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(56) Documents Cited
EP 0499313 A **WO 93/04040 A** **WO 91/18899 A**

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INT CL^5 **C07D 453/02**
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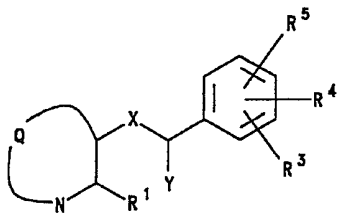
(54) Azabicyclic tachykinin-receptor antagonists

(57) Compounds of formula (I), and salts and prodrugs thereof:



(I)

wherein

Q is the residue of an optionally substituted azabicyclic ring system (preferably quinuclidine);

X represents O, S, CH_2 or CH;

Y represents H, OH, =O or halo;

R^1 represents phenyl optionally substituted by halo or trifluoromethyl; and

R^3, R^4 and R^5 independently represent H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SCH_3, $SOCH_3$, SO_2CH_3, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$

(where R^a and R^b independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl);

with the proviso that when X is O or S, Y is H; are tachykinin receptor antagonists useful in therapy.

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The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1990.

THERAPEUTIC AGENTS

This invention relates to a class of azabicyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azabicyclic ring system substituted by an arylmethyloxy or arylmethylthio moiety and by a phenyl moiety.

The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2

For example, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg et al, J. Med Chem, (1982) 25 1009) and in arthritis [Levine et al in Science (1984) 226 547-549]. These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as

inflammatory bowel disease [Mantyh et al in Neuroscience (1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri et al, Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne et al in Arthritis and Rheumatism (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing β-amyloid-mediated neurodegenerative changes [Yankner et al, Science (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et al, poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July 1992, in press], and in disorders of bladder function such as bladder detrusor hyper-reflexia (Lancet, 16th May, 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders:

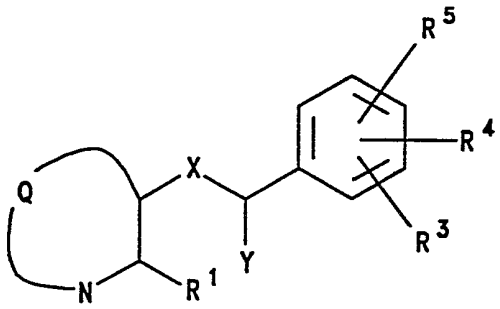
depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), opthalmic disease such as conjuctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989).

In view of their metabolic instability, peptide derivatives are likely to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin antagonists are sought.

WO-A-90/05729 describes inter alia a class of cis-3-[cyclic]methylamino-2-[(α-substituted)-arylmethyl]quinuclidine compounds which are stated to be useful as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. There is, however, no disclosure or suggestion in WO-A-90/05729 of the arylmethyloxy- or arylmethylthio-substituted azabicyclic derivatives provided by the present invention.

We have now found a further class of non-peptides which are potent antagonists of tachykinin.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

Q is the residue of an optionally substituted azabicyclic ring system;

X represents O, S, CH_2 or CH;

Y represents H, OH, =O or halo;

R^1 represents phenyl optionally substituted by halo or trifluoromethyl;

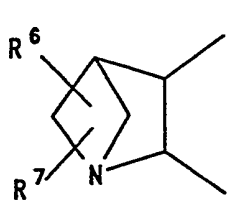
R^3, R^4 and R^5 independently represent H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SCH_3, $SOCH_3$, SO_2CH_3, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$; and

R^a and R^b independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl;

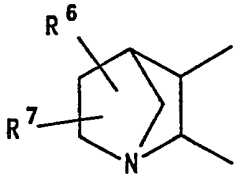
with the proviso that when X is O or S, Y is H.

The azabicyclic ring system of which Q is the residue is a non-aromatic ring system containing, as the sole heteroatom, the nitrogen atom indicated in formula (I) above. Suitably the ring system contains from 6 to 10 ring atoms, preferably from 7 to 9 ring atoms. The azabicyclic ring system may be fused, spiro or bridged, preferably bridged. The azabicyclic ring system may be substituted by one or more groups selected from carbonyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halo, hydroxy,

C_{1-4}alkoxy, carboxy or C_{2-4}alkoxycarbonyl. Examples of such azabicyclic ring systems include:



(A)



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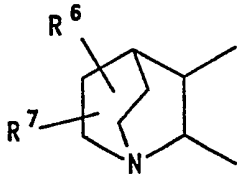

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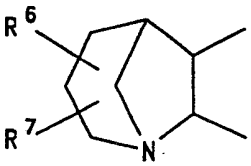

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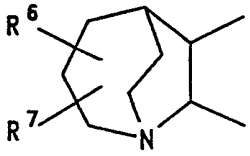

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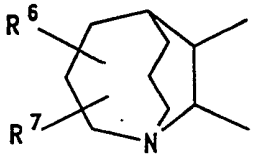


(F)

wherein

R^6 and R^7 independently represent H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, hydroxy, C_{1-4} alkoxy, carboxy or C_{2-4} alkoxycarbonyl; or R^6 and R^7 together represent carbonyl.

It will be appreciated that the nitrogen atom in the azabicyclic ring system will carry a lone pair of electrons.

It will also be appreciated that the R^6 and R^7 substituents may be present at any position in the azabicyclic ring system, including, where appropriate, the bridgehead carbon atom depicted in structures A to F above.

Suitably the group R^6 is H or methyl; and R^7 is H, C_{1-4} alkyl, hydroxy or C_{1-4} alkoxy, preferably H, methyl, hydroxy or methoxy. Preferably one or more preferably both of R^6 and R^7 is/are H.

Suitably the azabicyclic ring system of which Q is the residue is a 1-azabicyclo[2.2.1]heptanyl (1-azanorbornanyl), 1-azabicyclo[2.2.2]octanyl (quinuclidinyl) or 1-azabicyclo[3.2.1]octanyl ring system of formula B, C or D above, respectively, any of which is optionally substituted by methyl or hydroxy. A preferred ring system is quinuclidine of formula C above.

It will be appreciated that when X represents CH, there is a carbon-carbon double bond between X and the carbon atom of the azabicyclic ring system to which it is attached.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the formulae herein may represent straight, branched or cyclic groups. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo.

In one preferred group of compounds according to the invention, X is O.

In a further preferred group of compounds of formula (I), X is CH. When X is CH or CH_2, Y is preferably OH or halo, especially fluoro.

Preferably R^1 represents unsubstituted phenyl.

Suitably, R^3, R^4 and R^5 independently represent H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, $-OR^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$; and

R^a and R^b independently represent H or C_{1-6} alkyl.

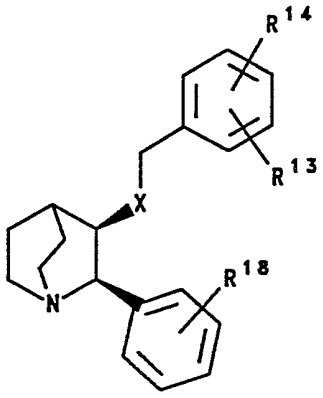
For example, suitable values for the groups R^3, R^4 and R^5 include H, amino, nitro, trifluoromethyl, trimethylsilyl, halo, cyano, methyl, ethyl, cyclopropyl, vinyl, carbonylmethoxy, methoxy and phenoxy, more suitably H, nitro, trifluoromethyl and halo, such as chloro.

Preferably, at least one of R^3, R^4 and R^5 is other than H. More preferably, two of R^3, R^4 and R^5 are other than H. The (non-H) substituents are preferably at the 3- and 5-positions of the phenyl ring. In a particularly preferred group of compounds of formula (I), two of R^3, R^4 and R^5 are trifluoromethyl and the other is H.

The compounds according to the invention have at least two asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. In particular, the relative orientation of the substituents on the azabicylic ring system in formula (I) above may give rise to cis and trans diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

It is believed that of the cis diastereomers, tachykinin receptor antagonist activity preferentially resides in the 2S,3S diastereomer, whereas of the trans diastereomers, activity preferentially resides in the 2R,3S diastereomers. Thus, it is believed that S stereochemistry at the 3-position of the azabicyle is crucial to tachykinin receptor antagonist activity.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

X represents O or S, preferably O;

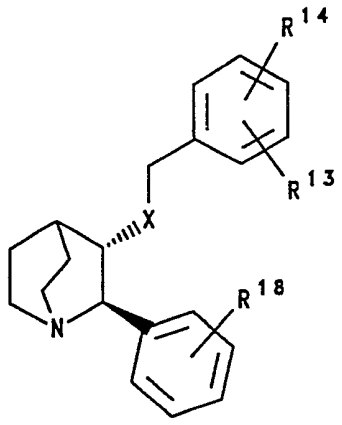
R^{13} and R^{14} independently represent H, C_{1-6}alkyl, C_{2-6}alkenyl, halo, cyano, nitro, $-CO_2(C_{1-6}alkyl)$, trifluoromethyl, trimethylsilyl, hydroxy, C_{1-6} alkoxy, phenoxy or amino; and

R^{18} represents H, halo or trifluoromethyl.

Particular values of R^{13} and R^{14} include H, C_{1-5}alkyl, especially methyl, ethyl and cyclopropyl, C_{2-6}alkenyl, especially vinyl, halo, nitro, trifluoromethyl, trimethylsilyl, cyano, methoxy and phenoxy. Preferably, R^{13} and R^{14} are selected from hydrogen, nitro, trifluoromethyl and halo, especially chloro. Preferably, at least one of R^{13} and R^{14} is other than H. More preferably, R^{13} and R^{14} are both other than H and are located at the 3- and 5-positions of the phenyl ring.

Preferably, R^{18} represents H.

A second sub-class of compounds according to the invention is represented by the compounds of formula (IIB), and salts and prodrugs thereof:



(IIB)

wherein X, R^{13}, R^{14} and R^{18} are as defined for formula (IIA) above.

Suitably, in formula (IIB) X represents O or S, preferably O;

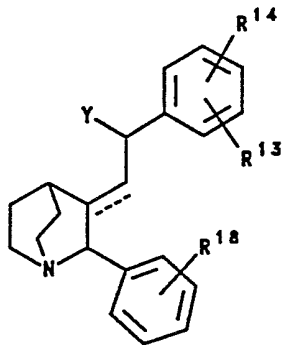
R^{13} and R^{14} independently represent phenoxy or, preferably, H, C_{1-6} alkyl, halo, cyano, nitro, trifluoromethyl, hydroxy, C_{1-6} alkoxy or amino.

R^{18} represents H, halo or trifluoromethyl.

A preferred group of compounds according to the invention are compounds of formula (IIB) wherein X is O and each of R^{13} and R^{14} represents a methyl or a trifluoromethyl group.

Also preferred are compounds of formula (IIB) wherein X is O and each of R^{13} and R^{14} is halo, especially chloro.

A further sub-class of compounds according to the invention is represented by the compounds of formula (IIC), and salts and prodrugs thereof:



(IIC)

wherein R^{13}, R^{14} and R^{18} are as defined for formula (IIA) above;

Y represents H, -OH, =O or halo, preferably OH or fluoro; and the dotted line represents an optional double bond.

Preferred are compounds of formula (IIC) wherein the double bond is present.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, oxalic acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where

the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage form such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories, for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the

composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

The present invention futher provides a process for the preparation of a pharmaceutical composition

comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example, diabetic and chemotherapy-induced neuropathy, and neuralgia; respiratory diseases such as chronic obstrucutive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as

ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

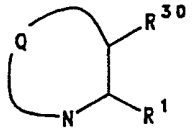
The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic or peripheral neuropathy and chemotherapy-induced neuropathy, asthma, osteroarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy. According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P. The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

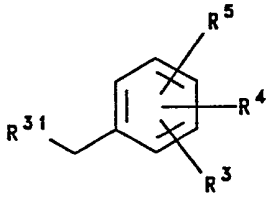
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10

mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds according to the invention wherein X is O or S may be prepared by a process which comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

wherein Q, R^1, R^3, R^4 and R^5 are as defined for formula (I) above, and one of R^{30} and R^{31} represents a leaving group and the other of R^{30} and R^{31} represents XH, where X is as defined for formula (I); in the presence of a base.

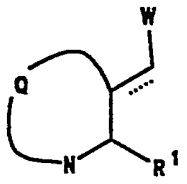
Suitably, R^{31} represents a leaving group and R^{30} represents XH.

Suitable leaving groups include halo, e.g. chloro, bromo or iodo, or sulphonate derivatives such as tosylate or mesylate.

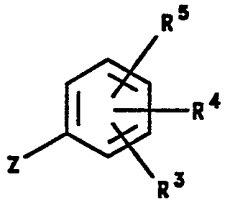
The reaction is conveniently carried out in a suitable organic solvent, such as an ether, e.g. 1,2-dimethoxyethane, at a temperature in the range of -5 to 25°C, preferably about 0°C. Favoured bases of use in the reaction include alkali metal amides and hydrides, such as potassium bis(trimethylsilyl)amide and potassium

hydride. Suitably, potassium bis(trimethylsilyl)amide is used.

The compounds according to the invention wherein X is CH or CH_2 and Y is OH may be prepared by a process which comprises reacting a compound of formula (V) with a compound of formula (VI):



(V)

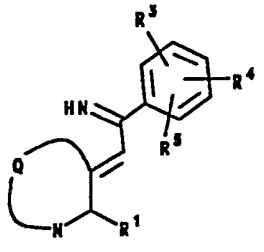


(VI)

wherein Q, R^1, R^3, R^4 and R^5 are as defined in formula (I) and the dotted line represents an optional double bond, W represents CHO (intermediates (VB)), and Z is a metal, such as aluminium or lithium, or metal halide.

The group Z in the reaction of (V) with (VI) suitably represents a metal such as aluminium or, preferably, the residue of a Grignard agent such as MgBr. The reaction is preferably carried out in an inert organic solvent such as an ether such as diethyl ether, tetrahydrofuran or a mixture thereof.

The compounds according to the invention wherein X is CH and Y is =O may be prepared by a process which comprises hydrolysing a compound of formula (VII):



(VII)

wherein Q, R^1, R^3, R^4 and R^5 are as defined in formula (I). The reaction may take place with dilute acid such as dilute mineral acid, for example, hydrochloric acid.

The compound of formula (VII) need not be isolated but may be hydrolized <u>in situ</u> after being prepared from the corresponding compound of formula (VA) wherein W represents CN by reaction with the corresponding compound of formula (VI) (wherein Z is preferably lithium) as described above in relation to preparing compounds of formula (I) wherein X is CH and Y is OH.

The compounds according to the invention wherein X is CH or CH_2 and Y is H may be prepared by reducing the corresponding compound of formula (I) wherein Y is OH. The reduction may be effected by standard methods known to those skilled in the art such as catalytic reduction by hydrogen in the presence of a catalyst such as platinum or palladium, preferably palladium dihydroxide. Such reduction is preferably carried out in the presence of a polar solvent such as an alcohol such as ethanol or an acid such as an inorganic acid, for example, hydrochloric acid, or a mixture thereof. Alternatively, the reduction may be carried out by, for example, lithium aluminium hydride/aluminium trichloride in the presence of a solvent such as an ether

such as diethyl ether or tetrahydrofuran or a mixture thereof, preferably at ambient temperature such as around 25°C.

The compounds according to the invention wherein Y is halo may be prepared from the corresponding compounds of formula (I) wherein Y is OH using conventional techniques, for example, by reaction with a suitable halogenating agent. Examples of halogenating agents include thionyl halides, phosphorous trihalides and phosphorous pentahalides.

A preferred halogenating agent for use in the reaction is diethylaminosulphurtrifluoride. The reaction is preferably conducted at low temperature, for example, at about -15 to +5°C.

The intermediates of formula (III) above wherein R^{30} is SH may be prepared from the corresponding intermediates of formula (III) wherein R^{30} represents OH by treating the latter compound with Lawesson's reagent or phosphorus pentasulphide in a suitable solvent, e.g. pyridine, at ambient or elevated temperatures, suitably at reflux temperature.

The intermediates of formula (III) above wherein R^{30} is OH may be prepared by the procedures described in J. Med. Chem., 1974, 17, 497, and J. Med. Chem., 1975, 18, 587; or by methods analogous thereto.

Intermediates of formula (III) wherein R^{30} is OH having cis stereochemistry may preferably be prepared from the corresponding ketones via a selective reduction using a suitable reducing agent such as a lithium aluminium hydride or a substituted borohydride such as triethylborohydride, as described in the accompanying examples.

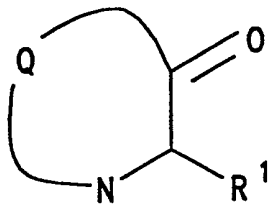
Intermediates of formula (III) wherein R^{30} is OH having trans sterochemistry may be obtained

selectively via a procedure involving non-selective reduction of the corresponding ketone, for example using sodium in an aromatic hydrocarbon solvent, e.g. toluene, preferably in the presence of an alcohol, e.g. iso-propyl alcohol, to give a mixture of cis and trans isomers, followed by selective oxidation of the cis isomer using a ketone in the presence of a base (Oppenauer oxidation). Suitable ketones include acetone, methyl ethyl ketone, cyclohexanone and, preferably, benzophenone. Suitable bases include alkali metal hydrides, e.g. potassium hydride.

Intermediates of formula (III) wherein R^{30} is a leaving group may be prepared from compounds of formula (III) wherein R^{30} is OH, for example, by reaction with a thionyl halide, a mesyl halide or a tosyl halide.

Where they are not commercially available, the intermediates of formula (IV) above may be prepared by conventional procedures which will be readily apparent to one skilled in the art.

The compounds of formula (VA) wherein the double bond is present and W represents CN may be prepared by reaction of a compound of formula (VIII) with a Wittig reagent:



(VIII)

wherein Q and R^1 are as defined in formula (I). Preferably, the compound of formula (VIII) is reacted with a reagent of formula $(alkoxy)_2PO(CH_2CN)$, such as

$(EtO)_2PO(CH_2CN)$ or $(iPrO)_2PO(CH_2CN)$ in the presence of an alkali or alkaline earth metal salt of an alcohol such as potassium t-butoxide in an inert organic solvent such as toluene at an elevated temperature in the range of from 25°C to 50°C, preferably around 50°C.

The compounds of formula (VA) wherein the double bond is absent and Y represents CN may be prepared from the corresponding compounds of formula (VA) wherein the double is present, by reduction. Suitable procedures and reagents will be readily apparent to one skilled in the art, and include dissolving metal reduction, for example, using magnesium in methanol.

The intermediates of formula (VB) above wherein W is CHO may be prepared by the procedures described in J. Med. Chem., 1974, 17, 497, and J. Med. Chem., 1975, 18, 587; or by methods analogous thereto. For example, from the corresponding intermediate of formula (VA) wherein W represents CN for example with a standard agent such as DIBAL-H (available from Aldrich).

Where they are not commercially available, the intermediates of formula (VI) above may be prepared by conventional procedures well known to those skilled in the art.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

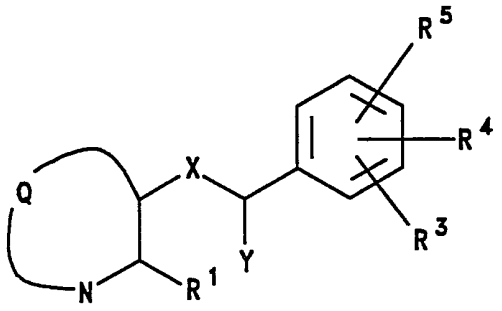
The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example, intermediate alcohols of formula (III), wherein X is O, may be resolved into their component enantiomers by standard techniques, such as the formation of

diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. The diastereomeric alcohols can then be used to prepare optically pure compounds of formula (I).

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

CLAIMS:

1. A compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

Q is the residue of an optionally substituted azabicyclic ring system;

X represents O, S, CH_2 or CH;

Y represents H, OH, =O or halo;

R^1 represents phenyl optionally substituted by halo or trifluoromethyl;

R^3, R^4 and R^5 independently represent H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SCH_3, $SOCH_3$, SO_2CH_3, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$; and

R^a and R^b independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl;

with the proviso that when X is O or S, Y is H.

2. A compound as claimed in claim 1 for use in therapy.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number

GB 9215527.4

Relevant Technical fields

(i) UK Cl (Edition L) C2C: CQS,CUL,CWC,CZF

(ii) Int Cl (Edition 5) C07D 453/02

Search Examiner

MISS D DAVIES

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES : CAS-ONLINE, EDOC

Date of Search

27 AUGUST 1993

Documents considered relevant following a search in respect of claims 1-2

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
A	EP 0499313 A (MERCK SHARP DOHME) quinuclideines 2-substituted by aryl methyl as tachykinin antagonists	
A,P	WO 9304040 A (MERCK SHARP DOHME) monoazacyclic compounds as tachkyninin antagonists	
A	WO 9118899 A (PFIZER INC) 3-arylmethyl amino quinuclidines as substance antagonists	

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).