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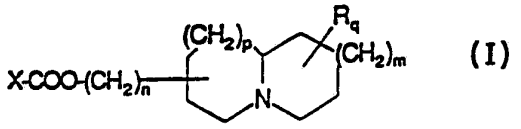
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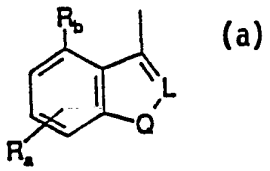
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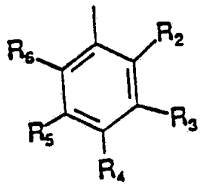
(54) Title: AZABICYCLIC COMPOUNDS AS 5-HT_4 RECEPTOR ANTAGONISTS



(I)



(a)



(b)

(57) Abstract

Compounds of formula (I), wherein X is (a), (b), wherein L is N or CR_c wherein R_c is hydrogen, alkoxy, halo, alkyl or cyano; Q is NR_1, CH_2, O or S; R_a is hydrogen, halo, alkyl, amino, nitro or alkoxy; R_b is hydrogen, halo, alkyl or alkoxy; R_1 is hydrogen, alkyl, alkenyl, aralkyl, alkanoyl, or alkanoylalkyl; R_2 is alkoxy; and R_3 is hydrogen, chloro or fluoro; R_4 is hydrogen, alkyl, amino optionally substituted by alkyl, halo, hydroxy or alkoxy; R_5 is hydrogen, halo, alkyl, alkoxy, nitro, amino or alkylthio; R_6 is hydrogen, halo, alkyl, alkoxy or amino; n is 0, 1, 2, 3 or 4; p and m are independently 0, 1 or 2; and R_q is hydrogen or alkyl. The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

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AZABICYCLIC COMPOUNDS AS 5-HT4 RECEPTOR ANTAGONISTS

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

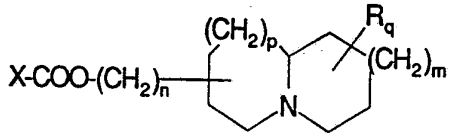
GB 2125398A (Sandoz Limited) describes a group of bridged piperidinyl ester and amide derivatives having 5-HT_3 receptor antagonist activity. GB 1593146 and EP-A-36269 (Beecham Group p.l.c.) describe groups of fused azabicyclic amide derivatives having gastric motility enhancing activity.

A class of novel, structurally distinct compounds has now been discovered, which compounds are fused azabicyclic ester derivatives. These compounds have 5-HT_4 receptor antagonist activity.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor.

PCT/GB91/00650 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

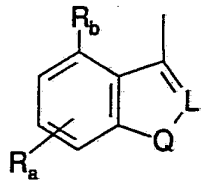
Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof



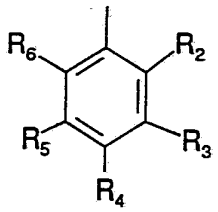
(I)

wherein

X is of sub-formula (a) or (b):



(a)



(b)

wherein

L is N or CR_c wherein R_c is hydrogen, C_{1-6} alkoxy, halo, C_{1-6} alkyl or cyano;

Q is NR_1, CH_2, O or S;

R_a is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkoxy;

R_b is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

R_1 is hydrogen, C_{1-10} alkyl, C_{2-6} alkenyl, aralkyl, C_{2-6} alkanoyl, or C_{2-6} alkanoyl C_{1-3} alkyl;

R_2 is C_{1-6} alkoxy; and

R_3 is hydrogen, chloro or fluoro;

R_4 is hydrogen, C_{1-6} alkyl, amino optionally substituted by a C_{1-6} alkyl group, halo, hydroxy or C_{1-6} alkoxy;

R_5 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_6 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

n is 0, 1, 2, 3 or 4;

p and m are independently 0, 1 or 2; and

R_q is hydrogen or C_{1-6} alkyl.

Examples of alkyl or alkyl containing groups include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 or C_{10} branched, straight chained or cyclic alkyl, as appropriate. C_{1-4} alkyl groups include methyl, ethyl *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Alkenyl includes all

suitable values including *E* and *Z* forms.

Aryl includes phenyl and naphthyl optionally substituted by one or two substituents selected from halo, C_{1-6} alkoxy and C_{1-6} alkyl.

Halo includes fluoro, chloro, bromo and iodo.

L in formula (a) is preferably CH, C-CH_3, C-Cl or $COCH_3$.

Q in formula (a) is preferably NR_1 and R_1 is preferably hydrogen or a methyl or ethyl group.

R_a is often hydrogen and R_b is often hydrogen or iodo.

R_2 is preferably methoxy.

R_4 is preferably amino.

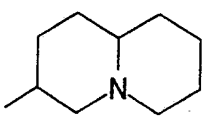
R_5 when halo is selected from fluoro, chloro, bromo and iodo, preferably chloro.

Suitable values for p and m include p = m = 1; p = 0, m = 1; p = 1, m = 2; p = 2, m = 1.

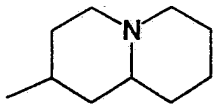
R_q is often hydrogen.

Preferably X-COO-$(CH_2)_n$- is attached such that the number of carbon atoms between the ester linkage and the azabicyclic nitrogen atom is from 2 to 4 carbon atoms.

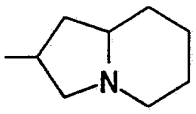
Specific values of the azabicycle which are of particular interest are as follows:



(i)



(ii)



(iii)

Other azacycles of interest are as described with reference to the Examples

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, a-keto glutaric, a-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_X-T wherein R_X is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_X include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

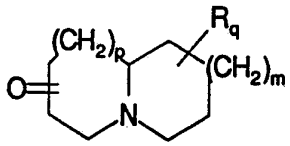
Some of the compounds of formula (I) have at least one asymmetric centre

and exist as more than one stereoisomeric form. The invention extends to each of these forms and to mixtures thereof including racemates.

It will also be realised that X-COO-$(CH_2)_n$- in compounds of formula (I) may adopt an α or β or configuration with respect to the fused azabicyclic moiety.

The compounds of formula (I) are prepared by linking together X-CO_2H or a reactive derivative thereof and the (azabicyclic side chain)-$(CH_2)_n$- moiety, usually by a conventional ester coupling with the -$(CH_2)_n$-OH derivative as described in the aforementioned patent publication reference in the name of Sandoz Limited.

The azabicyclic side chain $(CH_2)_n$-OH intermediates are known compounds or may be prepared from the ketones of formula (II):



(II)

according to conventional methods, such as those described in the Descriptions hereinafter.

Ketones of the formula (II) are known or are prepared by analogous methods to those used for preparing structurally related known compounds.

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the

treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

It is believed that platelet-derived 5-HT induces atrial arrhythmias which encourage atrial fibrillation and atrial disorders are associated with symptomatic cerebral and sytemic embolism. Cerebral embolism is the most common cause of ischaemic stroke and the heart the most common source of embolic material. Of particular concern is the frequency of embolism associated with atrial fibrillation.

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol. Pharmacol., 34, 880-887). Activity may be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof,

and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for enteral such as oral,nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or suspensions. Sublingual or transdermal administration is also envisaged. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily

suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof. In particular, the method comprises treatment of IBS or atrial arrhythmias and stroke.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature

and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70 kg adult will normally contain 0.05 to 1000 mg for example 0.5 to 500 mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50 mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

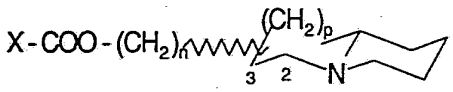
No adverse toxicological effects are indicated within the aforementioned dosage ranges.

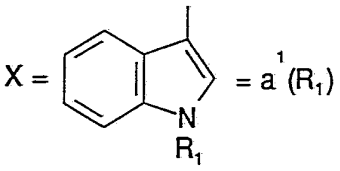
The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine, in particular IBS or atrial arrhythmias and stroke.

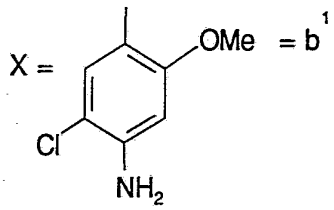
The invention also provides the use of a compound of formula (I) in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist in the treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine, in particular, IBS or atrial arrhythmias and stroke.

The following Examples illustrate the preparation of compounds of formula (I); the following Descriptions illustrate the preparation of intermediates.

Examples









Example	X	n	p	attach.	isomer(s)
E1	a^1(H)	1	1	3	α,β
E2	a^1(H)	2	1	3	α,β
E3	a^1(H)	0	1	3	α,β
E4	a^1(H)	0	1	4	α,β
E5	a^1(H)	1	0	3	α,β
E6	a^1(H)	2	0	3	α,β
E7	a^2	1	1	3	α,β
E8	b^1	1	1	3	α,β

Examples (cont'd.)

Example	X	n	p	attach.	isomer(s)
E9	a^1(H)	1	1	4	α,β
E10	a^1(H)	2	1	4	β
E11	a^1(H)	0	1	5	α,β
E12	a^1(H)	1	1	5	α,β
E13	a^1(H)	0	0	4	α,β
E14	a^1(H)	1	0	4	α,β
E15	a^1(Me)	1	1	4	β
E16	a^1(Et)	1	1	4	β
E17	a^1(^{n}Pr)	1	1	4	β
E18	a^1(^{i}Pr)	1	1	4	β
E19	a^1(allyl)	1	1	4	β
E20	a^1(^{i}Bu)	1	1	4	β
E21	a^1(Me)	1	0	3	α,β
E22	a^1(Et)	1	0	3	α,β

Examples (cont'd)

Example	X	n	p	attach.	isomer(s)
E23	$a^1(^nPr)$	1	0	3	α,β
E24	$a^1(H)$	1	2	4	α,β
E25	$a^1(H)$	1	2	5	α,β
E26	$a^1(H)$ (R_c=OCH_3)	1	1	4	β
E27	$a^1(^iPr)$ (R_b=I)	1	1	4	β
E28	a^1(cpm)	1	1	4	β
E29	a^1(chm)	1	1	4	β
E30	$a^1(COCH_3)$	1	1	4	β
E31	$a^1(CH_2Ac)$	1	1	4	β
E32	$a^1(^nPr)$	1	0	3	α,β*

cpm = cyclopropylmethyl
chm = cyclohexylmethyl
* = N-methyl iodide quaternary salt

Example 1

3-*ax*- and 3-*eq*-Quinolizidin-3-ylmethylindole-3-carboxylate (E1a and E1b)

A suspension of indole-3-carboxylic acid (400 mg, 0.0025 mole) in dichloromethane (25 ml) was treated with oxalyl chloride (0.24 ml, 0.0028 mole) plus 2 drops of DMF and stirred at room temperature for 2 hours, then concentrated *in vacuo* to give the acid chloride as a yellow solid. A solution of 3-hydroxymethylquinolizidine (H. Lewis and C. Shoppee J.C.S., 1956, 313) (mixture of isomers) (435 mg, 0.0025 mole) in THF (10 ml) at 5°C under nitrogen was treated with 1.6M n-butyllithium in hexane (1.56 ml, 0.0025 ml), stirred for 10 minutes, then treated with a solution of the above acid chloride in THF (5 ml). After 2 hours at room temperature, the mixture was treated with saturated $NaHCO_3$ solution (20 ml) and extracted with ethyl acetate (2 x 30 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel. The faster running component was obtained by elution with ethyl acetate and afforded the axial isomer (E1a) as a white solid mp 157-158°C.

^1H NMR ($CDCl_3$)

δ: 1.20-2.28 (m, 14H), 2.68-2.79 (m, 1H), 2.85-2.96 (m, 1H), 4.45-4.60 (m, 2H), 7.21-7.30 (m, 2H), 7.37-7.45 (m, 1H), 7.91 (d, 1H), 8.13-8.20 (m, 1H), 9.40 (br.s, 1H).

MS (EI) M^+ 312.

Elution with ethyl acetate:methanol (9:1) afforded the equatorial isomer (E1b) as a white solid mp 187-188°C.

^1H NMR ($CDCl_3$)

δ: 1.07-1.50 (m, 4H), 1.53-2.15 (m, 9H), 2.15-2.37 (m, 1H), 2.82-2.93 (m, 1H), 3.07-3.17 (m, 1H), 4.18 (d, 2H), 7.22-7.30 (m, 2H), 7.40-7.50 (m, 1H), 7.90 (d, 1H), 8.15-8.23 (m, 1H), 9.65 (br.s, 1H).

MS (EI) M^+ 312.

Example 2

3-*ax*- and 3-*eq*-Quinolizidin-3-ylethylindole-3-carboxylate (E2a and E2b)

The title compounds were prepared from 3-(2-hydroxyethyl)quinolizidine (D1) (mixture of isomers) and indole-3-carboxylic acid chloride using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ethyl acetate. Pooling of the fractions containing the faster running component afforded the axial isomer (E2a) as a colourless oil, which was converted to its hydrochloride salt mp 207-209°C (acetone).

Free base:- ^{1}H NMR ($CDCl_3$)

δ: 1.15-1.80 (m, 11H), 1.85-2.25 (m, 5H), 2.65-2.80 (m, 2H), 4.36 (t, 2H, J=7Hz), 7.20-7.30 (m, 2H), 7.35-7.45 (m, 1H), 7.87 (d, 1H), 8.10-8.18 (m, 1H), 9.30 (br.s, 1H).

MS (CI) MH^+ 327.

Fractions containing the lower running component afforded the equatorial isomer (E2b) as a colourless oil, which was converted to its hydrochloride salt mp. 224-225°C (acetone).

Free base:- ^{1}H NMR ($CDCl_3$)

δ: 0.90-1.45 (m, 5H), 1.45-2.12 (m, 11H), 2.78-2.98 (m, 2H), 4.35 (t, 2H, J=7Hz), 7.15-7.25 (m, 2H), 7.32-7.42 (m, 1H), 7.68 (d, 1H), 8.10-8.18 (m, 1H) and 10.0 (br.s, 1H).

MS (CI) MH^+ 327.

Example 3

3-*ax*- and 3-*eq*-Quinolizidin-3-ylindole-3-carboxylate (E3a and E3b)

3-Hydroxyquinolizidine (C. Rader et al., J.Org. Chem., 1964, 29, 2252) (mixture of isomers) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The product was chromatographed on silica gel eluting with ether. The faster running component proved to be the axial isomer (E3a), obtained as a white solid mp 202-204°C.

^{1}H NMR ($CDCl_3$)

δ: 1.20-2.60 (m, 13H), 2.86-3.00 (m, 1H), 3.33-3.45 (m, 1H), 5.21 (br.s, 1H), 6.94-7.10 (m, 2H), 7.16-7.25 (m, 1H), 7.52 (d, 1H), 7.82-7.90 (m, 1H) and 11.35 (br.s, 1H).

MS (CI) MH^+ 299.

The slower running component was the equatorial isomer (E3b) obtained as a beige solid mp 199-202°C (ethyl acetate/petrol).

^{1}H NMR ($CDCl_3$)

δ: 1.19-1.40 (m, 2H), 1.40-2.33 (m, 11H), 2.82-2.93 (m, 1H), 3.16-3.27 (m, 1H), 5.10-5.24 (m, 1H), 7.20-7.30 (m, 2H), 7.38-7.46 (m, 1H), 7.93 (d, 1H), 8.10-8.18 (m, 1H), 8.95 (br.s, 1H).

MS (CI) MH^+ 299.

Example 4

2-*ax*- and 2-*eq*-Quinolizidin-2-ylindole-3-carboxylate (E4a and E4b)

2-Hydroxyquinolizidine (C. Rader et al., J.Org. Chem., 1964, 29, 2252) (mixture of isomers) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The yellow oil obtained was treated with ether and the equatorial isomer (E4b) precipitated out as a white solid mp

215-216°C (ethyl acetate/petrol).

^{1}H NMR (d^6 DMSO)

δ: 1.18-2.23 (m, 13H), 2.80-2.95 (m, 2H), 4.84-5.00 (m, 1H), 7.22-7.35 (m, 2H), 7.53-7.60 (m, 1H), 8.04-8.10 (m, 1H), 8.15 (s, 1H), 12.0 (br.s, 1H).

MS (EI) M^+ 298.

The material contained in the filtrate was chromatographed on silica gel eluting with ethyl acetate and the fractions containing the slower running product afforded the axial isomer (E4a) as a white solid mp 67-72°C.

^{1}H NMR ($CDCl_3$)

δ: 1.20-1.43 (m, 2H), 1.48-1.85 (m, 5H), 1.90-2.40 (m, 5H), 2.52-2.67 (m, 1H), 2.71-2.83 (m, 1H), 2.87-2.98 (m, 1H), 5.35-5.43 (m, 1H), 7.23-7.37 (m, 2H), 7.39-7.48 (m, 1H), 7.96 (d, 1H), 8.18-8.27 (m, 1H), 8.97 (br.s, 1H).

MS (EI) M^+ 298.

Example 5

***cis*-2,9-H- and *trans*-2,9-H-Indolizidin-2-ylmethylindole-3-carboxylate** (E5a and E5b)

2-Hydroxymethylindolizidine (K. Winterfield et al., Arch. pharm., 1958, 291, 485) (mixture of isomers) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ethyl acetate:methanol (98:2). The faster running component gave the *cis* isomer E5a as a colourless oil and converted to its hydrochloride salt mp 191-194°C (acetone).

HCl salt:- ^{1}H NMR (d^{6}DMSO)

δ: 1.30-2.10 (m, 7H), 2.28-2.45 (m, 1H), 2.74-2.96 (m, 2H), 3.04-3.25 (m, 2H), 3.35-3.56 (m, 2H), 4.34 (d, 2H), 7.14-7.26 (m, 2H), 7.45-7.55 (m, 1H),

7.90-8.00 (m, 1H), 8.18 (d, 1H), 10.95 (br.s, 1H) and 12.10 (br.s, 1H).

MS (EI) M^+ 298.

The slower running component gave the *trans* isomer E5b as a colourless oil and converted to its hydrochloride salt, mp 199-201°C (acetone).

HCl salt:- ^1H NMR (d^6DMSO)

δ: 1.32-1.50 (m, 1H), 1.55-2.15 (m, 8H), 2.75-2.95 (m, 2H), 3.10-3.27 (m, 1H), 3.45-3.54 (m, 1H), 3.60-3.70 (m, 1H), 4.18-4.37 (m, 2H), 7.17-7.24 (m, 2H), 7.47-7.54 (m, 1H), 7.92-7.99 (m, 1H), 8.14 (d, 1H), 10.95 (br.s, 1H) and 12.15 (br.s, 1H).

MS (EI) M^+ 298.

Example 6

***cis*-2,9-H- and *trans*-2,9-H-Indolizidin-2-ylethylindole-3-carboxylate** (E6)

A mixture of the title compounds was prepared from 2-(2-hydroxyethyl)indolizidine (K. Winterfield et al., Arch. Pharm., 1958, 291, 485) (mixture of isomers) and indole-3-carboxylic acid chloride using the method of Example 1. The material was chromatographed on silica gel eluting with ethyl acetate:methanol (19:1), but the isomers were not separated. The colourless oil was converted to its hydrochloride salt, which proved to be a hygroscopic white solid mp 45-50°C. ^1H NMR showed a 3:2 mixture of isomers.

Free base:- ^1H NMR ($CDCl_3$)

δ: 1.10-1.35 and 1.45-2.45 (each m, together 14H), 2.85-2.95 (dd, 1H major isomer), 3.02-3.17 (m, 1H), 3.26-3.35 (m, 1H minor isomer), 4.33 (t, 2H), 7.20-7.30 (m, 2H), 7.37-7.45 (m, 1H), 7.87 (d, 1H minor isomer), 7.90 (d, 1H major isomer), 8.12-8.23 (m, 1H) and 9.60 (br.s, 1H).

MS (EI) M^+ 312.

Example 7

3-*ax*- and 3-*eq*-Quinolizidin-3-ylmethyl-1-methylindazole-3-carboxylate (E7a and E7b)

The title compounds were prepared from 3-hydroxymethylquinolizidine (H. Lewis and C. Shoppee J.Chem. Soc., 1956, 313) (mixture of isomers) and 1-methylindazole-3-carboxylic acid chloride using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ethyl acetate. Fractions containing the faster running component afforded the axial isomer (E7a) as a colourless oil, which was converted to its hydrochloride salt mp 238-239°C (acetone).

Free base:- ^{1}H NMR ($CDCl_3$)

δ: 1.19-1.35 (m, 2H), 1.38-2.03 (m, 10H), 2.16-2.32 (m, 2H), 2.65-2.75 (m, 1H), 2.80-2.90 (m, 1H), 4.18 (s, 3H), 4.62-4.75 (m, 2H), 7.29-7.37 (m, 1H), 7.43-7.49 (m, 2H), 8.19 (d, 1H).

MS (CI) MH^+ 328.

Fractions containing the lower running component afforded the equatorial isomer (E7b) as a colourless oil, which was converted to its hydrochloride salt mp 199-201°C (acetone).

HCl salt:- ^{1}H NMR (d^6DMSO)

δ: 1.30-1.95 (m, 11H), 2.73-3.05 (m, 3H), 3.25-3.42 (m, 2H), 4.18 (s, 3H), 4.22-4.35 (m, 2H), 7.33-7.42 (m, 1H), 7.48-7.57 (m, 1H), 7.80 (d, 1H), 8.06 (d, 1H), 10.9 (br.s, 1H).

MS (CI) MH^+ 328.

Example 8

3-*ax*- and 3-*eq*-Quinolizidin-3-ylmethyl-4-amino-5-chloro-2-methoxybenzoate (E8a and E8b)

A solution of 4-amino-5-chloro-2-methoxybenzoic acid (500 mg, 0.0025 mole) in acetonitrile (30 ml) was treated with N,N'-carbonyldiimidazole (400 mg, 0.0025 mole) and stirred at room temperature under nitrogen for 3 hours, then concentrated *in vacuo* to give a yellow oil containing the imidazolide. A solution of 3-hydroxymethylquinolizidine (H. Lewis and C. Shoppee J.Chem. Soc., 1956, 313) (mixture of isomers) (425 mg, 0.0025 mole) in THF (20 ml) at 5°C under nitrogen was treated with 1.6M n-butyllithium in hexane (1.6 ml, 0.0025 mole), stirred for 10 minutes, then treated with the above imidazolide. After 16 hours at room temperature, the mixture was treated with 10% Na_2CO_3 solution (20 ml) and extracted with ethyl acetate (2 x 30 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with ethyl acetate:ether (1:1). Fractions containing the faster running component afforded the axial isomer (E8a) as a white solid mp 158-161°C.

^1H NMR ($CDCl_3$+D_2O)

δ: 1.18-2.00 (m, 12H), 2.05-2.22 (m, 2H), 2.65-2.85 (m, 2H), 3.84 (s, 3H), 4.38-4.50 (m, 2H), 4.80 (br.s, 2H), 6.30 (s, 1H), 7.83 (s, 1H).

MS (CI) MH^+ 353.

Fractions containing the lower running component afforded the equatorial isomer (E8b) as a white solid mp 92-96°C.

^1H NMR ($CDCl_3$)

δ: 1.10-1.55 (m, 4H), 1.65-2.35 (m, 10H), 2.90-3.00 (m, 1H), 3.05-3.15 (m, 1H), 3.94 (s, 3H), 4.05-4.28 (m, 2H), 4.55 (br.s, 2H), 6.38 (s, 1H), 7.90 (s, 1H).

Example 9

a) ***ax*-Quinolizidin-2-ylmethylindole-3-carboxylate** (E9a)

The title compound was prepared from *ax*-2-hydroxymethylquinolizidine (D4) and indole-3-carboxylic acid chloride using the method of Example 1. The product was purified by chromatography on neutral alumina eluting with ethyl acetate, followed by crystallisation from ether/pentane, to give the title compound (E9a) as a white solid mp 156-157°C.

^{1}H NMR ($CDCl_3$)

δ: 9.40 (br.s, 1H), 8.10-8.20 (m,1H), 7.93 (d, 1H), 7.37-7.45 (m,1H), 7.22-7.33 (m,2H), 4.35-4.50 (m,2H), 2.77-2.93 (m,1H), 2.63-2.75 (m,1H), 2.23-2.43 (m,2H), 1.43-2.20 (m,10H), 1.17-1.40 (m,2H).

MS (EI) M^+ 312.

b) ***eq*-Quinolizidin-2-ylmethylindole-3-carboxylate** (E9b)

The title compound was prepared from *eq*-2-hydroxymethylquinolizidine (N.J. Leonard et al, J. Org. Chem., 1957, 22, 1445) and indole-3-carboxylic acid chloride using the method of Example 1. The yellow oil obtained was crystallised from ether to afford the title compound (E9b) as a beige solid mp 154-157°C.

^{1}H NMR ($CDCl_3$)

δ: 9.40 (br.s,1H), 8.10-8.20 (m,1H), 7.87 (d,1H), 7.35-7.45 (m,1H), 7.20-7.30 (m,2H), 4.20 (d,2H), 2.80-2.97 (m,2H), 1.43-2.20 (m,11H), 1.10-1.40 (m,3H).

MS (EI) M^+ 312.

Example 10

***eq*-Quinolizidin-2-ylethylindole-3-carboxylate** (E10)

eq-2-(2-Hydroxyethyl)quinolizidine (D5) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The product was chromatographed on silica gel eluting with ethyl acetate/methanol (95:5). The resulting beige solid was recrystallised from ethyl acetate/petrol (60-80) to afford the title compound (E10) as a white solid mp 170-172°C.

^{1}H NMR ($CDCl_3$)

δ: 9.15 (br.s,1H), 8.12-8.22 (m,1H), 7.91 (d,1H), 7.36-7.45 (m,1H), 7.20-7.30 (m,2H), 4.38 (t,2H), 2.80-2.92 (m,2H), 1.93-2.17 (m,3H), 1.20-1.83 (m,12H), 1.00-1.18 (m,1H).

MS (EI) M^+ 326.

Example 11

a) ***eq*-Quinolizidin-1-ylindole-3-carboxylate** (E11a)

eq-1-Hydroxyquinolizidine (H.S. Aaron et al, J. Org. Chem. 1964, 29, 2248) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The product was chromatographed on silica gel eluting with ether to afford the title compound (E11a) as a white solid, mp 230-232°C.

^{1}H NMR ($CDCl_3$)

δ: 8.88 (br.s,1H), 8.11-8.20 (m,1H), 7.93 (d,1H), 7.38-7.46 (m,1H), 7.22-7.32 (m,2H), 4.80-4.94 (m,1H), 2.75-2.98 (m,2H), 1.92-2.32 (m,5H), 1.38-1.88 (m,6H), 1.15-1.35 (m,2H).

MS (CI) MH^+ 299.

b) ***ax*-Quinolizidin-1-ylindole-3-carboxylate** (E11b)

ax-1-Hydroxyquinolizidine (H.S. Aaron et al, J. Org. Chem., 1964, 29, 2248) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The product was chromatographed on silica gel eluting with ether, followed by trituration with ether, to afford the title compound (E11b) as a white solid mp 80-85°C.

^{1}H NMR ($CDCl_3$)

δ: 9.75 (br.s, 1H), 8.27-8.36 (m,1H), 7.83 (d,1H), 7.17-7.45 (m,3H), 5.20 (s,1H), 2.90-3.05 (m,2H), 1.15-2.30 (m,13H).

MS (EI) MH^+ 299.

Example 12

***ax*-and *eq*-Quinolizidin-1-ylmethylindole-3-carboxylate** (E12a and E12b)

1-Hydroxymethylquinolizidine (G.R. Clemo et al, J. Chem. Soc., 1937, 965 and 1938, 1574) (mixture of isomers) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ethyl acetate/methanol (97:3). Fractions containing the faster running component afforded the axial isomer (E12a) as a white solid mp 173-177°C.

^{1}H NMR ($CDCl_3$)

δ: 9.75 (br.s, 1H), 8.12-8.23 (m,1H), 7.92 (s,1H), 7.36-7.47 (m,1H), 7.20-7.32 (m,2H), 4.60-4.72 (m,1H), 4.40-4.53 (m,1H), 2.80-2.95 (m,2H), 1.15-2.25 (m,14H).

MS (EI) M^+ 312.

Combining fractions containing the slower running component gave the equatorial isomer (E12b) as a white solid mp 55-60°C.

^{1}H NMR ($CDCl_3$)

δ: 10.35 (br.s,1H), 8.15-8.25 (m,1H), 7.94 (d,1H), 7.37-7.47 (m,1H), 7.22-7.32 (m,2H), 4.22-4.43 (m,2H), 2.83-2.97 (m,2H), 1.50-2.20 (m,11H), 1.20-1.46 (m,3H).

MS (CI) MH^+ 313.

Example 13

***cis*-1,9-H- and *trans*-1,9-H-Indolizidin-1-ylindole-3-carboxylate** (E13a and E13b)

1-Hydroxyindolizidine (H.S. Aaron, J. Org. Chem., 1966, 31, 3502) (mixture of isomers) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ether. The faster runing component was obtained as a white solid mp 169-170°C.

^{1}H NMR ($CDCl_3$)

δ: 8.85 (br.s,1H), 8.10-8.20 (m,1H), 7.95 (d,1H), 7.39-7.50 (m,1H), 7.20-7.35 (m,2H), 5.05-5.20 (m,1H), 3.00-3.20 (m,2H), 1.20-2.65 (m,11H).

MS (CI) MH^+ 285.

The slower running component was obtained as a white solid mp 179-181°C.

^{1}H NMR ($CDCl_3$)

δ: 10.70 (br.s,1H), 8.20-8.35 (m,1H), 8.10 (br.s,1H), 7.35-7.45 (m,1H), 7.20-7.33 (m,2H), 5.63-5.75 (m,1H), 3.25-3.50 (m,2H), 2.35-2.50 (m,1H), 1.50-2.30 (m,9H), 1.20-1.45 (m,1H).

MS (CI) MH^+ 285.

Example 14

***cis*-1,9-H-Indolizidin-1-ylmethylindole-3-carboxylate** (E14a)

cis-1,9-H-1-Hydroxymethylindolizidine (D6a) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The product was chromatographed on silica gel eluting with ethyl acetate/methanol (19:1) to afford a colourless oil, which was crystallised from ether to give E14a as a white solid mp 140-141°C.

^{1}H NMR ($CDCl_3$)

δ: 9.00 (br.s,1H), 8.15-8.25 (m,1H), 7.90 (d,1H), 7.37-7.45 (m,1H), 7.20-7.30 (m,2H), 4.40-4.50 (dd,1H), 4.08-4.20 (dd,1H), 3.00-3.20 (m,2H), 2.50-2.68 (m,1H), 1.35-2.15 (m,10H), 1.10-1.30 (m,1H).

MS (EI) M^+ 298.

***trans*-1,9-H-Indolizidin-1-ylmethylindole-3-carboxylate** (E14b)

trans-1,9-H-1-Hydroxymethylindolizidine (D6b) was reacted with indole-3-carboxylic acid chloride using the method of Example 1. The product was chromatographed on silica gel eluting with ethyl acetate/methanol (19:1) followed by crystallisation from ether to afford the title compound (E14b) as a white solid mp 116-118°C.

^{1}H NMR ($CDCl_3$)

δ: 9.30 (br.s,1H), 8.12-8.23 (m,1H), 7.90 (d,1H), 7.37-7.47 (m,1H), 7.22-7.33 (m,2H), 4.28-4.40 (m,2H), 3.05-3.18 (m,2H), 1.95-2.35 (m,5H), 1.47-1.85 (m,5H), 1.13-1.43 (m,2H).

MS (EI) M^+ 298.

Example 15

***eq*-Quinolizidin-2-ylmethyl-1-methylindole-3-carboxylate** (E15)

eq-2-Hydroxymethylquinolizidine (N.J. Leonard et al, J. Org. Chem., 1957, 22, 1445) was reacted with the acid chloride of 1-methylindole-3-carboxylic acid using the method of Example 1. The product was chromatographed on silica gel eluting with ethyl acetate. The resulting pale yellow oil was crystallised from n-pentane to afford the title compound (E15) as a white crystalline solid mp 115-116°C.

^{1}H NMR ($CDCl_3$)

δ: 8.12-8.20 (m,1H), 7.80 (s,1H), 7.23-7.38 (m,3H), 4.18 (d,2H), 3.84 (s,3H), 2.80-2.93 (m,2H), 1.42-2.15 (m,11H), 1.08-1.35 (m,3H).

MS (EI) M^+ 326.

Example 16

***eq*-Quinolizidin-2-ylmethyl-1-ethylindole-3-carboxylate** (E16)

eq-2-Hydroxymethylquinolizidine (N.J. Leonard et al, J. Org. Chem., 1957, 22, 1445) was reacted with the acid chloride of 1-ethylindole-3-carboxylic acid using the method of Example 1. The product was chromatographed on silica gel eluting with ethyl acetate to afford the title compound (E16) as a pale yellow oil. This was converted to its hydrochloride salt mp 168-172°C.

^{1}H NMR (HCl salt) ($CDCl_3$)

δ: 12.10 (br.s,1H), 8.14 (s,1H), 8.07-8.18 (m,1H), 7.35-7.43 (m,1H), 7.23-7.32 (m,2H), 4.18-4.28 (d,2H and q,2H), 3.38-3.55 (m,2H), 2.30-2.83 (m,5H), 2.00-2.22 (m,3H), 1.75-2.00 (m,5H), 1.55 (t,3H), 1.35-1.60 (m,1H).

MS (EI) M^+ 340.

Example 17

***eq*-Quinolizidin-2-ylmethyl-1-n-propylindole-3-carboxylate** (E17)

eq-2-Hydroxymethylquinolizidine (N.J. Leonard et al, J. Org. Chem, 1957, 22, 1445) was reacted with the acid chloride of 1-n-propylindole-3-carboxylic acid using the method of Example 1. The product was chromatographed on silica gel eluting with ethyl acetate. The resulting yellow oil was crystallised from n-pentane to afford the title compound (E17) as a white solid mp 75-76°C.

^{1}H NMR ($CDCl_3$)

δ: 8.12-8.20 (m,1H), 7.84 (s,1H), 7.33-7.42 (m,1H), 7.23-7.32 (m,2H), 4.18 (d,2H), 4.10 (t,2H), 2.80-2.95 (m,2H), 1.42-2.15 (m,13H), 1.06-1.36 (m,3H), 0.95 (t,3H).

MS (EI) M^+ 354.

Example 18

***eq*-Quinolizidin-2-ylmethyl-1-isopropylindole-3-carboxylate** (E18)

A solution of *eq*-quinolizidin-2-ylmethylindole-3-carboxylate (E9b) (320 mg, 1.08 mmole) in dry THF (15 ml) at room temperature under nitrogen was treated with potassium t-butoxide (125 mg, 1.1 mmole) and stirred for 20 minutes. The solution was then treated with 2-iodopropane (0.11 ml, 1.1 mmole) and stirred for 18h. The reaction mixture was treated with 10% Na_2CO_3 solution (25 ml) and extracted with ethyl acetate (2x50 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting initially with ether, then with ethyl acetate, to afford the title compound (E18) as a colourless oil (240 mg, 63%). This was converted to the hydrochloride salt mp 235-238°C (acetone).

^{1}H NMR (HCl salt) (d^6DMSO)

δ: 10.60 (br.s,1H), 8.32 (s,1H), 8.00-8.05 (m,1H), 7.62-7.67 (m,1H), 7.20-7.30 (m,2H), 4.84 (septet,1H), 4.15 (d,2H), 3.25-3.40 (m,2H), 2.77-3.12 (m,3H), 2.05-2.18 (m,1H), 1.70-1.95 (m,7H), 1.55-1.70 (m,2H), 1.53 (d,6H), 1.40-1.52 (m,1H).

MS (EI) + 354.

Example 19

***eq*-Quinolizidin-2-ylmethyl-1-allylindole-3-carboxylate** (E19)

eq-Quinolizidin-2-ylmethylindole-3-carboxylate (E9b) was alkylated with allyl iodide using the method in Example 18. The product was chromatographed on silica gel eluting initially with ether, then with ethyl acetate, to afford the title compound (E19) as a colourless oil. This was converted to its hydrochloride salt mp 190-192°C (acetone)

^{1}H NMR (HCl salt) (d^6DMSO)

δ: 10.45 (br.s,1H), 8.26 (s,1H), 7.98-8.05 (m,1H), 7.52-7.57 (m,1H), 7.20-7.28 (m,2H), 5.98-6.10 (m,1H), 5.20 (d,1H,J=10Hz), 5.10 (d,1H,J=16Hz), 4.93 (d,2H,J=6Hz), 4.14 (d,2H), 3.25-3.38 (m,2H), 2.77-3.13 (m,3H), 2.04-2.17 (m,1H), 1.70-1.95 (m,7H), 1.37-1.68 (m,3H).

MS (EI) M^+ 352.

Example 20

***eq*-Quinolizidin-2-ylmethyl-1-isobutylindole-3-carboxylate** (E20)

eq-Quinolizidin-2-ylmethylindole-3-carboxylate (E9b) was alkylated with 1-bromo-2-methylpropane using the method in Example 18. The product was chromatographed on silica gel eluting initially with ether, then with ethyl acetate, to afford the title compound (E20) as a colourless oil. This was converted to its hydrochloride salt mp 174-175°C (acetone/ether).

^{1}H NMR (HCl salt) (d^{6}DMSO)

δ: 10.55 (br.s,1H), 8.28 (s,1H), 7.98-8.04 (m,1H), 7.58-7.63 (m,1H), 7.20-7.28 (m,2H), 4.13 (d,2H), 4.08 (d,2H), 3.25-3.40 (m,2H), 2.78-3.13 (m,3H), 2.05-2.23 (m,2H), 1.70-1.95 (m,7H), 1.52-1.70 (m,2H), 1.38-1.50 (m,1H), 0.85 (d,6H).

MS (EI) M^+ 368.

Example 21

***cis*-2,9-H- and *trans*-2,9-H-Indolizidin-2-ylmethyl-1-methylindole-3-carboxylate** (E21a and E21b)

2-Hydroxymethylindolizidine (H. Kato et al, Chem. Pharm. Bull., 1980, 28(7), 2194) (mixture of isomers) was reacted with the acid chloride of 1-methylindole-3-carboxylic acid using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ethyl acetate. The faster running isomer was crystallised from ether/pentane to afford the *cis* isomer (E21a) as a white solid mp 109-110°C.

^{1}H NMR ($CDCl_3$)

δ: 8.13-8.20 (m,1H), 7.78 (s,1H), 7.25-7.36 (m,3H), 4.21-4.33 (m,2H), 3.82 (s,3H), 3.00-3.08 (m,2H), 2.48-2.60 (m,1H), 2.31 (t,1H), 2.04-2.12 (m,1H), 1.92-2.00 (m,1H), 1.72-1.90 (m,3H), 1.52-1.67 (m,2H), 1.17-1.25 (m,3H).

MS (EI) M^+ 312.

The slower running component gave the trans isomer (E21b) as a white solid from ether/pentane mp 94-96°C.

^{1}H NMR ($CDCl_3$)

δ: 8.10-8.18 (m,1H), 7.78 (s,1H), 7.25-7.38 (m,3H), 4.18-4.31 (m, 2H), 3.84 (s,3H), 3.32 (t,1H), 3.05-3.13 (m,1H), 2.65-2.78 (m,1H), 1.50-2.06 (m,9H), 1.17-1.30 (m,2H).

MS (EI) M^+ 312.

Example 22

***cis*-2,9-H- and *trans*-2,9-H-Indolizidin-2-ylmethyl 1-ethylindole-3-carboxylate** (E22a and E22b)

2-Hydroxymethylindolizidine (H. Kato et al, Chem. Pharm. Bull., 1980, 28(7), 2194) (mixture of isomers) was reacted with the acid chloride of 1-ethylindole-3-carboxylic acid using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ethyl acetate. The faster running component gave the *cis* isomer (E22a) as a colourless oil and converted to its hydrochloride salt mp 168-169°C.

^{1}H NMR (HCl salt) (d^6DMSO)

δ: 10.90 (br.s,1H), 8.29 (s,1H), 7.92-8.02 (m,1H), 7.56-7.66 (m,1H), 7.20-7.32 (m,2H), 4.22-4.38 (m,4H), 3.32-3.57 (m,2H), 3.05-3.23 (m,2H), 2.73-2.96 (m,2H), 2.30-2.44 (m,1H), 1.40 (t,3H), 1.25-2.05 (m,7H).

MS (EI) M^+ 326.

The slower running component afforded the *trans* isomer (E22b). Hydrochloride salt mp 146-148°C.

^{1}H NMR (HCl salt) (d^6DMSO)

δ: 10.90 (br.s,1H), 8.20 (s,1H), 7.93-8.03 (m,1H), 7.55-7.65 (m,1H), 7.15-7.33 (m,2H), 4.15-4.40 (m,4H), 3.40-3.75 (m,2H), 2.70-3.30 (m,4H), 1.38 (t,3H), 1.15-2.10 (m,8H).

MS (EI) M^+ 326.

Example 23

***cis*-2,9-H- and *trans*-2,9-H-Indolizidin-2-ylmethyl-1-n-propylindole-3-carboxylate** (E23a and E23b)

2-Hydroxymethylindolizidine (H. Kato et al, Chem. Pharm. Bull., 1980, 28(7), 2194) (mixture of isomers) was reacted with the acid chloride of 1-n-propylindole-3-carboxylic acid using the method of Example 1. The isomers were separated by chromatography on silica gel eluting with ethyl acetate. The faster running component gave the *cis* isomer (E23a), which was crystallised from pentane mp 54-55°C. HCl salt mp 172-173°C (acetone/ether).

^{1}H NMR (HCl salt) (d^{6}DMSO)

δ: 10.90 (br.s,1H), 8.28 (s,1H), 7.91-8.01 (m,1H), 7.56-7.66 (m,1H), 7.18-7.31 (m,2H), 4.31 (d,2H), 4.24 (t,2H), 3.34-3.54 (m,2H), 3.04-3.24 (m,2H), 2.72-2.94 (m,2H), 2.28-2.43 (m,1H), 1.94-2.06 (m,1H), 1.30-1.90 (m,8H), 0.83 (t,3H).

MS (EI) M^+ 340.

The slower running component afforded the *trans* isomer (E23b), which also crystallised from pentane mp 81-82°C.

^{1}H NMR (free base) ($CDCl_3$)

δ: 8.10-8.20 (m,1H), 7.83 (s,1H), 7.34-7.42 (m,1H), 7.23-7.33 (m,2H), 4.18-4.32 (m,2H), 4.12 (t,2H), 3.28-3.38 (t,1H), 3.04-3.15 (m,1H), 2.64-2.81 (m,1H), 1.47-2.07 (m,11H), 1.13-1.35 (m,2H), 0.95 (t,3H).

MS (EI) M^+ 340.

Example 24

***cis*-4,7-H- and *trans*-4,7-H-1-Azabicyclo[5.4.0]undecan-4-ylmethylindole-3-carboxylate** (E24a and E24b)

The two title compounds (E24a and E24b) were prepared by reaction of indole-3-carboxylic acid chloride with *cis*-4,7-H-4-hydroxymethyl-1-azabicyclo[5.4.0]undecane (D2a) and *trans*-4,7-H-4-hydroxymethyl-1-azabicyclo[5.4.0]undecane (D2b) respectively, using the method of Example 1. Each product was purified by chromatography on silica gel eluting with chloroform/methanol (19:1) to give a colourless oil. The two isomers had different rf values.

Higher rf isomer:- HCl salt mp 130-135°C.

^{1}H NMR (HCl salt) ($CDCl_3$)

δ: 11.30 (br.s,1H), 10.10 (br.s,1H), 8.03-8.15 (m,2H), 7.48-7.58 (m,1H), 7.20-7.30 (m,2H), 4.12 (d,2H), 3.30-3.55 (m,2H), 2.50-2.93 (m,3H), 1.60-2.50 (m,12H), 1.30-1.50 (m,1H).

MS (CI) MH^+ 327.

Lower rf isomer:- HCl salt mp 160-162°C (acetone)

^{1}H NMR (HCl salt) (d^6 DMSO)

δ: 12.05(s,1H), 10.30(br.s,1H), 8.10(d,1H), 7.94-8.02(m,1H), 7.45-7.54(m,1H), 7.14-7.25(m,2H), 4.08(d,2H), 2.85-3.60(m,5H), 1.30-2.65(m,13H).

MS (FAB) MH^+ 327

Example 25

***cis*-5,7-H- and *trans*-5,7-H-1-Azabicyclo[5.4.0]undecan-5-ylmethylindole-3-carboxylate** (E25a and E25b)

Indole-3-carboxylic acid chloride was reacted separately with *cis*-5,7-H-5-hydroxymethyl-1-azabicyclo[5.4.0]undecane (D3a) and *trans*-5,7-H-5-hydroxymethyl-1-azabicyclo[5.4.0]undecane (D3b) using the method of Example 1. Each product was purified by chromatography on silica gel eluting with ethyl acetate then ethyl acetate, methanol (95:5). The two isomers had different rf values.

Higher rf isomer:- off-white solid mp 109-110°C.

^{1}H NMR ($CDCl_3$)

δ: 9.05 (br.s,1H), 8.15-8.23 (m,1H), 7.92 (d,1H), 7.35-7.45 (m,1H), 7.20-7.30 (m,2H), 4.15 (d,2H), 2.80-2.90 (m,1H), 2.45-2.72 (m,2H), 2.18-2.42 (m,3H), 1.90-2.05 (m,1H), 1.35-1.87 (m,9H), 1.10-1.35 (m,2H).

MS (CI) MH^+ 327.

Lower rf isomer:- white solid mp 138-140°C.

^{1}H NMR ($CDCl_3$)

δ: 9.30 (br.s,1H), 8.11-8.21 (m,1H), 7.92 (s,1H), 7.38-7.47 (m,1H), 7.22-7.32 (m,2H), 4.07-4.26 (m,2H), 2.83-2.98 (m,2H), 2.05-2.60 (m,5H), 1.15-1.98 (m,11H).

MS (CI) MH^+ 327.

Example 26

***eq*-Quinolizidin-2-ylmethyl-2-methoxyindole-3-carboxylate** (E26)

A stirred solution of N-chlorosuccinimide (220 mg, 0.0016 mole) in chloroform (6 ml) at room temperature under nitrogen was treated with a solution of *eq*-quinolizidin-2-ylmethylindole-3-carboxylate (E9b) (330 mg, 0.0011 mole) in chloroform (6 ml) and stirred for 2h. The solution was then treated with methanol (0.71 ml, 0.022 mole) and stirring continued. After 3h a beige precipitate began to form and after a further 1h this was filtered off, washed with chloroform, and dried to afford the title compound (E26) as its hydrochloride salt mp 212-213°C.

^{1}H NMR (HCl salt) (d^{6}DMSO)

δ: 12.10 (s,1H), 10.20 (br.s,1H), 7.80 (d,1H), 7.30 (d,1H), 7.01-7.17 (m,2H), 4.10 (s,3H), 4.07 (d,2H), 3.23-3.43 (m,2H), 2.73-3.15 (m,3H), 2.00-2.15 (m,1H), 1.35-1.95 (m,10H).

MS (EI) MH^+ 343.

Example 27

4-Iodo-3-(*eq*-quinolizidin-2-yl)methyl-1-isopropylindole carboxylate (E27)

To a solution of *eq*-quinolizidin-2-ylmethyl-1-isopropyl-indole-3-carboxylate (E18) (122 mg) in TFA (5 ml), was added thallium trifluoroacetate (170 mg). The reaction mixture was stirred at room temperature for 2 hours then the solvent was removed *in vacuo*. The residue was treated with Et_2O to give a grey solid that was collected by filtration. This was suspended in H_2O (5 ml) and a solution of KI (500 mg) in H_2O (2 ml) was added. The reaction mixture was stirred at room temperature overnight then extracted thoroughly with $CHCl_3$ (pH 9). The $CHCl_3$ extracts were dried and concentrated *in vacuo* to give a yellow gum that was purified by column chromatography on SiO_2 ($CHCl_3$ 95%, MeOH 5%). The product was isolated as the HCl salt.

^{1}H NMR (250 MHz) ($CDCl_3$) (free base)

δ: 7.79 (s, 1H), 7.8 (dd, 1H), 7.4 (dd, 1H), 6.95 (t, 1H), 4.6-4.77 (m, 1H), 4.2 (d, 2H), 2.98-3.15 (m, 2H), 1.2-2.35 (m, 20H inc. d, 6H).

Example 28

***eq*-Quinolizidin-2-ylmethyl 1-cyclopropylmethylindole-3-carboxylate** (E28)

eq-Quinolizidin-2-ylmethyl indole-3-carboxylate (E9b) was alkylated with cyclopropylmethyl bromide using the method in Example 18. The product was chromatographed on silica gel eluting initially with ether, then with ethyl acetate, to afford the title compound (E28) as a colourless oil. This was converted to its hydrochloride salt mp 167-169°C (acetone/ether).

^{1}H NMR (HCl salt) (d^6DMSO)

δ: 10.55 (br.s,1H), 8.35 (s,1H), 7.97-8.05 (m,1H), 7.60-7.70 (m,1H), 7.20-7.30 (m,2H), 4.13 (d,2H and d,2H), 3.22-3.40 (m,2H), 2.74-3.15 (m,3H), 2.02-2.20 (m,1H), 1.25-1.98 (m,11H), 0.40-0.60 (m,4H).

MS (EI) M^+ 366.

Example 29

***eq*-Quinolizidin-2-ylmethyl 1-cyclohexylmethylindole-3-carboxylate** (E29)

eq-Quinolizidin-2-ylmethyl indole-3-carboxylate (E9b) was alkylated with cyclohexylmethyl bromide using the method of Example 18. The product was chromatographed on silica gel eluting initially with ether, then with ethyl acetate, to afford a colourless oil, which crystallised from n-pentane to give the title compound (E29) as a white solid mp 98-100°C.

^{1}H NMR ($CDCl_3$)

δ: 8.13-8.20 (m,1H), 7.79 (s,1H), 7.20-7.40 (m,3H), 4.18 (d,2H), 3.96 (d,2H), 2.80-2.95 (m,2H), 1.42-2.18 (m,17H), 0.93-1.38 (m,8H).

MS (EI) M^+ 408.

Example 30

***eq*-Quinolizidin-2-ylmethyl 1-acetylindole-3-carboxylate** (E30)

eq-Quinolizidin-2-ylmethyl indole-3-carboxylate (E9b) was acylated with acetyl chloride using the method of Example 18. The product was chromatographed on silica gel eluting with ethyl acetate to give a pale yellow oil, which crystallised from ether to afford the title compound (E30) as a white solid mp 127-129°C.

^{1}H NMR ($CDCl_3$)

δ: 8.42-8.47 (m,1H), 8.10-8.20 (m,2H), 7.35-7.45 (m,2H), 4.23 (d,2H), 2.85-3.00 (m,2H), 2.72 (s,3H), 1.55-2.20 (m,11H), 1.15-1.45 (m,3H).

MS (EI) M^+ 354.

Example 31

***eq*-Quinolizidin-2-ylmethyl 1-acetylmethylindole-3-carboxylate** (E31)

A stirred solution of *eq*-quinolizidin-2-ylmethylindole-3-carboxylate (E9b) (300 mg, 0.96 mmole) in acetone (10 ml) was treated with anhydrous potassium carbonate (270 mg, 2 mmole) and bromoacetone (150 mg, 1.1 mmole) and kept at room temperature for 3 days. The mixture was treated with 10% Na_2CO_3 solution (10 ml) and extracted with ethyl acetate (2x25 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel

eluting with ethyl acetate/methanol (95:5). The pale yellow oil obtained was crystallised from ether to afford the title compound (E31) as a beige solid (14 mg) mp 139-142^{O}C.

^{1}H NMR ($CDCl_3$)

δ: 8.17-8.25 (m,1H), 7.81 (s,1H), 7.26-7.35 (m,2H), 7.14-7.22 (m,1H), 4.88 (s,3H), 4.19 (d,2H), 2.82-2.97 (m,2H), 2.14 (s,3H), 1.45-2.20 (m,11H), 1.10-1.40 (m,3H).

MS (EI) M^+ 368.

Example 32

***cis*-2,9-H-N-Methylindolizidin-2-ylmethyl l-n-propylindole-3-carboxylate iodide** (E32)

A stirred solution of *cis*-2,9-H-indolizidin-2-ylmethyl indole-3-carboxylate (E23), 100 mg, 0.30 mmole) in acetone (10 ml) was treated with iodomethane (0.095 ml, 1.5 mmole) and heated under reflux for 4h. The solution was then concentrated *in vacuo* and the residual solid recrystallised from acetone to afford the title compound as a white solid (60 mg, 42%) mp 195-196^{o}C.

M.S. (CI) 341

Description 1 (intermediate for Example 2)

3-(2-Hydroxyethyl)quinolizidine (D1)

a) A stirred solution of diisopropylamine (2.25 ml, 0.016 mole) in dry THF (20 ml) at -50°c under nitrogen was treated with 1.6M n-butyllithium in hexane (9.4 ml, 0.015 mole). After 10 minutes the solution was cooled to -65°C and treated with a solution of quinolizidin-4-one (I. Murakoshi, Yakugaku Zasshi, 1958, 78, 594) (2.0g, 0.013 mole) in ether (20 ml), stirred for a further 10 minutes and then ethylene oxide (1.23g, 0.028 mole) bubbled into the solution, which was allowed to warm to room temperature over 1 hour and then heated under reflux for 1.5 hours. The reaction mixture was treated with concentrated potassium carbonate solution (30 ml) and extracted with ethyl acetate (2 x 60 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with chloroform/methanol (98:2) to afford 3-(2-hydroxyethyl)quinolizidin-4-one as a pale yellow oil (1.4g, 55%).

^1H NMR ($CDCl_3$)

δ: 1.16-2.10 (m, 12H), 2.30-2.58 (m, 2H), 3.18-3.36 (m, 1H), 3.62-3.85 (m, 2H), 4.20-5.20 (v.br.s, 1H, OH) and 4.70-4.85 (m, 1H).

b) A solution of 3-(2-hydroxyethyl)quinolizidin-4-one (1.4g, 0.0071 mole) in THF (40 ml) was added to a stirred suspension of lithium aluminium hydride (0.5g, 0.013 mole) in THF (50 ml) under nitrogen and the mixture heated under reflux for 2.5 hours, then cooled to ice bath temperature and treated dropwise with water (0.5 ml), 10% sodium hydroxide solution (0.5 ml) and water (1.5 ml). The mixture was filtered through kieselguhr and the filtrate concentrated *in vacuo*. The residue was distilled in a Kugelröhr apparatus (bp approx. 140°C at 2 mmHg) to give the title compound as a colourless oil (0.97g, 75%).

^1H NMR ($CDCl_3$)

δ: 0.88-1.07 and 1.15-2.25 (each m, together 17H), 2.65-2.86 (m, 2H), 3.59-3.85 (m, 2H).

Description 2 (intermediate for Example 24)

a) **Diethylpiperidine-1,2-dipropionate**

A stirred solution of ethyl piperidinyl-2-propionate (I Murakoshi, Yakugaku Zasshu, 1958, 78, 598) (0.12 mole) in ethanol (350 ml) was treated with ethyl acrylate (26 ml, 0.24 mole) and heated under reflux for 4 h. The solution was concentrated *in vacuo* and the residue chromatographed on silica gel eluting with ether to afford the title compound as an yellow oil 9.6g, (28%).

^{1}H NMR ($CDCl_3$)

δ: 4.14 (q, 4H), 2.93-3.17 (m, 1H), 2.70-2.88 (m, 2H), 2.46 (t, 2H), 2.18-2.40 (m, 4H), 1.40-2.00 (m, 6H), 1.25 (t, 6H), 1.15-1.38 (m, 2H)

b) **1-Azabicyclo[5.4.0]undecan-4-one**

A solution of diethyl piperidine-1,2-dipropionate (9.60g, 0.034 mole) in xylene (100 ml) was added dropwise over 4h to a flask containing 250 ml of xylene, which was being fed *via* a continuous extraction apparatus to a stirred, refluxing, suspension of sodium hydride (4.2g of 80%, 0.14 mole) in xylene (100 ml) containing ethanol (0.5 ml) under nitrogen. The reaction mixture was heated under reflux for a total of 40 h, then cooled in an ice bath and treated with 5M HCl acid (250 ml). The aqueous layer was separated, treated with concentrated HCl acid (30 ml) and heated under reflux for 18 h. The solution was cooled, basified with potassium carbonate and extracted with ether (3 x 100 ml). The combined extracts were dried (Na_2CO_3), concentrated *in vacuo* and the residue distilled in a Kugelröhr apparatus to give the title compound as a colourless oil (4.6 g, 84%) bp approx. 110°C at 0.25 mm Hg.

^{1}H NMR ($CDCl_3$)

δ: 2.75-3.05 (m, 4H), 2.44-2.70 (m, 4H), 2.15-2.30 (m, 1H), 2.00-2.15 (m, 1H), 1.15-1.90 (m, 7H)

c) ***cis*-4,7-H- and *trans*-4-7-H-4-cyano-1-azabicyclo[5.4.0]undecane**

A stirred solution of 1-azabicyclo[5.4.0]undecan-4-one (4.60 g, 0.028 mole) and 4-toluenesulphonylmethyl isocyanide (6.73 g, 0.035 mole) in dimethoxyethane (125 ml) together with ethanol (3.2 ml., 0.055 mole) at 5°C under nitrogen was treated portionwise over 15 minutes with potassium t-butoxide (6.17g, 0.055 mole) keeping the temperature below 15°C. The mixture was allowed to warm to room temperature over 2h, then warmed to 45°C for 0.75h followed by 18h at room temperature. The solution was concentrated *in vacuo* and basified with 10% Na_2CO_3 solution, then extracted with ethyl acetate (3 x 100 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on a short neutral alumina column eluting with ethyl acetate to afford a mixture of the title compounds as a pale yellow oil (4.18g, 84%). This was used without further purfication.

^1H NMR ($CDCl_3$)

δ: 2.60-2.95 (m, 4H), 1.15-2.55 (m, 14H)

d) **Ethyl *cis*-4,7-H- and *trans*-4,7-H-1-Azabicyclo[5.4.0]-undecan-4-ylcarboxylate**

A mixture of *cis*-4,7-H and *trans*-4,7-H-4-cyano-1-azabicyclo[5.4.0]undecane (D2a and D2b) (3.18 g, 0.018 mole) in concentrated HCl acid (80 ml) was heated under reflux for 12 h, then concentrated *in vacuo*. The residue was treated with ethanol (80 ml) and concentrated HCl acid (2 ml) and heated under reflux for 6 h, then concentrated *in vacuo*. The residue was basified with 10% Na_2CO_3 solution (100 ml) and extracted with ethyl acetate (2 x 100 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to leave a brown oil, which was chromatographed on silica gel eluting initially with ether, then ethyl acetate, to separate each title compound as a yellow oil.

Higher rf isomer: ^1H NMR ($CDCl_3$)

δ: 4.10 (q, 2H), 2.62-2.90 (m, 2H), 2.35-2.60 (m, 2H), 1.25 (t, 3H), 1.15-2.30 (m, 14H)

Lower rf isomer: ^{1}H NMR ($CDCl_3$)

δ: 4.12 (q, 2H), 2.53-2.93 (m, 4H), 2.18-2.36 (m, 1H), 1.92-2.15 (m, 4H), 1.25 (t, 3H), 1.15-1.90 (m, 9H)

e) ***cis*-4,7-H- and *trans*-4,7-H-4-Hydroxymethyl-1-azabicyclo[5.4.0]undecane** (D2a and D2b)

A stirred suspension of lithium aluminium hydride (232 mg, 0.0061 mole) in THF (20 ml) at room temperature under nitrogen was treated with a solution of one isomer of ethyl 1-azabicyclo[5.4.0]undecan-4-ylcarboxylate (1.10 g, 0.0049 mole) in THF (20 ml). The mixture was stirred for 1 h then treated with water (0.2 ml), 10% NaOH solution (0.2 ml) and water (0.6 ml). The mixture was filtered through a plug of Kieselguhr, the filtrate concentrated *in vacuo* and the residue distilled in a Kugelröhr apparatus to give one of the title compounds as a colourless oil. The alternative title compound was prepared from the alternative isomer of ethyl 1-azabicyclo[5.4.0]undecan-4-ylcarboxylate using the same procedure, as a colourless oil. The two isomers had different rf values.

Higher rf isomer; ^{1}H NMR ($CDCl_3$)

δ: 3.50 (d, 2H), 2.82-2.95 (m, 1H), 2.68-2.80 (m, 1H), 2.41-2.55 (m, 1H), 2.14-2.30 (m, 1H), 1.95-2.10 (m, 1H), 1.78-1.95 (m, 2H), 1.20-1.77 (m, 12H)

Lower rf isomer: ^{1}H NMR ($CDCl_3$)

δ: 3.45 (d, 2H), 2.65-2.90 (m, 2H), 2.48-2.62 (m, 1H), 2.20-2.35 (m, 1H), 1.15-2.05 (m, 15H)

Description 3 (intermediate for Example 25)

a) **Ethyl-1-(3-ethoxycarbonylpropyl)piperidin-2-ylacetate**

A stirrred solution of ethyl piperidin-2-ylacetate (8.0g, 0.047 mole) and ethyl 4-bromobutyrate (6.7 ml, 0.047 mole) in acetone (100 ml) was treated with potassium carbonate (13g, 0.094 mole) and heated under reflux for 32 h. A further 1.5 ml of ethyl 4-bromobutyrate and 3g of potassium carbonate was added and reflux continued for 16 h. The mixture was concentrated *in vacuo* and the residue treated with water (100 ml) and extracted with ethyl acetate (2 x 100 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with ether/petrol (60-80) to afford the title compound as a pale yellow oil (11.5g, 86%)

^1H NMR ($CDCl_3$)

δ: 4.13 (q, 4H), 2.87-3.02 (m, 1H), 2.25-2.75 (m, 8H), 1.25 (t, 6H), 1.15-1.87 (m, 8H)

b) **1-Azabicyclo[5,4,0]undecan-5-one**

The title compound was prepared from ethyl-1-(3-ethoxycarbonylpropyl)piperidin-2-ylacetate using the method of Description 2b). The crude product was purified by distillation in a Kugelröhr apparatus (bp approx, 105°C at 0.5 mm Hg) to give a colourless oil.

^1H NMR ($CDCl_3$)

δ: 2.80-3.20 (m, 3H), 1.55-2.65 (m, 12H), 1.18-1.50 (m, 2H).

c) ***cis*-5,7-H- and *trans*-5,7-H-5-Cyano-1-azabicyclo[5.4.0]undecane**

The title compounds were prepared from 1-azabicyclo[5.4.0]undecan-5-one using the method of Description 2c). The crude product was purified by chromatography on neutral alumina eluting with ethylacetate to afford a

yellow oil containing a mixture of the title compounds.

^{1}H NMR ($CDCl_3$)

δ: 2.97-3.10 (m), 2.75-2.90 (m), 2.55-2.68 (m), 2.23-2.45 (m), 1.20-2.15 (m).

IR (film) C=N 2240 cm^{-1}.

d) **Ethyl *cis*-5,7-H- and *trans*-5,7-H-1-azabicyclo[5.4.0]undecan-5-ylcarboxylate**

The title compounds were prepared from a mixture of *cis*-5,7-H-5-cyano-1-azabicyclo[5.4.0]undecane and *trans*-5,7-H-5-cyano-1-azabicyclo[5.4.0]undecane (mixture from Description 3c)) using the method of Description 2d).

The mixture was chromatographed on silica gel eluting initially with ether, then ethylacetate, to afford the separate isomers as yellow oils.

Higher rf isomer:- ^{1}H NMR ($CDCl_3$) δ: 4.12 (q, 2H), 2.75-2.86 (m, 2H), 2.59-2.71 (m, 1H), 2.42-2.55 (m, 1H), 2.15-2.32 (m, 2H), 1.80-2.05 (m, 3H), 1.25 (t, 3H), 1.15-1.78 (m, 9H).

Lower rf isomer:- ^{1}H NMR ($CDCl_3$)

δ: 4.12 (q, 2H), 2.95-3.10 (m, 1H), 2.78-2.90 (m, 1H), 2.59-2.73 (m, 1H), 2.37-2.49 (m, 1H), 2.15-2.28 (m, 1H), 1.25 (t, 3H), 1.20-2.10 (m, 13H).

e) ***cis*-5,7-H- and *trans*-5,7-H-5-Hydroxymethyl-1-azabicyclo[5.4.0]undecane**

The title compounds (D3a and D3b) were prepared respectively from ethyl cis-5,7-H-1-azabicyclo[5.4.0]undecan-5-ylcarboxylate and ethyl-*trans*-5,7-H-1-azabicyclo[5.4.0]undecan-5-ylcarboxylate using the method of Description 2e). Each isomer was distilled in a kügelröhr apparatus to give the title compounds as colourless oils.

The isomers had different rf values.

Higher rf isomer:- ^{1}H NMR ($CDCl_3$)

δ: 3.45-3.60 (m, 2H), 2.78-2.92 (m, 1H), 2.63-2.74 (m, 1H), 2.35-2.56 (m, 3H), 1.92-2.08 (m, 1H), 1.20-1.85 (m, 13H).

Lower rf isomer:-

δ: 3.40-3.60 (m, 2H), 2.93-3.10 (m, 1H), 2.68-2.90 (2H, m), 2.38-2.52 (m, 1H), 2.15-2.30 (m, 1H), 1.15-2.10 (m, 14H).

Description 4 (Intermediate for Example 9)

***ax*-2-Hydroxymethylquinolizidine**

Ethyl *ax*-quinolizidin-2ylcarboxylate (E. Koshinaka et al, Yakugaku Zasshi, 1980, 100(1), 88) was reduced with lithium aluminium hydride using the method of Description 2e). The crude product was distilled in a kugelröhr apparatus (bp approx. 140°C at 0.2 mm Hg) to afford the title compound (D4) as a colourless oil.

^{1}H NMR ($CDCl_3$)

δ: 3.70 (d, 2H), 2.75-2.86 (m, 1H), 2.55-2.66 (m, 1H), 1.40-2.24 (m, 13H), 1.15-1.37 (m, 2H).

Description 5 (Intermediate for Example 10)

***eq*-2-(2-Hydroxyethyl)quinolizidine**

Ethyl-*eq*-quinolizidin-2-ylacetate (U.S.A. Patent 3692791) was reduced with lithium aluminium hydride using the method of Description 2e). The product was purified by distillation in a Kugelröhr apparatus (bp approx. 120°C at 0.15 mm Hg) to afford the title compound (D5) as a colourless oil.

^1H NMR ($CDCl_3$)

δ: 3.63-3.75 (m, 2H), 2.84 (dt, 2H), 1.90-2.13 (m, 2H), 1.15-1.80 (m, 14H), 0.90-1.10 (m, 1H).

Description 6 (intermediate for Example 14)

***cis*-1,9-H-and *trans*-1,9-H-1-Hydroxymethylindolizidine** (D6a and D6b)

The title compounds (D6a and D6b) were prepared respectively from ethyl *cis*-1,9-H- and *trans*-1,9-H-indolizidin-1-ylcarboxylates (H. Kato et al, Chem Pharm Bull., 1980, 28, 2194) using the method of Description 2e). Each isomer was obtained as a colourless oil.

cis isomer:- ^1H NMR ($CDCl_3$)

δ: 4.50 (br.s, 1H), 3.86 (dd, 1H), 3.46 (dd, 1H), 3.03-3.18 (m, 2H), 1.38-2.17 (m, 11H), 1.15-1.32 (m, 1H).

trans isomer:- ^1H NMR ($CDCl_3$)

δ: 3.57-3.72 (m, 2H), 2.97-3.13 (m, 2H), 1.74-2.20 (m, 7H), 1.40-1.70 (m, 4H), 1.12-1.35 (m, 2H).

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}M and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10^{-9}M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, pIC_{50} values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist.

Compounds were generally active in the range of concentrations of the order of pIC_{50}=6 or more, E22a and E26 showing particularly good activity.

2) Piglet Atria

Compounds were tested in the piglet spontaneous beating screen (Naunyn-Schmiedeberg's Arch. Pharmacol 342, 619-622). pK_B ($-\log_{10} K_B$) value for the compounds were generally 6 or more, E5a, E9b,

E16, E18, E21a, E22a, E24a, E24b, E26, E27 and E30 showing particularly good activity.

3) Rat oesophagus

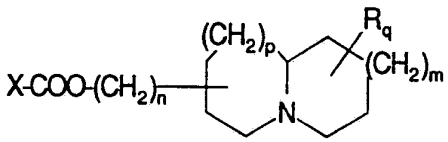
Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

4) 5-HT-induced motility in dog gastric pouch

Compounds are tested for inhibition in the *in vivo* method described in "Stimulation of canine motility by BRL 24924, a new gastric prokinetic agent", Bermudez *et al*, J. Gastrointestinal Motility, 1990, 2(4), 281-286.

Claims

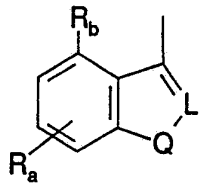
1. A compound of formula (I), or a pharmaceutically acceptable salt thereof



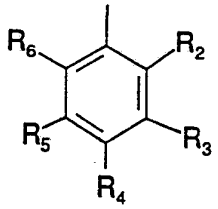
(I)

wherein

X is of sub-formula (a) or (b):



(a)



(b)

wherein

L is N or CR_c wherein R_c is hydrogen, C_{1-6} alkoxy, halo, C_{1-6} alkyl or cyano;

Q is NR_1, CH_2, O or S;

R_a is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkoxy;

R_b is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

R_1 is hydrogen, C_{1-10} alkyl, C_{2-6} alkenyl, aralkyl, C_{2-6} alkanoyl, or C_{2-6} alkanoyl C_{1-3} alkyl;

R_2 is C_{1-6} alkoxy; and

R_3 is hydrogen, chloro or fluoro;

R_4 is hydrogen, C_{1-6} alkyl, amino optionally substituted by a C_{1-6} alkyl

group, halo, hydroxy or C_{1-6} alkoxy;

R_5 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_6 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

n is 0, 1, 2, 3 or 4;

p and m are independently 0, 1 or 2; and

R_q is hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 wherein X is of sub-formula (a) and L is CH, C-CH_3, C-Cl or $COCH_3$.

3. A compound according to claim 1 or 2 wherein X is of sub-formula (a) and Q is NR_1 wherein R_1 is hydrogen or a methyl or ethyl group.

4. A compound according to any one of claims 1, 2 or 3 wherein X is of sub-formula (a) and R_a is hydrogen and R_b is hydrogen or iodo.

5. A compound according to claim 1 wherein X is of sub-formula (b) and R_2 is methoxy, R_4 is amino and R_5 is halo.

6. A compound according to any one of claims 1 to 5 wherein p = m = 1; p = 0, m = 1; p = 1 or m = 2; p = 2, m = 1.

7. A compound according to any one of claims 1 to 6 wherein R_q is hydrogen.

8. A compound according to any one of claims 1 to 7 wherein the X-COO-$(CH_2)_n$- is attached such that the number of carbon atoms between the ester linkage and the azabicyclic nitrogen atom is from 2 to 4 carbon atoms.

9. A compound according to claim 1 selected from the compounds E1 to E32 inclusive, as described herein, including pharmaceutically acceptable salts thereof.

10. A process for the preparation of a compound according to claim 1 which process comprises linking together X-CO_2H or a reactive derivative thereof and the (azabicyclic side chain)-$(CH_2)_n$- moiety, by a conventional ester coupling with the -$(CH_2)_n$-OH derivative

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, and a pharmaceutically acceptable carrier.

12. A compound according to claim 1 for use as an active therapeutic substance.

13. The use of a compound according to claim 1 in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

14. The use according to claim 13 for use as a 5-HT_4 antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

15. The use according to claim 14 for use in the treatment of IBS.

16. The use according to claim 14 for use in the treatment of atrial arrhythmias and stroke.

17. A method of treatment of IBS in mammals which comprises the administration of an effective amount of a compound according to claim 1.

18. A method of treatment of atrial arrhythmias and stroke in mammals which comprises the administration of an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01612

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D455/02; C07D471/04; A61K31/435; C07D487/04
//(C07D471/04,221:00,209:00)(C07D471/04,223:00,221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	WO,A,8 400 166 (SANDOZ) 19 January 1984 cited in the application see page 44, line 9 - page 46, line 4; claim 1 & GB,A,2 125 398	1,11
A	EP,A,0 036 269 (BEECHAM) 23 September 1981 cited in the application see claims 1,11	1,11

° Special categories of cited documents :[10]

"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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 NOVEMBER 1992	15. 01. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201612 SA 63959

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 25/11/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8400166	19-01-84	AT-B- 391136	27-08-90
		AU-B- 570002	03-03-88
		AU-A- 1628683	05-01-84
		AU-B- 603399	15-11-90
		AU-A- 8243487	28-04-88
		CH-A- 669792	14-04-89
		CH-A- 669954	28-04-89
		DE-A,C 3322574	29-12-83
		DE-A,C 3348331	31-08-89
		DE-A,C 3348332	07-09-89
		DE-A,C 3348333	24-08-89
		DE-A,C 3348334	31-08-89
		FR-A,B 2531083	03-02-84
		GB-A,B 2125398	07-03-84
		GB-A,B 2166726	14-05-86
		GB-A,B 2166727	14-05-86
		GB-A,B 2166728	14-05-86
		NL-A- 8302253	16-01-84
		SE-B- 463210	22-10-90
		SE-A- 8303651	30-12-83
		US-A- 4803199	07-02-89
		US-A- 4910207	20-03-90
		US-A- 5017582	21-05-91
		BE-A- 897117	23-12-83
		CA-A,C 1257870	25-07-89
		JP-A- 59067284	16-04-84
		JP-A- 59036675	28-02-84
		US-A- 4789673	06-12-88
EP-A-0036269	23-09-81	JP-A- 56140992	04-11-81