mL flask. The mixture of secondary amine + DIEA is added to the triphosgene solution at 0 °C. Stirring is maintained for 1 hour at 0 °C then 1 hour at room temperature. The carbamoyl chloride thus formed is added to a mixture (of formula IV) RNH_2 (1.1 eq.) + DIEA (1.4 eq.) in dichloromethane at 0 °C. Stirring is maintained for 1 hour at 0 °C then 20 hours at room temperature. Urea formation is controlled by TLC.

Once the reaction has ended, the aqueous phase is extracted with dichloromethane, and the combined organic phases are washed with brine then dried over $MgSO_4$ and finally evaporated.

The crude product thus obtained is purified by chromatography over a silica column or over a preparation plate with an eluent CH_2Cl_2/AcOEt or heptane/AcOEt, depending on the product obtained.

Method D). By action of CDI on a product of formula (IV) and addition of 3,3-diphenylpropyl-(2-morpholin-4-ylethyl)amine or other secondary amine of formula (II).

1.5 eq. of carbonyl diimidazole are dissolved in CH_2Cl_2, then 1 eq. of product of formula (IV), dissolved in CH_2Cl_2, is added dropwise under argon. A white precipitate appears. The suspension is stirred for 15 hours at room temperature. 1.2 eq. of 3,3-(diphenylpropyl)(2-morpholin-4-ylethyl)amine or other secondary amine of formula (II) in solution in CH_2Cl_2 are added to the reaction mixture. The solution, which has become clear again, is stirred for 5 hours at room temperature. A sodium bicarbonate solution is added and the aqueous phase is extracted with dichloromethane. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product obtained is subjected to chromatography over silica gel.

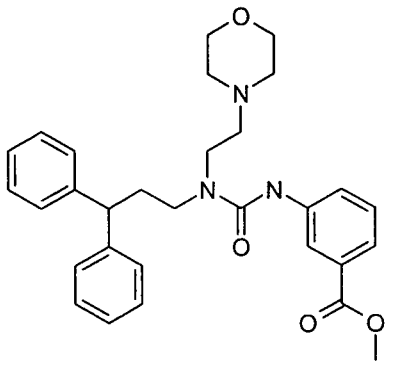
Method E). By action of diphenylphosphoryl azide (DPPA) on a carboxylic acid of formula (A') to form an isocyanate of formula (A) and addition of 3,3-diphenylpropyl-(2-morpholin-4-ylethyl)amine or other secondary amine of formula (II).

1 eq. of carboxylic acid formula (A') are dissolved in toluene. 1.1 eq. of triethylamine are added. After checking the basicity of the medium, 1.05 eq. of diphenylphosphoryl azide (DPPA) are added to the medium. The mixture is heated to 80 °C for 2 hours then 1.2 eq. of (3,3-diphenylpropyl)(2-morpholin-4-ylethyl)amine or other secondary amine of formula (II) are added. Heating is maintained for 1 hour. The mixture is then left to return to room temperature and stirring is maintained for one night. A saturated $NaHCO_3$ solution is added and the aqueous phase is extracted with DCM. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The products are purified over an alumina column, and the yields are approximately 40 %.

Non-limiting practical examples of the invention will now be described.

EXAMPLE 1

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester



0.36 g (1.11 mmol, 1 eq.) of 3,3-(diphenylpropyl)(2-morpholin-4-ylethyl)amine are dissolved in 27 mL of dichloromethane under an argon atmosphere in a 50 mL flask. 0.232 g (1.31 mmol, 1.2 eq.) of 3-(methoxycarbonyl)phenylisocyanate are then added. The mixture is stirred for 2 hours at room temperature, then taken up in water. The aqueous phase is extracted with dichloromethane, washed with brine, dried over $MgSO_4$, filtered and concentrated. The oil obtained is subjected to chromatography over silica gel (eluent: 4/1 DCM/AcOEt) in order to obtain the expected product in the form of white crystals (0.46 g, yield = 83 %).

This procedure is hereinafter called method "A".

^{1}H NMR (400 MHz, $CDCl_3$): ppm 2.41 (q, 2H, CH2), 2.73 (sl, 6H, 3xCH2), 3.32 (t, 2H, CH2), 3.39 (sl, 2H, CH2), 3.72 (sl, 4H, CH2), 3.93 (s, 3H, CH3), 3.98 (t, 1H, CH), 7.15-7.34 (m, 10H, aromatic H), 7.47 (t, 1H, aromatic H), 7.69 (d, 1H, aromatic H), 7.80 (d, 1H, aromatic H), 7.93 (s, 1H, aromatic H), 9.19-9.63 (sl, 1H, NH).

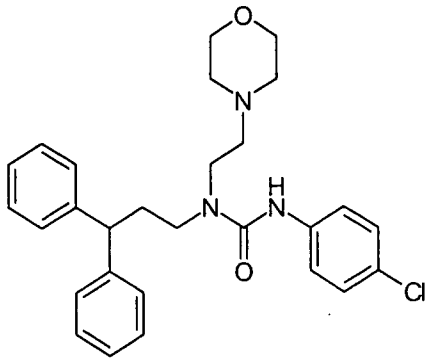
MS: 501.7^+ $(M+H)^+$

TLC: Rf = 0.15 (eluent: DCM/AcOEt 4/1)

EXAMPLE 2

3-(4-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



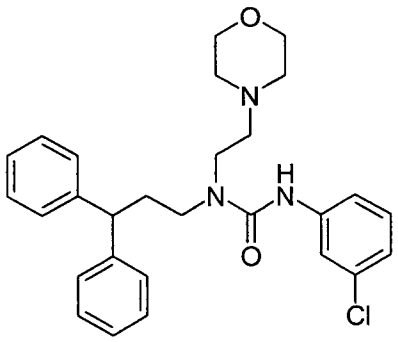
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.61 (m, 6H, 3xCH_2), 3.29 (t, 2H, CH_2), 3.39 (m, 2H, CH_2), 3.77 (m, 4H, 2xCH_2), 3.96 (t, 1H, CH), 7.13-7.37 (m, 14H, aromatic H), 9.15 (bs, 1H, NH).

MS: 478^+ $(M+H)^+$

EXAMPLE 3

3-(3-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



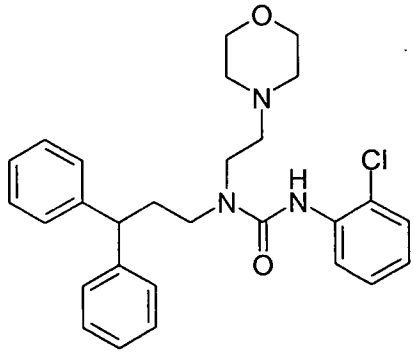
1H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.63 (m, 6H, 3xCH_2), 3.29 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.96 (t, 1H, CH), 6.98 (d, 1H, aromatic H), 7.15-7.36 (m, 12H, aromatic H), 7.47 (s, 1H, aromatic H), 9.22 (bs, 1H, NH).

MS: 478^+ $(M+H)^+$

EXAMPLE 4

3-(2-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



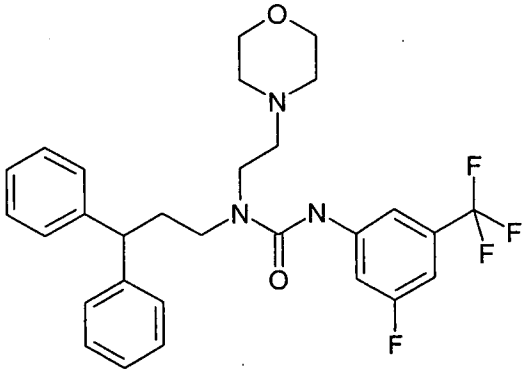
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.45 (q, 2H, CH_2), 2.56 (m, 6H, 3xCH_2), 3.34 (t, 2H, CH_2), 3.50 (m, 2H, CH_2), 3.69 (m, 4H, 2xCH_2), 3.99 (t, 1H, CH), 6.99 (t, 1H, aromatic H), 7.13-7.40 (m, 12H, aromatic H), 8.10 (d, 1H, aromatic H).

MS: 478^+ $(M+H)^+$

EXAMPLE 5

1-(3,3-diphenylpropyl)-3-(3-fluoro-5-trifluoromethylphenyl)-1-(2-morpholin-4-yl)urea

Method "A" was used to prepare the title compound having the following formula:



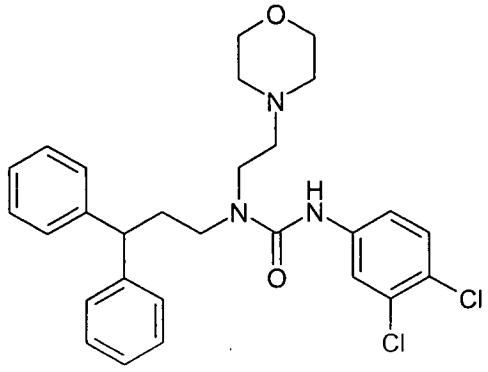
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.41 (q, 2H, CH_2), 2.67 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.41 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 6.95 (d, 1H, aromatic H), 7.15-7.24 (m, 2H, aromatic H), 7.25-7.37 (m, 9H, aromatic H), 7.59 (d, 1H, aromatic H), 9.63 (bs, 1H, NH).

MS: 530^+ $(M+H)^+$

EXAMPLE 6

3-(3,4-dichlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



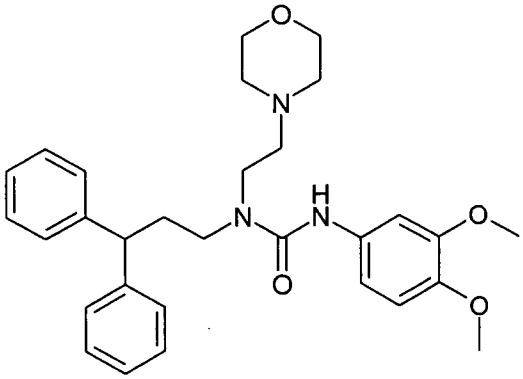
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.39 (q, 2H, CH_2), 2.67 (m, 6H, 3xCH_2), 3.31 (t, 2H, CH_2), 3.43 (m, 2H, CH_2), 3.82 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.15- 7.37 (m, 12H, aromatic H), 7.58 (s, 1H, aromatic H), 9.34 (bs, 1H, NH).

MS: 512^+ $(M+H)^+$

EXAMPLE 7

3-(3,4-dimethoxyphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



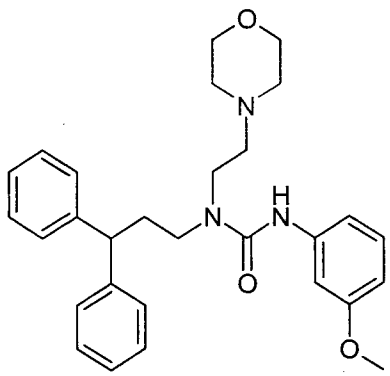
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.41 (q, 2H, CH_2), 2.63 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.79 (m, 4H, 2x CH_2), 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.97 (t, 1H, CH), 6.75 (dd, 1H, aromatic H), 6.80 (d, 1H, aromatic H), 7.13-7.23 (m, 3H, aromatic H), 7.25-7.34 (m, 8H, aromatic H), 8.95 (bs, 1H, NH).

MS: 504^+ $(M+H)^+$

EXAMPLE 8

1-(3,3-diphenylpropyl)-3-(3-methoxyphenyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



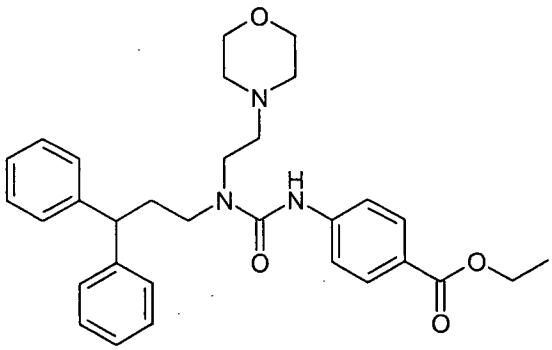
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.41 (q, 2H, CH_2), 2.62 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.81 (m, 7H, 2xCH_2, OCH_3), 3.98 (t, 1H, CH), 6.58 (dd, 1H, aromatic H), 6.89 (d, 1H, aromatic H), 7.11 (s, 1H, aromatic H), 7.15-7.35 (m, 11H, aromatic H), 9.05 (bs, 1H, NH).

MS: 474^+ $(M+H)^+$

EXAMPLE 9

4-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid ethyl ester

Method "A" was used to prepare the title compound having the following formula:



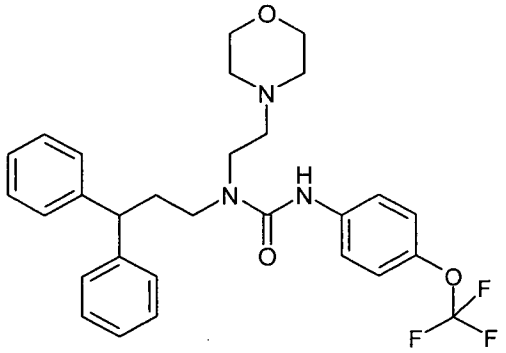
^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.40 (t, 3H, CH_3), 2.41 (q, 2H, CH_2), 2.64 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.81 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 4.37 (q, 2H, CH_2), 7.16-7.25 (m, 2H, aromatic H), 7.26-7.36 (m, 8H, aromatic H), 7.45 (d, 2H, aromatic H), 7.98 (d, 2H, aromatic H), 9.45 (bs, 1H, NH).

MS: 516^+ $(M+H)^+$

EXAMPLE 10

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(4–trifluoromethoxyphenyl)urea

Method "A" was used to prepare the title compound having the following formula:



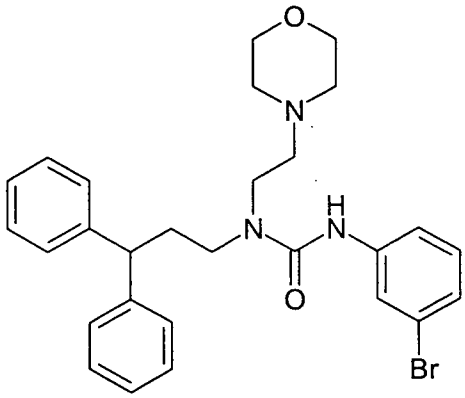
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.60 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.38 (m, 2H, CH_2), 3.77 (m, 4H, 2xCH_2), 3.96 (t, 1H, CH), 7.15 (d, 2H, aromatic H), 7.17-7.23 (m, 2H, aromatic H), 7.25-7.35 (m, 8H, aromatic H), 7.39 (d, 2H, aromatic H), 9.26 (bs, 1H, NH).

MS: 528^+ $(M+H)^+$

EXAMPLE 11

3-(3-Bromophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



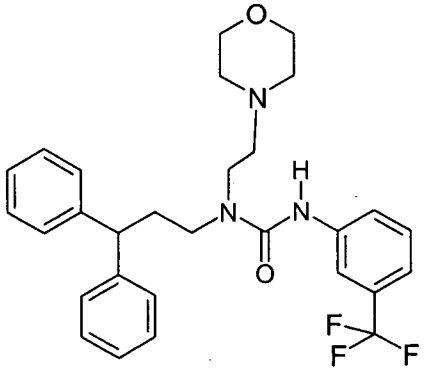
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.61 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.36 (m, 2H, CH_2), 3.78 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 7.10-7.17 (m, 2H, aromatic H), 7.17-7.23 (m, 2H, aromatic H), 7.26-7.35 (m, 9H, aromatic H), 7.62 (s, 1H, aromatic H), 9.20 (bs, 1H, NH).

MS: 523^+ $(M+H)^+$

EXAMPLE 12

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-trifluoromethylphenyl)urea

Method "A" was used to prepare the title compound having the following formula:



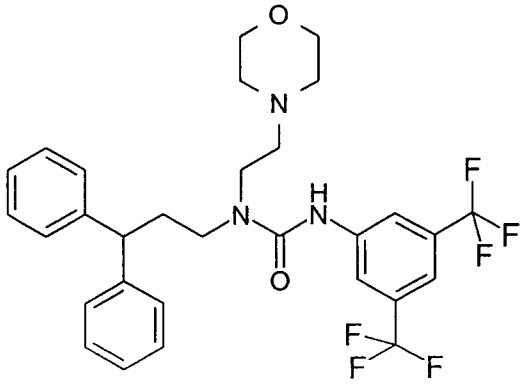
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.61 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.80 (t, 4H, 2xCH_2), 3.99 (t, 1H, CH), 7.10-7.35 (m, 11H, aromatic H), 7.40 (t, 1H, aromatic H), 7.62 (d, 2H, aromatic H).

MS: 512^+ $(M+H)^+$

EXAMPLE 13

3-(3,5-bis-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



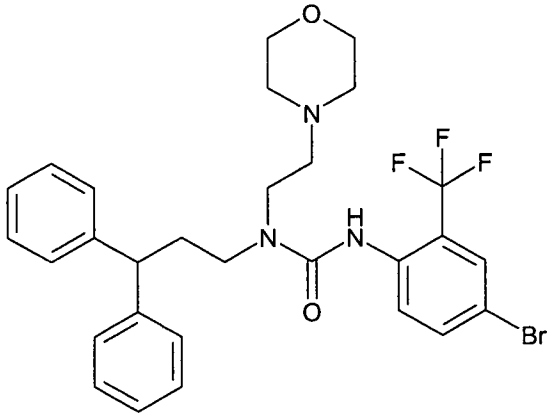
^{1}H NMR(400 MHz, $CDCl_3$) ppm 7.90 (s, 2H, aromatic H), 7.50 (s, 1H, aromatic H), 7.00-7.35 (m, 10H, aromatic H), 3.99 (t, 1H, CH), 3.80 (t, 4H, 2xCH_2), 3.40 (m, 2H, CH_2), 3.30 (t, 2H, CH_2), 2.61 (m, 6H, 3xCH_2), 2.40 (q, 2H, CH_2).

MS: 580^+ $(M+H)^+$

EXAMPLE 14

3-(4-bromo-6-trifluoromethyl-phenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



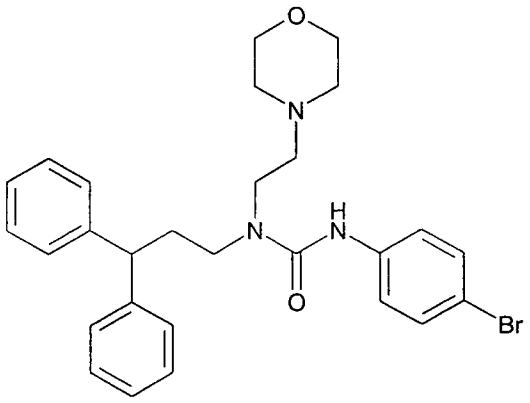
MS: 590.3^+ $(M+H)^+$

TLC: Rf = 0.27 (eluent: DCM/AcOEt 4/1)

EXAMPLE 15

3-(4-bromophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:

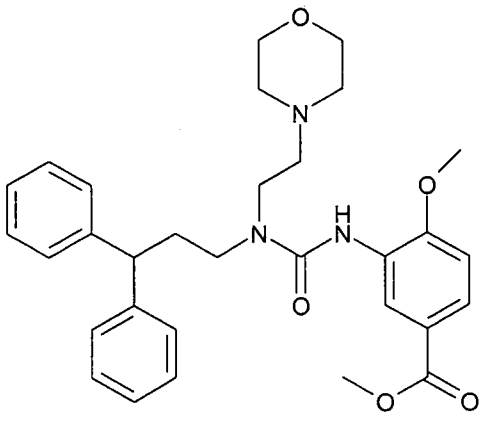


MS: 524.2^{+} $(M+H)^{+}$

TLC: Rf = 0.38 (eluent: 2/1 DCM/AcOEt)

EXAMPLE 16

4-methoxy-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester



33 mg (0.11 mmol, 0.6 eq.) of triphosgene and 200 μL of CH_2Cl_2 are introduced in succession into a flask placed under argon. A solution of 34 mg (0.19 mmol, 1 eq.) of 3-amino-4-methoxybenzoic acid methyl ester and 29.5 μL (0.334 mmol, 1.8 eq.) of diisopropylethylamine, in 200 μL of CH_2Cl_2 is added to the mixture. The mixture is stirred for 1 hour at room temperature. 133 eq. (0.41 mmol, 2.2 eq.) of secondary amine dissolved in 400 μL of CH_2Cl_2 are then added, and stirring is maintained for one night. The reaction medium is neutralised by a saturated solution of $NaHCO_3$ and dichloromethane. The organic phases are combined, then washed with a saturated NaCl solution. After drying over $MgSO_4$, filtration and concentration to dryness, the crude reaction product is purified by column chromatography over silica gel (eluent: DCM/AcOEt 4/1 to 1/1) leading to the desired urea in a yield of 90 %.

This procedure is hereinafter called method "B".

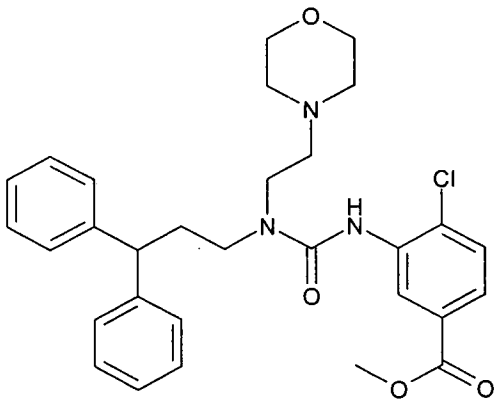
MS: 532.1^+ $(M+H)^+$

TLC: Rf = 0.18 (eluent: DCM/AcOEt 2/1)

EXAMPLE 17

4-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester

Method "B" was used to prepare the title compound having the following formula:



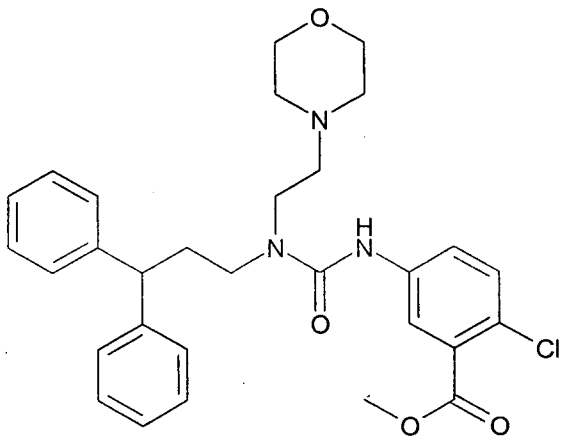
MS: 536.0^+ $(M+H)^+$

TLC: Rf = 0.15 (eluent: DCM/AcOEt 4/1)

EXAMPLE 18

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester

Method "B" was used to prepare the title compound having the following formula:



^{1}H NMR (400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH2), 2.53-2.79 (m, 6H, CH2), 3.24-3.46 (m, 4H, CH2), 3.67-3.90 (m, 4H, CH2), 3.94 (s, 3H, CH3), 3.97 (t, 1H, CH), 7.16-7.40 (m, 11H, aromatic H), 7.59-7.69 (m, 1H, aromatic H), 7.84 (s, 1H, aromatic H), 9.30-9.90 (m, 1H, NH).

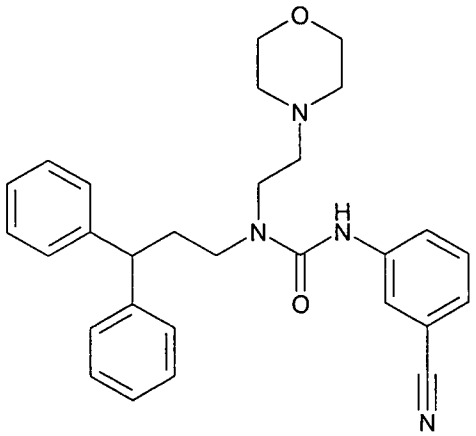
MS: 536.0^+ $(M+H)^+$

TLC: Rf = 0.21 (eluent: DCM/AcOEt 4/1)

EXAMPLE 19

3-(3-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$) ppm 2.40 (q, 2H, CH_2), 2.61 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.80 (t, 4H, 2xCH_2), 3.99 (t, 1H, CH), 7.10-7.50 (m, 12H, aromatic H), 7.53 (d, 1H, aromatic H), 7.78 (s, 1H, aromatic H).

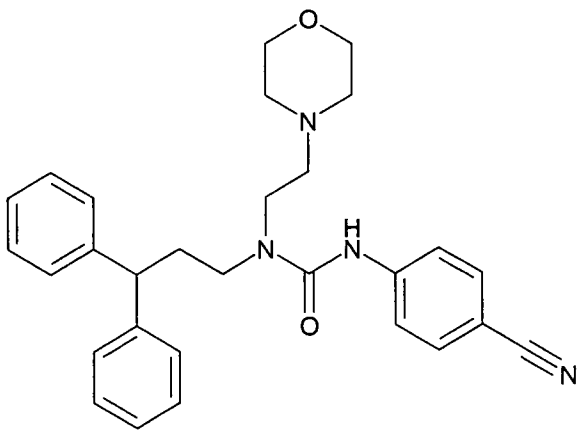
MS: 469.0^+ $(M+H)^+$

TLC: Rf = 0.21 (eluent: DCM/AcOEt 4/1)

EXAMPLE 20

3-(4-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



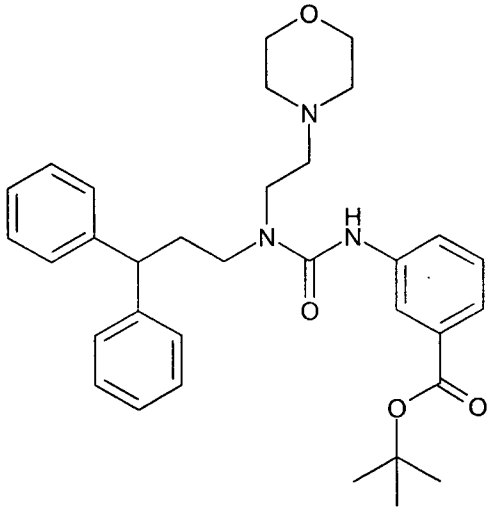
MS: 469.0^+ $(M+H)^+$

TLC: Rf = 0.21 (eluent: DCM/AcOEt 4/1)

EXAMPLE 21

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester

Method "B" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.51 (s, 9H, CH3), 2.40 (q, 2H, CH2), 2.61 (m, 6H, CH2), 3.31 (t, 2H, CH2), 3.36 (m, 2H, CH2), 3.82 (sl, 4H, CH2), 3.98 (t, 1H, CH), 7.16-7.23 (m, 2H, aromatic H), 7.26-7.32 (m, 8H, aromatic H), 7.37 (t, 1H, aromatic H), 7.66 (d, 1H, aromatic H), 7.77 (s, 1H, aromatic H), 7.86 (d, 1H, aromatic H), 9.40-9.53 (sl, 1H, NH).

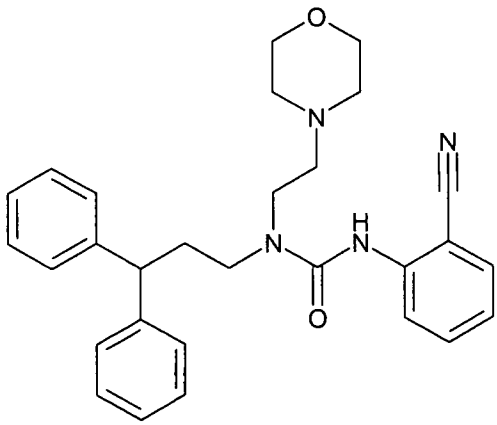
MS: 544.0^+ $(M+H)^+$

TLC: Rf = 0.16 (eluent: DCM/AcOEt 4/1)

EXAMPLE 22

3-(2-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



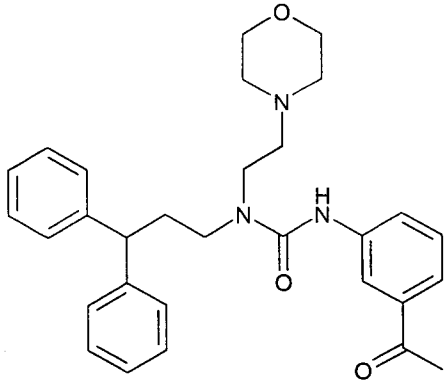
MS: 469.0^+ $(M+H)^+$

TLC: Rf = 0.24 (eluent: DCM/AcOEt 2/1)

EXAMPLE 23

3-(3-acetylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



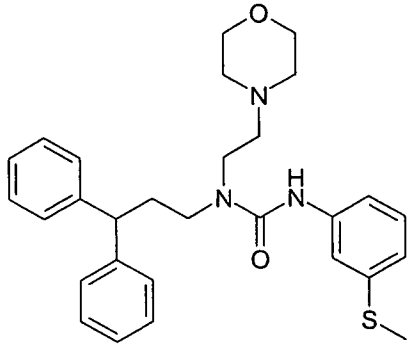
MS: 486.0^+ $(M+H)^+$

TLC: Rf = 0.10 (eluent: DCM/AcOEt 2/1)

EXAMPLE 24

1-(3,3-diphenylpropyl)-3-(3-methylsulphanylphenyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.41 (q, 2H, CH2), 2.49 (s, 3H, CH3), 2.57 (bs, 6H, CH2), 3.29 (t, 2H, CH2), 3.35 (t, 2H, CH2), 3.77 (bs, 4H, CH2), 3.98 (t, 1H, CH), 6.93 (d, 1H, aromatic H), 7.13 (d, 1H, aromatic H), 7.16-7.24 (m, 3H, aromatic H), 7.27-7.33 (m, 8H, aromatic H), 7.40 (s, 1H, aromatic H), 8.92-9.15 (bs, 1H, NH).

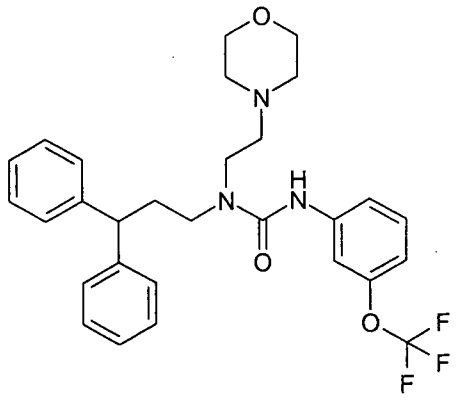
MS: 490^+ $(M+H)^+$

TLC: Rf = 0.39 (eluent: DCM/AcOEt 1/1)

EXAMPLE 25

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3–trifluoromethoxyphenyl)urea

Method "B" was used to prepare the title compound having the following formula:



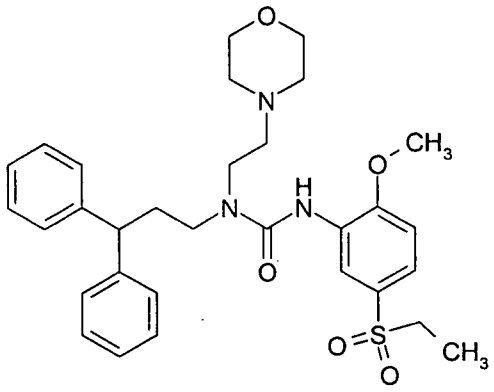
MS: 528.20^+ $(M+H)^+$

TLC: Rf = 0.31 (eluent: DCM/AcOEt 4/1)

EXAMPLE 26

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3–ethylsulphonyl-6-methoxyphenyl)urea

Method "B" was used to prepare the title compound having the following formula:

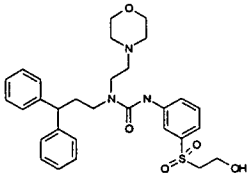
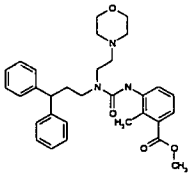
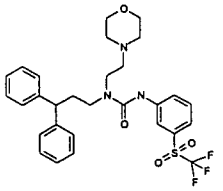
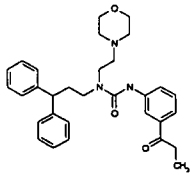


MS: 566.2^{+} $(M+H)^{+}$

TLC: Rf = 0.07 (eluent: DCM/AcOEt 4/1)

EXAMPLES 27 TO 30

Method "B" was used to prepare the products shown in the following table

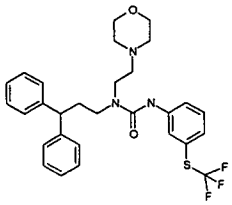
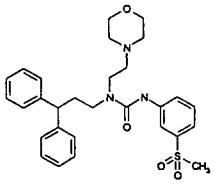
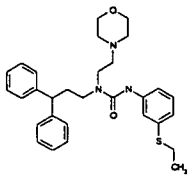
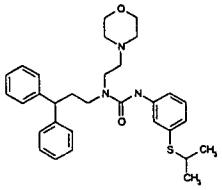
Formula	MS	Rf =	EXAMPLE
	553.2^{+}	0.17 (95/5 DCM/MeOH)	Example 27
	516.2^{+}	0.15 (4/1 DCM/AcOEt)	Example 28
	576.1^{+}	0.24 (4/1 DCM/AcOEt)	Example 29
	500.0^{+}	0.16 (4/1 DCM/AcOEt)	Example 30

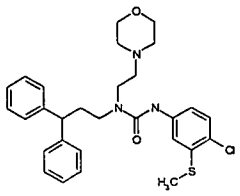
Product of example 30:

^{1}H NMR(400 MHz, $CDCl_3$) ppm 1.24 (t, 3H, CH3), 2.40 (q, 2H, CH2), 2.63 (m, 6H, CH2), 3.02 (q, 2H, $COCH_2$), 3.32 (t, 2H, CH2), 3.41 (m, 2H, CH2), 3.82 (m, 4H, CH2), 3.97 (t, 1H, CH), 7.16-7.24 (m, 2H, aromatic H), 7.25-7.35 (m, 8H, aromatic H), 7.39 (t, 1H, aromatic H), 7.61 (d, 1H, aromatic H), 7.74 (d, 1H, aromatic H), 7.92 (s, 1H, aromatic H), 9.43 (bs, 1H, NH).

EXAMPLES 31 TO 35

Method "B" was used to prepare the products shown in the following table:

Formula	MS	Rf =	EXAMPLE
	544.2^+	0.41 (4/1 DCM/AcOEt)	Example 31
	522.2^+	0.14 (95/5 DCM/MeOH)	Example 32
	504.5^+	0.36 (4/1 DCM/AcOEt)	Example 33
	518.5^+	0.31 (4/1 DCM/AcOEt)	Example 34

	524.4^+	0.17 (4/1 DCM/AcOEt)	Example 35

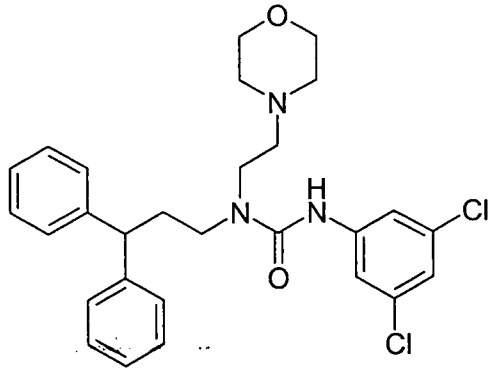
Product of example 35.

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH2), 2.50 (s, 3H, SCH3), 2.54-2.68 (m, 6H, CH2), 3.30 (t, 2H, CH2), 3.34-3.42 (m, 2H, CH2), 3.73-3.82 (m, 4H, CH2), 3.98 (t, 1H, CH), 7.00 (d, 2H, aromatic H), 7.16-7.35 (m, 10H, aromatic H), 7.43 (s, 1H, aromatic H), 8.95-9.40 (m, 1H, NH).

EXAMPLE 36

3-(3,5-dichlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



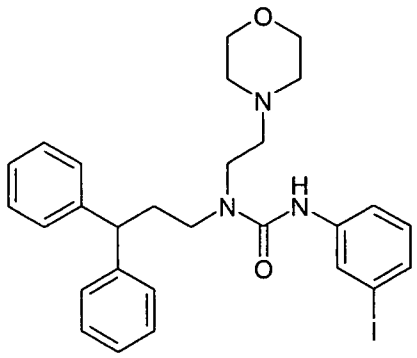
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.38 (q, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.38 (bs, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.95 (t, 1H, CH), 7.00 (s, 1H, aromatic H), 7.20 (m, 2H, aromatic H), 7.30 (m, 10H, aromatic H), 9.30 (bs, 1H, NH).

MS: 512.0^+ $(M+H)^+$

EXAMPLE 37

1-(3,3-diphenylpropyl)-3-(3-iodophenyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



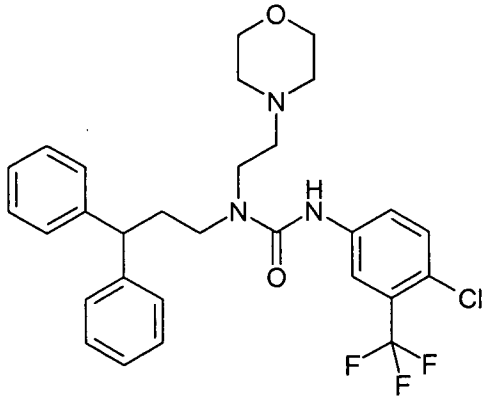
H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.62 (m, 6H, 3xCH_2), 3.37 (m, 2H, CH_2), 3.30 (t, 2H, CH_2), 3.78 (m, 4H, 2xCH_2), 3.96 (t, 1H, CH), 7.00 (t, 1H, aromatic H), 7.16-7.24 (m, 2H, aromatic H), 7.26-7.40 (m, 10H, aromatic H), 7.77 (s, 1H, aromatic H), 9.14 (bs, 1H, NH).

MS: 570.0^+ $(M+H)^+$

EXAMPLE 38

3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.64 (m, 6H, 3xCH_2), 3,32 (t, 2H, CH_2), 3.41 (m, 2H, CH_2), 3.79 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 7.17-7.23 (m, 2H, aromatic H),

7.26-7.35 (m, 8H, aromatic H), 7.40 (d, 1H, aromatic H), 7.64 (m, 2H, aromatic H), 9.58 (bs, 1H, H11).

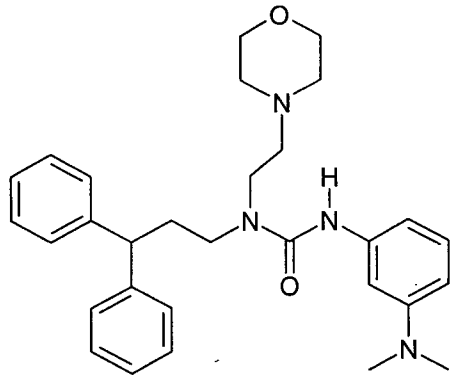
MS: 546^+ $(M+H)^+$

TLC: Rf = 0.35 (eluent: DCM/AcOEt 4/1)

EXAMPLE 39

3-(3-dimethylaminophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:

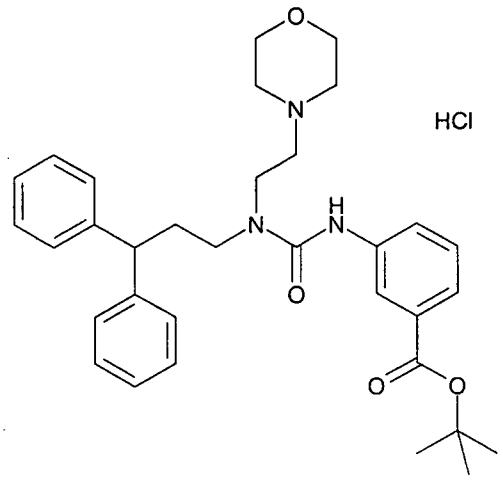


^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.60 (m, 6H, 3xCH_2), 3.00 (d, 6H, 2xNCH_3), 3.30 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.70 (m, 4H, 2xCH_2), 3.99 (t, 1H, CH), 7.15-7.35 (m, 14H, aromatic H).

MS: 487.0^+ $(M+H)^+$

EXAMPLE 40

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester hydrochloride (of the product described in example 21)



217 mg (0.41 mmol, 1 eq.) of product obtained in example 21 are dissolved in 3 mL of dichloromethane. 310 µL (0.41 mmol, 1 eq.) of 2N HCl in diethyl ether are added. The mixture is stirred for 10 sec then concentrated to dryness. The residue is taken up in the minimum of dichloromethane (2 mL) then 3 mL of diethyl ether are added to precipitate the product. The insoluble matter is filtered then washed with diethyl ether (m = 224 mg, yield = 96 %).

This procedure is hereinafter called method "F".

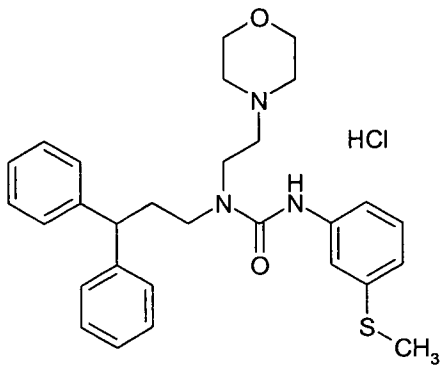
^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.61 (s, 9H, CH3), 2.07-2.21 (m, 2H, CH2), 2.36-2.54 (m, 2H, CH2), 2.79-3.02 (m, 2H, CH2), 3.05-3.28 (m, 2H, CH2), 3.31-3.60 (m, 2H, CH2), 3.80-4.07 (m, 5H, CH2+CH), 4.12-4.28 (m, 2H, CH2), 6.78-6.96 (m, 1H, aromatic H), 7.17-7.38 (m, 10H, aromatic H), 7.55-7.63 (m, 1H, aromatic H), 7.67 (d, 1H, aromatic H), 7.80-7.90 (m, 1H, aromatic H).

MS: 544.21^+ $(M+H-HCl)^+$

EXAMPLE 41

Hydrochloride of the product of example 24

Method "F", but using 3 eq. of HCl instead of 1 eq., was used to prepare the title compound having the following formula:



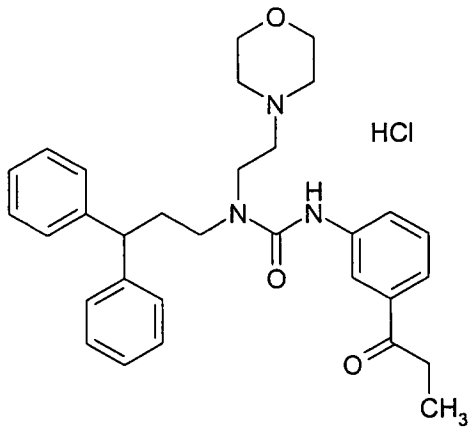
^{1}H NMR(400 MHz, DMSO): ppm 2.33 (q, 2H, CH2), 2.43 (s, 3H, SCH3), 2.96-3.13 (m, 2H, CH2), 3.15-3.30 (m, 4H, CH2), 3.34-3.50 (m, 2H, CH2), 3.64-3.82 (m, 4H, CH2), 3.87-3.98 (m, 2H, CH2), 4.00 (t, 1H, CH), 6.84 (d, 1H, aromatic H), 7.12-7.21 (m, 3H, aromatic H), 7.23-7.40 (m, 9H, aromatic H), 7.47 (s, 1H, aromatic H), 8.38 (bs, 1H, NH), 10.95-11.13 (m, 1H, NH^+Cl^-).

MS: 490^+ $(M+H-HCl)^+$

EXAMPLE 42

Hydrochloride of the product of Example 30

Method "F", but using 3 eq. of HCl instead of 1 eq., was used to prepare the title compound having the following formula:

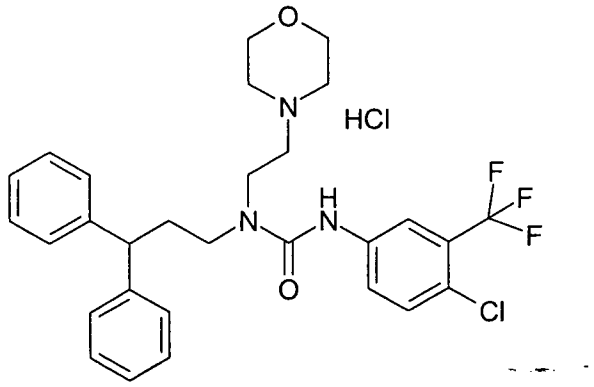


^{1}H NMR(400 MHz, CD_3OD): ppm 1.20 (t, 3H, CH3), 2.45-2.55 (m, 2H, CH2), 3.06 (q, 2H, $COCH_2$), 3.10-3.20 (m, 2H, CH2), 3.25-3.35 (m, 2H, CH2), 3.38-3.48 (m, 2H, CH2), 3.55-3.65 (m, 2H, CH2), 3.66-3.82 (m, 4H, CH2), 4.00-4.12 (m, 3H, CH+CH2), 7.20 (t, 2H, aromatic H), 7.26-7.40 (m, 8H, aromatic H), 7.44 (t, 1H, aromatic H), 7.63 (d, 1H, aromatic H), 7.72 (d, 1H, aromatic H), 8.00 (s, 1H, aromatic H).

EXAMPLE 43

3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea hydrochloride (product described in example 38)

Method "F", but using 3 eq. of HCl instead of 1 eq., was used to prepare the title compound having the following formula:



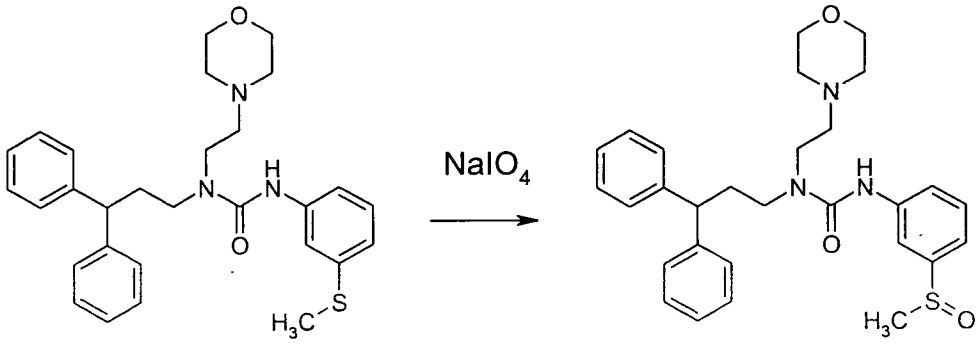
^{1}H NMR(400 MHz, CD_3OD): ppm 2.48 (q, 2H, CH2), 3.05-3.22 (m, 2H, CH2), 3.24-3.32 (m, 2H, CH2), 3.44 (t, 2H, CH2), 3.51-3.65 (m, 2H, CH2), 3.70 (t, 2H, CH2), 3.71-3.83 (m, 2H, CH2), 3.98-4.15 (m, 3H, CH+CH2), 7.19 (t, 2H, aromatic H), 7.24-7.38 (m, 8H, aromatic H), 7.51 (d, 1H, aromatic H), 7.64 (d, 1H, aromatic H), 7.87 (s, 1H, aromatic H).

MS: 546.03^+ $(M+H-HCl)^+$

EXAMPLE 44

1-(3,3-diphenylpropyl)-3-(3-methanesulphinylphenyl)-1-(2-morpholin-4-ylethyl)urea

Starting from the product of Example 24, the corresponding sulphoxide was prepared: 1-(3,3-diphenylpropyl)-3-(3-methanesulphinylphenyl)-1-(2-morpholin-4-ylethyl)urea, using the following reaction scheme:



50 mg (0.102 mmol, 1 eq.) of product obtained in Example 24 are dissolved hot in 0.6 mL of methanol, then the solution is cooled to 0 °C. 33 mg (0.153 mmol, 1.5 eq.) of $NaIO_4$ dissolved in 0.3 mL of H_2O are added. The suspension is stirred for 6 hours from 0 °C to room temperature then for 16 hours at room temperature. The suspension is taken up in water and extracted with dichloromethane. The organic phase is washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica gel (eluent: 95/5 dichloromethane/methanol) (m = 49 mg, yield = 94 %).

This procedure is hereinafter called method "G".

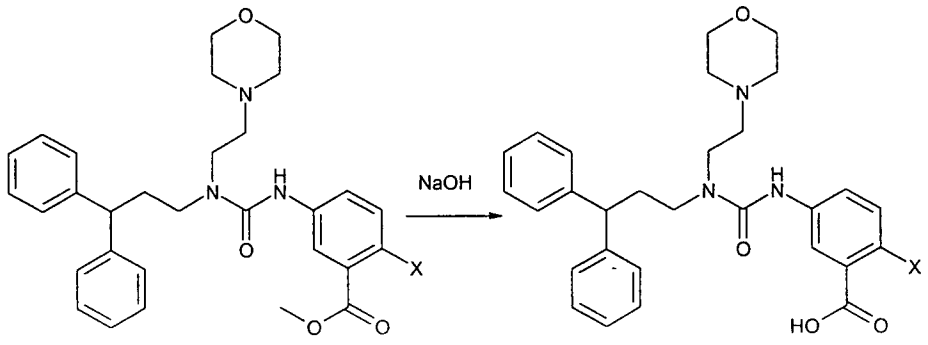
MS: 506.3^+ $(M+H)^+$

TLC: Rf = 0.38 (eluent: DCM/MeOH 9/1)

EXAMPLES 45-46

Proceeding in the manner described in the following scheme, 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid (Example 45) is prepared from 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester (obtained in Example 1) and 2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)-

ureido]benzoic acid (Example 46) is obtained from 2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester (obtained in Example 18):



X=H, **Example 1** X=H, **Example 45**

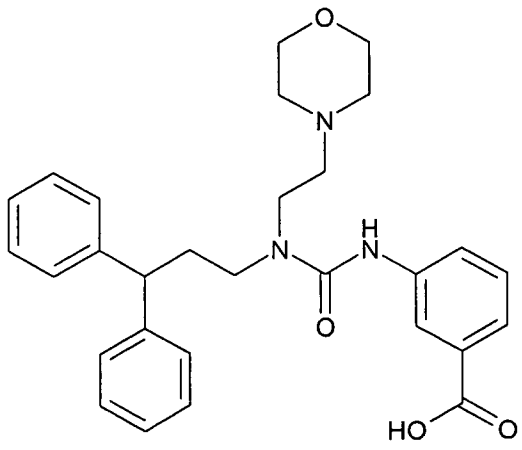
X=Cl, **Example 18** X=Cl, **Example 46**

EXAMPLE 45

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid

60 mg (0.12 mmol, 1 eq.) of 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)-ureido]benzoic acid methyl ester (obtained in Example 1) are dissolved in 2 mL of methanol in a 10 mL flask equipped with a condenser. 240 µL of 1 N (0.24 mmol, 2 eq.) sodium hydroxide are added to the mixture and the mixture is heated under reflux for 2 hours 30 min. The methanol is evaporated and water is added. This aqueous solution is acidified with 1 N HCl to pH=6, then extracted with ethyl acetate. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. 53 mg of a white solid are obtained (yield = 92 %).

This procedure is hereinafter called method "H".



^{1}H NMR(400 MHz, CD_3OD): ppm 2.44 (q, 2H, CH2), 2.85 (sl, 6H, CH2), 3.38 (t, 2H, CH2), 3.54 (t, 2H, CH2), 3.68 (t, 4H, CH2), 4.03 (t, 1H, CH), 7.14-7.36 (m, 10H, aromatic H), 7.39 (t, 1H, aromatic H), 7.64 (d, 1H, aromatic H), 7.72(d, 1H, aromatic H), 8.03 (s, 1H, aromatic H).

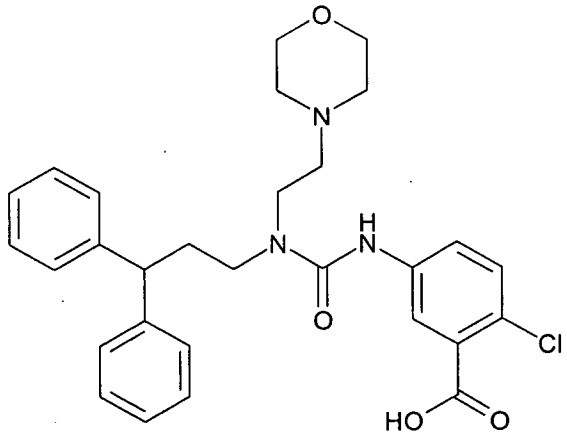
MS: 488.0^+ $(M+H)^+$

TLC: Rf = 0.32 (eluent: DCM/MeOH/NH_4OH 90/10/0.1)

EXAMPLE 46

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid

Method "H" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, CD_3OD): ppm 2.45 (q, 2H, CH2), 3.16-3.23 (m, 2H, CH2), 3.17-3.32 (m, 4H, CH2), 3.41 (t, 2H, CH2), 3.63-3.73 (m, 2H, CH2), 3.83-3.95 (m, 4H, CH2), 4.04 (t, 1H, CH), 7.18 (t, 2H, aromatic H), 7.26-7.41 (m, 9H, aromatic H), 7.54 (d, 1H, aromatic H), 7.85 (s, 1H, aromatic H).

MS: 521.9^+ $(M+H)^+$

TLC: Rf = 0.48 (eluent: DCM/MeOH 4/1)

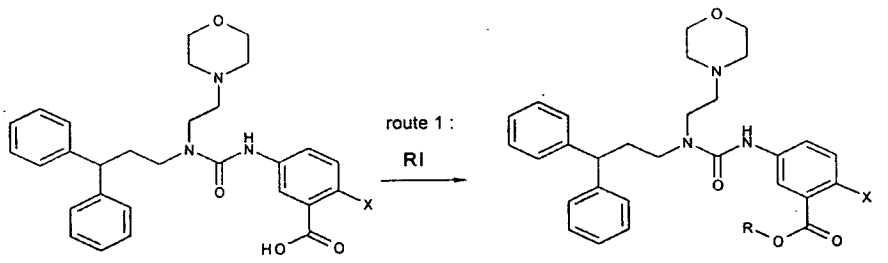
EXAMPLES 47-54

Proceeding as indicated in the following scheme, and starting from:

the product obtained in Example 45, 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid and

the product obtained in Example 46, 2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid,

a plurality of esters are prepared by two different methods called *method "I", route 1* (Examples 47-50) and *method "I", route 2* (Examples 52-54):

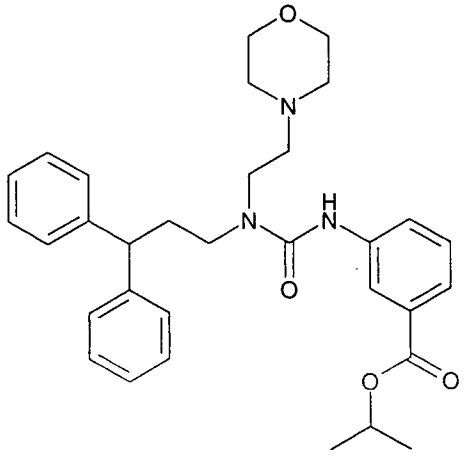


EXAMPLE 47

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester

200 mg (0.41 mmol, 1 eq.) of product of Example 45 are dissolved in 2 mL of acetone and 2 mL of dry DMF under argon. 283 mg (2.05 mmol, 5 eq.) of K_2CO_3 and 328 μL (3.28 mmol, 8 eq.) of 2-iodopropane, the mixture is heated under reflux for 2 hours. The medium is then concentrated and taken up in water and the aqueous phase is extracted with ethyl acetate. The organic phase is washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The oil obtained is freed from DMF by entraining the DMF to the rotary evaporator with ethyl acetate, then dried with a vane pump. The product is obtained in the form of white crystals (m = 214 mg, yield = 99 %).

This method is hereinafter identified as: *Method I route 1*. This method was used to prepare the title compound having the following formula:



MN ^{1}H (400 MHz, $CDCl_3$): ppm 1.38 (d, 6H, CH3), 2.40 (q, 2H, CH2), 2.52 (m, 6H, CH2), 3.32 (t, 2H, CH2), 3.37 (m, 2H, CH2), 3.83 (t, 4H, CH2), 3.98 (t, 1H, CH), 5.28 (sept, 1H, CH), 7.16-7.23 (m, 2H, aromatic H), 7.26-7.34 (m, 8H, aromatic H), 7.38 (t, 1H, aromatic H), 7.69 (d, 1H, aromatic H), 7.85 (s, 1H, aromatic H), 7.94 (d, 1H, aromatic H).

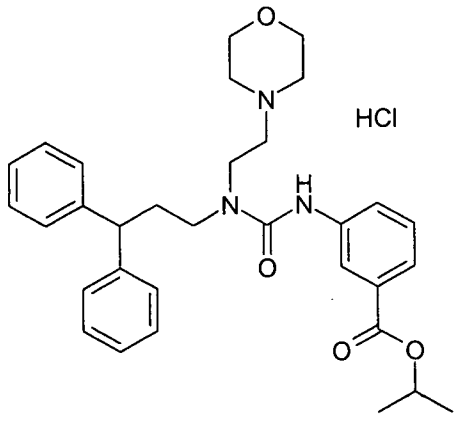
MS: 530.1^+ $(M+H)^+$

TLC: Rf = 0.48 (eluent: DCM/AcOEt 1/1)

EXAMPLE 48

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester hydrochloride

Starting from the product obtained in Example 47, method "F" was used to prepare the title compound having the following formula:



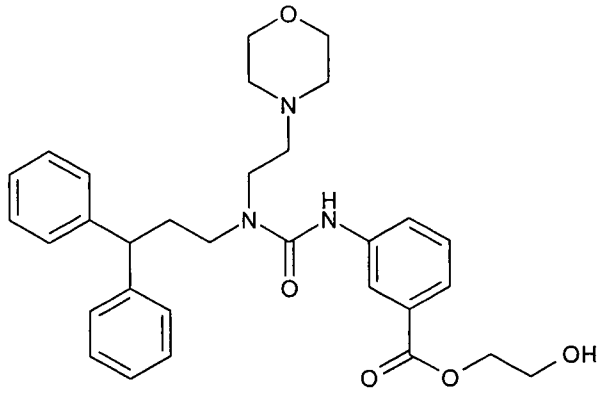
^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.39 (d, 6H, CH3), 1.95-2.13 (m, 2H, CH2), 2.37-2.58 (m, 2H, CH2), 2.76-3.02 (m, 2H, CH2), 3.04-3.30 (m, 2H, CH2), 3.32-3.65 (m, 2H, CH2), 3.80-4.10 (m, 5H, CH2+CH), 4.12-4.32 (m, 2H, CH2), 5.26 (sept, 1H, CH), 6.70-6.90 (m, 1H, aromatic H), 7.14-7.45 (m, 10H, aromatic H), 7.58-7.69 (m, 1H, aromatic H), 7.71 (d, 1H, aromatic H), 7.80-7.90 (m, 1H, aromatic H).

MS: 530^+ $(M+H-HCl)^+$

EXAMPLE 49

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid 2-hydroxy ester.

Method "I" route 1 was used to prepare the product described hereinafter:



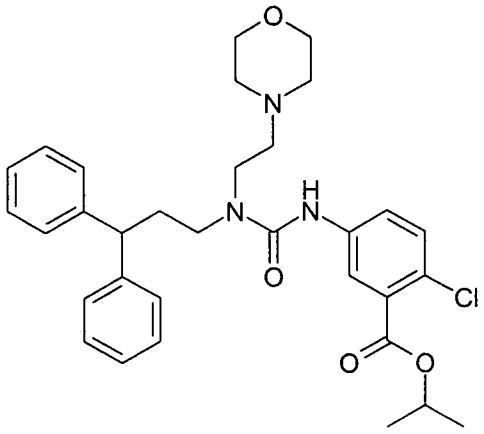
MS: 531.9^+ $(M+H)^+$

TLC: Rf = 0.36 (eluent: DCM/MeOH 95/5)

EXAMPLE 50

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester

The product described hereinafter was prepared using *Method "I" route 1*, but starting from 2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid (product of Example 46):



^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.40 (d, 6H, CH3), 2.39 (q, 2H, CH2), 2.50-2.75 (m, 6H, CH2), 3.31 (t, 2H, CH2), 3.32-3.45 (m, 2H, CH2), 3.73-3.88 (m, 4H, CH2), 3.97 (t, 1H, CH), 5.30 (sept, 1H, CH), 7.13-7.23 (m, 2H, aromatic H), 7.25-7.40 (m, 9H, aromatic H), 7.69 (s, 1H, aromatic H), 7.71-7.78 (m, 1H, aromatic H), 9.40-9.90 (m, 1H, NH).

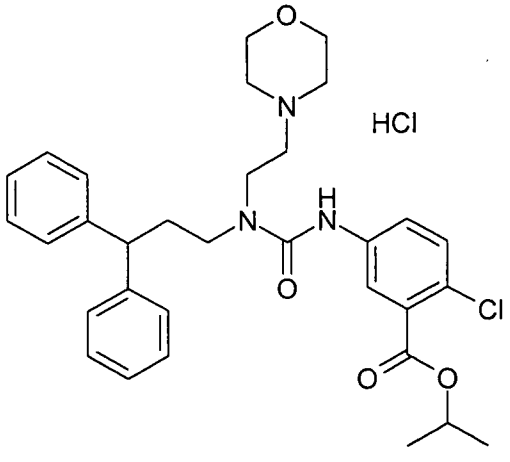
MS: 565.3^+ $(M+H)^+$

TLC: Rf = 0.63 (eluent: DCM/MeOH 95/5)

EXAMPLE 51

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester hydrochloride

Starting from the product obtained in Example 50, method "F" was used to prepare the title compound having the following formula



^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.41 (d, 6H, CH3), 2.32-2.55 (m, 2H, CH2), 2.75-2.98 (m, 2H, CH2), 3.00-3.27 (m, 2H, CH2), 3.29-3.60 (m, 4H, CH2), 3.78-4.07 (m, 5H, CH2,CH), 4.10-4.30 (m, 2H, CH2), 5.27 (sept, 1H, CH), 7.00-7.40 (m, 11H, aromatic H), 7.46-7.59 (m, 1H, aromatic H), 7.66-7.78 (m, 1H, aromatic H).

MS: 565.26$^+$ $(M+H-HCl)^+$

TLC: Rf = 0.63 (eluent: Rf = 0.48 (eluent: DCM/MeOH 95/5)

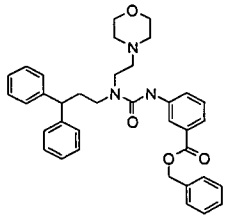
EXAMPLES 52 TO 54

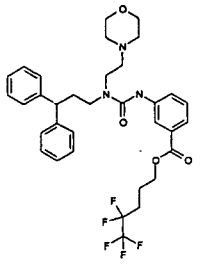
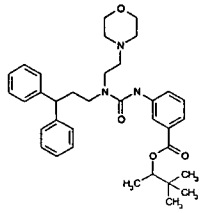
EXAMPLE 52

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid benzyl ester

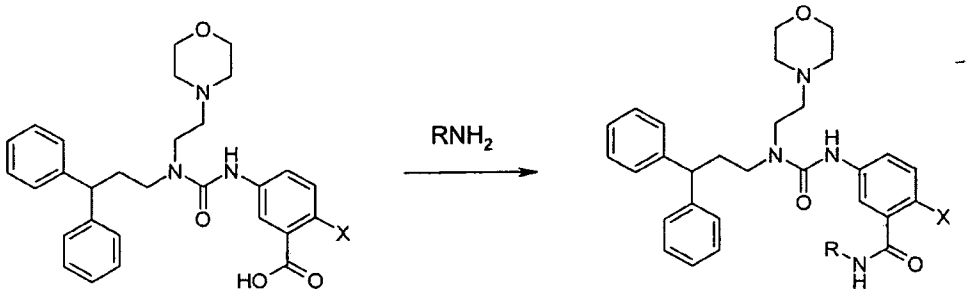
20 mg (0.041 mmol, 1 eq.) of the acid of Example 45 are dissolved in 1 mL of dichloromethane under argon. 0.5 mg (0.004 mmol, 0.1 eq.) of DMAP and 9.3 mg (0.045 mmol, 1.1 eq.) of DCC are added to the medium. After stirring for 30 min. at room temperature, 4.2 µL (0.045 mmol, 1.1 eq.) of benzyl alcohol are added and the mixture is stirred for a further 24 hours. The mixture is neutralised with water and the aqueous phase is extracted with dichloromethane. The organic phase is washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica gel (eluent: 2/1 DCM/AcOEt) (m = 18.5 mg, yield = 77 %).

This method is hereinafter identified as: *Method I route 2*. This method was used to prepare the compounds having the following formulae:

Formula	MS	Rf =	EXAMPLE
	$[M+H]^+$ 578.0	Rf = = 0.23 (2/1 dichloromethane/	Example 52

	648.0	Rf = 0.64 (95/5 DCM/MeOH)	Example 53
	572.0	Rf = 0.23 (2/1 DCM/AcOEt)	Example 54

Starting from the benzoic acids obtained in Examples 45 or 46, amides were prepared by two different routes, hereinafter called "Method J, route 1" or "Method J, route 2". The following scheme illustrates these two routes of synthesis.



route 1 :	X=Cl	Example 46	R = H, H_2O R= Me	R=H, R=Me,	Example 55 Example 56
route 2 :	X=H	Example 45	R = $(CH_2)_2OH$	R=$(CH_2)_2OH$,	Example 57

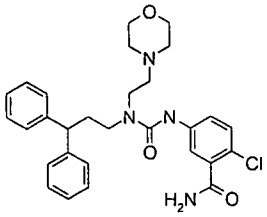
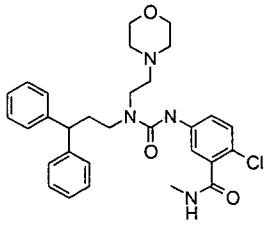
EXAMPLE 55

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzamide

25 mg (0.048 mmol, 1 eq.) of 2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid (obtained in Example 46) are dissolved in 0.5 mL of dry THF. Once the mixture had been cooled to -15 °C, 5.5μL (0.057 mmol, 1.2 eq.) of ethyl chloroformate and 8 μL (0.057 mmol, 1.2 eq.) of triethylamine are added to the medium. The mixture is stirred for 7 min. at -15 °C and 46 μL (0.24 mmol, 5 eq.) of 20 % eq. NH_4OH are added. The temperature is raised to 0 °C for 3 hours and then to room temperature for 15 min.

Water is added and the aqueous phase is extracted with dichloromethane. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica gel (eluent: AcOEt then 9/1: dichloromethane/methanol) (m = 17 mg, yield = 85 %).

This procedure is hereinafter called method "J", route 1.

Formula	MS	Rf =	EXAMPLE
	$(M+H)^+$ = 521.0	0.34 (9/1 DCM/MeOH)	Example 55
	535.0	0.48 (eluent: 9/1 DCM/MeOH)	Example 56

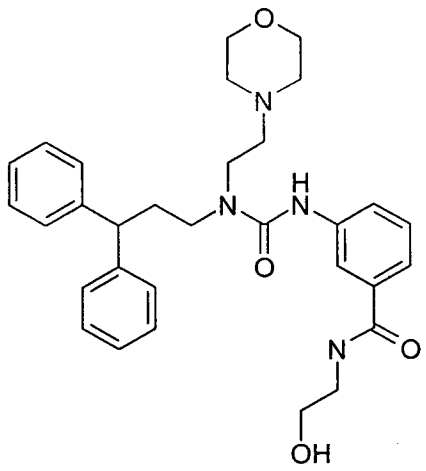
EXAMPLE 57

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-N-(2-hydroxy-ethyl)-benzamide

80 mg (0.164 mmol, 1 eq.) of 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid (obtained in Example 45) dissolved in dichloromethane are introduced into a 100 mL flask under an argon atmosphere, then HOBt (27 mg, 1.2 eq.), EDC (37 mg, 1.2 eq.), and ethanolamine (12 mg, 1 eq.) are added to the medium. After reacting

for 14 hours, the mixture is neutralised with water, then with a saturated $NaHCO_3$solution and the aqueous phase is extracted with dichloromethane. The organic phases are combined and washed with brine, then, dried over $MgSO_4$ and concentrated. The crude product thus obtained is purified by silica column chromatography (eluent: CH_2Cl_2/MeOH 99/1 to 96/4). The desired amide, 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-N-(2-hydroxyethyl)benzamide, is obtained in a yield of 52 %.

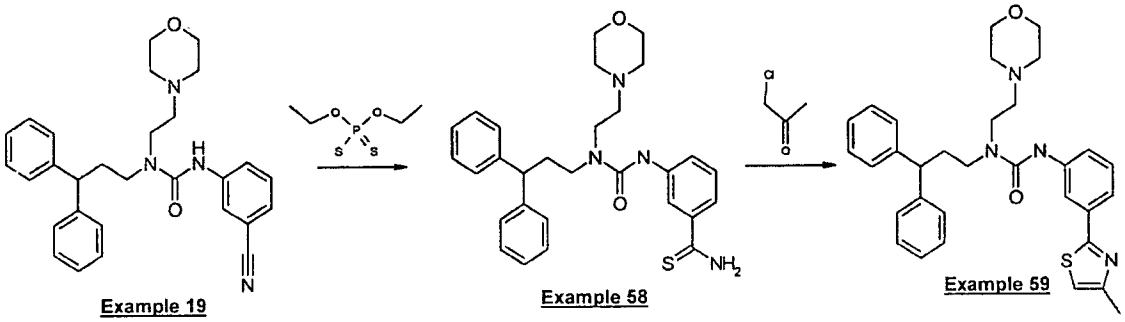
This procedure is hereinafter called method "J", route 2.



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2) 2.58 (m, 6H, 3xCH_2), 3.28 (t, 2H, CH_2), 3.35 (t, 2H, CH_2), 3.53 (t, 2H, CH_2), 3.75 (m, 6H, 3xCH_2), 3.95 (t, 1H, CH), 7.35-7.10 (m, 10H, aromatic H), 7.50-7.35 (m, 3H, aromatic H), 7.80 (s, 1H, aromatic H).
MS: 531^+ $(M+H)^+$

Starting from nitriles such as those obtained in Example 19 it is possible to prepare a thioamide derivative by a procedure hereinafter called procedure "K" illustrated below:

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiobenzamidethioamide (Example 58) then 1-(3,3-diphenylpropyl)-3-[3-(4-methylthiazol-2-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea (Example 59) are prepared from 3-(3-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea (obtained in Example 19):

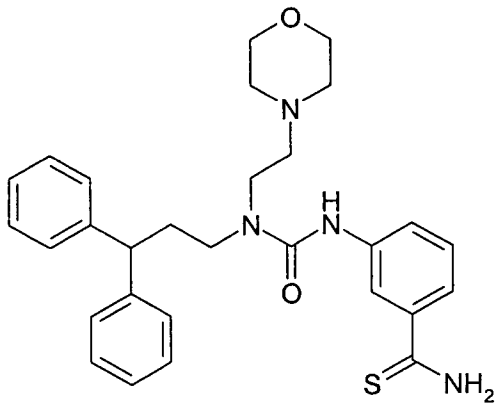


EXAMPLE 58

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiobenzamide

70 mg (0.15 mmol, 1 eq.) of 3-(3-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea (obtained in Example 19) are dissolved in 0.5 mL of THF under argon. 142 μL (0.90 mmol, 6 eq.) of diethyldithiophosphate and 50 μL (0.01 mmol, 0.1 eq.) of water are added. The mixture is stirred for 27 hours at 40 °C. Water is added to the medium and the aqueous phase is extracted with dichloromethane, washed twice with water then brine, dried over $MgSO_4$, filtered and concentrated. The oil obtained is subjected to chromatography over silica gel (eluent: 97/3 dichloromethane/methanol) in order to obtain the expected product in the form of a yellow powder (55 mg, yield = 73 %).

This procedure is hereinafter called method "K".



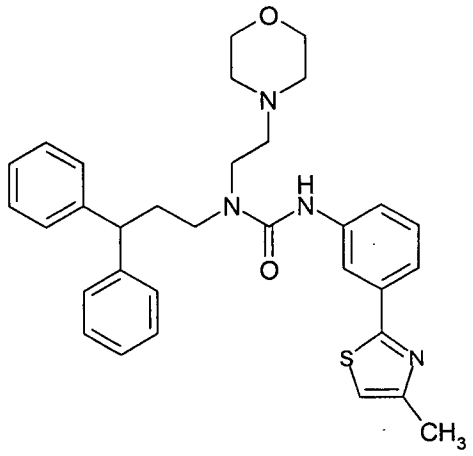
MS: 503.4^+ $(M+H)^+$

TLC: Rf = 0.20 (eluent: Rf = 0.48 (eluent: DCM/MeOH 9/1)

EXAMPLE 59

1-(3,3-diphenylpropyl)-3-[3-(4-methylthiazol-2-yl)-phenyl]-1-(2-morpholin-4-ylethyl)urea

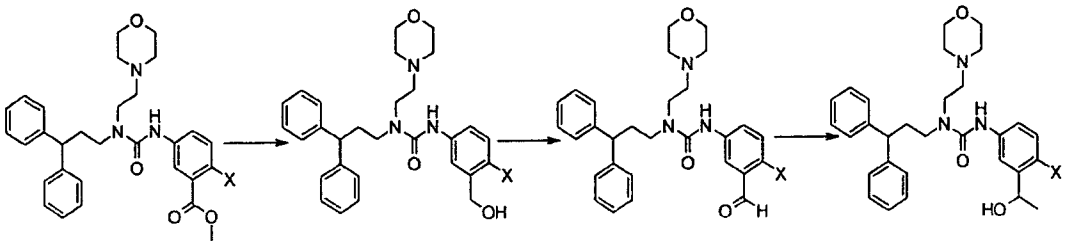
30 mg (0.060 mmol, 1 eq.) of 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiobenzamide (obtained in Example 58) are dissolved in 0.3 mL of DMF under argon and 19 μL (0.240 mmol, 4 eq.) of chloroacetone are added. The mixture is stirred for 16 hours at room temperature. Water is added to the medium and the aqueous phase is extracted with ethyl acetate. The organic phase is washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over a silica preparation plate (eluent: 85/15 AcOEt/heptane).



MS: 541.5^+ $(M+H)^+$

TLC: Rf = 0.25 (eluent: Rf = 0.48 (eluent: AcOEt/ heptane 4/1)

Starting from the methyl ester of the products obtained in Examples 1 or 18, it is possible to prepare the corresponding primary alcohol, aldehyde and secondary alcohol derivatives:



X = H, Example 1
X = Cl, Example 18

Example 60
Example 61

Example 62
Example 63

Example 64

EXAMPLE 60

1-(3,3-diphenylpropyl)-3-(3-hydroxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea

135.1 mg (0.269 mmol, 1 eq.) of 3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester (obtained in Example 1) and 6 mL of anhydrous THF are introduced in succession into a 30 mL flask under an argon atmosphere while stirring. The mixture is cooled to -78 °C, then 300 µL of a 1 M solution of DIBAL in dichloromethane (0.296 mmol, 1.1 eq.) are added slowly, the mixture is subsequently stirred for 2 hours at -78 °C, then for one night in a freezer at -27 °C. 300 µL of a 1 M solution of $LiAlH_4$ in THF are therefore added at -78 °C. After 30 minutes at this temperature, the reaction medium is plunged into an ice bath at 0 °C for 1 hour. Complete disappearance of the ester in favour of the alcohol is observed by TLC.

6 mL of a saturated solution of sodium and potassium tartrate are added at 0 °C and, after stirring for one hour at room temperature, the mixture is extracted with dichloromethane. The organic phases are combined, washed with water then a saturated NaCl solution and dried over $MgSO_4$. After filtration and concentration to dryness, the crude reaction product is purified by flash chromatography over silica gel (eluent: CH_2Cl_2/MeOH 95/5) leads to the desired alcohol in a yield of 90 %.

^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.88 (bs, 1H, OH) 2.40 (q, 2H, CH_2), 2.61 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.39 (m, 2H, CH_2), 3.79 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 4.69 (s, 2H, CH_2), 7.01 (d, 1H, aromatic H), 7.35-7.15 (m, 12H, aromatic H), 7.45 (s, 1H, aromatic H), 9.09 (bs, 1H, NH).

MS: 474^+ $(M+H)^+$

EXAMPLE 61

3-(4-chloro-3-hydroxymethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

The title compound was obtained by proceeding as in Example 60, but starting from the product obtained in Example 18.

MS: 508^+ $(M+H)^+$

TLC: Rf = 0.57 (eluent: DCM/MeOH 90/10)

EXAMPLE 62

1-(3,3-diphenylpropyl)-3-(3-formylphenyl)-1-(2-morpholin-4-ylethyl)urea

105.2 mg (0.222 mmol, 1 eq.) of 1-(3,3-diphenylpropyl)-3-(3-hydroxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea (obtained in Example 60), 6 mL of chloroform, and 193 mg (2.22 mmol, 10 eq.) of manganese oxide are introduced in succession into a 50 mL flask under an argon atmosphere while stirring. The mixture is heated under reflux for one night, then the reaction medium is filtered over Celite®. After rinsing with dichloromethane then concentrating to dryness, the crude reaction product is purified by flash chromatography over silica gel (elution gradient: CH_2Cl_2/AcOEt 4/1 then 1/1), leading to the desired aldehyde in a yield of 84 %.

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2) 2.63 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.35-7.15 (m, 10H, aromatic H), 7.46 (t, 1H, aromatic H), 7.52 (d, 1H, aromatic H), 7.71 (d, 1H, aromatic H), 7.90 (s, 1H, aromatic H), 9.43 (bs, 1H, NH), 10.00 (s, 1H, CHO).

MS: 472^+ $(M+H)^+$

EXAMPLE 63

3-(4-chloro-3-formylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

The title compound was obtained by proceeding as in Example 62, but starting from the product obtained in Example 61.

MS: 506^+ $(M+H)^+$

TLC: Rf = 0.46 (eluent: DCM/MeOH 95/5)

EXAMPLE 64

3-[4-chloro-3-(1-hydroxyethyl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

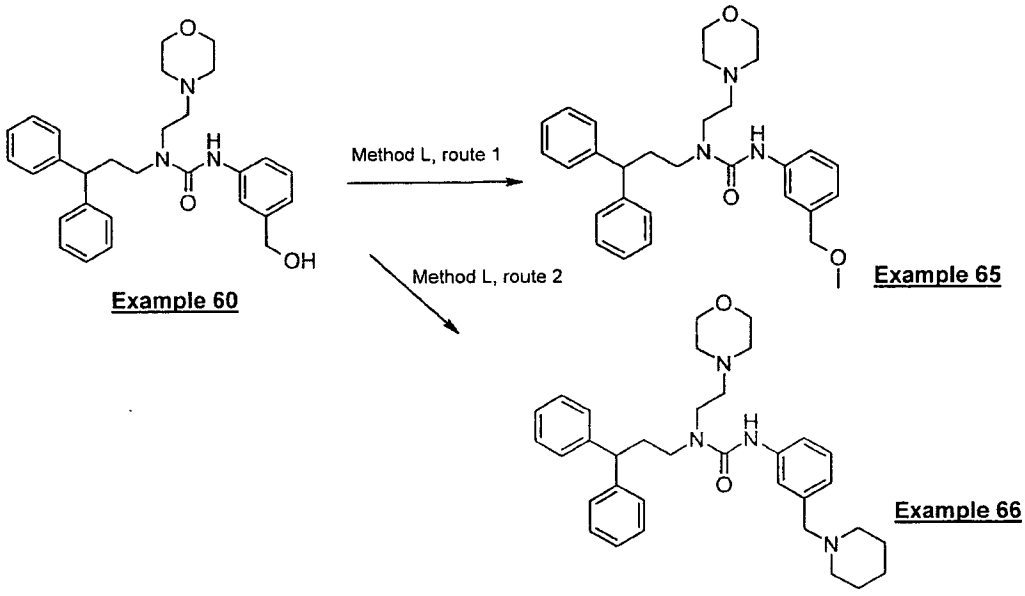
16 mg (0.033 mmol, 1 eq.) of 3-(4-chloro-3-formylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea (obtained in Example 63) are dissolved in 0.7 mL of dry THF. Once the solution has been cooled to 0 °C, 17 µL (0.049 mmol, 1.5 eq.) of magnesium methyl bromide in solution (3 M in diethyl ether) are added to the medium. After stirring for 20 min. at 0 °C, the reaction is neutralised with a saturated ammonium chloride solution at 0 °C. The aqueous phase is extracted with dichloromethane, the organic phases are washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica gel (eluent: 1/1 heptane/AcOEt). 11.4 mg of expected product are obtained (yield = 67 %).

^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.48 (d, 3H, CH3), 2.37 (q, 2H, CH2), 2.50-2.76 (m, 6H, CH2), 3.29 (t, 2H, CH2), 3.33-3.48 (m, 2H, CH2), 3.72-3.88 (m, 4H, CH2), 3.96 (t, 1H, CH), 5.24 (q, 1H, CH), 7.13-7.38 (m, 11H, aromatic H), 7.41 (d, 1H, aromatic H), 7.50 (s, 1H, aromatic H).

MS: 522.0^+ $(M+H)^+$

TLC: Rf = 0.69 (eluent: Rf = 0.48 (eluent: DCM/MeOH 9/1)

Starting from a primary alcohol of formula (I) such as that obtained in Example 60, an diethyl ether (method L, route 1) or piperidine (method L, route 2) derivative can be prepared in accordance with the following scheme:

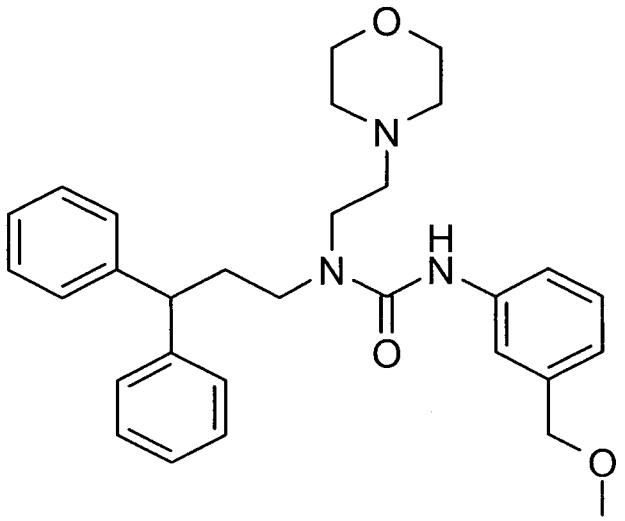


EXAMPLE 65

1-(3,3-diphenylpropyl)-3-(3-methoxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea

20 mg (0.042 mmol, 1 eq.) of 1-(3,3-diphenylpropyl)-3-(3-hydroxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea (obtained in Example 60) are dissolved in 3 mL of THF under argon. 3.4 mg (0.084 mmol, 2 eq.) of 60 % NaH in oil and 11 μL (0.169 mmol, 4 eq.) of methyl iodide are added. The solution is stirred for 1 hour at room temperature then 2 hours under reflux. Water is added and the aqueous phase is extracted with dichloromethane, the organic phases are washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over a preparation plate (eluent: 1/2 DCM/AcOEt) to give 2.5 mg of desired product (yield = 12 %)

(procedure "L", route 1)



MS: 489.2$^+$ $(M+H)^+$

TLC: Rf = 0.26 (eluent: Rf = 0.48 (eluent: DCM/AcOEt 1/2)

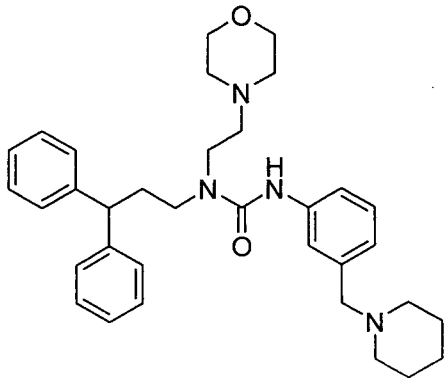
EXAMPLE 66

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-piperidin-1-ylmethyl-phenyl)urea

63 mg (0.133 mmol, 1 eq.) of 1-(3,3-diphenylpropyl)-3-(3-hydroxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea (obtained in Example 60) are dissolved in 1.5 mL of dichloromethane under argon. 24 μL (0.173 mmol, 1.3 eq.) of triethylamine are added to the medium. Once the mixture has been cooled to 0 °C, 18.4 μL (0.243 mmol, 1.8 eq.) of methane sulphonyl chloride are added. The reaction mixture is stirred for 3 hours at 0 °C and is then neutralised with water. The aqueous phase is extracted with dichloromethane, the organic phases are washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product is used as it is for the reaction sequence (m = 73 mg, yield = 100 %)

30 mg (0.054 mmol, 1 eq.) of this mesylate derivative are dissolved in 200 μL of DMF under argon. 23 mg (0.163 mmol, 3 eq.) of K_2CO_3 and 16 μL (0.163 mmol, 3 eq.) of piperidine are added. The mixture is stirred for 3 hours at room temperature. Water is added and the aqueous phase is extracted with ethyl acetate, the organic phases are washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction product is subjected to chromatography over silica (eluent: 95/5 dichloromethane/methanol). (m = 17.2 mg, yield = 59 %).

(Procedure "L", route 2)



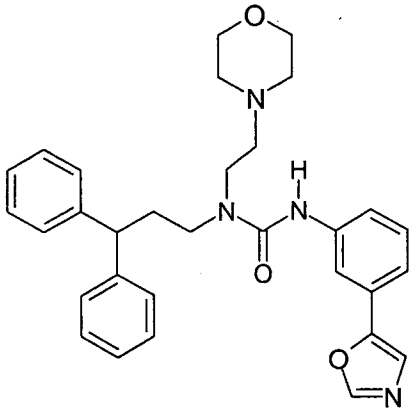
MS: 541.6^{+} $(M+H)^{+}$

TLC: Rf = 0.13 (eluent: Rf = 0.48 (eluent: DCM/MeOH 9/1)

EXAMPLE 67

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea

Method "B" was used to prepare the title compound having the following formula:



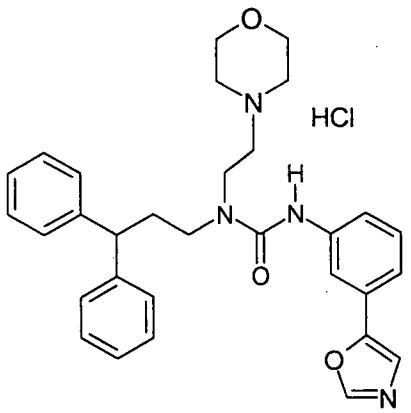
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2) , 2.90 (m, 6H, 3xCH_2), 3.38 (m, 2H, CH_2), 3.60 (d, 2H, CH_2), 3.95 (m, 5H, CH, 2xCH_2), 7.20 (m, 2H, aromatic H), 7.40-7.22 (m, 12H, aromatic H), 7.78 (s, 1H, $H_{oxazole}$), 7.90 (s, 1H, $H_{oxazole}$), 9.32 (bs, 1H, NH).

MS: $511.4^{+}(M+H)^{+}$

EXAMPLE 68

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea hydrochloride

Method "F", but using 3 eq. of HCl instead of 1 eq., was used to prepare the title compound having the following formula:



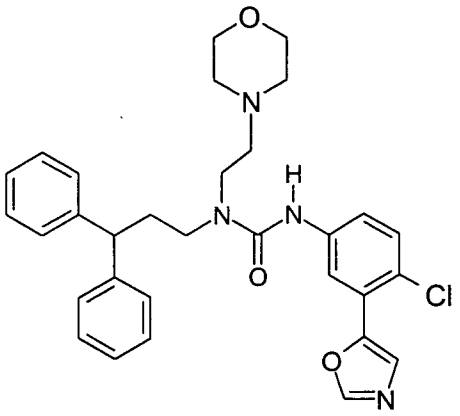
^{1}H NMR(400 MHz, CD_3OD): ppm 2.50 (q, 2H, CH_2), 3.15 (m, 4H, 2xCH_2), 3.45 (t, 2H, CH_2), 3.60 (m, 2H, CH_2), 3.75 (d, 4H, 2xCH_2), 4.05 (m, 3H, CH, CH_2), 7.20 (m, 2H, aromatic H), 7.48-7.25 (m, 11H, aromatic H), 7.60 (s, 1H, aromatic H), 7.80 (s, 1H, $H_{oxazole}$), 8.45 (s, 1H, $H_{oxazole}$).

MS: $511.4^{+}(M+H-HCl)^{+}$

EXAMPLE 69

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-yl-4-chlorophenyl)urea

Method "B" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH2), 2.55-2.72 (m, 6H, CH2), 3.32 (t, 2H, CH2), 3.35-3.43 (m, 2H, CH2), 3.78-3.88 (m, 4H, CH2), 3.98 (t, 1H, CH), 7.14-7.35 (m, 10H, aromatic H), 7.38 (d, 1H, aromatic H), 7.45 (d, 1H, aromatic H), 7.82 (s, 1H, aromatic H), 7.85 (s, 1H, aromatic H), 7.96 (s, 1H, aromatic H), 9.20-9.80 (m, 1H, NH).

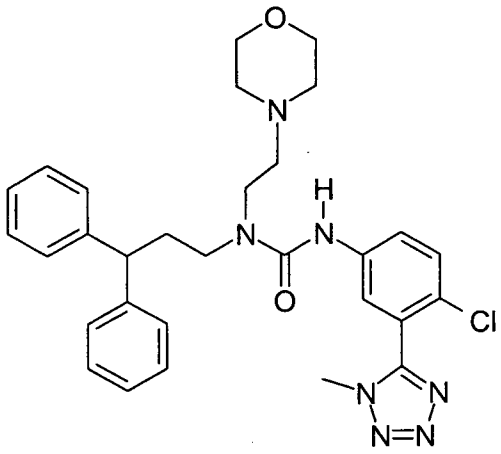
MS: 545.4^+ $(M+H)^+$

TLC: Rf = 0.05 (eluent: DCM/AcOEt 4/1)

EXAMPLE 70

3-[4-Chloro-3-(1-methyl-1H-tetrazol-5-yl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the product of the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.37 (q, 2H, CH2), 2.54-2.65 (m, 6H, CH2), 3.27 (t, 2H, CH2), 3.32-3.40 (m, 2H, CH2), 3.69-3.77 (m, 4H, CH2), 3.95 (t, 1H, CH), 4.01 (s, 3H, CH3), 7.14-7.33 (m, 10H, aromatic H), 7.39-7.52 (m, 2H, aromatic H), 7.64 (s, 1H, aromatic H), 9.30-9.80 (m, 1H, NH).

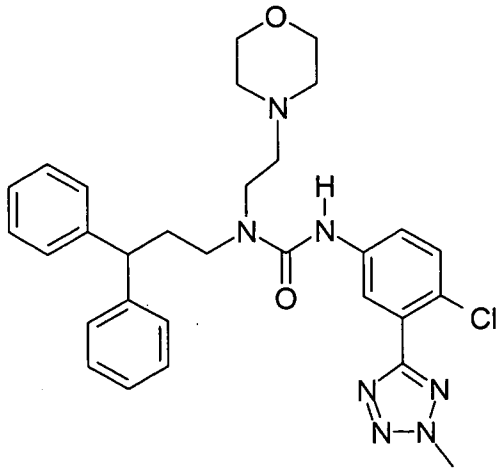
MS: 560.22^+ $(M+H)^+$

TLC: Rf = 0.11 (eluent: DCM/AcOEt 4/1)

EXAMPLE 71

3-[4-Chloro-3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH2), 2.52-2.68 (m, 6H, CH2), 3.30 (t, 2H, CH2), 3.33-3.40 (m, 2H, CH2), 3.73-3.86 (m, 4H, CH2), 3.96 (t, 1H, CH), 4.44 (s, 3H, CH3), 7.15-7.23 (m, 2H, aromatic H), 7.26-7.35 (m, 8H, aromatic H), 7.45 (d, 1H, aromatic H), 7.67 (d, 1H, aromatic H), 7.94 (s, 1H, aromatic H), 9.26-9.80 (m, 1H, NH).

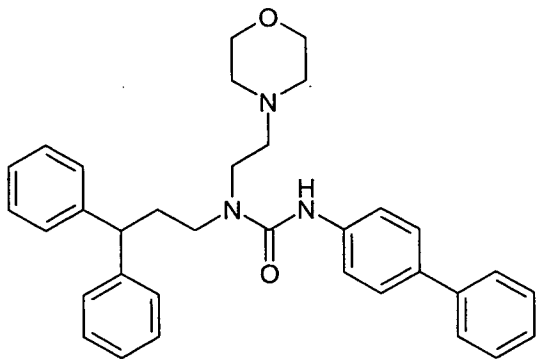
MS: 560.22^+ $(M+H)^+$

TLC: Rf: 0.21 (eluent: DCM/AcOEt 4/1)

EXAMPLE 72

3-Biphenyl-4-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:

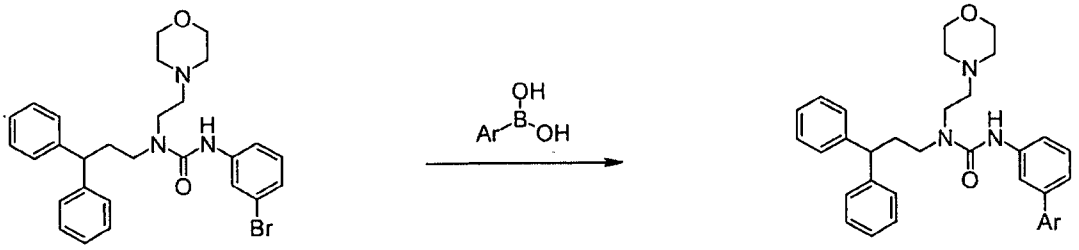


^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.43 (q, 2H, CH_2), 2.61 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.81 (m, 4H, 2xCH_2), 3.99 (t, 1H, CH), 7.17-7.38 (m, 11H, aromatic H), 7.40-7.48 (m, 4H, aromatic H), 7.55 (d, 2H, aromatic H), 7.59 (d, 2H, aromatic H), 9.18 (bs, 1H, NH).

MS: 520^+ $(M+H)^+$

In order to obtain biaryl derivatives of formula (I) in which R_3 represents a phenyl radical substituted by an aryl group or a heterocycle, saturated or unsaturated, mono-, bi- or tricyclic, optionally containing from 1 to 5 heteroatoms and optionally being substituted by a halogen atom, an alkyl or alkoxy group containing from 1 to 6 carbon atoms, a product such as the one obtained in Example 11 can be made to react by Suzuki coupling with a boric acid

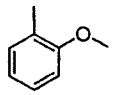
derivative of formula Ar-B-$(OH)_2$ in accordance with the following scheme. The modes of procedure "M" or "N" below are employed.



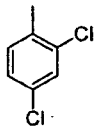
Example 11

Ar =

Example 73



Example 79

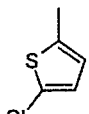


Example 80

Example 74

Example 75

Example 76



Example 77

Example 78

Method "M":

1 eq. of bromine derivative, obtained in Example 11, 1 eq. of boronic acid, 2 mL of THF, 2 mL of a 2 M solution of sodium carbonate in water and 0.1 eq. of palladium tetrakis are introduced into a Radley tube under nitrogen while stirring. The mixture is heated under reflux for one night. The THF is evaporated and the reaction medium is extracted with ethyl acetate. Then the organic phase is washed with water and a saturated NaCl solution. After drying over $MgSO_4$, filtration and concentration to dryness, the crude product is purified by

column chromatography over silica gel (elution gradient: DCM/AcOEt 9/1 to 4/1) (yields ranging from 16 % to 79 %).

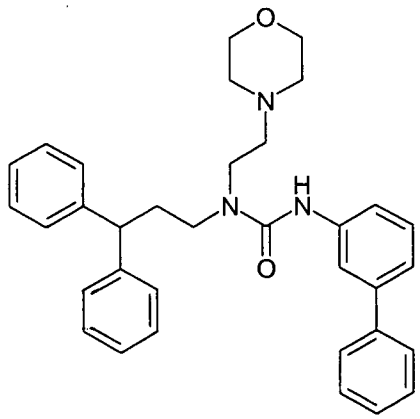
Method "N":

1 eq. of bromine derivative obtained in Example 11, 0.1 eq. of palladium tetrakis, 0.7 mL of dioxane, 0.7 mL of a 2 M solution of sodium carbonate in water and 1.5 eq. of boric acid are introduced in succession into a sealed 2-5 mL tube, adapted for microwave treatment. The mixture is stirred and heated to 100 °C for 3 to 10 minutes depending on the R group which introduces diversity. The reaction medium is subsequently extracted with ethyl acetate, then the organic phase is washed with water and a saturated NaCl solution. After drying over $MgSO_4$, filtration and concentration to dryness, the crude product is purified by chromatography over silica gel (yields ranging from 69 % to 95 %).

EXAMPLE 73

Biphenyl-3-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "M", starting with the product obtained in Example 11, was used to prepare the title compound having the following formula:



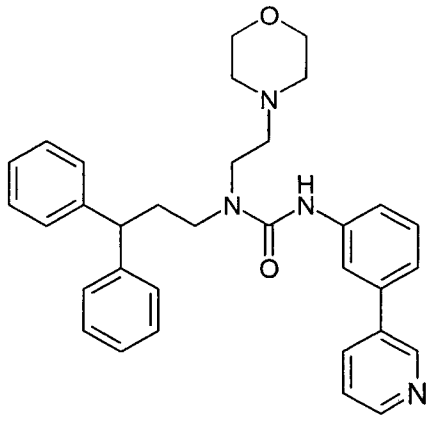
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.43 (q, 2H, CH_2), 2.69 (m, 6H, 3xCH_2), 3.33 (t, 2H, CH_2), 3.47 (m, 2H, CH_2), 3.82 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.20 (m, 2H, aromatic H), 7.28 (m, 8H, aromatic H), 7.48 (m, 4H, aromatic H), 7.58 (m, 3H, aromatic H), 7.70 (m, 2H, aromatic H), 9.02 (bs, 1H, NH).

MS: 520.2^+ $(M+H)^+$

EXAMPLE 74

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-pyridin-3-ylphenyl)urea

Method "M", starting with the product obtained in Example 11, was used to prepare the title compound having the following formula:



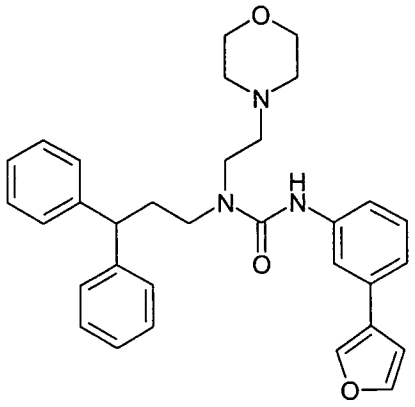
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2), 2.73 (m, 6H, 3xCH_2), 3.35 (t, 2H, CH_2), 3.52 (m, 2H, CH_2), 3.85 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.18-7.39 (m, 14H, aromatic H), 7.65 (s, 1H, aromatic H), 7.90 (d, 1H, aromatic H), 8.60 (d, 1H, aromatic H), 8.85 (s, 1H, aromatic H).

MS: 521.2^+ $(M+H)^+$

EXAMPLE 75

(1-(3,3-diphenylpropyl)-3-(3-furan-3-ylphenyl)-1-(2-morpholin-4-ylethyl)urea

Method "N", starting from the product obtained in Example 11, was used to prepare the title compound having the following formula:



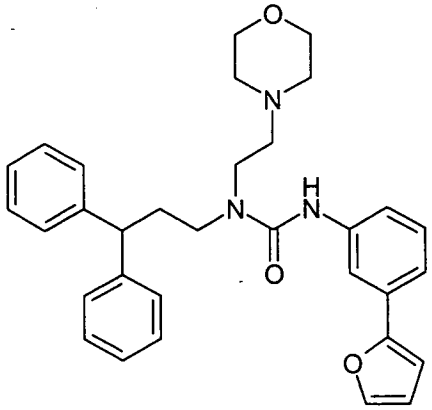
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2), 2.60 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 6.70 (s, 1H, H_{furan}), 7.12 (d, 1H, aromatic H), 7.20 (m, 2H, aromatic H), 7.29 (m, 5H, aromatic H), 7.49 (m, 3H, aromatic H), 7.55 (m, 2H, aromatic H), 7.70 (m, 3H, aromatic H), 9.09 (bs, 1H, NH).

MS: 510.2$^+$ $(M+H)^+$

EXAMPLE 76

1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea

Method "N", starting from the product obtained in Example 11, was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 3.33 (t, 2H, CH_2), 3.41 (m, 2H, CH_2), 3.85 (m, 4H, 2xCH_2), 3.99 (t, 1H, CH), 6.48 (m, 1H, $H_{oxazole}$), 6.65 (m,

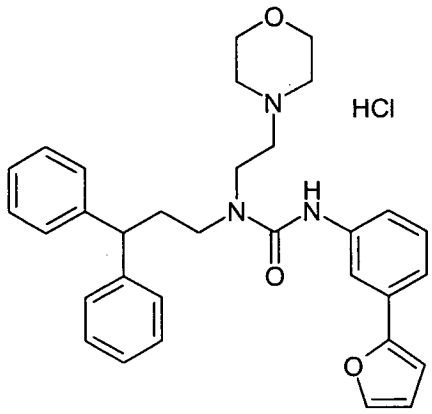
1H, $H_{oxazole}$), 7.20 (m, 2H, aromatic H), 7.30 (m, 5H, aromatic H), 7.49 (m, 3H, aromatic H), 7.58 (m, 2H, aromatic H), 7.69 (m, 3H, aromatic H).

MS: 510.24^{+} $(M+H)^{+}$

EXAMPLE 76A

1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea hydrochloride

Method "F", starting from the product obtained in Example 76, was used to prepare the title compound having the following formula:



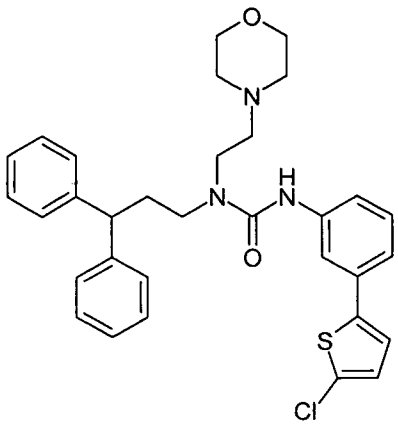
1H NMR(400 MHz, CD_3OD): ppm 2.50 (q, 2H, CH2), 3.12 (t, 2H, CH2), 3.30 (m, 2H, CH2), 3.43 (t, 2H, CH2), 3.60 (d, 2H, CH2), 3.75 (m, 4H, 2xCH2), 4.05 (m, 3H, CH2, CH), 6.52 (d, 1H, Hoxazole), 6.75 (d, 1H, Hoxazole), 7.20 (t, 2H, aromatic H), 7.32 (m, 6H, aromatic H), 7.40 (d, 1H, Hoxazole), 7.48 (m, 2H, aromatic H), 7.68 (m, 4H, aromatic H).

MS: 510.40^{+} $(M+H-HCl)^{+}$

EXAMPLE 77

3-[3-(5-chlorothiophen-2-yl)-phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "N", starting from the product obtained in Example 11, was used to prepare the title compound having the following formula:



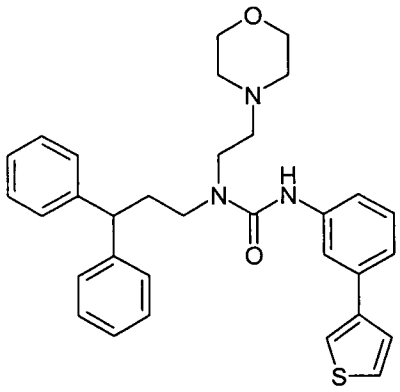
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.43 (q, 2H, CH_2), 2.75 (m, 6H, 3xCH_2), 3.35 (m, 4H, 2xCH_2), 3.90 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 6.89 (d, 1H, aromatic H), 7.09 (d, 1H, aromatic H), 7.15-7.35 (m, 13H, aromatic H), 7.52 (s, 1H, aromatic H).

MS: 560.2$^+$ $(M+H)^+$

EXAMPLE 78

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-thiophen-3-ylphenyl)urea

Method "N", starting from the product obtained in Example 11, was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2), 2.64 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.82 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.20 (m, 2H, aromatic H), 7.30

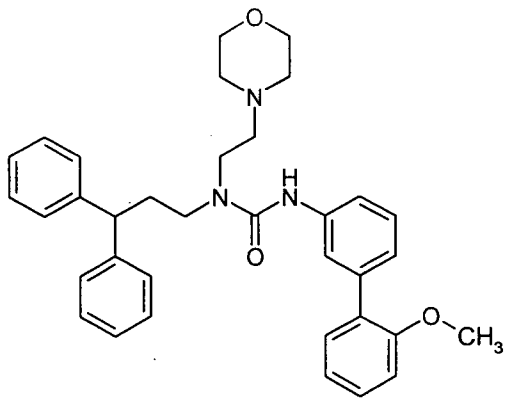
(m, 7H, aromatic H), 7.38 (s, 1H, aromatic H), 7.49 (m, 3H, aromatic H), 7.58 (m, 1H, aromatic H), 7.68 (m, 3H, aromatic H), 3.10 (m, 1H, NH).

MS: 526.2^{+} $(M+H)^{+}$

EXAMPLE 79

1-(3,3-diphenylpropyl)-3-(2'-methoxybiphenyl-3-yl)-1-(2-morpholin-4-ylethyl)urea

Method "N", starting from the product obtained in Example 11, was used to prepare the title compound having the following formula:



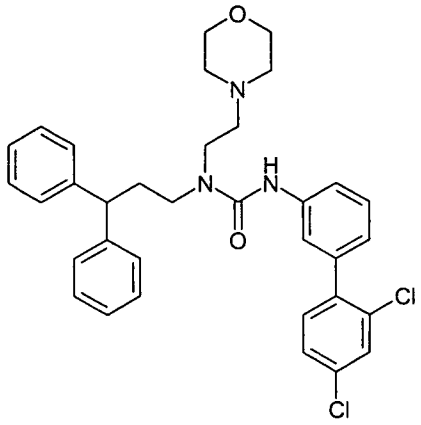
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2), 2.62 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.82 (s, 3H, OCH_3), 3.97 (t, 1H, CH), 6.99 (d, 1H, aromatic H), 7.03 (t, 1H, aromatic H), 7.18 (m, 2H, aromatic H), 7.30 (m, 8H, aromatic H), 7.40 (m, 1H, aromatic H), 7.48 (m, 2H, aromatic H), 7.56 (m, 1H, aromatic H), 7.70 (m, 2H, aromatic H), 9.15 (bs, 1H, NH).

MS: 550.5^{+} $(M+H)^{+}$

EXAMPLE 80

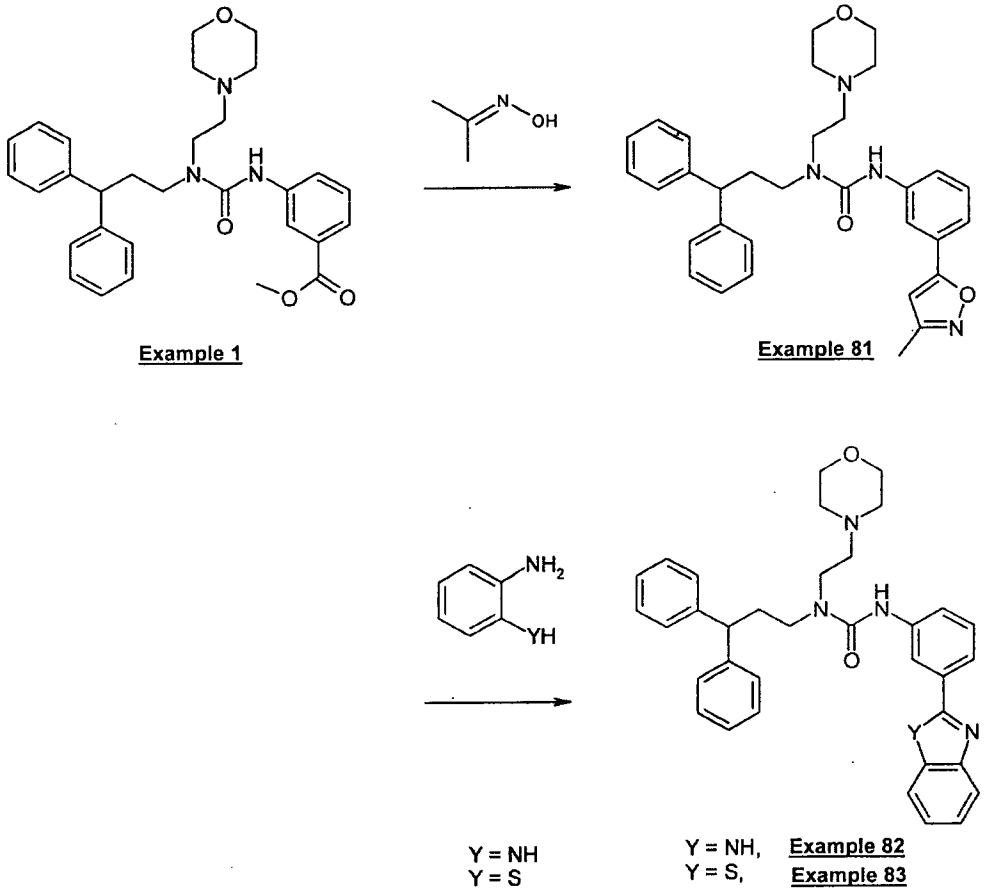
3-(2',4'-dichlorobiphenyl-3-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "N", starting from the product obtained in Example 11, was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2), 2.62 (m, 6H, 3xCH_2), 3.30 (t, 2H, CH_2), 3.41 (m, 2H, CH_2), 3.79 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 7.06 (d, 1H, aromatic H), 7.20 (m, 2H, aromatic H), 7.30 (m, 7H, aromatic H), 7.35 (m, 2H, aromatic H), 7.49 (m, 2H, aromatic H), 7.55 (m, 1H, aromatic H), 7.70 (m, 2H, aromatic H), 9.17 (bs, 1H, NH).
MS: 588.5$^+$ $(M+H)^+$

Biaryl derivatives of formula (I), in which R^3 represents an isoxazolylphenyl, benzimidazolylphenyl or benzothiazolylphenyl radical, can also be prepared starting from a methyl ester such as the one obtained in Example 1 by proceeding in accordance with the following scheme.

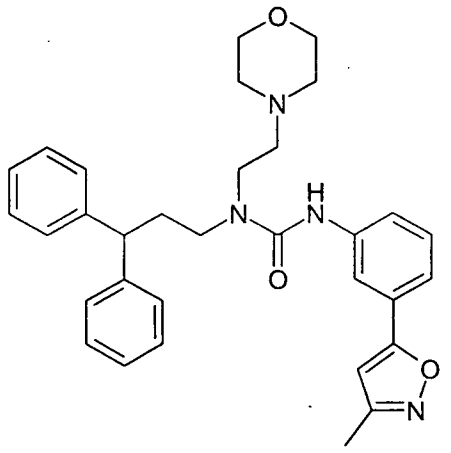


EXAMPLE 81

1-(3,3-diphenylpropyl)-3-[3-(3-methylisoxazol-5-yl)-phenyl]-1-(2-morpholin-4-ylethyl)urea

22 mg (0.3 mmol, 3 eq.) of oxime acetone, 0.4 mL of anhydrous THF and 376 µL of a 1.6 M solution of butyl lithium in hexane (0.6 mmol, 6 eq.) are introduced in succession into a 10 mL flask at 0 °C under argon. The mixture is stirred for 1 hour at 0 °C. A solution of 50 mg (0.1 mmol, 1 eq.) of methyl ester obtained in Example 1, in 0.4 mL of anhydrous THF is then added dropwise at 0 °C. Stirring is maintained for 20 hours, with the temperature passing progressively from 0 °C to room temperature. A solution of concentrated sulphuric acid (31 µL , d = 1.83) in THF (0.3 mL) and water (0.1 mL) is poured into the reaction medium and the complete mixture is heated under reflux for 2 hours. After cooling, the pH of the solution is rendered basic by addition of a saturated potassium carbonate solution. The mixture is extracted with ethyl acetate and the organic phase is washed with a saturated NaCl

solution. After drying over $MgSO_4$, filtration and concentration to dryness, the crude reaction product is purified by column chromatography over silica gel (elution gradient: CH_2Cl_2 then CH_2Cl_2/AcOEt 9/1 to 1/1), leading to 17.9 mg (yield= 34 %) of expected 3-methylisoxazole derivative.



^{1}**H NMR**(400 MHz, $CDCl_3$): ppm 2.37 (s, 3H, CH_3), 2.42 (q, 2H, CH_2), 2.66 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.43 (m, 2H, CH_2), 3.84 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 6.39 (s, 1H, $H_{isoxazole}$), 7.20 (m, 2H, aromatic H), 7.28 (m, 6H, aromatic H), 7.39 (m, 2H, aromatic H), 7.49 (d, 1H, aromatic H), 7.52 (m, 1H, aromatic H), 7.75 (m, 2H, aromatic H).
MS: 525.5$^+$ $(M+H)^+$

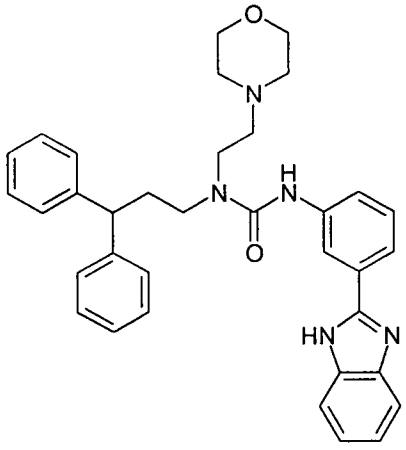
EXAMPLE 82

3-[3-(1H-benzimidazole-2-yl)-phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

1 mL of anhydrous toluene and 250 mL (0.5 mmol, 5 eq.) of a 2 M solution of trimethyl aluminium in toluene are introduced in succession into a 10 mL flask under argon and previously placed in an oven. The solution is cooled to 0 °C, then 16.2 mg (0.15 mmol, 1.5 eq.) of 1.2-phenylenediamine are added. Stirring is continued for 30 minutes at 0 °C, then for 45 minutes at room temperature. 50 mg (0.1 mmol, 1 eq.) of methyl ester obtained in Example 1 are then added and the mixture is heated under reflux for 12 hours. The reaction medium is cooled in an ice bath and 2 mL of water are added. The insoluble matter is filtered

over a frit and rinsed with ethyl acetate. The organic phase is subsequently washed with saturated NaCl solution and dried over $MgSO_4$, then evaporated.

Purification of the crude reaction product by flash chromatography over silica gel (elution gradient: CH_2Cl_2 then CH_2Cl_2/MeOH 98/2 to 90/10) allows 34.5 mg of a mixture of the desired product and impurities to be obtained. The desired product is again purified by preparation LCMS, leading to 12.9 MG (yield = 34 %) of expected benzimidazole.

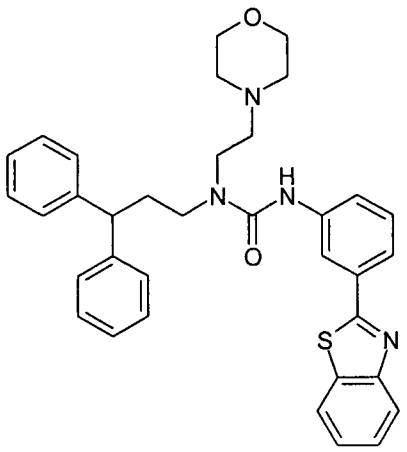


^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.42 (q, 2H, CH_2), 2.54 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.78 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 7.13-7.32 (m, 15H, aromatic H), 7.62 (m, 2H, aromatic H), 7.77 (d, 1H, aromatic H), 8.22 (s, 1H, NH), 9.32 (bs, 1H, NH).
MS: 560.5$^+$ $(M+H)^+$

EXAMPLE 83

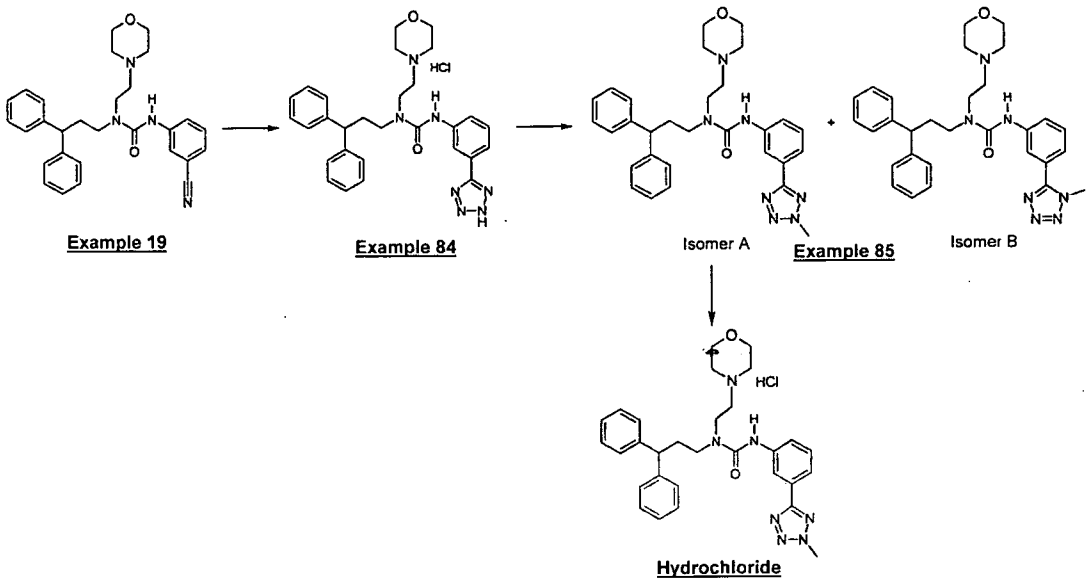
3-(3-Benzothiazol-2-ylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

The title compound was prepared by proceeding as indicated in Example 82 but using 2-aminothiophenol instead of 1,2-phenylenediamine.



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.43 (q, 2H, CH_2), 2.68 (m, 6H, 3xCH_2), 3.33 (t, 2H, CH_2), 3.48 (m, 2H, CH_2), 3.90 (m, 4H, 2xCH_2), 3.99 (t, 1H, CH), 7.20 (m, 2H, aromatic H), 7.30 (m, 8H, aromatic H), 7.41 (q, 2H, aromatic H), 7.51 (t, 1H, aromatic H), 7.72 (m, 2H, aromatic H), 7.93 (d, 1H, aromatic H), 8.08 (m, 2H, aromatic H), 9.46 (bs, 1H, NH).
MS: 577.5$^+$ $(M+H)^+$

Biaryl derivatives of general formula (I) in which R^3 represents a phenyl radical substituted by a tetrazolyl or N-Me tetrazolyl group can be prepared starting from the corresponding nitrile by proceeding in accordance with the following reaction scheme.



EXAMPLE 84

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-[3-(2H-tetrazol-5-yl)phenyl]urea hydrochloride

76.7 mg (0.164 mmol, 1 eq.) of nitrile derivative obtained in Example 19, 2.5 mL of toluene, and 90 µl (0.328 mmol, 2 eq.) of tributyl tin azide are introduced in succession into a 30 mL flask in an argon atmosphere while stirring. The mixture is heated under reflux for 16 hours, then the reaction medium is evaporated. 2 mL of 2 M HCl in diethyl ether are added to the mixture, the precipitate thus formed is washed with pentane, the crude reaction product is purified by flash chromatography over silica gel (elution gradient: CH_2Cl_2 then CH_2Cl_2/MeOH 95/5 then 90/10), leading to the expected derivative in hydrochloride form in a yield of 65 %.

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.38 (q, 2H, CH2), 2.62-2.77 (m, 6H, CH2), 3.24-3.37 (m, 4H, CH2), 3.75-3.83 (m, 4H, CH2), 3.96 (t, 1H, CH), 7.15-7.33 (m, 12H, aromatic H), 7.63-7.69 (m, 1H, aromatic H), 8.05 (s, 1H, aromatic H).

MS: 512.4$^+$ $(M+H)^+$

TLC: Rf = 0.27 (eluent: DCM/MeOH 90/10)

EXAMPLE 85

1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea (Isomer A) and its hydrochloride, and

1-(3,3-diphenylpropyl)-3-[3-(1-methyl-1H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea (Isomer B)

536 mg (0.978 mmol, 1 eq.) of tetrazole derivative, obtained in Example 84, 1 mL of acetonitrile, and 73.4 μL (1.173 mmol, 1.2 eq.) of methyl iodide and 162 mg of K_2CO_3 (1.173 mmol, 1.2 eq.) are introduced in succession into a 100 mL flask under an argon atmosphere while stirring. The mixture is heated under reflux for 30 minutes, the reaction being incomplete, 0.6 eq. (0.587 mmol) of methyl iodide are still added to the reaction mixture, stirring is maintained for 30 minutes under reflux. The reaction medium is cooled to room temperature then neutralised with water. The organic phase is extracted repeatedly with dichloromethane at pH 8 and, after washing with NaCl, drying over $MgSO_4$ and evaporation of the solvent, the crude product obtained is purified by flash chromatography over silica gel (elution gradient: heptane/AcOEt 1/1 to 1.6 then pure AcOEt) to lead to the expected product in the form of isomer A with a yield of 34 % and isomer B with a yield of 10 %.

Isomer A

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.60 (m, 6H.3xCH_2), 3.30 (m, 2H, CH_2), 3.38 (m, 2H, CH_2), 3.82 (t, 4H, 2xCH_2), 4.00 (t, 1H, CH), 4.40 (s, 3H, NCH_3), 7.20 (m, 2H, aromatic H), 7.30 (m, 8H, aromatic H), 7.43 (t, 1H, aromatic H), 7.70 (d, 1H, aromatic H), 7.78 (d, 1H, aromatic H), 8.08 (s, 1H, aromatic H), 9.40 (bs, 1H, NH).

MS: 526^+ $(M+H)^+$

Hydrochloride of isomer A

^{1}H NMR(400 MHz, CD_3OD): ppm 2.50 (q, 2H, CH_2), 3.15 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 3.45 (t, 2H, CH_2), 3.60 (d, 2H, CH_2), 3.75 (m, 4H, 2xCH_2), 4.10 (m, 3H, CH, CH_2), 4.42 (s, 3H, NCH_3), 7.20 (t, 2H, aromatic H), 7.35-7.25 (m, 8H, aromatic H), 7.48 (t, 1H, aromatic H), 8.18 (s, 1H, aromatic H), 7.80 (d, 1H, aromatic H), 7.52 (bd, 1H, aromatic H).

MS: 526^+ $(M+H-2HCl)^+$

Isomer B

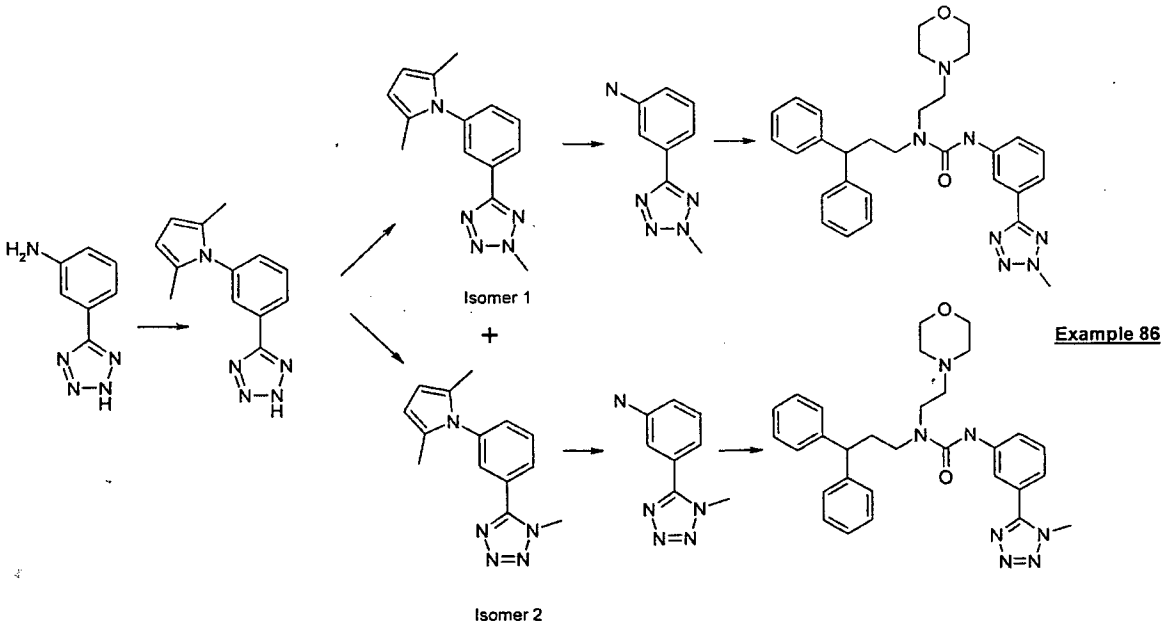
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.60 (m, 6H, 3xCH_2), 3.30 (m, 2H, CH_2), 3.38 (m, 2H, CH_2), 3.78 (t, 4H, 2xCH_2), 3.98 (t, 1H, CH), 4.20 (s, 3H, NCH_3), 7.20 (m, 2H, aromatic H), 7.30 (m, 8H, aromatic H), 7.38 (m, 1H, aromatic H), 7.48 (d, 2H, aromatic H), 8.00 (s, 1H, aromatic H), 9.50 (bs, 1H, NH) .

MS: 526^+ $(M+H)^+$

EXAMPLE 86

1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea (Isomer A) and 1-(3,3-diphenylpropyl)-3-[3-(1-methyl-1H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea (Isomer B)

The title compounds (products identical to the products obtained in Example 85) were prepared by an alternative to the process of the invention, in accordance with the following scheme.



1) Synthesis of 5-[3-(2,5-dimethylpyrrol-1-yl)phenyl]-2H-tetrazole

8 g (49.64 mmol, 1 eq.) of 5-(3-aminophenyl)-tetrazole are introduced into a 500 mL flask equipped with a Dean Stark trap, with 200 mL of toluene and 0.80 mL of acetic acid.

6.89 µL (58.57 mmol, 1.18 eq.) acetonyl acetone are added. The mixture is heated under reflux for 1 hour 30 min. The initially insoluble mixture dissolves during the reaction and becomes red. The solution is left to return to room temperature and the product crystallises in the medium. The solvent is concentrated to half and the insoluble matter is filtered and rinsed 4 times with toluene (m = 9.45 g, yield = 80%).

2) Synthesis of isomer 1 5-[3-(2,5-Dimethylpyrrol-1-yl)phenyl]-2-methyl-2H-tetrazole and isomer 2 5-[3-(2,5-Dimethylpyrrol-1-yl)phenyl]-1-methyl-1H-tetrazole:

9 g (37.61 mmol, 1 eq.) of 5-[3-(2,5-dimethylpyrrol-1-yl)phenyl]-2H-tetrazole are dissolved in 45 mL of acetonitrile in a flask equipped with a condenser. 6.24 g (45.14 mmol, 1.2 eq.) of potassium carbonate are added. The mixture is heated to 80 °C, and 2.82 mL (45.14 mmol, 1.2 eq.) of methyl iodide are added. The mixture is stirred for 15 min. at 80 °C and a further 0.94 mL (15.05 mmol, 0.4 eq.) of methyl iodide are added. The mixture is stirred for 15 min. at 80 °C then left to rest for one night at room temperature. The medium is concentrated and taken up in DMF. Water is added and the basic aqueous phase is extracted with DCM. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by chromatography over silica gel (eluent: pure heptane to heptane/AcOEt 2/1) (6 g of ***Isomer 1***, yield = 63%; 3.54 g of ***Isomer 2***, yield = 37%).

3) Synthesis of 3-(2-methyl-2H-tetrazol-5-yl)phenylamine

5.71 g (22.54 mmol, 1 eq.) of isomer 1 obtained above are dissolved hot in 61 mL of ethanol and 23 mL of water. 7.83 g (113 mmol, 5 eq.) of hydroxylamine hydrochloride are added and the mixture is stirred for 24 h under reflux. 7.83 g (113 mmol, 5 eq.) of hydroxylamine hydrochloride are added again and the reflux is maintained for a further 24 hours. The ethanol is concentrated and a 2 N solution of hydrochloric acid is added. Diethyl ether is added and the aqueous phase is repeatedly extracted with Et_2O. The aqueous phase is recovered, basified with 2 N NaOH then concentrated NaOH. It is extracted with ethyl acetate. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by chromatography over silica gel (eluent: heptane/AcOEt 1/1) (m = 3.11 g, yield = 79%).

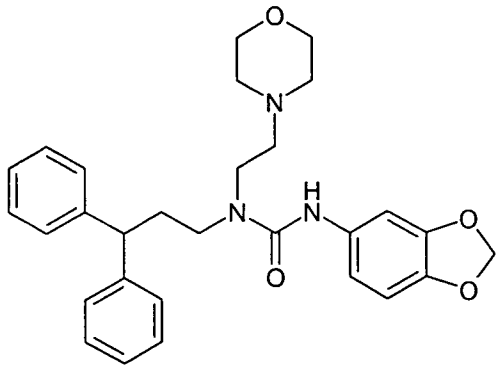
4): Synthesis of 1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea (Isomer 1)

Starting from the 3-(2-methyl-2H-tetrazol-5-yl)phenylamine obtained above, the expected product was prepared by method "D" (m = 238 mg, yield = 91%).

EXAMPLE 87

3-benzo[1,3]dioxol-5-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the title compound having the following formula:



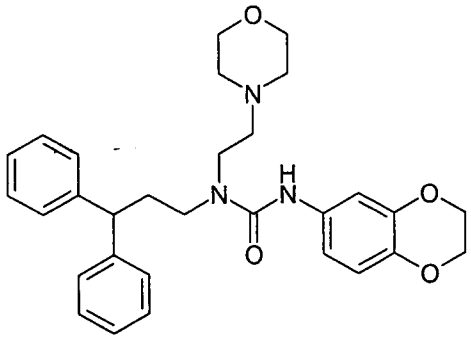
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.62 (m, 6H, 3xCH_2), 3.29 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.78 (m, 4H, 2xCH_2), 3.97 (t, 1H, CH), 5.92 (s, 2H, CH_2), 6.64 (d, 1H, aromatic H), 6.72 (d, 1H, aromatic H), 7.03 (s, 1H, aromatic H), 7.15-7.23 (m, 2H, aromatic H), 7.25-7.34 (m, 8H, aromatic H), 9.00 (bs, 1H, NH).

MS: 488^+ $(M+H)^+$

EXAMPLE 88

3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

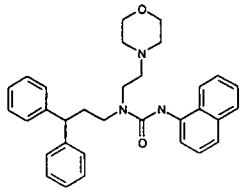
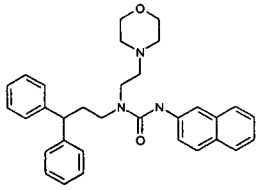
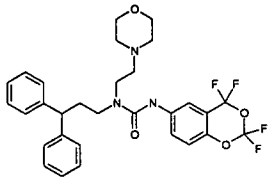
Method "A" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.60 (bs, 6H, 3xCH_2), 3.28 (t, 2H, CH_2), 3.35 (bs, 2H, CH_2), 3.78 (bs, 4H, 2xCH_2), 3.95 (t, 1H, CH), 4.22 (bs, 4H, 2xCH_2), 6.78 (s, 2H, aromatic H), 6.92 (s, 1H, aromatic H), 7.20 (m, 2H, aromatic H), 7.30 (m, 8H, aromatic H), 8.85 (bs, 1H, NH).

MS: 502^+ $(M+H)^+$

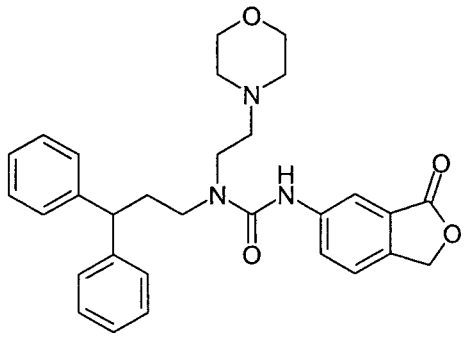
Method "A" was used to prepare the title compounds of the following formulae:

Formula	$[M+H]^+$	Rf = (DCM/AcOEt)	EXAMPLE
	494.1	0.18 (4/1)	Example 89
	494.1	0.14 (4/1)	Example 90
	574.2	= 0.48 (95/5 DCM/MeOH)	Example 91

EXAMPLE 92

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxo-1,3-dihydroisobenzofuran-5-yl)urea

Method "B" was used to prepare the title compounds of the following formulae:



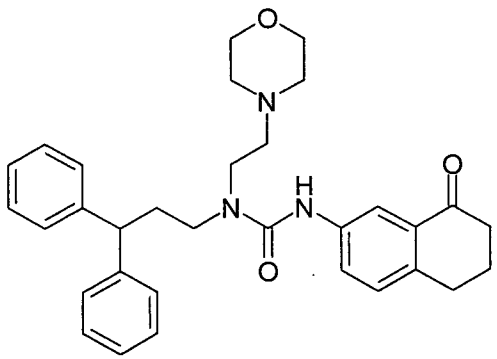
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.62 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.40 (bs, 2H, CH_2), 3.78 (bs, 4H, 2xCH_2), 3.98 (t, 1H, CH), 5.28 (s, 2H, CH_2), 7.20 (m, 2H, aromatic H), 7.30 (m, 8H, aromatic H), 7.40 (d, 1H, aromatic H), 7.75 (s, 1H, aromatic H), 7.85 (d, 1H, aromatic H), 9.50 (bs, 1H, NH).

MS: 500.8^+ $(M+H)^+$

EXAMPLE 93

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(8-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)urea

Method "B" was used to prepare the title compound having the following formula:



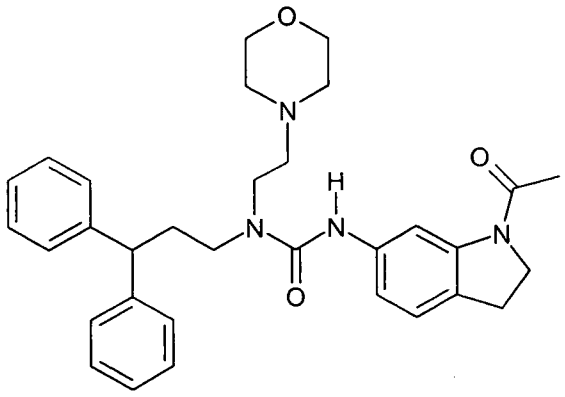
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.12 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 2.60 (m, 8H, 4xCH_2), 2.92 (t, 2H, CH_2), 3.30 (m, 2H, CH_2), 3.38 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.20 (m, 2H, aromatic H), 7.30 (m, 9H, aromatic H), 7.72 (s, 1H, aromatic H), 7.78 (d, 1H, aromatic H), 9.30 (bs, 1H, NH).

MS: 512^+ $(M+H)^+$

EXAMPLE 94

3-(1-acetyl-2,3-dihydro-1H-indol-6-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



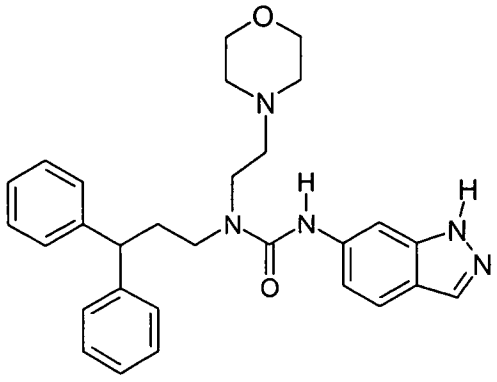
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.22 (s, 3H, CH_3), 2.40 (q, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 3.15 (t, 2H, CH_2), 3.30 (t, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.87 (m, 4H, 2xCH_2), 3.99 (t, 1H, CH), 4.05 (t, 2H, CH_2), 7.10 (d, 1H, aromatic H), 7.20 (m, 2H, aromatic H), 7.30 (m, 9H, aromatic H), 7.45 (1H, aromatic H), 8.00 (s, 1H, aromatic H), 9.30 (bs, 1H, NH).

MS: 527^+ $(M+H)^+$

EXAMPLE 95

1-(3,3-diphenylpropyl)-3-(1H-indazol-6-yl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



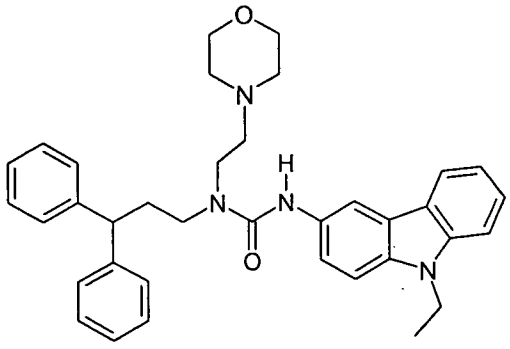
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.45 (q, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 3.35 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 4.00 (t, 1H, CH), 6.88 (d, 1H, aromatic H), 7.20 (m, 2H, aromatic H), 7.30 (m, 8H, aromatic H), 7.60 (d, 1H, aromatic H), 7.98 (s, 1H, aromatic H), 8.01 (s, 1H, aromatic H), 9.25 (bs, 1H, NH), 10.40 (bs, 1H, NH).

MS: 484^+ $(M+H)^+$

EXAMPLE 96

1-(3,3-diphenylpropyl)-3-(9-ethyl-9H-carbazol-3-yl)-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



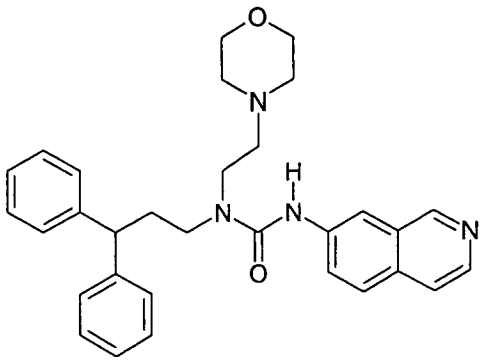
^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.45 (t, 3H, CH_3), 2.48 (q, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 3.35 (t, 2H, CH_2), 3.45 (m, 2H,CH_2), 3.80 (m, 4H, 2xCH_2), 4.00 (t, 1H, CH), 4.35 (q, 2H, CH_2), 7.20 (m, 3H, aromatic H), 7.25-7.34 (m, 9H, aromatic H), 7.36-7.50 (m, 3H, aromatic H), 8.05 (s, 1H, aromatic H), 8.10 (s, 1H, aromatic H), 8.90 (bs, 1H, NH).

MS: 561^+ $(M+H)^+$

EXAMPLE 97

1-(3,3-diphenylpropyl)-3-isoquinolin-7-yl-1-(2-morpholin-4-ylethyl)urea

Method "B" was used to prepare the title compound having the following formula:



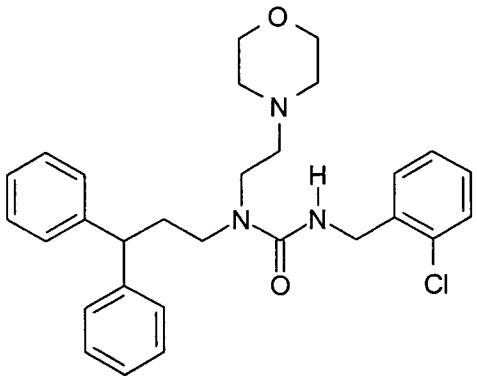
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.48 (q, 2H, CH_2), 2.70 (m, 6H, 3xCH_2), 3.40 (t, 2H, CH_2), 3.65 (m, 6H, 3xCH_2), 4.00 (t, 1H, CH), 7.20 (m, 2H, aromatic H), 7.30 (m, 9H, aromatic H), 7.62 (m, 2H, aromatic H), 7.80 (d, 1H, aromatic H), 7.88 (d, 1H, aromatic H), 8.52 (bs, 1H, aromatic H), 9.25 (bs, 1H, NH).

MS: 495^+ $(M+H)^+$

EXAMPLE 98

3-(2-chloro-benzyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "A" was used to prepare the product of the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.35 (q, 2H, CH2), 2.39-2.44 (m, 4H, CH2), 2.46 (t, 2H, CH2), 3.23 (t, 2H, CH2), 3.26 (t, 2H, CH2), 3.45 (m, 4H, CH2), 3.94 (t, 1H, CH), 4.48 (d, 2H, CH2), 7.15-7.33 (m, 12H, aromatic H), 7.37 (d, 1H, aromatic H), 7.42 (d, 1H, aromatic H).

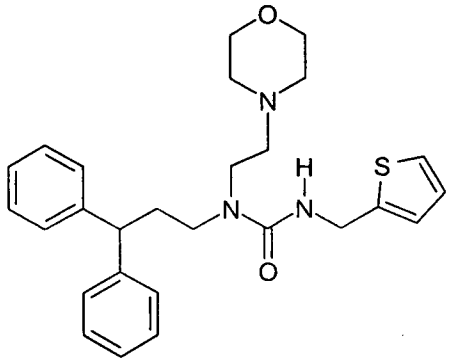
MS: 492.2^+ $(M+H)^+$

TLC: Rf = 0.10 (eluent: DCM/AcOEt 4/1)

EXAMPLE 99

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-thiophen-2-ylmethylurea

Method "C" was used to prepare the product of the following formula:



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.35 (q, 2H, CH2), 2.45 (m, 6H, CH2), 3.22 (m, 4H, CH2), 3.40 (m, 4H, CH2), 3.95 (t, 1H, CH), 4.55 (d, 2H, CH2), 6.95 (m, 2H, aromatic H), 7.12-7.32 (m, 11H, aromatic H).

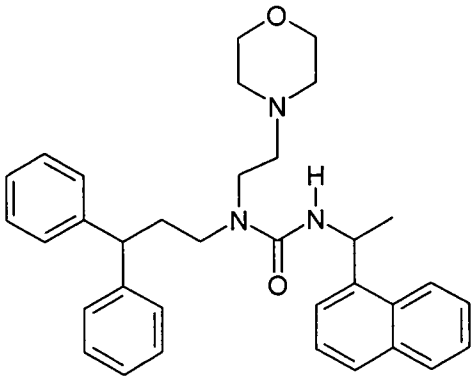
MS: 463.6$^+$ $(M+H)^+$

TLC: Rf = 0.27 (eluent: DCM/MeOH 95/5)

EXAMPLE 100

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(1-naphthalen-1-ylethyl)urea

Method "A" was used to prepare the product of the following formula:



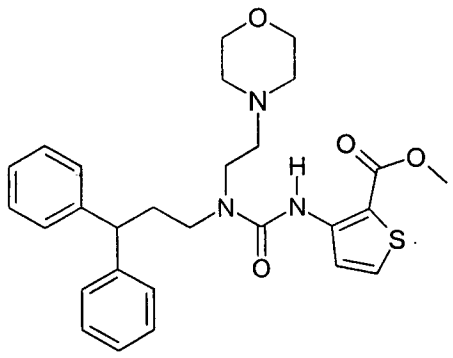
MS: 522.0$^+$ $(M+H)^+$

TLC: Rf = 0.32 (eluent: DCM/MeOH 95/5)

EXAMPLE 101

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiophene-2-carboxylic acid methyl ester

Method "B" was used to prepare the title compound having the following formula:



^{1}H NMR (400 MHz, CDCl3) : ppm 10.02-9.95 (s el, 1H, NH), 8.03 (d, 1H, aromatic H), 7.44 (d, 1H, aromatic H), 7.36-7.26 (m, 8H, aromatic H), 7.24-7.16 (m, 2H, aromatic H), 4.08 (t, 1H, CH), 3.90 (s, 3H, CH3), 3.70-3.55 (m, 4H, CH2), 3.50-3.35 (m, 4H, CH2), 2.60-2.30 (m, 8H, CH2).

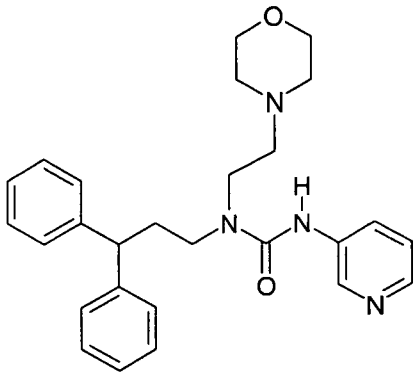
MS: 507.3$^+$ $(M+H)^+$

TLC: Rf = 0.19 (eluent: DCM/AcOEt 1/1)

EXAMPLE 102

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-pyridin-3-ylurea

Method "B" was used to prepare the title compound having the following formula:



^{1}**H NMR**(400 MHz, $CDCl_3$): ppm 2.40 (q, 2H, CH_2), 2.65 (m, 6H, 3xCH_2), 3.32 (t, 2H, CH_2), 3.43 (m, 2H, CH_2), 3.80 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.15-7.35 (m, 11H, aromatic H), 7.98 (d, 1H, aromatic H), 8.35 (bs, 1H, aromatic H), 8.48 ((bs, 1H, aromatic H), 9.30 (bs, 1H, NH).

MS: 445^+ $(M+H)^+$

EXAMPLE 103

1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea

125 mg (0.77 mmol, 1.5 eq.) of carbonyl diimidazole are dissolved in 0.4 mL of DCM then 82 mg (0.51 mmol, 1 eq.) of 3-(2-methyl-2H-tetrazol-5-yl)phenylamine, in 0.4 mL of DCM are added dropwise under argon. A white precipitate appears. The suspension is stirred for 15 hours at room temperature. 200 mg (0.615 mmol, 1.2 eq.) of [3,3-diphenylpropyl)(2-morpholin-4-ylethyl)amine] in 0.4 mL of DCM are added. The solution, which has become clear again, is stirred for 3 hours at room temperature. A sodium bicarbonate solution is added and the aqueous phase is extracted with dichloromethane. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The oil obtained is subjected to chromatography over silica gel (eluent: 1/0 to 1/1 heptane/ AcOEt) (238 mg, yield = 91%).

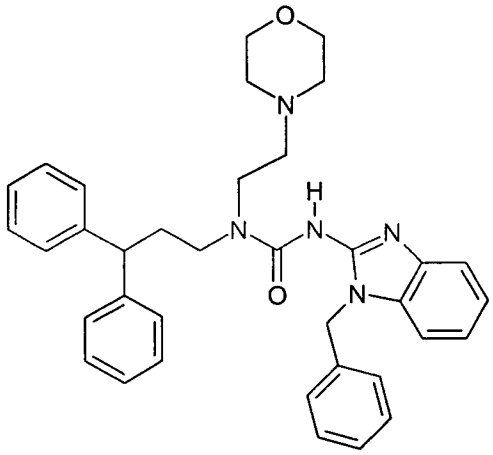
The product obtained is identical to the product obtained in Example 86.

This procedure is hereinafter called method "D".

EXAMPLE 104

3-(1-benzyl-1H-benzimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : ppm 12.00-11.85 (s el, 1H, NH), 7.50-7.05 (m, 19H, aromatic H), 5.31 (s, 1H, CH), 5.20 (s, 1H, CH), 4.07-3.95 (m, 1H, CH), 3.62 (t, 1H, CH), 3.57-3.40 (m, 6H, CH2), 3.36 (t, 1H, CH), 2.52-2.32 (m, 6H, CH2), 2.30-2.20 (m, 2H, CH2).

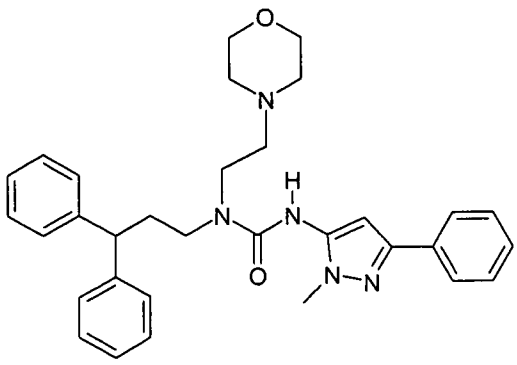
MS: 574.54$^+$ $(M+H)^+$

TLC: Rf = 0.13 (eluent: DCM/MeOH 97/3)

EXAMPLE 105

1-(3,3-diphenylpropyl)-3-(2-methyl-5-phenyl-2,5-dihydro-1H-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : ppm 9.70-9.45 (s el, 1H, NH), 7.81 (d, 2H, aromatic H), 7.42-7.23 (m, 11H, aromatic H), 7.18 (t, 2H, aromatic H), 6.41 (s, 1H, H pyrazole), 4.04 (t, 1H, CH), 3.70 (s, 3H, CH3), 3.63-3.56 (m, 4H, CH2), 3.55-3.50 (m, 2H, CH2), 3.34 (t, 2H, CH2), 2.67-2.60 (m, 2H, CH2), 2.58-2.50 (m, 4H, CH2), 2.44 (q, 2H, CH2).

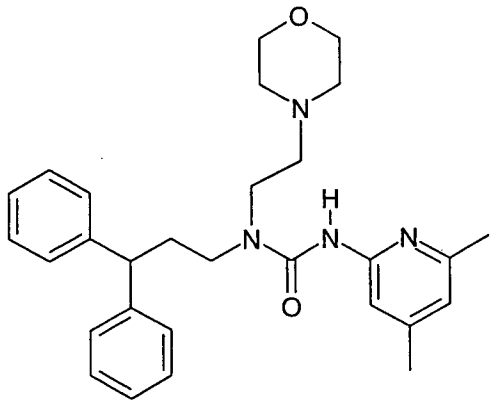
MS: 524.54$^+$ $(M+H)^+$

TLC: Rf = 0.17 (eluent: DCM/MeOH 97/3)

EXAMPLE 106

3-(4,6-dimethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(morpholin-4-ylethyl)urea

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : ppm 10.70-10.50 (s el, 1H, NH), 7.62 (s, 1H, aromatic H), 7.39 (d, 4H, aromatic H), 7.30 (t, 4H, aromatic H), 7.18 (t, 2H, aromatic H), 6.62 (s, 1H, aromatic H), 4.05 (t, 1H, CH), 3.98-3.87 (m, 4H, CH2), 3.47-3.40 (m, 2H, CH2), 3.30 (t, 2H, CH2), 2.65-2.52 (m, 6H, CH2), 2.43 (q, 2H, CH2), 2.33 (s, 3H, CH3), 2.26 (s, 3H, CH3).

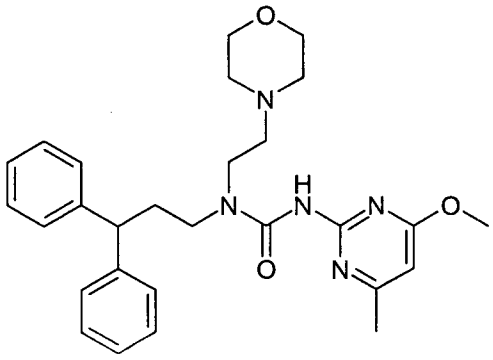
MS: 473.51$^+$ $(M+H)^+$

TLC: Rf = 0.36 (eluent: DCM/MeOH 97/3)

EXAMPLE 107

1-(3,3-diphenylpropyl)-3-(4-methoxy-6-methylpyrimidin-2-yl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the product of the following formula:

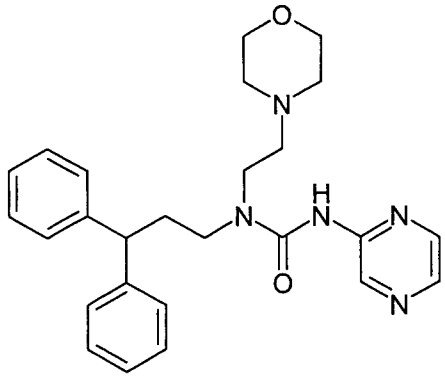


^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.37 (s, 3H, CH3), 2.42 (q, 2H, CH2), 2.51 (m, 2H, CH2), 2.61 (m, 4H, 2xCH2), 3.29 (t, 2H, CH2), 3.34 (t, 2H, CH2), 3.96 (m, 8H, CH, OCH3, 2xCH2), 6.20 (s, 1H, aromatic H), 7.19 (m, 2H, aromatic H), 7.28 (m, 8H, aromatic H).
MS: 490^+ $(M+H)^+$

EXAMPLE 108

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-pyrazin-2-ylurea

Method "D" was used to prepare the product of the following formula:



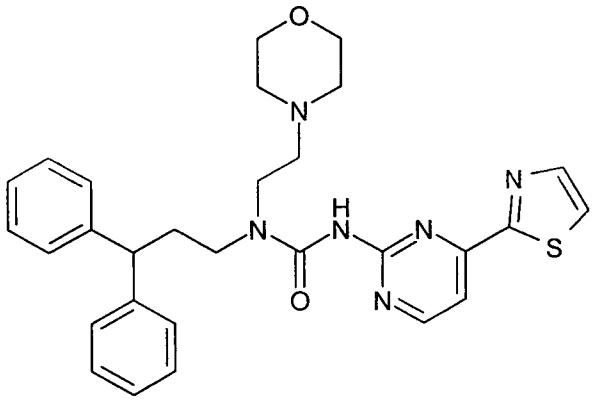
^{1}H NMR(400 MHz, DMSO): 2.35 (q, 2H, H5), 2.52 (m, 6H, 3xCH2), 3.32 (m, 4H, 2xCH2), 3.71 (m, 4H, 2xCH2), 4.03 (m, 1H, CH), 7.16 (m, 2H, aromatic H), 7.31 (m, 8H, aromatic H), 8.19 (s, 1H, aromatic H), 8.28 (s, 1H, aromatic H), 9.03 (s, 1H, aromatic H).

MS: 446^+ $(M+H)^+$

EXAMPLE 109

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(4-thiazol-2-ylpyrimidin-2-yl)urea

Method "D" was used to prepare the product of the following formula:



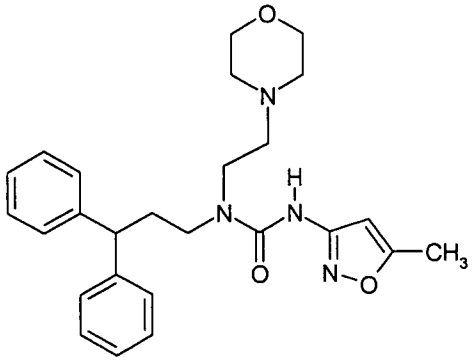
MS: 529.2^+ $(M+H)^+$

TLC: Rf = 0.33 (eluent: AcOEt 100%)

EXAMPLE 110

1-(3,3-diphenylpropyl)-3-(5-methylisoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : ppm 11.57-11.40 (s el, 1H, NH), 7.37 (d, 4H, aromatic H), 7.29 (t, 4H, aromatic H), 7.17 (t, 2H, aromatic H), 6.56 (s, 1H, aromatic H), 4.03 (t, 1H,

CH), 3.86-3.76 (m, 4H, CH2), 3.46-3.41 (m, 2H, CH2), 3.30 (t, 2H, CH2), 2.66-2.52 (m, 6H, CH2), 2.40 (q, 2H, CH2), 2.35 (s, 3H, CH3).

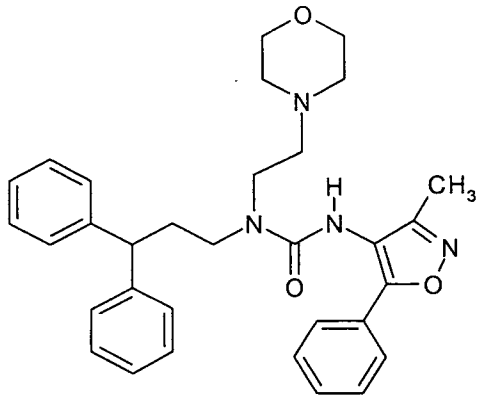
MS: 449.46^{+} $(M+H)^{+}$

TLC: Rf = 0.30 (eluent: DCM/MeOH 97/3)

EXAMPLE 111

1-(3,3-diphenylpropyl)-3-(3-methyl-5-phenylisoxazol-4-yl)-1-(2-morpholin-4-ylethyl)urea

Method "E" was used to prepare the product of the following formula:



60 mg (0.30 mmol, 1 eq.) of 3-methyl-5-phenyl-4-isoxazole carboxylic acid are dissolved in 3 mL of toluene. 46 µL (0.32 mmol, 1.1 eq.) of triethylamine are added. After checking the basicity of the medium, 67 µL (0.31 mmol, 1.05 eq.) of diphenylphosphoryl azide are added to the medium. This mixture is brought to 80 °C for two hours then 115 mg (0.35 mmol, 1.2 eq.) of (3,3-diphenylpropyl)(2-morpholin-4-ylethyl)-amine are added. Heating is maintained for 1 hour. The mixture is then left to return to room temperature and stirring is maintained for one night. A saturated $NaHCO_3$ solution is added and the aqueous phase is extracted with DCM. The organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The product is purified over an alumina column (eluent: 1/1 heptane/AcOEt) (m = 59 mg, yield = 38%).

This procedure is hereinafter called method "E".

^{1}H NMR(400 MHz, CD_3COCD_3): ppm 2.20 (s, 3H, CH3), 2.37-2.44 (m, 4H, CH_2), 2.46 (q, 2H, CH_2), 2.60 (t, 2H, CH_2), 3.26-3.35 (t, 4H, CH_2), 3.38 (t, 2H,CH_2), 3.53 (t, 2H, CH2), 4.06

(t, 1H, CH), 7.18 (t, 2H, aromatic H), 7.30 (t, 4H, aromatic H), 7.38 (d, 4H, aromatic H), 7.43-7.52 (m, 3H, aromatic H), 7.86 (d, 2H, aromatic H), 8.80-9.13 (bs, 1H, NH).

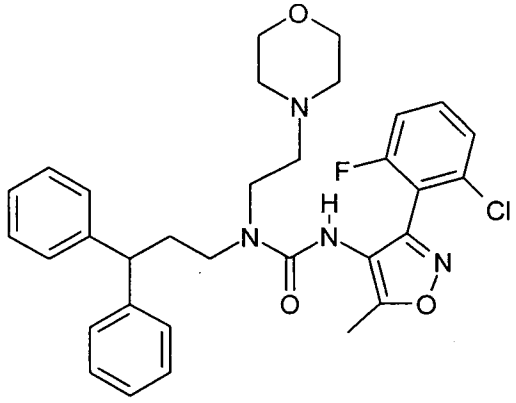
MS: 525.50^{+} $(M+H)^{+}$

TLC: Rf = 0.11 (eluent: DCM/MeOH 97/3)

EXAMPLE 112

3-[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "E" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : ppm 8.36-8.22 (s el, 1H, NH), 7.50-7.43 (m, 1H, aromatic H), 7.36 (d, 1H, aromatic H), 7.32-7.15 (m, 11H, aromatic H), 3.91 (t, 1H, CH), 3.49-3.42 (m, 4H, CH2), 3.30 (t, 2H, CH2), 3.18 (t, 2H, CH2), 2.45-2.39 (m, 5H, CH2+CH3), 2.37-2.30 (m, 4H, CH2), 2.23 (q, 2H, CH2).

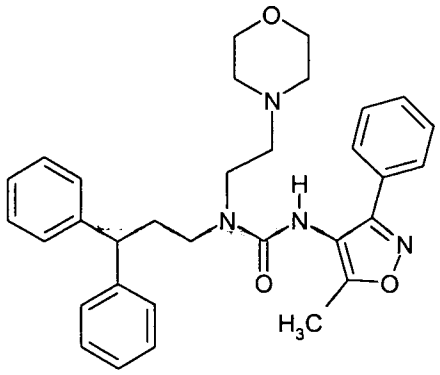
MS: 577.48^{+} $(M+H)^{+}$

TLC: Rf = 0.11 (97/3 DCM/MeOH)

EXAMPLE 113

1-(3,3-diphenylpropyl)-3-(5-methyl-3-phenylisoxazol-4-yl)-1-(2-morpholin-4-ylethyl)urea

Method "E" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : ppm 8.85-8.55 (s el, 1H, NH), 7.80-7.72 (m, 2H, aromatic H), 7.50-7.41 (m, 3H, aromatic H), 7.40-7.25 (m, 8H, aromatic H), 7.21-7.13 (m, 2H, aromatic H), 4.07-3.98 (m, 1H, CH), 3.51-3.43 (m, 2H, CH2), 3.39-3.22 (m, 6H, CH2), 2.57-2.48 (m, 2H, CH2), 2.46-2.27 (m, 9H, CH2+CH3).

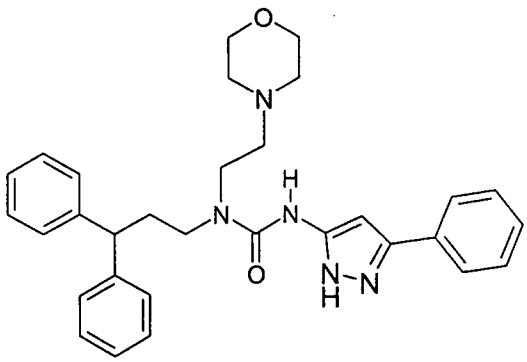
MS: 525.50$^+$ $(M+H)^+$

TLC: Rf = 0.11 (eluent: DCM/MeOH 97/3)

EXAMPLE 114

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-phenyl-2H-pyrazol-3-yl)urea

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : 7.80 (d, 2H, aromatic H), 7.42-7.24 (m, 11H, aromatic H), 7.17 (t, 2H, aromatic H), 5.88-5.82 (s el, 3H, aromatic H+NH), 4.08 (t, 1H, CH), 3.81-3.70 (m, 2H, CH2), 3.63-3.53 (m, 2H, CH2), 3.52-3.46 (m, 4H, CH2), 2.72-2.58 (m, 4H, CH2), 2.36-2.28 (m, 4H, CH2).

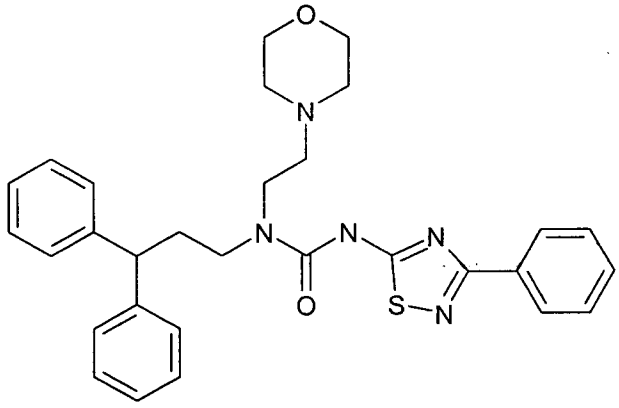
MS: 510.45$^+$ $(M+H)^+$

Rf = 0.50 (eluent: DCM/MeOH 97/3)

EXAMPLE 115

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-phenyl-[1,2,4]thiadiazol-5-yl)urea

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : 8.26 (d, 2H, aromatic H), 7.53-7.43 (m, 3H, aromatic H), 7.39 (d, 4H, aromatic H), 7.30 (t, 4H, aromatic H), 7.19 (t, 2H, aromatic H), 4.16-3.96 (m, 5H, CH+CH2), 3.63-3.57 (m, 2H, CH2), 3.43 (t, 2H, CH2), 2.88-2.65 (m, 6H, CH2), 2.44 (q, 2H, CH2).

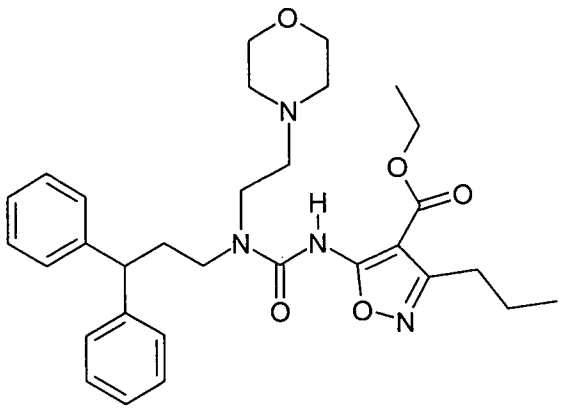
MS: 528.40^+ $(M+H)^+$

TLC: Rf = 0.66 (eluent: DCM/MeOH 97/3)

EXAMPLE 116

5-[3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-3-propyl-isoxazole-4-carboxylic acid ethyl ester

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : 11.00-10.20 (s el, 1H, NH), 7.40 (d, 4H, aromatic H), 7.30 (t, 4H, aromatic H), 7.18 (t, 2H, aromatic H), 4.32 (q, 2H, CH2), 4.10 (t, 1H, CH), 3.60-3.52 (m, 4H, CH2), 3.50 (t, 2H, CH2), 3.37 (t, 2H, CH2), 2.75 (t, 2H, CH2), 2.62-2.40 (m, 8H, CH2), 1.72 (sextuplet, 2H, CH2), 1.34 (t, 3H, CH3), 0.99 (t, 3H, CH3).

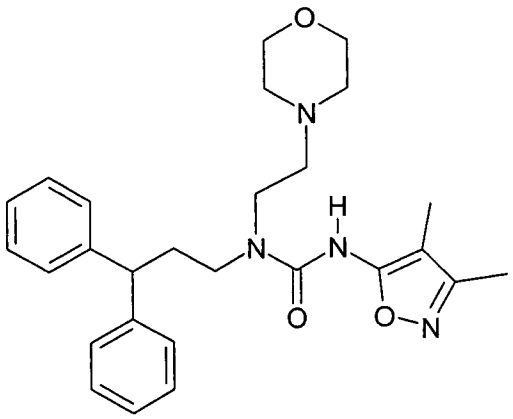
MS: 549.46$^+$ $(M+H)^+$

TLC: Rf = 0.20 (eluent: DCM/MeOH 97/3)

EXAMPLE 117

3-(3,4-dimethyl-isoxazol-5-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea.

Method "D" was used to prepare the product of the following formula:



^{1}H NMR (400 MHz, acetone D6) : 11.30-10.80 (s el, 1H, NH), 7.38 (d, 4H, aromatic H), 7.30 (t, 4H, aromatic H), 7.18 (t, 2H, aromatic H), 4.04 (t, 1H, CH), 3.71-3.62 (m, 4H, CH2),

3.50-3.45 (m, 2H, CH2), 3.32 (t, 2H, CH2), 2.66-2.50 (m, 6H, CH2), 2.42 (q, 2H, CH2), 2.13 (s, 3H, CH3), 1.84 (s, 3H, CH3).

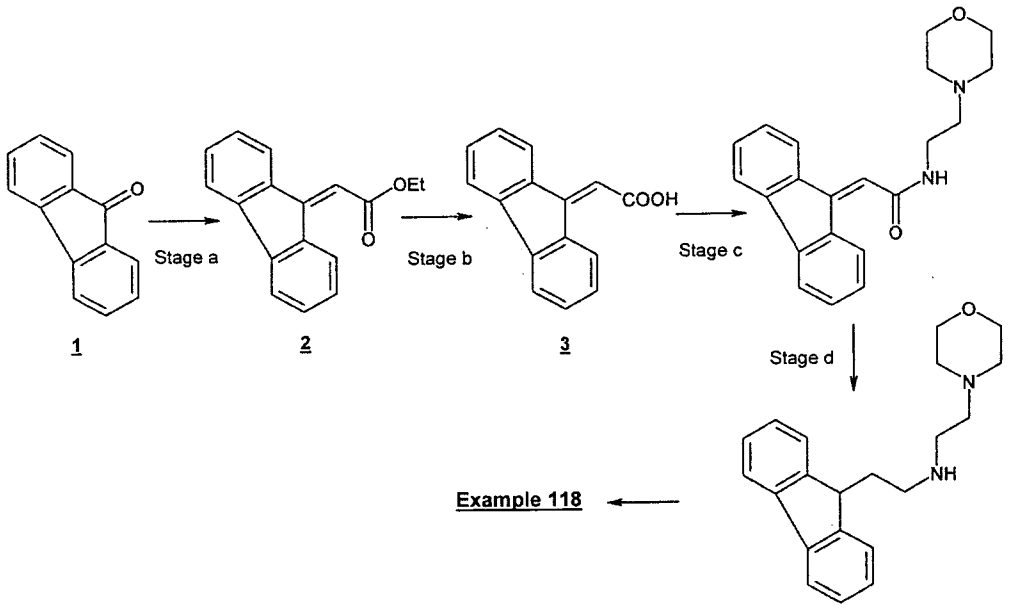
MS: 463.40^{+} $(M+H)^{+}$

TLC: Rf = 0.26 (eluent: DCM/MeOH 97/3)

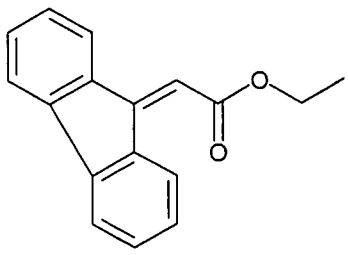
EXAMPLE 118

3-[3-[2-(9H-fluoren-9-yl)-ethyl]-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester

Proceeding as indicated in the following scheme, 3-[3-[2-(9H-fluoren-9-yl)-ethyl]-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester is prepared from fluorenone 1 (Method II-a).



Stage a): Synthesis of fluoren-9-ylidene-acetic acid ethyl ester 2



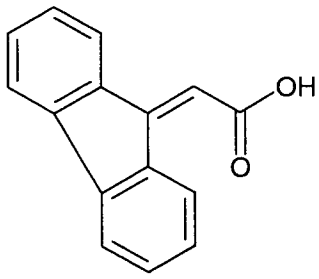
2 g (11.1 mmol, 1 eq.) of 9-fluorenone, **1** in 15 mL of dry THF are dissolved in a flask equipped with a condenser, under argon. 2.86 mL (14.43 mmol, 1.3 eq.) of triethylphosphonoacetate are introduced and 577 mg (14.43 mmol, 1.3 eq.) of 60 % NaH in oil are added batchwise to the solution. The mixture is heated to 70-80 °C for 3 hours, 1.10 mL (5.55 mmol, 1 eq.) of triethylphosphonoacetate and 222 mg (5.55 mmol, 1 eq.) of 60 % NaH in oil are added to the medium. The mixture is stirred for 2 hours at 70-80 °C. Water is added, then the THF is concentrated. The basic aqueous phase is extracted with AcOEt and the organic phase is washed with brine, dried over $MgSO_4$, filtered and concentrated. The oil obtained is subjected to chromatography over silica gel (eluent: heptane/DCM: 1/0 to 0/1) to give the desired product in the form of yellow crystals (m = 1.86 g, yield = 67 %).

^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.42 (t, 3H, CH3), 4.37 (q, 2H, CH2), 6.77 (s, 1H, CH alkene), 7.24-7.47 (m, 7H, aromatic H), 7.60-7.72 (m, 3H, aromatic H), 8.92 (d, 1H, aromatic H).

MS: 251.05$^+$ $(M+H)^+$

TLC: Rf = 0.81 (eluent: DCM 100%)

Stage b: Synthesis of fluoren-9-ylidene-acetic acid **3**



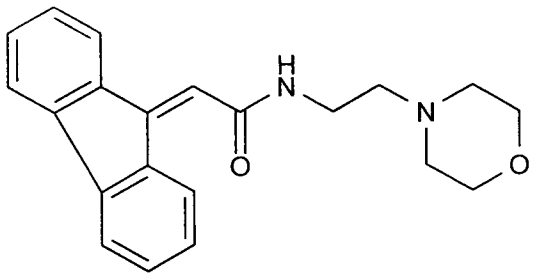
1.85 g (7.39 mmol, 1 eq.) of **2** are introduced into 40 mL of EtOH. 14.8 mL (14.78 mmol, 2 eq.) of 1 N sodium hydroxide are added and the mixture is stirred for 45 min. at 60 °C. The reagent dissolves completely while hot. The ethanol is concentrated, the residue is taken up in the water and AcOEt is added. The aqueous phase is acidified to pH 3, then extracted with AcOEt. The organic phase is washed with brine, dried, filtered and concentrated (m = 1.62 g, yield = 99 %).

^{1}**H NMR**(400 MHz, CD_3OD): ppm 6.87 (s, 1H, CH alkene), 7.26-7.33 (m, 2H, aromatic H), 7.39-7.46 (m, 2H, aromatic H), 7.71 (t, 2H, aromatic H), 7.78 (d, 1H, aromatic H), 8.76 (d, 1H, aromatic H).

MS: 221.18$^-$ $(M-H)^-$

TLC: Rf = 0.31 (eluent: DCM/MeOH 9/1)

Stage c): 2-fluoren-9-ylidene-*N*-(2-morpholin-4-ylethyl)acetamide,



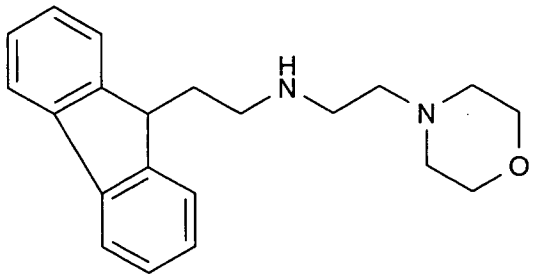
1.62 g (7.28 mmol, 1 eq.) of **3** are dissolved in 30 mL of DCM and 6 mL of DMF under argon. 1.083 g (8.01 mmol, 1.1 eq.) of HOBt and 1.536 g (8.01 mmol, 1.1 eq.) of EDC, HCl are then introduced in succession. The mixture is stirred for 30 min. at room temperature and 1.054 mL (8.01 mmol, 1.1 eq.) of 2-(4-morpholino)ethylamine are added. The mixture is stirred for 5 hours at room temperature. 670 µL (5.10 mmol, 0.7 eq.) of 2-(4-morpholino)ethylamine and 980 mg (5.10 mmol, 0.7 eq.) of EDC, HCl are added. The mixture is stirred for one night at room temperature. Dichloromethane is added, the organic phase is washed with a 0.1 N HCl solution, with a saturated $NaHCO_3$ solution then finally with brine. It is dried over $MgSO_4$, filtered and concentrated. The oil obtained is subjected to chromatography over silica gel (eluent: DCM/MeOH 90/10). The product obtained is recrystallised in AcOEt (yellow crystals, m = 1.86, yield = 76%).

^{1}**H NMR**(400 MHz, $CDCl_3$): ppm 2.44-2.55 (m, 4H, CH2), 2.60 (t, 2H, CH2), 3.58 (q, 2H, CH2), 3.66-3.77 (m, 4H, CH2), 6.44-6.57 (m, 1H, NH), 6.78 (s, 1H, CH alkene), 7.28 (t, 2H, aromatic H), 7.40 (t, 2H, aromatic H), 7.67 (d, 3H, aromatic H), 8.60 (d, 1H, aromatic H).

MS: 335.04$^+$ $(M+H)^+$

TLC: Rf = 0.46 (eluent: DCM/MeOH/NH_4OH: 90/10/0.5)

Stage d): [2-(9H-fluoren-9-yl)ethyl](2-morpholin-4-ylethyl)amine



1 g (2.99 mmol, 1 eq.) of product obtained in stage c) above are dissolved in 24 ml of THF in a 250 mL flask placed in an argon atmosphere. After cooling the solution to 0 °C, 200 mg (1.50 mmol, 0.5 eq.) of $AlCl_3$ are added batchwise. Once the medium has become homogeneous, 7.48 mL (7.48 mmol, 2.5 eq.) of $LiAlH_4$ in a 1 M solution in THF are added smoothly. The mixture is kept at 0 °C during addition. The mixture is subsequently heated under reflux (60 °C) for 1 hour then cooled to 0 °C. 7 mL of water are then added very slowly to the solution to avoid a violent reaction. The salts are filtered and rinsed with ethyl acetate. The filtrate is recovered, water is added and the aqueous phase is extracted with ethyl acetate. The organic phase is washed once with water then once with brine, is subsequently dried over $MgSO_4$, filtered and concentrated. The paste obtained is subjected to chromatography over silica gel (eluent: DCM/MeOH gradient: 99/1 to 7/3) (colourless oil, m = 801 mg, yield = 83 %).

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.30 (q, 2H, CH2), 2.34-2.40 (m, 4H, CH2), 2.41 (t, 2H, CH2), 2.50 (t, 2H, CH2), 2.61 (t, 2H, CH2), 3.63-3.70 (m, 4H, CH2), 4.09 (t, 1H, CH), 7.32 (t, 2H, aromatic H), 7.39 (t, 2H, aromatic H), 7.54 (d, 2H, aromatic H), 7.77 (d, 2H, aromatic H).

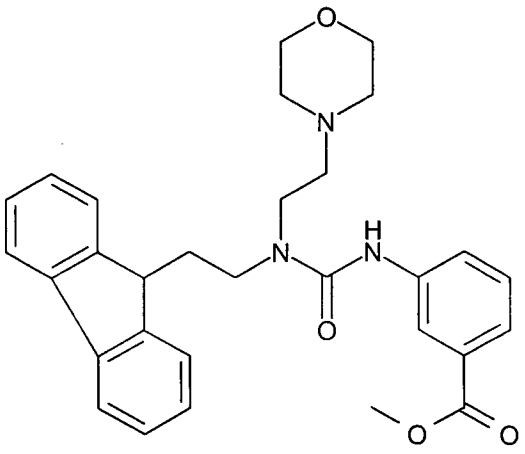
MS: 323.27^+ $(M+H)^+$

TLC: Rf = 0.38 (eluent: DCM/MeOH 90/10)

EXAMPLE 118

3-[3-[2-(9H-fluoren-9-yl)ethyl]-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester

Method "A", but replacing (3,3-di-propyl)(2-morpholin-4-ylethyl)amine with [2-(9H-fluoren-9-yl)ethyl](2-morpholin-4-ylethyl)amine, was used to prepare the title compound having the following formula:



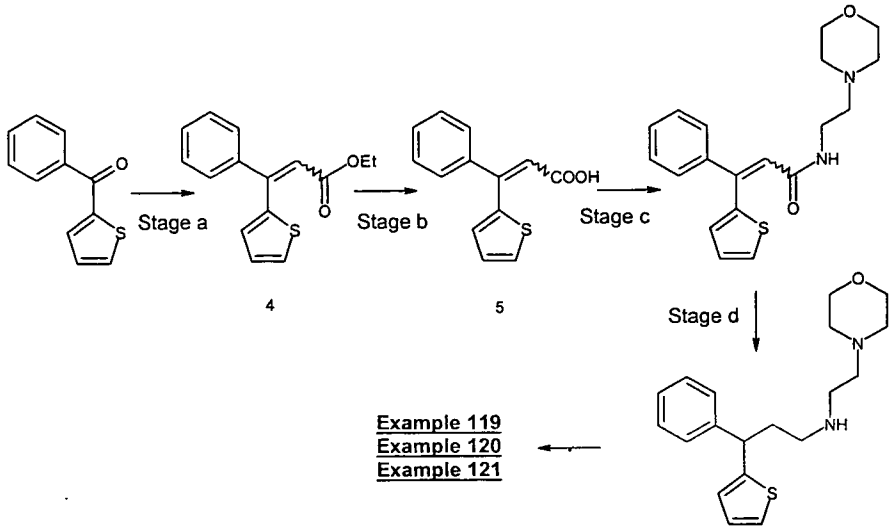
^{1}H NMR(400 MHz, CD_3COCD_3): ppm 2.40 (q, 2H, CH2), 2.48-2.56 (m, 4H, CH2), 2.58 (t, 2H, CH2), 3.28 (t, 2H, CH2), 3.44 (t, 2H, CH2), 3.66 (t, 4H, CH2), 3.89 (s, 3H, CH3), 4.10 (t, 1H, CH), 7.32-7.45 (m, 5H, aromatic H), 7.59 (d, 1H, aromatic H), 7.73 (d, 2H, aromatic H), 7.83-7.90 (m, 3H, aromatic H), 8.14 (s, 1H, aromatic H), 9.25-9.35 (m, 1H, NH).

MS: 500.27^+ $(M+H)^+$

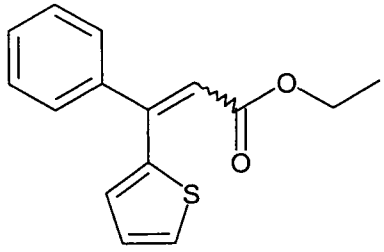
TLC: Rf = 0.30 (eluent: AcOEt 100%)

The secondary amine (2-morpholin-4-ylethyl)(3-phenyl-3-thiophen-2-ylpropyl)-amine (product obtained in stage d) of Example 119) is synthesised in the same way as the secondary amine [2-(9H-fluoren-9-yl)ethyl](2-morpholin-4-ylethyl)amine obtained in stage 3) of the present Example using method IIa.

EXAMPLES 119-121



Stage a): Synthesis of 3-phenyl-3-thiophen-2-ylacrylic acid ethyl ester, **4**
(mixture of 2 isomers Z and E) (proportion: 1/1)

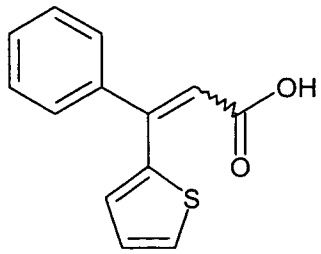


^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.12 (t, 3H, CH3), 1.25 (t, 3H, CH3), 4.05 (q, 2H, CH2), 4.18 (q, 2H, CH2), 6.22 (s, 1H, CH alkene), 6.43 (s, 1H, CH alkene), 6.88 (d, 1H, aromatic H), 6.99 (t, 1H, aromatic H), 7.08 (t, 1H, aromatic H), 7.19 (d, 1H, aromatic H), 7.27-7.33 (m, 2H, aromatic H), 7.35-7.49 (m, 10H, aromatic H)

MS: 259.0^+ $(M+H)^+$

TLC: Rf: = 0.64 (Alumina, eluent: heptane/DCM 2/1)

Stage b): Synthesis of 3-phenyl-3-thiophen-2-ylacrylic acid, **5**
(mixture of 2 isomers Z and E) (proportion: 1/1)

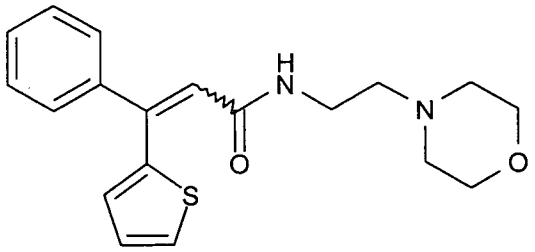


^{1}H NMR(400 MHz, $CDCl_3$): ppm 6.17 (s, 1H, CH alkene), 6.41 (s, 1H, CH alkene), 6.90 (d, 1H, aromatic H), 7.00 (t, 1H, aromatic H), 7.08 (t, 1H, aromatic H), 7.25 (d, 1H, aromatic H), 7.27-7.34 (m, 2H, aromatic H), 7.35-7.45 (m, 9H, aromatic H), 7.48 (d, 1H, aromatic H).

MS: 229.17$^-$ $(M-H)^-$

TLC: Rf = 0.46 (**isomer 1**) and 0.53 (**isomer 2**) (eluent: DCM/MeOH 9/1)

Stage c): N-(2-morpholin-4-ylethyl)-3-phenyl-3-thiophen-2-ylacrylamide (mixture of 2 isomers Z and E) (proportion: 1/1).

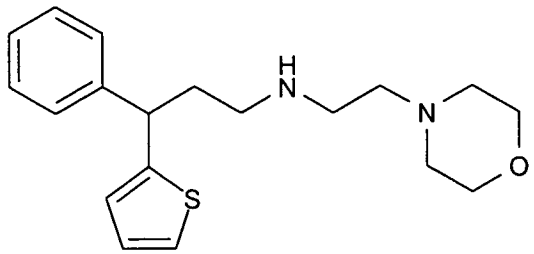


^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.19 (t, 2H, CH2), 2.20-2.27 (m, 4H, CH2), 2.28-2.40 (m, 6H, CH2), 3.21 (q, 2H, CH2), 3.33 (q, 2H, CH2), 3.56-3.68 (m, 8H, CH2), 5.61-5.73 (m, 1H, NH), 6.01-6.13 (m, 1H, NH), 6.32 (s, 1H, CH alkene), 6.47 (s, 1H, CH alkene), 6.80 (d, 1H, aromatic H), 6.97 (t, 1H, aromatic H), 7.07 (t, 1H aromatic H), 7.16 (d, 1H, aromatic H), 7.30-7.50 (m, 12H, aromatic H).

MS: 343.10$^+$ $(M+H)^+$

TLC: Rf = 0.44 (eluent: DCM/MeOH 95/5)

Stage d): (2-morpholin-4-ylethyl)(3-phenyl-3-thiophen-2-ylpropyl)amine



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.18-2.38 (m, 2H, CH2), 2.39-2.50 (m, 6H, CH2), 2.56-2.70 (m, 4H, CH2), 3.71 (t, 4H, CH2), 4.25 (t, 1H, CH), 6.84 (d, 1H, aromatic H), 6.92 (t, 1H, aromatic H), 7.15 (d, 1H, aromatic H), 7.19-7.35 (m, 4H, aromatic H).

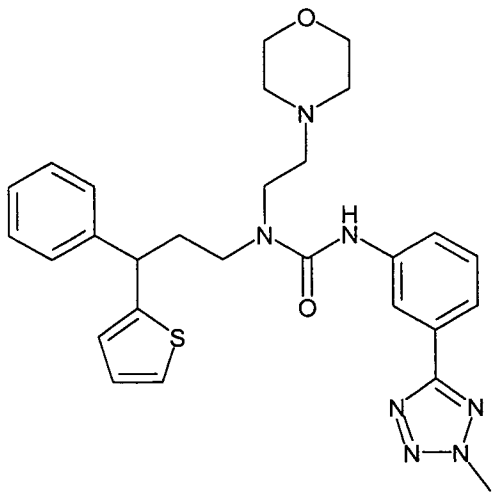
MS: 331.14$^+$ $(M+H)^+$

TLC: Rf = 0.37 (eluent: DCM/MeOH 9/1)

EXAMPLE 119

3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)-1-(3-phenyl-3-thiophen-2-ylpropyl)urea

Method "D" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, CD_3COCD_3): ppm 2.40-2.58 (m, 6H, CH2), 2.62 (t, 2H, CH2), 3.30-3.54 (m, 4H, CH2), 3.69 (t, 4H, CH2), 4.32 (t, 1H, CH), 4.44 (s, 3H, CH3), 6.96 (t, 1H,

aromatic H), 7.04 (s, 1H, aromatic H), 7.23 (t, 1H, aromatic H), 7.28 (d, 1H, aromatic H), 7.34 (t, 2H, aromatic H), 7.38-7.46 (m, 3H, aromatic H), 7.68-7.76 (m, 2H, aromatic H), 8.31 (s, 1H, aromatic H), 9.16-9.26 (m, 1H, NH).

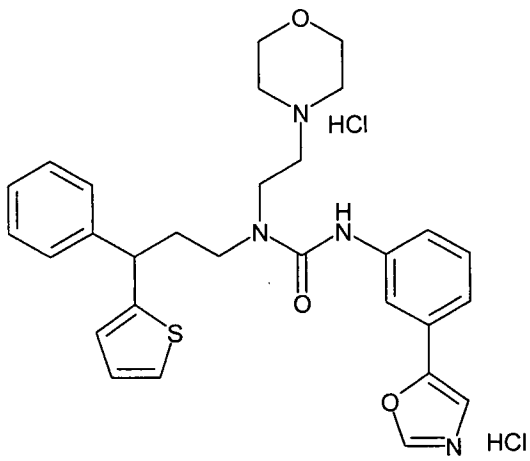
MS: 532.09^{+} $(M+H)^{+}$

TLC: Rf = 0.59 (eluent: AcOEt)

EXAMPLE 120

1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)-1-(3-phenyl-3-thiophen-2-yl-propyl)urea dihydrochloride

Method "D" then "F" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, DMSO): ppm 2.28-2.45 (m, 2H, CH2), 3.00-3.16 (m, 2H, CH2), 3.19-3.29 (m, 2H, CH2), 3.33-3.57 (m, 4H, CH2), 3.64-3.80 (m, 4H, CH2), 3.90-4.03 (m, 2H, CH2), 4.31 (t, 1H, CH), 6.96 (t, 1H, aromatic H), 7.04 (s, 1H, aromatic H), 7.23 (t, 1H, aromatic H), 7.28-7.42 (m, 7H, aromatic H), 7.46-7.55 (m, 1H, aromatic H), 7.60 (s, 1H, aromatic H), 7.87-7.92 (m, 1H, aromatic H), 8.45 (s, 1H, aromatic H), 8.50-8.56 (m, 1H, NH).

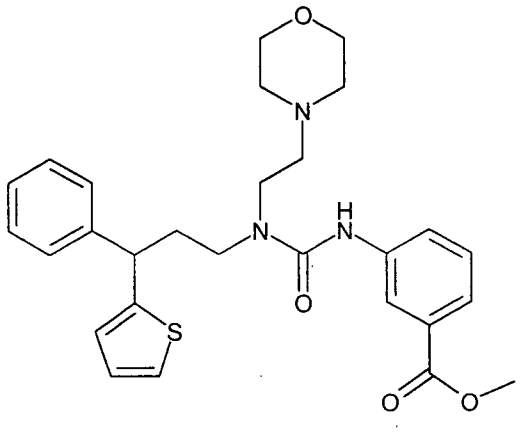
MS: 517.15^{+} $(M+H-2HCl)^{+}$

TLC: Rf = 0.30 (eluent: AcOEt 100%)

EXAMPLE 121

3-[3-(2-morpholin-4-ylethyl)-3-(3-phenyl-3-thiophen-2-ylpropyl)ureido]benzoic acid methyl ester

Method "A" was used to prepare the title compound having the following formula:



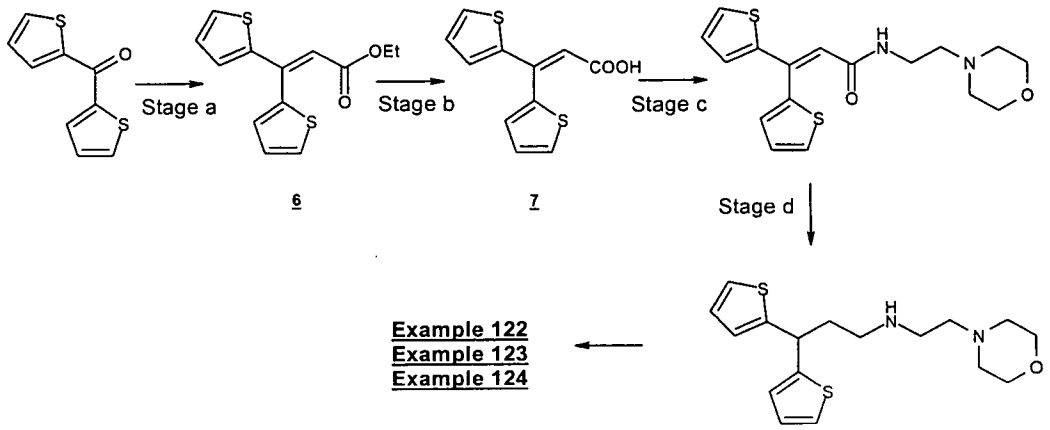
^{1}H NMR(400 MHz, CD_3COCD_3): ppm 2.39-2.51 (m, 2H, CH2), 2.52-2.57 (m, 4H, CH2), 2.61 (t, 2H, CH2), 3.29-3.38 (m, 1H, CH), 3.38-3.47 (m, 1H, CH), 3.48-3.53 (m, 2H, CH2), 3.68 (t, 4H, CH2), 3.88 (s, 3H, CH3), 4.31 (t, 1H, CH), 6.95 (t, 1H, aromatic H), 7.03 (s, 1H, aromatic H), 7.23 (t, 1H, aromatic H), 7.28 (d, 1H, aromatic H), 7.30-7.43 (m, 5H, aromatic H), 7.59 (d, 1H, aromatic H), 7.87 (d, 1H, aromatic H), 8.14 (s, 1H, aromatic H), 9.20-9.30 (m, 1H, NH).

MS: 508.23$^+$ $(M+H)^+$

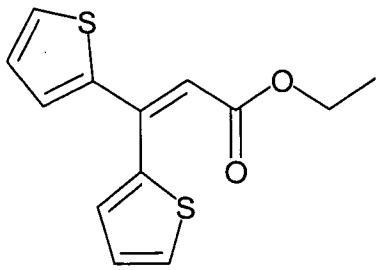
TLC: Rf = 0.32 (eluent: AcOEt 100%)

The secondary amine (3,3-dithiophen-2-yl-propyl)(2-morpholin-4-ylethyl)amine (product obtained in stage d) of Example 122) is synthesised in the same way as the secondary amine [2-(9H-fluoren-9-yl)ethyl](2-morpholin-4-ylethyl)amine obtained in stage d) of Example 118 using method IIa.

EXAMPLES 122-124



Stage a): Synthesis of 3,3-dithiophen-2-ylacrylic acid diethyl ester, **6**

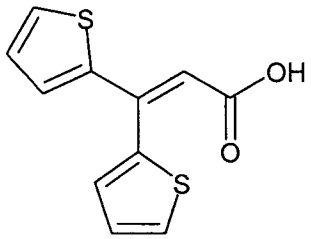


^{1}H NMR(400 MHz, $CDCl_3$): ppm 1.20 (t, 3H, CH3), 4.12 (q, 2H, CH2), 6.42 (s, 1H, CH alkene), 7.02 (t, 1H, aromatic H), 7.07-7.13 (m, 2H, aromatic H), 7.14-7.18 (m, 1H, aromatic H), 7.38 (d, 1H, aromatic H), 7.46 (d, 1H, aromatic H).

MS: 265.0^+ $(M+H)^+$

TLC: Rf: = 0.61 (Alumina, eluent: heptane/AcOEt 8/1)

Stage b): Synthesis of 3,3-dithiophen-2-ylacrylic acid, **7**

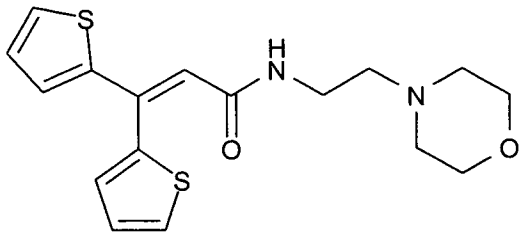


^{1}H NMR(400 MHz, $CDCl_3$): ppm 6.38 (s, 1H, CH alkene), 7.05 (t, 1H, aromatic H), 7.08-7.16 (m, 2H, aromatic H), 7.18-7.22 (m, 1H, aromatic H), 7.43 (d, 1H, aromatic H), 7.48 (d, 1H, aromatic H).

MS: 235.11$^-$ $(M-H)^-$

TLC: Rf = 0.41 (eluent: DCM/MeOH 9/1)

Stage c): *N*-(2-morpholin-4-ylethyl)-3,3-dithiophen-2-ylacrylamide

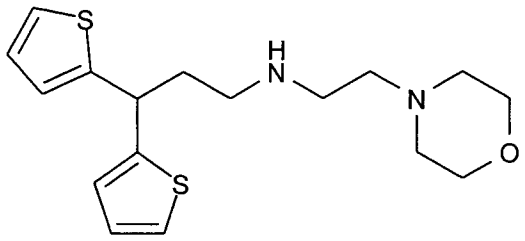


^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.24-2.36 (m, 6H, CH2), 3.28 (q, 2H, CH2), 3.64 (t, 4H, CH2), 5.92-6.04 (m, 1H, NH), 6.48 (s, 1H, CH alkene), 6.98-7.03 (m, 2H, aromatic H), 7.11 (t, 1H, aromatic H), 7.21 (d, 1H, aromatic H), 7.34 (d, 1H, aromatic H), 7.46 (d, 1H, aromatic H).

MS: 349.06$^+$ $(M+H)^+$

TLC: Rf = 0.43 (eluent: DCM/MeOH 90/10)

Stage d): (3,3-dithiophen-2-ylpropyl)(2-morpholin-4-ylethyl)amine



^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.33 (q, 2H, CH2), 2.38-2.46 (m, 4H, CH2), 2.48 (t, 2H, CH2), 2.68 (q, 4H, CH2), 3.71 (t, 4H, CH2), 4.61 (t, 1H, CH), 6.89-6.96 (m, 4H, aromatic H), 7.17 (d, 2H, aromatic H).

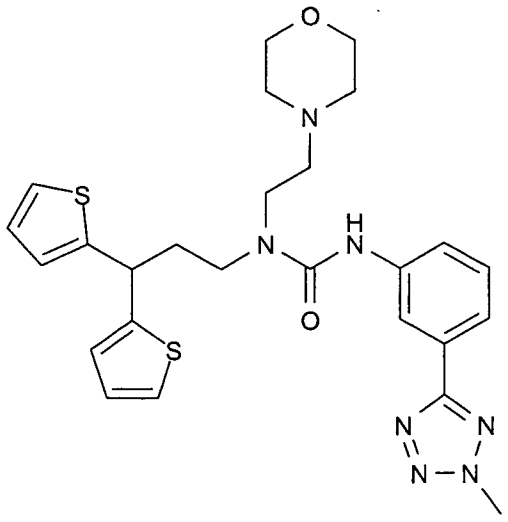
MS: 337.16^+ $(M+H)^+$

TLC: Rf = 0.39 (eluent: DCM/MeOH 9/1)

EXAMPLE 122

1-(3,3-di-thiophen-2-ylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, CD_3COCD_3): ppm 2.49 (q, 2H, CH2), 2.54-2.59 (m, 4H, CH2), 2.61-2.66 (m, 2H, CH2), 3.44 (t, 2H, CH2), 3.54 (t, 2H, CH2), 3.67-3.74 (m, 4H, CH2), 4.45 (s, 3H, CH3), 4.66 (t, 1H, CH), 6.94-7.00 (m, 2H, aromatic H), 7.07 (s, 2H, aromatic H), 7.32 (d,

2H, aromatic H), 7.43 (t, 1H, aromatic H), 7.68-7.77 (m, 2H, aromatic H), 8.32 (s, 1H, aromatic H), 9.19-9.28 (m, 1H, NH).

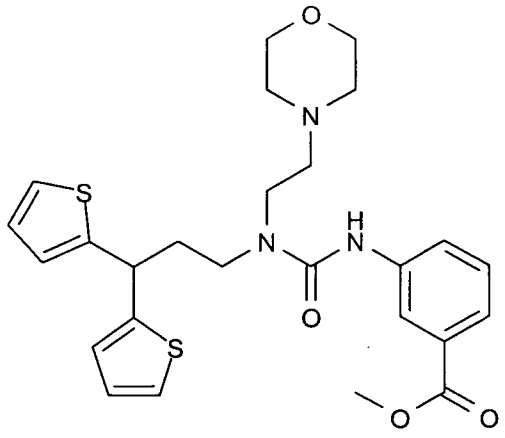
MS: 538.15^{+} $(M+H)^{+}$

TLC: Rf = 0.26 (eluent: Rf = 0.48 (eluent: AcOEt 100%)

EXAMPLE 123

3-[3-(3,3-dithiophen-2-yl-propyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester

Method "A" was used to prepare the title compound having the following formula:



^{1}H NMR(400 MHz, CD_3COCD_3): ppm 2.47 (q, 2H, CH2), 2.52-2.59 (m, 4H, CH2), 2.63 (t, 2H, CH2), 3.42 (t, 2H, CH2), 3.52 (t, 2H, CH2), 3.66-3.73 (m, 4H, CH2), 3.88 (s, 3H, CH3), 4.65 (t, 1H, CH), 6.94-6.99 (m, 2H, aromatic H), 7.06 (s, 2H, aromatic H), 7.32 (d, 2H, aromatic H), 7.40 (t, 1H, aromatic H), 7.60 (d, 1H, aromatic H), 7.88 (d, 1H, aromatic H), 8.15 (s, 1H, aromatic H), 9.23-9.32 (m, 1H, NH).

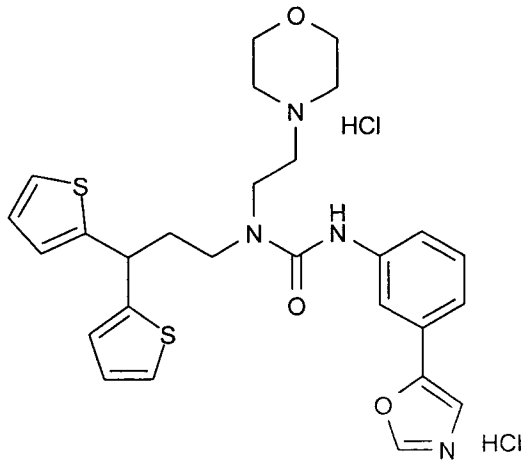
MS: 514.21^{+} $(M+H)^{+}$

TLC: Rf = 0.33 (eluent: AcOEt 100%)

EXAMPLE 124

1-(3,3-dithiophen-2-ylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea dihydrochloride

Method "D" then "F" was used to prepare the title compound having the following formula:



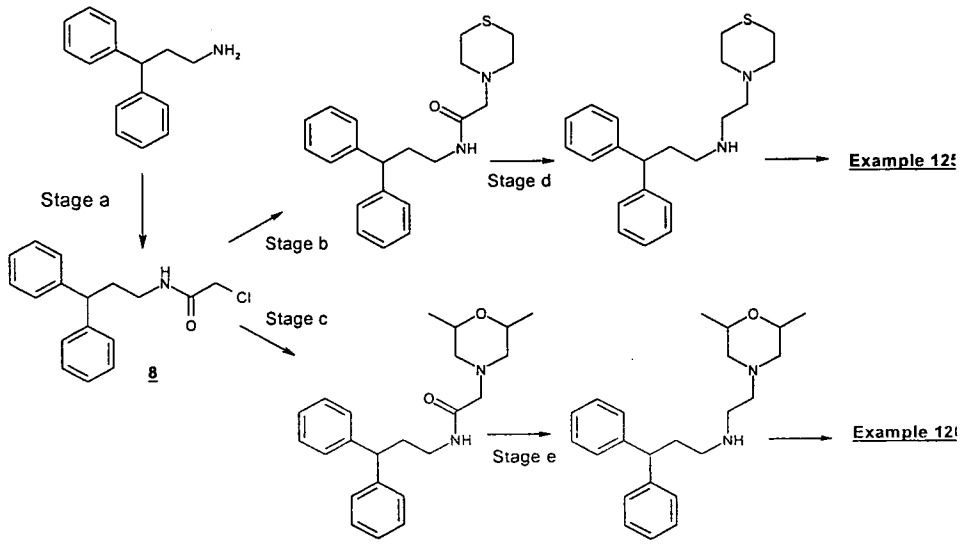
^{1}H NMR(400 MHz, DMSO): ppm 2.36 (q, 2H, CH2), 3.02-3.17 (m, 2H, CH2), 3.20-3.30 (m, 2H, CH2), 3.38 (t, 2H, CH2), 3.42-3.63 (m, 2H, CH2), 3.68-3.81 (m, 4H, CH2), 3.90-4.04 (m, 2H, CH2), 4.66 (t, 1H, CH), 6.94-6.99 (m, 2H, aromatic H), 7.06 (s, 2H, aromatic H), 7.30-7.45 (m, 4H, aromatic H), 7.49-7.56 (m, 1H, aromatic H), 7.60 (s, 1H, aromatic H), 7.86-7.94 (m, 1H, aromatic H), 8.45 (s, 1H, aromatic H), 8.56 (m, 1H, NH).

MS: 523.11^+ $(M+H)^+$

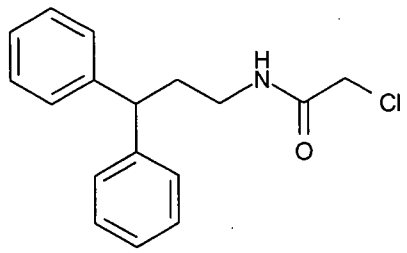
TLC: Rf = 0.27 (eluent: AcOEt 100%)

Synthesis of a thiomorpholine derivative and a dimethylmorpholine derivative using method IV.

EXAMPLES 125 - 126



Stage a): Synthesis of *N*-chloromethyl-3,3-diphenylpropionamide, **8**:



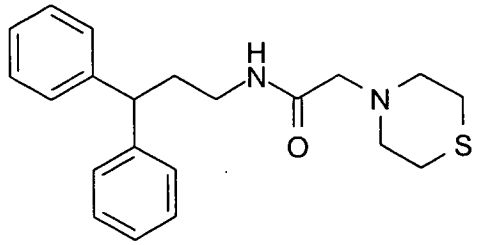
1 g (4.73 mmol, 1 eq.) of 3,3-diphenylpropylamine and 732 µL (5.21 mmol, 1.1 eq.) of triethylamine are diluted in 30 mL of DCM at 0 °C under argon. 300 µL (3.77 mmol, 0.8 eq.) of chloroacetyl chloride are added dropwise. White fumes form then gradually dissipate. The mixture is stirred for 45 min. at 0 °C, the solution becomes red. A dilute HCl solution is added then the aqueous phase is extracted with DCM. The organic phase is washed once with water then once with brine, dried over $MgSO_4$, filtered and concentrated. The product is obtained in the form of an oil (m = 1.36 g, yield = 100%).

^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.24 (q, 2H, CH2), 3.21 (q, 2H, CH2), 3.82-3.92 (m, 3H, CH+CH2), 6.37-6.50 (m, 1H, NH), 7.06-7.25 (m, 10H, aromatic H).

MS: 288.09$^+$ $(M+H)^+$, 329.11$^+$ $(M+H+CH_3CN)^+$

TLC: Rf = 0.73 (eluent: DCM/MeOH 95/5)

Stage b: N-(3,3-diphenylpropyl)-2-thiomorpholin-4-ylacetamide



700 mg (2.43 mmol, 1 eq.) of *N*-chloromethyl-3,3-diphenylpropionamide, **8**, 508 µL (2.92 mmol, 1.2 eq.) of diisopropylethylamine, 245 µL (2.43 mmol, 1 eq.) of thiomorpholine and 5 mL of DMF are introduced into a sealed tube. The mixture is heated for 8 min. under microwaves at 180 °C. A saturated sodium bicarbonate solution is added to the mixture and the aqueous phase is extracted with ethyl acetate. The organic phase is washed with brine, dried, filtered concentrated. The solid obtained is recrystallised in diethyl ether (m = 769 mg, yield = 89%).

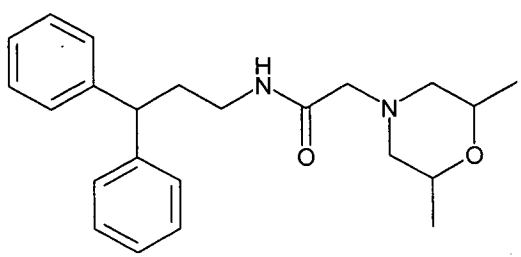
^{1}H NMR(400 MHz, $CDCl_3$): ppm 2.32 (q, 2H, CH2), 2.55-3.10 (m, 10H, CH2), 3,28 (q, 2H, CH2), 3.99 (t, 1H, CH), 7.16-7.23 (m, 2H, aromatic H), 7.24-7.36 (m, 8H, aromatic H).

MS: 355.12$^+$ $(M+H)^+$

TLC: Rf = 0.20 (eluent: heptane/AcOEt 1/1)

Stage c): 2-(2,6-dimethylmorpholin-4-yl)-*N*-(3,3-diphenylpropyl)acetamide (mixture of 3 isomers)

Method IV, but replacing the thiomorpholine with 2,6-dimethylmorpholine (cis/trans mixture), was used to prepare the title compound having the following formula:

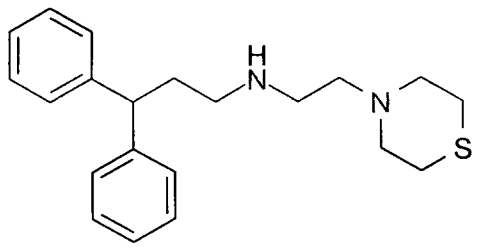


MS: 367.17^{+} $(M+H)^{+}$

TLC: Rf: 0.17 (eluent: heptane/AcOEt 1/1)

Stage d): (3,3-diphenylpropyl)(2-thiomorpholin-4-ylethyl)amine

Starting from the product obtained in stage b), method II, route b was used to obtain the title compound having the following formula:



^{1}H NMR(300 MHz, $CDCl_3$): ppm 2.20 (q, 2H, CH2), 2.40 (t, 2H, CH2), 2.46-2.64 (m, 12H, CH2), 3.92 (t, 1H, CH), 7.06-7.24 (m, 10H, aromatic H).

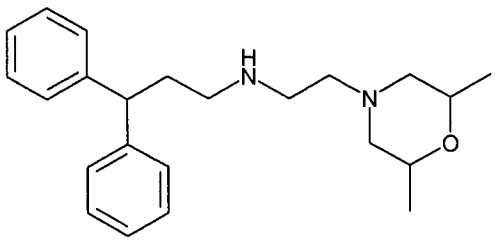
MS: 341.25^{+} $(M+H)^{+}$

TLC: Rf = 0.30 (eluent: DCM/MeOH 95/5)

(mixture of 3 isomers)

Stage e): [2-(2,6-dimethylmorpholin-4-yl)ethyl](3,3-diphenylpropyl)amine

Starting from the product obtained in stage c), method II, route b was used to obtain the title compound having the following formula:



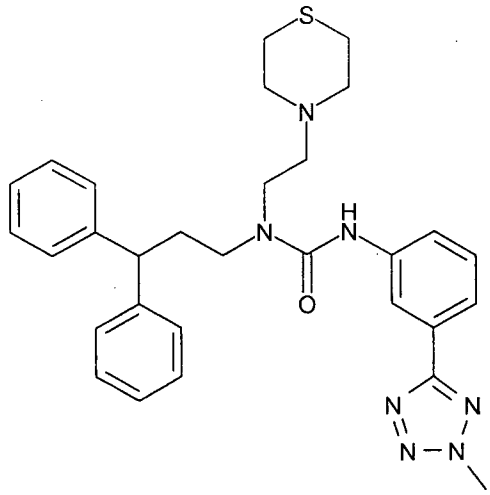
MS: 353.3^{+} $(M+H)^{+}$

TLC: Rf = 0.28 (eluent: DCM/MeOH 95/5)

EXAMPLE 125

1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-thiomorpholin-4-ylethyl)urea

Method "D" was used to prepare the title compound having the following formula:



^{1}H NMR(300 MHz, CD_3COCD_3): ppm 2.46 (q, 2H, CH2), 2.62 (t, 2H, CH2), 2.66-2.72 (m, 4H, CH2), 2.76-2,86 (m, 4H, CH2), 3.36 (t, 2H, CH2), 3.50 (t, 2H, CH2), 4.06 (t, 1H, CH), 4.44 (s, 3H, CH3), 7.18 (t, 2H, aromatic H), 7.31 (t, 4H, aromatic H), 7.36-7.46 (m, 5H, aromatic H), 7.70 (d, 2H, aromatic H), 8.30 (s, 1H, aromatic H), 9.10-9.17 (m, 1H, NH).

MS: 542.15^{+} $(M+H)^{+}$

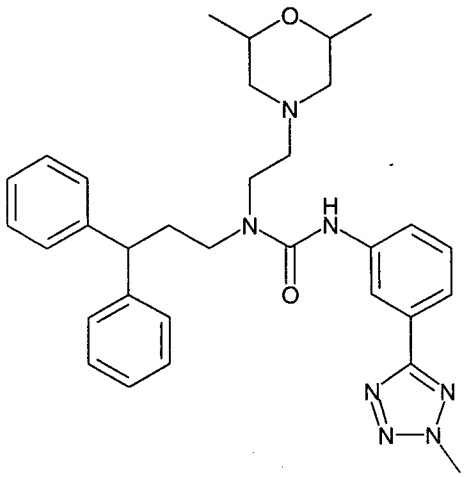
TLC: Rf = 0.22 (eluent: heptane/AcOEt 1/1)

(mixture of 3 isomers)

EXAMPLE 126

1-[2-(2,6-dimethylmorpholin-4-yl)-ethyl]-1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]urea

Method "D" was used to prepare the title compound having the following formula:



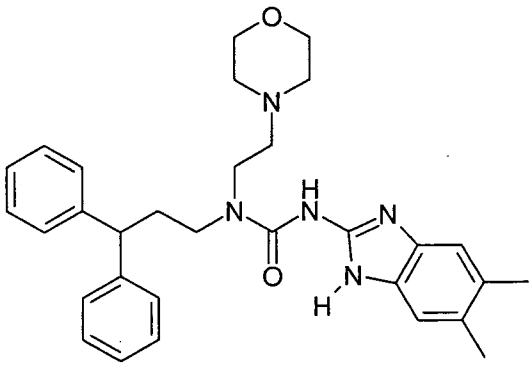
MS: 554.2^{+} $(M+H)^{+}$

TLC: Rf = 0.16 (eluent: heptane/AcOEt 1/1)

EXAMPLE 127

3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the title compound having the following formula:



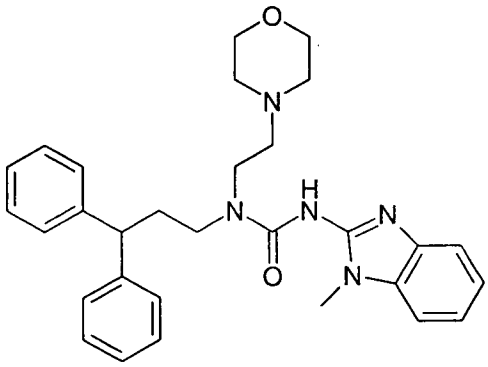
^{1}H NMR (400 MHz, DMSO) ppm 2.20 (s, 6H, 2xCH3), 2.30-2.42 (m, 8H, 4xCH_2), 3.25 (m, 2H, CH_2), 3.40 (m, 2H, CH_2), 3.58 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.03 (s, 2H, aromatic H), 7.16 (m, 2H, aromatic H), 7.29 (m, 4H, aromatic H), 7.32 (m, 4H, aromatic H), 11.50 (brs, 1H, NH)

MS: ES^{+} 512.25^{+} $(M+H)^{+}$

EXAMPLE 128

1-(3,3-Diphenylpropyl)-3-(1-methyl-1H-benzoimidazol-2-yl)-1-(2-morpholin-4-ylethyl)-urea

Method "D" was used to prepare the title compound having the following formula:



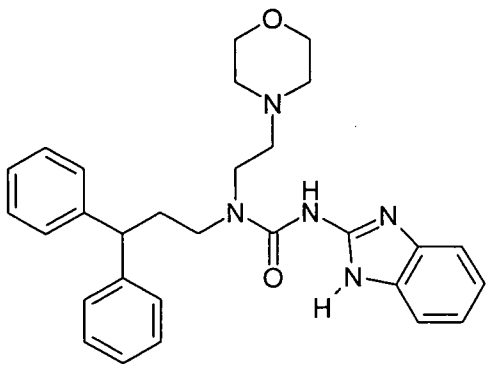
^{1}H NMR (400 MHz, DMSO) ppm 2.30-2.47 (m, 8H, 4xCH_2), 3.21 (m, 1H, CH), 3.28 (s, 2H, CH_2), 3.39 (m, 1H, CH), 3.40 (m, 2H, CH_2), 3.49 (m, 4H, CH_3, CH), 3.57 (m, 1H, CH), 3.97 (t, 1H, CH), 7.08 (m, 2H, aromatic H), 7.16 (m, 3H, aromatic H), 7.29 (m, 5H, aromatic H), 7.32 (m, 4H, aromatic H), 11.80 (s, 1H, NH).

MS: ES^+ 498.3$^+$ $(M+H)^+$

EXAMPLE 129

3-(1H-Benzoimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the title compound having the following formula:



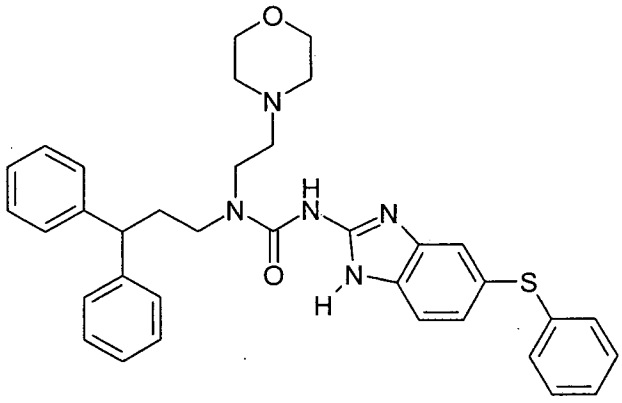
^{1}H NMR (400 MHz, DMSO) ppm 2.30-2.47 (m, 8H, 4xCH_2), 3.28 (m, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.62 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.08 (m, 2H, aromatic H), 7.00 (m, 2H, aromatic H), 7.16 (m, 2H, aromatic H), 7.29 (m, 6H, aromatic H), 7.32 (m, 4H, aromatic H), 11.70 (brs, 1H, NH).

MS: ES^+ 484.34^+ $(M+H)^+$

EXAMPLE 130

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)-3-(5-phenylsulfanyl-1H-benzoimidazol-2-yl)-urea

Method "D" was used to prepare the title compound having the following formula:



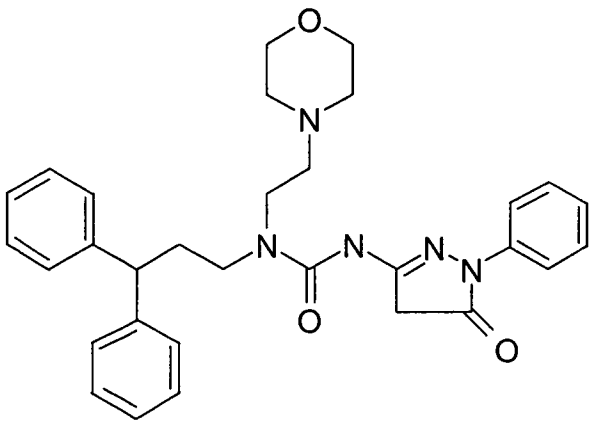
^{1}H NMR (400 MHz, DMSO) ppm 2.31 (q, 2H, CH_2), 2.45 (m, 6H, 3xCH_2), 3.28 (m, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.65 (m, 4H, 2xCH_2), 3.98 (t, 1H, CH), 7.10 (m, 2H, aromatic H), 7.15 (m, 4H, aromatic H), 7.28 (m, 6H, aromatic H), 7.35 (m, 6H, aromatic H), 11.80 (brs, 1H, NH).

MS: ES^+ 592.37^+ $(M+H)^+$

EXAMPLE 131

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)urea

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column Ascentis RP amide 5cm 2.1mn 5 microns (Supelco)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.70

MS: ES+ 526 (M+1) 524 (M-H)

^{1}H NMR (400 MHz, DMSO) ppm

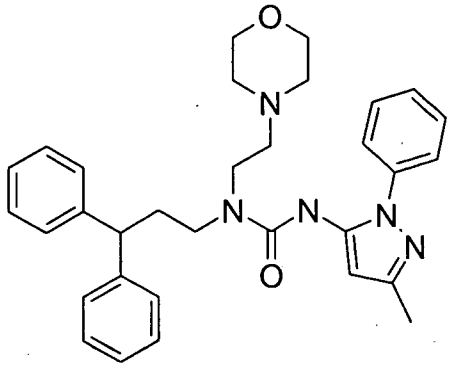
2.3(q,2H) 2.5(m,6H) 3.17(m,2H) 3.35(m,2H s,2H) 3.75(m,4H) 3.95(t,1H)

7.15(m,3H) 7.3(m,4H) 7.35(m,4H) 7.4(m,2H) 7.7(d,1H) 7.82(d,1H)

EXAMPLE 132

1-(3,3-Diphenylpropyl)-3-(5-methyl-2-phenyl-2H-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.46 mn

MS: ES+ 524 (M+H)

522 (M-H)

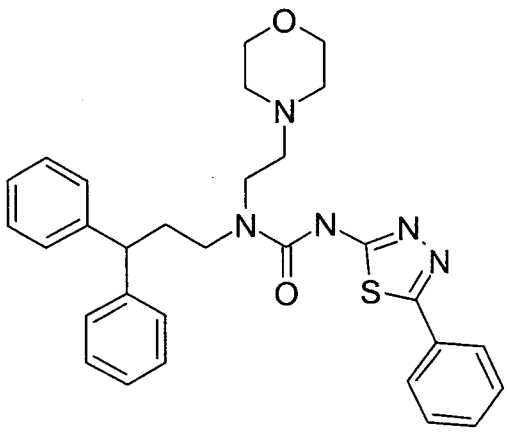
^{1}H NMR (400 MHz, MeOD) ppm

En ppm 2.35(m,6H) 3.5(s,3H) 2.44(t,2H) 3.25(m,2H) 3.5(m, 4H) 3.46(m,3H) 3.95(t,1H) 6.22(s,1H) 7.23(m,2H) 7.33(m,8H) 7.4(m,1H) 7.5(m,2H) 7.55(m,2H)

EXAMPLE 133

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-phenyl[1,3,4] thiadiazol-2-yl)-urea

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.89 mn

MS: ES+ 528 (M+H) 325

^{1}H NMR (400 MHz, DMSO) ppm

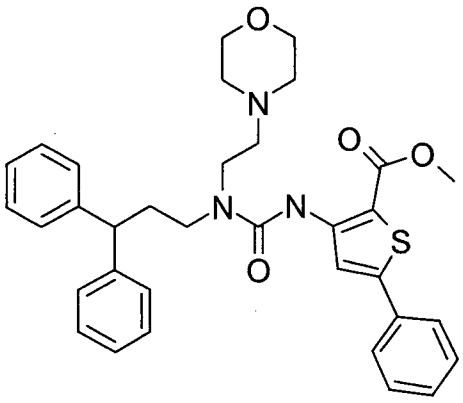
2.33(q,4H) 2.5(m,2H) 3.3(m,4H) 3.45(pic large 4H) 3.72 (large 4H) 3.98(t,1H)

7.17(t,2H) 7.3(m,4H) 7.35(m,4H) 7.5(m,2H) 7.88(m,2H)

EXAMPLE 134

3-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-yl-ethyl)ureido]-5-phenylthiophene-2-carboxylic acid methyl ester

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.97mn

MS: ES+ = 584 (M+H)

^{1}H NMR (400 MHz, MeOD) ppm

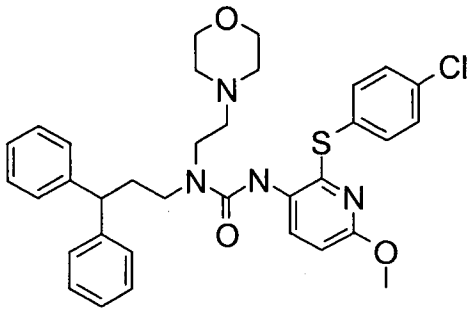
2.45(m,4H) 2.55(m,4H) 3.35(m,4H) 3.5(m,4H) 3.63(m;4H) 3.95(s,3H) 4.15(m,1H)

7.22(m,2H) 7.35(m,4H) 7.4(m,4H) 7.48(m,3H) 7.73(m,2H) 8.25(s,1H)

EXAMPLE 135

3-[2-(4-Chlorophenylsulfanyl)-6-methoxypyridin-3-yl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)urea

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.96 mn

MS: ES+ 618-619 (M+H)

^{1}H NMR (400 MHz, DMSO) ppm

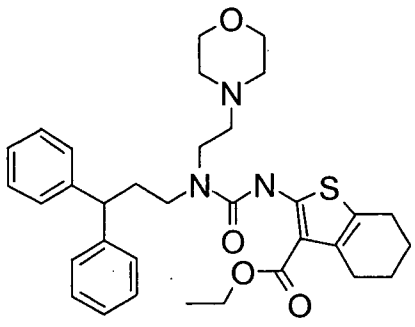
2.32(m,4H) 2.42(t,2H) 3.2(m,2H) 3.35(m,4H) 3.45(m,4H) 3.5(s,3H) 4.0(t,1H)

6.6(d,1H) 7.15(m,2H) 7.28(m,4H) 7.35(m,4H) 7.45(s,4H) 7.54(d,1H)

EXAMPLE 136

2-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid ethyl ester

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 2.44 mn

MS: ES+ 576 (M+H)

^{1}H NMR (400 MHz, MeOD) ppm

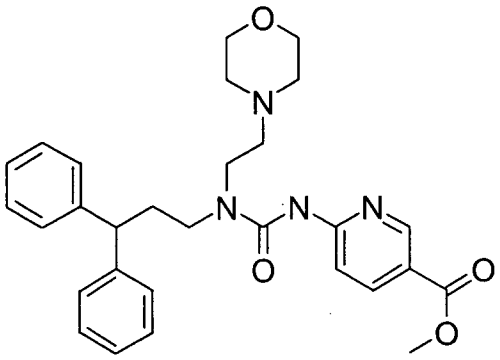
1.42(t,3H) 1.85(large 4H) 2.44 (m,4H) 2.53(m,4H) 2.65(m,2H) 2.82(m,2H)

3.45(m,4H) 3.61(t,4H) 4.12(m,1H) 4.37(q,2H) 7.22(m,2H) 7.35(m,4H) 7.4(m,4H)

EXAMPLE 137

6-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]nicotinic acid methyl ester

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column Ascentis RP amide 5cm 2.1mn 5 microns (Supelco)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.67 MS: ES+503$^+$ (M+H)

^{1}H NMR (400 MHz, DMSO) ppm

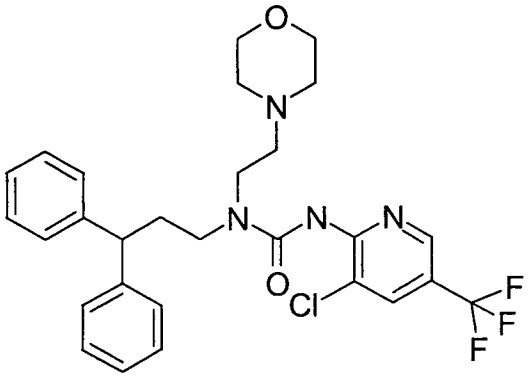
2.32 (q,2H) 2.47(m,6H) 3.32(m,2H) 3.39(m,2H) 3.7(m,4H) 3.97t(1H)

7.15(m,2H) 7.27(m,4H) 7.35(m,4H) 7.9(d,1H) 8.15(dd,1H) 8.75(d,1H)

EXAMPLE 138

3-(3-Chloro-5-trifluoromethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-urea

Method "D" was used to prepare the title compound having the following formula



LC MS

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.68mn

MS: ES+ 547(M+H) 545 (M-H)

^{1}**H NMR** (400 MHz, MeOD) ppm

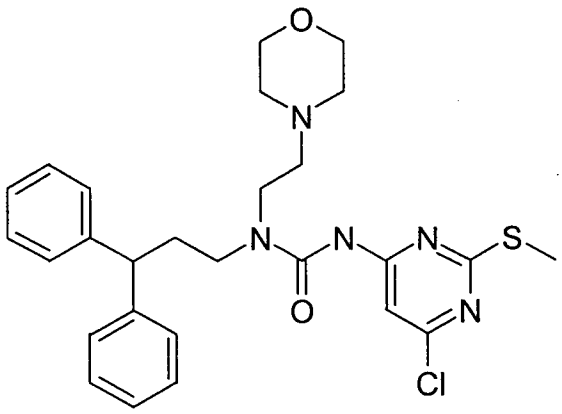
2.49(m,2H) 2.65(m,6H) 3.38(m,2H) 3.58(m,2H) 3.8(m,4H) 4.08(t,1H)

7.22(m,2H) 7.35(m,8H) 8.21(s,1H) 8.63(s,1H)

EXAMPLE 139

3-(6-Chloro-2-methylsulfanylpyrimidin-4-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-urea

Method "D" was used to prepare the title compound having the following formula



LC SM

Column Ascentis RP amide 5cm 2.1mn 5 microns (Supelco)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 4.08

MS: ES+ 527 (M+H)

^{1}H NMR (400 MHz, DMSO) ppm

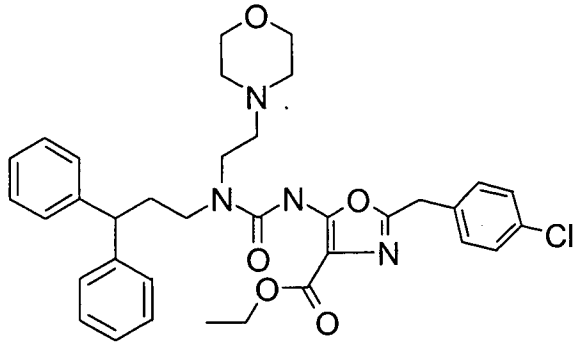
2.3 (q,2H) 2.5(s,3H + m,6H) 3.2(m,2H) 3.38(m,2H) 3.71(m,4H) 3.95(t,1H)

7.15(m,2H) 7.28(m,4H) 7.35(m,2H) 7.51(s,1H)

EXAMPLE 140

2-(4-Chlorobenzyl)-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)-ureido]oxazole-4-carboxylic acid ethyl ester

Method "D" was used to prepare the title compound having the following formula



LC SM

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt=3.82

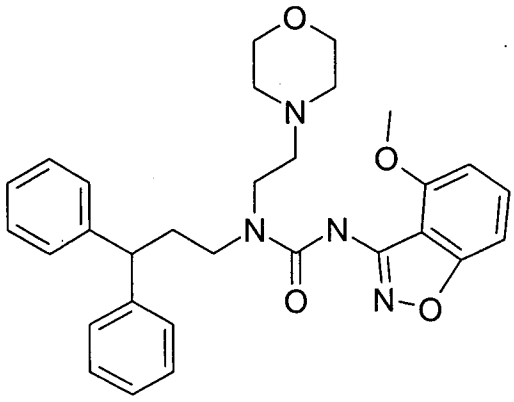
MS: ES+ 632 (M+H)

^{1}H NMR (400 MHz, MeOD) ppm 1.35(t,3H, CH3 ester), 2.45(q,2H), 2.5(m, 4H) , 2.6 (m ,2H) 3.47 (t 2,H) 3.57(m, 3H) 3.35(4H) 4.1(t ,1H) 4.15(s, 2H) 4.35(q, 2H, ester) 7.2(m, 2H,) 7.35(m, 12H,)

EXAMPLE 141

1-(3,3-Diphenylpropyl)-3-(4-methoxybenzo[d]isoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the title compound having the following formula



LC SM

Column Ascentis RP amide 5cm 2.1mn 5 microns (Supelco)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.47

MS: ES+ 515 (M+H) 513 (M-H)

^{1}**H NMR** (400 MHz, DMSO) ppm

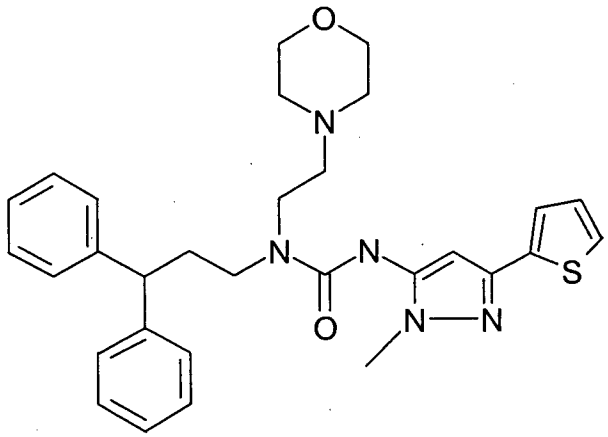
2.37(m,6H) 2.47(m,2H) 3.22(m,2H) 3.41(m,2H) 3.5(m,4H) 3.78(s,3H) 4.0(t,1H)

6.68(d,1H) 7.16(m,3H) 7.3(m,4H) 7.46(m,4H) 7.52(t,1H)

EXAMPLE 142

1-(3,3-Diphenylpropyl)-3-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea

Method "D" was used to prepare the title compound having the following formula



LC SM

Column Ascentis RP amide 5cm 2.1mn 5 microns (Supelco)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.50

MS: ES+ 530 (M+H) 528 (M-H)

^{1}**H NMR** (400 MHz, DMSO) ppm

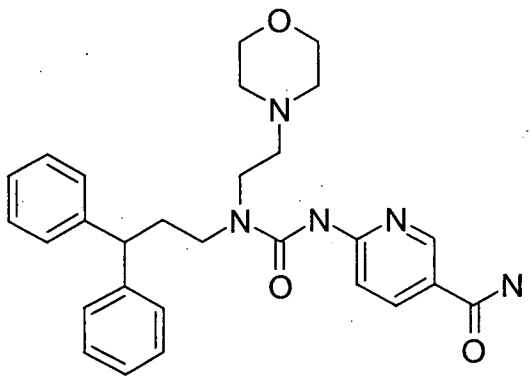
2.32(m,6H) 2.4(t,2H) 3.22(m,2H) 3.35(t ,2H) 3.45(m,4H) 3.95(t,1H)

6.36(s,1H) 7.05(m,1H) 7.17(m,2H) 7.3(m,4H) 7.33(d,1H) 7.36(m,4H) 7.4(d,1H)

EXAMPLE 143

6-[3-(3,3-Diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]nicotinamide

Method "D" was used to prepare the title compound having the following formula:



LC SM

Column Ascentis RP amide 5cm 2.1mn 5 microns (Supelco)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.4 MS:

ES+ 488 (M+H)

^{1}H NMR (400 MHz, DMSO) ppm

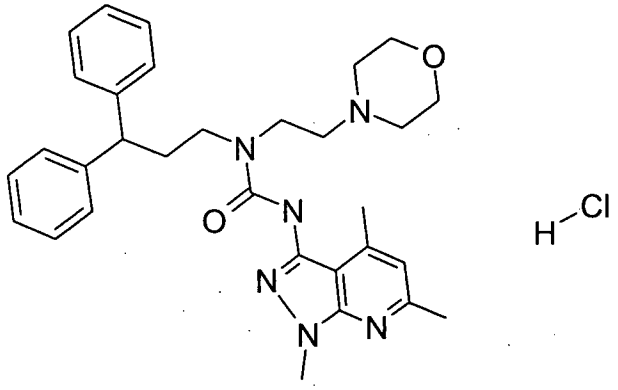
2.3(m,4H) 2.48(m,4H) 3.2(,2H) 3.38(m ;2H) 3.72(,4H) 3.98(t,1H)

7.15(m,2H) 7.3(m,4H) 7.35(m,4H) 7.83(d,1H) 7.95 (H mobile) 8.1(dd,1H) 8.72(d,1H)

EXAMPLE 144

1-(3,3-Diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(1,4,6-trimethyl-1H-pyrazolo[3,4-b]pyridin-3-yl)urea hydrochloride

Method "D" was used to prepare the title compound having the following formula :



LC SM

Column synergi polar RP ref: 00B 4336-B0

50mm 2.0mn 4 microns (Phenomenex)

Flow : 0.4ml/mn Gradient H_20/ CH_3CN

T=0	% CH_3CN 20
5.5 mn	100
8.00 mn	100

Rt = 3.95 masse : 527 M(+H)

EXAMPLE 145

Pharmaceutical Composition

Tablets were prepared, which contained

Product of Example 68 30 mg

Excipient, sufficient for 1 g

Details of the excipient: starch, talc, magnesium stearate.

Injectable solutions were also prepared from the salified products.

EXAMPLE 146

Pharmaceutical Composition

Tablets were prepared, which contained

Product of Example 76A 30 mg

Excipient, sufficient for 1 g

Details of the excipient: starch, talc, magnesium stearate

EXAMPLE 147

Pharmaceutical Composition

Tablets were prepared, which contained

Product of Example 85 50 mg

Excipient, sufficient for 1 g

Details of the excipient: starch, talc, magnesium stearate.

EXAMPLE 148

BIOLOGICAL ACTIVITY

***In vivo* evaluation of the compounds of the present invention:**

I- PTH measurement on intact rats

After fasting for 16 hours, some male rats (Sprague-Dawley, 250-300 g, Charles River France or CERJ) received an oral administration of the compounds to be tested or their vehicle.

30 min. after this bolus, the animals were slaughtered by decapitation using a guillotine.

The arterial and venous blood was collected at 4 °C and centrifuged cold, then the sera were frozen at -20 °C.

After thawing, the serum level of PTH (1-34 + 1-84) was measured by a radioimmunology test (IRMA kit, rat, Immutopics).

In this test, oral administration of the compound of Example 68 in a dose of 30 mg/kg enabled the PTH level to be reduced by 94 % relative to the control group.

II- Rats with chronic renal failure

Chronic renal failure (CRF) was induced in male rats (220-250 g, Sprague-Dawley, CERJ) by ablation of 5/6 of the total renal mass.

After anaesthesia (Imalgene 1000), the rats were subjected to exeresis of the right kidney and ablation of both ends of the left kidney, representing approximately 2/3 of the organ).

The incision was cauterised by application of dry ice. To compensate for the loss of blood volume, the animals received an intravenous injection of physiological serum.

Two days after the procedure and for the remainder of the trial, the rats were fed with a standard diet (UAR or Safe) and drank phosphate-enriched (1.2%) Volvic® water at will.

The procedure was carried out either at the supplier's or at the laboratory.

Ten days after nephrectomy, the animals which had been fasting for 16 hours entered the trial.

The compounds to be tested or their vehicle were administered orally 30 min. prior to slaughter.

The arterial and venous blood was at 4 °C after decapitation using a guillotine and was centrifuged cold. The sera were frozen a -20 °C.

After thawing, the serum level of PTH (1-34 + 1-84) was measured by a radioimmunology test (IRMA kit, rat, Immutopics).

Example	Dose (mg/kg)	% PTH reduction at 30 min. relative to the untreated group (intact rat)	Dose (mg/kg)	% PTH reduction at 30 min. relative to the untreated group (CRF rat)
Example 1	30	56		
Example 85	30	88	10	70
Example 76A	30	14		
Example 40	30	21		
Example 42	30	69		
Example 43	30	43		
Example 48	30	32		
Example 51	30	13		
Example 68	30	94	10	67

EXAMPLE 149

BIOLOGICAL ACTIVITY

The activities of the compounds of the present invention on calcium receptors were measured in accordance with the method described hereinbelow.

Human Ca^{2+} receptor cDNA was subcloned into the mammalian expression vector PECE (1). The luciferase reporter was subcloned into the mammalian expression vector pGL3basic (Promega). Resistance to neomycin (pSV2-neo) and resistance to puromycin (pSG5-puro) were used as selection markers. All these plasmids were simultaneously transfected into CHO cells by calcium phosphate precipitation. Transfected cells were grown in F12 medium containing 7.5% foetal bovine serum, 100U/ml penicillin and 100 μg/ml streptomycin (as 1% Pen-Strep, BioWithaker), neomycin (750μg/ml) and puromycin (5μg/ml). Neomycin and puromycin resistant colonies were subcloned and assayed for activation against a range of calcium concentration. Clone 8-5-5 was used to assess the effects of compounds on $[Ca^{2+}]_i$. This stably transfected cell line was termed ET8-5-5.

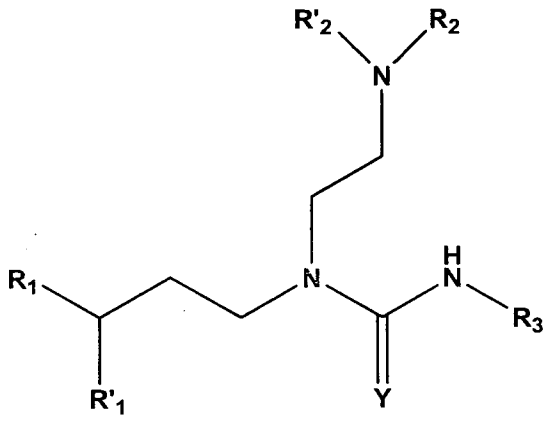
For measurements of $[Ca^{2+}]_i$, the cells were recovered from tissue culture flasks by brief treatment with Trypsin-EDTA (Invitrogen; containing 0.53mM EDTA•4Na in HBSS) and then seeded in culture-treated 96-well plates (Greiner) at 50k cells per well in the growth media (same as above, except neomycin 400µg/ml). Cells were grown in 37°C TC incubator for 24h. The culture medium was then removed and replaced with F12 medium, 1% Pen-Strep for an overnight foetal bovine serum starvation in 37°C TC incubator. Then the starvation medium was removed and replaced with a test buffer (20 mM HEPES pH 7.4, 125 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 5.5 mM Glucose, 2g/l lysosyme and 0.3 mM $CaCl_2$) supplemented with a range of test compound concentrations crossed against a super-added range of $CaCl_2$ concentrations. The cells were incubated with the test compounds for 5h in 37°C TC incubator. Then the test buffer was discarded, and cells were added with the substrate for Luciferase from SteadyLite Kit (Perkin-Elmer). The luminescence was recorded.

The compounds of Examples 1 to 144 were tested according to this procedure described above and all were found to have an EC_{50} of 10 µM or less.

Ref 1 : Replacement of Insulin Receptor tyrosine Residues 11621 and 1163 compromises Insulin-Stimulated Kinase activity and Uptake of 2-deoxyglucose (1986)
L. Ellis, E. Clauser, D.O. Morgan, M. Edery, R.A. Roth and W.J. Rutter
Cell vol. 45, 721-732

Claims:

1. A compound of formula (I):

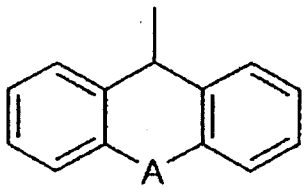


(I)

wherein:

Y is oxygen or sulphur;

R_1 and R'_1 are the same or different, and each represents an aryl group, a heteroaryl group, or R_1 and R'_1, together with the carbon atom to which they are linked, form a fused ring structure of formula:



in which A represents a single bond, a methylene group, a dimethylene group, oxygen, nitrogen or sulphur, said sulphur optionally being in the sulphoxide or sulphone forms,

wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group *c*

wherein the group *c* consists of: halogen atoms, hydroxyl, carboxyl, linear and branched alkyl, hydroxyalkyl, haloalkyl, thioalkyl, alkenyl, and alkynyl groups; linear and branched alkoxyl groups; linear and branched alkylthio

groups; hydroxycarbonylalkyl; alkylcarbonyl; alkoxycarbonylalkyl; alkoxycarbonyl; trifluoromethyl; trifluoromethoxyl; -CN; -NO_2; alkylsulphonyl groups optionally in the sulphoxide or sulphone forms; wherein any alkyl component has from 1 to 6 carbon atoms, and any alkenyl or alkynyl components have from 2 to 6 carbon atoms,

and wherein, when there is more than one substituent, then each said substituent is the same or different,

R_2 and R'_2, which may be the same or different, each represents: a hydrogen atom ; a linear or branched alkyl group containing from 1 to 6 carbon atoms and optionally substituted by at least one halogen atom, hydroxy or alkoxy group containing from 1 to 6 carbon atoms; an alkylaminoalkyl or dialkylaminoalkyl group wherein each alkyl group contains from 1 to 6 carbon atoms,

or R_2 and R'_2, together with the nitrogen atom to which they are linked, form a saturated or unsaturated heterocycle containing 0, 1 or 2 additional heteroatoms and having 5, 6, or 7 ring atoms, said heterocycle being optionally substituted by at least one substituent selected from the group ***c*** defined above,

and wherein, when there is more than one substituent, said substituent is the same or different,

R_3 represents a group of formula $-(CH_2)_p$-Ar-R_n,

in which p is 0 or 1 and, when p is 1, $(CH_2)_p$ may be substituted by methyl, chlorine, fluorine, hydroxy, or trimethyl, Ar represents an aryl or heteroaryl group, n is equal to the number of positions that can be substituted on Ar, and wherein each R, which may be the same or different, represents a hydrogen atom or a substituent selected from the group consisting of:

group ***a***, in which group ***a*** consists of: halogen atoms; hydroxyl; trifluoromethyl; linear and branched alkyl, alkenyl, alkynyl, and alkoxyl groups, all optionally further substituted by one or more of hydroxy groups, halogen atoms, alkoxy groups, amino groups, and alkylthio groups; linear and branched alkoxyl groups; linear and branched thioalkyl groups; aryl groups; aralkyl groups; aralkoxy groups; aryloxy groups; perfluoroalkyl; perfluoroalkoxy; -CN;

the groups -NR_4R_5, -C(=X)NR_4R_5,–O-C(=X)NR_4R_5, -$SO_2NR_4R_5$, or -Alk-NR_4R_5,

in which X is oxygen or sulphur,

Alk is an alkyl group, and

R_4 and R_5 are the same or different and are H, alkyl, aralkyl, aryl, heteroaryl or heteroaralkyl and are optionally further substituted by one or more substituents selected from trifluoromethyl, halogen atoms and hydroxyl groups;

the groups $-NZC(=X)(NH)_qR_6$, $-Alk-NZC(=X)(NH)_qR_6$, $-C(=X)R_6$, or $-Alk-C(=X)(NH)_qR_6$,

in which Z is H or $C(=X)R_6$ wherein each X and each R_6 is the same or different,

q is 0 or 1 and, when q is 1, $(NH)_q$ is optionally substituted with a methyl, ethyl, or trifluoromethyl group,

X is oxygen or sulphur,

Alk is an alkyl group, and

R_6 is H, OH, alkyl, aralkyl, aryl, heteroaryl or heteroaralkyl and is optionally further substituted by one or more substituents selected from trifluoromethyl, halogen atoms and hydroxyl groups or,

when C(=X) is CO, then $C(=X)R_6$ may form an ester or thioester grouping;

the groups $-NHSO_2R_7$, $-SO_2R_7$, $-SOR_7$, or $-SR_7$,

in which R_7 is OH or amino, or R_7 is alkyl, aralkyl, alkylamino, aralkylamino, aryl, heteroaryl or heteroaralkyl, optionally further substituted by one or more substituents selected from trifluoromethyl, halogen atoms and hydroxyl groups;

and saturated or unsaturated heterocyclyl groups, said heterocyclyl groups being mono- or bi- cyclic and being optionally substituted by one or more substituents, which may be the same or different, selected from the group ***b***,

wherein the group ***b*** consists of: halogen atoms; hydroxyl; carboxyl; aldehyde groups; linear and branched alkyl, alkenyl, alkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, haloalkyl, haloalkenyl, and haloalkynyl groups; linear and branched alkoxyl groups; linear and branched thioalkyl groups; alkoxycarbonyl; hydroxycarbonylalkyl; alkoxycarbonylalkyl; perfluoroalkyl; perfluoroalkoxy; -CN; acyl; amino, alkylamino, dialkylamino, acylamino, and diacylamino groups; alkyl groups substituted with an amino, alkylamino, dialkylamino, acylamino, or diacylamino group; $CONH_2$; alkylamido groups;

alkylthio and the oxidised sulphoxide and sulphone forms thereof; sulphonyl, alkylsulphonyl groups; and sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups,

wherein, in groups ***a*** and ***b***, any alkyl components contain from 1 to 6 carbon atoms, and any alkenyl or alkynyl components contain from 2 to 6 carbon atoms, and are optionally substituted by at least one halogen atom or hydroxy group, and wherein any aryl component is optionally a heteroaryl group,

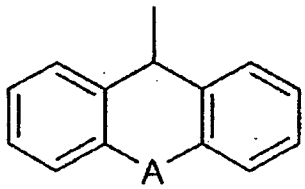
and when n is at least two, then two adjacent groups R may form a 5, 6, or 7 membered fused carbocyclic or heterocyclic ring with Ar, said fused ring being optionally further substituted with an oxo group or a substituent selected from group ***b*** as defined above,

provided that, when p is 0, Ar is not thiazolyl or oxazolyl, either unfused or fused with a monocyclic aryl or a monocyclic heteroaryl in which the or any heteroatom is nitrogen,

and salts and esters thereof.

2. A compound, salt, or ester, according to claim 1, wherein Y is oxygen.

3. A compound, salt, or ester, according to claim 1 or 2, wherein R_1 and R'_1 are the same or different, and each represents a monocyclic aryl group, a monocyclic heteroaryl group, or R_1 and R'_1, together with the carbon atom to which they are linked, form a fused ring structure of formula:



in which A is as defined in claim 1,

wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group ***c*** as defined in claim 1.

4. A compound, salt, or ester, according to claim 3, wherein R_1 and R'_1 each represents a

phenyl, pyridinyl, or thienyl radical, or R_1 and R'_1 represents a fused ring structure as defined in claim 1, wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted as defined in claim 1.

5. A compound, salt, or ester, according to claim 3 or 4, wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group ***c'***: fluorine and chlorine atoms, hydroxyl, linear and branched alkyl, alkylthio, hydroxyalkyl, and fluoroalkyl groups; linear and branched alkoxyl groups; trifluoromethyl; trifluoromethoxyl; -CN; alkylcarbonyl groups; alkylsulphonyl groups, and any alkyl component has from 1 to 4 carbon atoms,

and wherein, when there is more than one substituent, then each said substituent is the same or different.

6. A compound, salt, or ester, according to claim 3 or 4, wherein each of R_1 and R'_1, or said fused ring structure formed thereby, is optionally substituted by at least one substituent selected from the group consisting of: fluorine and chlorine atoms, hydroxy groups, linear or branched alkoxy groups containing from 1 to 5 carbon atoms, linear or branched alkyl groups containing from 1 to 5 carbon atoms, trifluoromethyl and trifluoromethoxy groups, and -CN groups,

and wherein, when there is more than one substituent, then each said substituent is the same or different.

7. A compound, salt, or ester, according to any preceding claim, wherein each of R_1 and R'_1 represents an, optionally substituted, phenyl, pyridinyl, or thienyl group.

8. A compound, salt, or ester, according to any preceding claim, wherein R_2 and R'_2, together with the nitrogen atom to which they are linked, form a saturated heterocycle containing 5, 6, or 7 ring atoms, said heterocycle being optionally substituted by at least one substituent selected from the group ***c*** defined in claim 1.

9. A compound, salt, or ester, according to any of claims 1 to 7, wherein R_2 and R'_2, which may be the same or different, each represents a methyl or ethyl group, or, together with

the nitrogen atom to which they are linked, form a morpholinyl, thiomorpholinyl, piperazinyl, homopiperazinyl, or piperidinyl group, optionally substituted at least one substituent selected from the group consisting of: chlorine atoms, hydroxyl groups, trifluoromethyl groups, alkoxy groups, hydroxyalkyl groups, and alkyl groups.

10. A compound, salt, or ester, according to claim 9, wherein R_2 and R'_2, together with the nitrogen atom to which they are linked, form a morpholinyl group optionally substituted by at least one substituent selected from the group consisting of: trifluoromethyl groups and alkyl groups.

11. A compound, salt, or ester, according to any preceding claim, wherein R_2 and R'_2, together with the nitrogen atom to which they are linked, form a morpholinyl group.

12. A compound, salt, or ester, according to any of claim 1 to 9, wherein R_2 and R'_2, together with the nitrogen atom to which they are linked, form a thiomorpholinyl group.

13. A compound, salt, or ester, according to any preceding claim, wherein each Ar is an aryl or heteroaryl group selected from the group consisting of: phenyl, naphthyl, monocyclic heteroaryls, and bicyclic heteroaryls.

14. A compound, salt, or ester, according to claim 13, wherein each Ar is selected from the group consisting of: phenyl, naphthyl, thienyl, thiazolyl, isothiazolyl, furanyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, indolyl, pyrrolyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyridazinyl groups.

15. A compound, salt, or ester, according to claim 14, wherein Ar is phenyl.

16. A compound, salt, or ester, according to any preceding claim, wherein p is 0.

17. A compound, salt, or ester, according to any of claims 1 to 15, wherein p is 1 and $(CH_2)_p$ is unsubstituted.

18. A compound, salt, or ester, according to any of claims 1 to 15, wherein p is 1 and $(CH_2)_p$ is substituted by methyl.

19. A compound, salt, or ester, according to any preceding claim, wherein at least one R comprises the moiety C(=X) wherein X is oxygen.

20. A compound, salt, or ester, according to claim 19, wherein every C(=X) is CO.

21. A compound, salt, or ester, according to any preceding claim, wherein at least one R comprises Alk, wherein Alk is methylene or ethylene.

22. A compound, salt, or ester, according to any preceding claim, wherein at least one R comprises the moiety NR_4R_5 wherein each of R_4 and R_5 is selected from the group consisting of hydrogen, methyl, ethyl, hydroxymethyl and hydroxyethyl.

23. A compound, salt, or ester, according to claim 22, wherein each R_4 and R_5 is hydrogen or methyl.

24. A compound, salt, or ester, according to any preceding claim, wherein at least one R represents the group $-NZC(=X)(NH)_qR_6$ or $-Alk-NZC(=X)(NH)_qR_6$ wherein Z is hydrogen.

25. A compound, salt, or ester, according to claim 24, wherein every Z is hydrogen.

26. A compound, salt, or ester, according to any preceding claim, wherein at least one R comprises the moiety R_6, wherein R_6 is hydrogen, hydroxy, alkyl, or trifluoromethyl.

27. A compound, salt, or ester, according to any preceding claim, wherein at least one R represents a group $-NZC(=X)(NH)_qR_6$, $-Alk-NZC(=X)(NH)_qR_6$, $-C(=X)(NH)_qR_6$, or $-Alk-C(=X)(NH)_qR_6$, wherein q is 1.

28. A compound, salt, or ester, according to claim 27, wherein $(NH)_qR_6$ is a dimethylamino group.

29. A compound, salt, or ester, according to any of claims 1 to 26, wherein at least one R represents a group $-NZC(=X)(NH)_qR_6$, $-Alk-NZC(=X)(NH)_qR_6$, $-C(=X)(NH)_qR_6$, or $-Alk-C(=X)(NH)_qR_6$, wherein q is 0.

30. A compound, salt, or ester, according to any of claims 1 to 26, wherein at least one R represents a group $-NZC(=X)(NH)_qR_6$, $-Alk-NZC(=X)(NH)_qR_6$, $-C(=X)(NH)_qR_6$, or $-Alk-C(=X)(NH)_qR_6$, wherein $-C(=X)(NH)_qR_6$ represents a carboxylic ester moiety.

31. A compound, salt, or ester, according to claim 30, wherein R_6 is an alkoxy group optionally substituted by one or more substituents selected from the group consisting of chlorine, fluorine, hydroxy, and phenyl.

32. A compound, salt, or ester, according to any preceding claim, wherein at least one R represents a group $-NHSO_2R_7$, $-SO_2R_7$, $-SOR_7$, or $-SR_7$, wherein R_7 is OH, amino, alkyl, hydroxyalkyl, or trifluoromethyl.

33. A compound, salt, or ester, according to any preceding claim, wherein at least one R represents an aryl, aralkyl, heteroaryl, or heteroaralkyl group.

34. A compound, salt, or ester, according to claim 33, wherein only one R represents an aryl or heteroaryl group.

35. A compound, salt, or ester, according to any preceding claim, wherein at least one R represents a group selected from the group consisting of: oxazolyl, methyltetrazolyl, isoxazolyl, furanyl, isoxazolyl, benzimidazolyl, and thiophene.

36. A compound, salt, or ester, according to any preceding claim, wherein no more than two substituents R are selected from said substituents ***a***.

37. A compound, salt, or ester, according to any preceding claim, wherein each R is selected from hydrogen and substituents ***a'***: fluorine atoms; chlorine atoms; hydroxyl groups;

carboxyl groups; aldehyde groups; linear and branched alkyl, hydroxyalkyl, and fluoroalkyl groups; linear and branched alkoxyl groups; linear and branched thioalkyl groups; alkoxycarbonyl groups; benzylcarbonyl groups; hydroxycarbonylalkyl groups; alkoxycarbonylalkyl groups; trifluoromethyl groups; trifluoromethoxy groups; -CN groups; amino, alkylamino, dialkylamino, acylamino, and diacylamino groups; alkoxycarbonylamino, alkylcarbonylamino groups; alkylaminocarbonyloxy groups; alkyl groups substituted with an amino, alkylamino, dialkylamino, acylamino, or diacylamino group; $CONH_2$; alkylamido groups; alkylthio; alkylsulphoxide; sulphonyl, and alkylsulphonyl groups; sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups; trifluoromethylsulphoxide; trifluoromethylsulphonyl groups; trifluoromethylsulphonamide, and di(trifluoromethylsulphonyl)amino groups; alkylcarbonylalkyl; and saturated monocyclic heterocyclyl groups, said heterocyclyl groups being optionally substituted by one or more substituents, which may be the same or different, selected from the group ***b*** as defined in claim 1.

38. A compound, salt, or ester, according to claim 37, wherein each R is selected from hydrogen and substituents ***a''***: chlorine atoms; hydroxyl groups; carboxyl groups; linear and branched alkyl, hydroxyalkyl; linear and branched alkoxyl groups; alkoxycarbonyl groups; hydroxycarbonylalkyl groups; alkoxycarbonylalkyl groups; trifluoromethyl groups; trifluoromethoxy groups; -CN groups; amino, alkylamino, and dialkylamino groups; alkoxycarbonylamino, alkylcarbonylamino groups; alkylaminocarbonyloxy groups; alkyl groups substituted with an amino, alkylamino, or dialkylamino group; $CONH_2$; alkylcarbonylalkyl; alkylthio; sulphonyl and alkylsulphonyl groups; sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups; trifluoromethylsulphoxide; trifluoromethylsulphonyl groups; trifluoromethylsulphonamide, and di(trifluoromethylsulphonyl)amino groups; pyrrolidinyl, piperidinyl piperazinyl, morpholinyl, and thiomorpholinyl groups optionally substituted by one or more substituents, which may be the same or different, selected from the group ***b*** as defined in claim 1.

39. A compound, salt, or ester, according to any preceding claim, wherein substituents ***b*** are selected from substituents ***b'*** consisting of: chlorine atoms; hydroxyl groups; linear and branched alkyl, hydroxyalkyl, and alkoxyl groups; trifluoromethyl groups; trifluoromethoxy

groups; -CN groups; amino, alkylamino, and dialkylamino groups; sulphonyl, alkylsulphonyl groups; and sulphonamide, alkylsulphonamide, and di(alkylsulphonyl)amino groups.

40. A compound, salt, or ester, according to any preceding claim, wherein each R is selected from hydrogen and the group consisting of substituents ***a''*** as defined in claim 17, and wherein any pyrrolidinyl, piperidinyl piperazinyl, morpholinyl, and thiomorpholinyl groups are not further substituted.

41. A compound, salt, or ester, according to any preceding claim, wherein any alkyl, alkenyl or alkynyl component has no more than 4 carbon atoms.

42. A compound, salt, or ester, according to any preceding claim, wherein any alkylsulphonyl substituent is a methylsulphonyl substituent.

43. A compound, salt, or ester, according to claim 1, selected from:
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;
3-(4-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(3-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(2-chlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-fluoro-5-trifluoromethylphenyl)-1-(2-morpholin-4-yl)urea;
3-(3,4-dichlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(3,4-dimethoxyphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-methoxyphenyl)-1-(2-morpholin-4-ylethyl)urea;
4-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid ethyl ester;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(4–trifluoromethoxyphenyl)urea;
3-(3-bromophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-trifluoromethylphenyl)urea;
3-(3,5-bis-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(4-bromo-6-trifluoromethyl-phenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(4-bromophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
4-methoxy-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

4-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

3-(3-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester;

3-(2-cyanophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(3-acetylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-methylsulphanylphenyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3–trifluoromethoxyphenyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3–ethylsulphonyl-6-methoxyphenyl)urea;

1-(3,3-diphenylpropyl)-3-[3-(2-hydroxyethanesulfonyl)phenyl]-1-(2-morpholin-4-yl-ethyl)urea;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-2-methylbenzoic acid methyl ester;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-trifluoromethanesulfonyl-phenyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-propionylphenyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-trifluoromethylsulfanyl-phenyl)urea;

1-(3,3-diphenylpropyl)-3-(3-methanesulfonylphenyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-ethylsulfanylphenyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-isopropylsulfanylphenyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-chloro-3-methylsulfanylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)urea;

3-(3,5-dichlorophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-iodophenyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-(3-dimethylaminophenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester hydrochloride;

3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea hydrochloride;

1-(3,3-diphenylpropyl)-3-(3-methanesulphinylphenyl)-1-(2-morpholin-4-ylethyl)urea;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester hydrochloride;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid 2-hydroxy ester.;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester hydrochloride;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid benzyl ester;

2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzamide;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-n-(2-hydroxy-ethyl)-benzamide;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiobenzamide;

1-(3,3-diphenylpropyl)-3-[3-(4-methylthiazol-2-yl)-phenyl]-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-hydroxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-chloro-3-hydroxymethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-formylphenyl)-1-(2-morpholin-4-ylethyl)urea;

3-(4-chloro-3-formylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-[4-chloro-3-(1-hydroxyethyl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-methoxymethylphenyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-piperidin-1-ylmethyl-phenyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea hydrochloride;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-yl-4-chlorophenyl)urea;

3-[4-chloro-3-(1-methyl-1h-tetrazol-5-yl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

3-[4-chloro-3-(2-methyl-2h-tetrazol-5-yl)phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-biphenyl-4-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
biphenyl-3-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-pyridin-3-ylphenyl)urea;
(1-(3,3-diphenylpropyl)-3-(3-furan-3-ylphenyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea hydrochloride;
3-[3-(5-chlorothiophen-2-yl)-phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-thiophen-3-ylphenyl)urea;
1-(3,3-diphenylpropyl)-3-(2'-methoxybiphenyl-3-yl)-1-(2-morpholin-4-ylethyl)urea;
3-(2',4'-dichlorobiphenyl-3-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(3-methylisoxazol-5-yl)-phenyl]-1-(2-morpholin-4-ylethyl)urea;
3-[3-(1h-benzimidazole-2-yl)-phenyl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(3-benzothiazol-2-ylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-[3-(2h-tetrazol-5-yl)phenyl]urea hydrochloride;
1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2h-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(1-methyl-1h-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2h-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-[3-(1-methyl-1h-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
3-benzo[1,3]dioxol-5-yl-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxo-1,3-dihydroisobenzofuran-5-yl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(8-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)urea;

3-(1-acetyl-2,3-dihydro-1h-indol-6-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(1h-indazol-6-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(9-ethyl-9h-carbazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-isoquinolin-7-yl-1-(2-morpholin-4-ylethyl)urea;

3-(2-chloro-benzyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-thiophen-2-ylmethylurea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(1-naphthalen-1-ylethyl)urea;

3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]thiophene-2-carboxylic acid methyl ester;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-pyridin-3-ylurea;

1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2h-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;

3-(1-benzyl-1h-benzimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(2-methyl-5-phenyl-2,5-dihydro-1h-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;

3-(4,6-dimethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(4-methoxy-6-methylpyrimidin-2-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-pyrazin-2-ylurea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(4-thiazol-2-ylpyrimidin-2-yl)urea;

1-(3,3-diphenylpropyl)-3-(5-methylisoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(3-methyl-5-phenylisoxazol-4-yl)-1-(2-morpholin-4-ylethyl)urea;

3-[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-3-(5-methyl-3-phenylisoxazol-4-yl)-1-(2-morpholin-4-ylethyl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-phenyl-2h-pyrazol-3-yl)urea;

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-phenyl-[1,2,4]thiadiazol-5-yl)urea;

5-[3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-3-propyl-isoxazole-4-carboxylic acid ethyl ester;

3-(3,4-dimethyl-isoxazol-5-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea.;

3-[3-[2-(9h-fluoren-9-yl)-ethyl]-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;

3-[3-[2-(9h-fluoren-9-yl)ethyl]-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;
3-[3-(2-methyl-2h-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)-1-(3-phenyl-3-thiophen-2-ylpropyl)urea;
1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)-1-(3-phenyl-3-thiophen-2-yl-propyl)urea dihydrochloride;
3-[3-(2-morpholin-4-ylethyl)-3-(3-phenyl-3-thiophen-2-ylpropyl)ureido]benzoic acid methyl ester;
1-(3,3-di-thiophen-2-ylpropyl)-3-[3-(2-methyl-2h-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea;
3-[3-(3,3-dithiophen-2-yl-propyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester;
1-(3,3-dithiophen-2-ylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea dihydrochloride;
1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2h-tetrazol-5-yl)phenyl]-1-(2-thiomorpholin-4-ylethyl)urea;
1-[2-(2,6-dimethylmorpholin-4-yl)-ethyl]-1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2h-tetrazol-5-yl)phenyl]urea;
3-(5,6-dimethyl-1h-benzoimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(1-methyl-1h-benzoimidazol-2-yl)-1-(2-morpholin-4-ylethyl)-urea;
3-(1h-benzoimidazol-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)-3-(5-phenylsulfanyl-1h-benzoimidazol-2-yl)-urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-oxo-1-phenyl-4,5-dihydro-1h-pyrazol-3-yl)urea;
1-(3,3-diphenylpropyl)-3-(5-methyl-2-phenyl-2h-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(5-phenyl[1,3,4] thiadiazol-2-yl)-urea;
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-yl-ethyl)ureido]-5-phenylthiophene-2-carboxylic acid methyl ester;
3-[2-(4-chlorophenylsulfanyl)-6-methoxypyridin-3-yl]-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-yl-ethyl)urea;

2-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid ethyl ester;
6-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]nicotinic acid methyl ester;
3-(3-chloro-5-trifluoromethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-urea;
3-(6-chloro-2-methylsulfanylpyrimidin-4-yl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-urea;
2-(4-chlorobenzyl)-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)-ureido]oxazole-4-carboxylic acid ethyl ester;
1-(3,3-diphenylpropyl)-3-(4-methoxybenzo[d]isoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;
1-(3,3-diphenylpropyl)-3-(2-methyl-5-thiophen-2-yl-2h-pyrazol-3-yl)-1-(2-morpholin-4-ylethyl)urea;
6-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]nicotinamide; and
1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(1,4,6-trimethyl-1h-pyrazolo[3,4-b]pyridin-3-yl)urea hydrochloride.

44. A compound, salt, or ester, according to claim 1, selected from:
3-[3-(3,3diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid methyl ester and the hydrochloride thereof,
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester and the hydrochloride thereof,
2-chloro-5-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid isopropyl ester and the hydrochloride thereof,
3-[3-(3,3-diphenylpropyl)-3-(2-morpholin-4-ylethyl)ureido]benzoic acid tertbutyl ester and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-(3-ethylcarbonylphenyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
3-(4-chloro-3-trifluoromethylphenyl)-1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,

1-(3,3-diphenylpropyl)-1-(2-morpholin-4-ylethyl)-3-(3-oxazol-5-ylphenyl)urea and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-(3-furan-2-ylphenyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
1-(3,3-diphenylpropyl)-3-(3-methylsulphanylphenyl)-1-(2-morpholin-4-ylethyl)urea and the hydrochloride thereof,
3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]-1-(2-morpholin-4-ylethyl)-1-(3-phenyl-3-thiophen-2-ylpropyl)urea,
3-[3-(2-morpholin-4-ylethyl)-3-(3-phenyl-3-thiophen-2-ylpropyl)ureido]benzoic acid methyl ester,
1-(3,3-diphenylpropyl)-3-(4-methoxy-6-methylpyrimidin-2-yl)-1-(2-morpholin-4-ylethyl)urea,
3-(4,6-dimethylpyridin-2-yl)-1-(3,3-diphenylpropyl)-1-(morpholin-4-ylethyl)urea, and
1-(3,3-diphenylpropyl)-3-(5-methylisoxazol-3-yl)-1-(2-morpholin-4-ylethyl)urea.

45. Use of a compound according to any preceding claim in therapy.

46. A pharmaceutically acceptable composition comprising a compound according to any of claims 1 to 44.

47. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the treatment or the prevention of diseases or disorders linked to abnormal physiological behaviour of inorganic ion receptors and in particular of the calcium receptor.

48. Use according to claim 47, characterised in that the calcium receptor is expressed in the parathyroid, the thyroid, the bone cells, the renal cells, the lung, the brain, the pituitary gland, the hypothalamus, the gastrointestinal cells, the pancreas cells, the skin cells, the cells of the central or peripheral nervous system and the smooth muscle cells.

49. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of cancers, in particular of the parathyroid and the digestive tract.

50. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of neurodegenerative diseases.

51. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of bone and articular metabolism diseases, in particular osteoporosis, osteopaenia and Paget's disease, rheumatoid arthritis and osteoarthritis.

52. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of abnormal calcium homeostasis.

53. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of hyperplasia and parathyroid adenoma.

54. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of intestinal malabsorption.

55. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of biliary lithiasis and renal lithiasis.

56. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of hyperparathyroidism.

57. Use according to claim 56, characterised in that secondary hyper-parathyroidism is observed in the event of renal insufficiency.

58. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of ionised serum calcium level reduction during the treatment of hypercalcaemia.

59. Use of a compound according to any of claims 1 to 44 in the manufacture of a

medicament for the prevention or treatment of cardiovascular diseases and more particularly hypertension.

60. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of vascular calcification.

61. Use of a compound according to any of claims 1 to 44 in the manufacture of a medicament for the prevention or treatment of diarrhoea.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/012245

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5375 A61K31/5377 C07D213/38 C07D213/75 C07D213/80
C07D213/82 C07D217/22 C07D231/52 C07D231/56 C07D235/14
C07D235/30 C07D239/46 C07D257/04 C07D261/08 C07D261/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 02/059102 A (AVENTIS PHARMA S.A; DEPREZ, PIERRE; PATEK, MARCEL) 1 August 2002 (2002-08-01) claims 1,9	1-61
A	WO 97/37967 A (NPS PHARMACEUTICALS, INC; SMITHKLINE BEECHAM PLC; SMITHKLINE BEECHAM) 16 October 1997 (1997-10-16) claims 1,13	1-61
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2007	12/03/2007

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/012245

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