

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-009984

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **543** DE

FECHA **01 DE SEPTIEMBRE DE 2004** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **29 DE NOVIEMBRE DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO__ _X_ _____



US005998409A

United States Patent [19]

Gaster et al.

[11] **Patent Number:** 5,998,409[45] **Date of Patent:** *Dec. 7, 1999[54] **CONDENSED INDOLE DERIVATIVES AS 5HT₄-RECEPTOR ANTAGONISTS**

[75] Inventors: Laramie Mary Gaster, Bishop's Stortford; Paul Adrian Wyman, Epping, both of United Kingdom

[73] Assignee: SmithKline Beecham plc, Middlesex, United Kingdom

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: 08/459,934

[22] Filed: Jun. 2, 1995

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/302,784, filed as application No. PCT/GB93/00506, Mar. 10, 1993, abandoned.

[30] Foreign Application Priority Data

Mar. 12, 1992	[GB]	United Kingdom	9205428
Sep. 5, 1992	[GB]	United Kingdom	9218846
Dec. 29, 1992	[GB]	United Kingdom	9227045
Aug. 5, 1993	[GB]	United Kingdom	9316195
Jul. 28, 1994	[WO]	WIPO	PCT/EP94/02514

[51] Int. Cl.⁶ A61K 31/535; C07D 498/04

[52] U.S. Cl. 514/230.2; 514/211; 514/224.5; 514/294; 514/321; 540/547; 540/586; 544/32; 544/89; 546/94; 546/198

[58] Field of Search 544/89, 32; 514/230.2, 514/224.5, 321, 211, 294; 546/198, 94; 540/547, 586

[56] References Cited**U.S. PATENT DOCUMENTS**

4,314,058	2/1982	Hayami et al.	542/455
5,001,133	3/1991	Richardsen	514/304

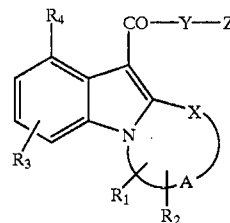
FOREIGN PATENT DOCUMENTS

0144986	6/1984	European Pat. Off.
WO91/16045	10/1991	WIPO
WO93/02677	2/1993	WIPO
WO93/03725	3/1993	WIPO
WO93/05038	3/1993	WIPO
WO93/05040	3/1993	WIPO
WO93/08187	4/1993	WIPO

WO93/12785	7/1993	WIPO
WO93/14745	8/1993	WIPO
WO93/16072	8/1993	WIPO
9318036	9/1993	WIPO
WO93/18027	9/1993	WIPO
WO93/18036	9/1993	WIPO
WO93/24117	12/1993	WIPO
WO94/00113	1/1994	WIPO
WO94/01095	1/1994	WIPO
WO94/05654	3/1994	WIPO
WO94/07859	4/1994	WIPO
WO94/08965	4/1994	WIPO
WO94/08994	4/1994	WIPO
WO94/08995	4/1994	WIPO
WO94/08998	4/1994	WIPO
WO94/10174	5/1994	WIPO
WO94/17071	8/1994	WIPO
WO94/19344	9/1994	WIPO
WO94/27987	12/1994	WIPO
WO94/29298	12/1994	WIPO
WO95/04737	2/1995	WIPO

OTHER PUBLICATIONSSaxena, P.R. *Pharmacology and Therapeutics*, vol 66, pp. 339-368 (1995).Dhasmona, K.M. et al. *Life Sci.*, vol. 53, pp. 1651-1661 (1993).*Primary Examiner*—Richard L. Raymond*Attorney, Agent, or Firm*—Soma G Simon; William T King; Charles M Kinzig**[57] ABSTRACT**

Compounds of formula (I) and pharmaceutically acceptable salts thereof:



(I)

and their use as pharmaceuticals in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.**21 Claims, No Drawings**

CONDENSED INDOLE DERIVATIVES AS 5HT₄ -RECEPTOR ANTAGONISTS

This is a continuation-in-part of U.S. Ser. No. 08/302,784, filed Sep. 12, 1994, now abandoned which is a §371 application of PCT/GB93/00506, filed Mar. 10, 1993.

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

This is a continuation-in-part application of U.S. Ser. No. 08/302,784, filed Sep. 12, 1994. U.S. Ser. No.

EP-A-429984 (Nisshin Flour Milling Co., Ltd.) describes indole derivatives having 5-HT₃ receptor antagonist activity.

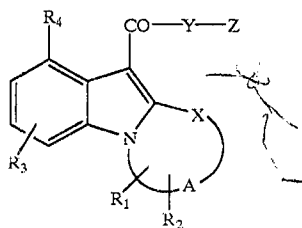
European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT₄ receptor, and that ICS 205-930, which is also a 5-HT₄ receptor antagonist, acts as an antagonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT₄ receptor antagonists in the treatment of atrial arrhythmias and stroke.

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT₄ antagonist activity.

A class of novel, structurally distinct compounds has now been discovered, which compounds are indole derivatives 1,2-disubstituted by alkyleneoxy, with an azacyclic, fused azabicyclic or aminoalkyl moiety. These compounds have 5-HT₄ receptor antagonist activity.

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



wherein

X is O, S, SO, SO₂, CH₂, CH or NR wherein R is hydrogen, N or C₁₋₆ alkyl;

A is a saturated or unsaturated polymethylene chain of 2-4 carbon atoms;

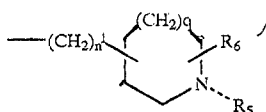
R₁ and R₂ are hydrogen or C₁₋₆ alkyl;

R₃ is hydrogen, halo, C₁₋₆ alkyl, amino, nitro or C₁₋₆ alkoxy;

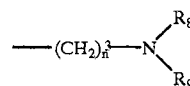
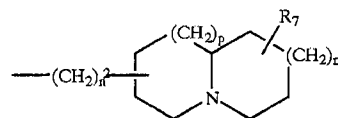
R₄ is hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ alkoxy;

Y is O or NH;

Z is of sub-formula (a), (b) or (c):



-continued



wherein

n¹ is 1, 2, 3 or 4; n² is 0, 1, 2, 3 or 4; n³ is 2, 3, 4 or 5; q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2;

R₅ is hydrogen, C₁₋₁₂ alkyl, aralkyl or R₅ is (CH₂)_z-R₁₀ wherein z is 2 or 3 and

R₁₀ is selected from cyano, hydroxyl, C₁₋₆ alkoxy, phenoxy, C(O)C₁₋₆ alkyl, COC₆H₅, -CONR₁₁R₁₂, NR₁₁COR₁₂, SO₂NR₁₁R₁₂ or NR₁₁SO₂R₁₂

wherein R₁₁ and R₁₂ are hydrogen or C₁₋₆ alkyl; and

R₆, R₇ and R₈ are independently hydrogen or C₁₋₆ alkyl; and

R₉ is hydrogen or C₁₋₁₀ alkyl;

or a compound of formula (I) wherein the CO—Y linkage is replaced by a heterocyclic bioisostere;

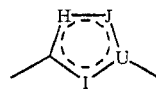
having 5-HT₄ receptor antagonist activity.

Examples of alkyl or alkyl containing groups include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ or C₁₂ branched, straight chained or cyclic alkyl, as appropriate. C₁₋₄ 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.

Aryl includes phenyl and naphthyl optionally substituted by one or more substituents selected from halo, C₁₋₆ alkyl and C₁₋₆ alkoxy.

Halo includes fluoro, chloro, bromo and iodo.

A suitable bioisostere for the amide or ester linkage containing Y in formula (I), is of formula (d):



wherein the dotted circle represents one or two double bonds in any position in the 5-membered ring; H, J and I independently represent oxygen, sulphur, nitrogen or carbon, provided that at least one of H, J and I is other than carbon; U represents nitrogen or carbon.

Suitable examples of (d) are as described for X, Y and Z in EP-A-328200 (Merck Sharp & Dohme Ltd.), such as an oxadiazole moiety.

X is often O.

Values for A include —CH₂—(CH₂)_r—CH₂— wherein r is 0, 1 or 2; —CH₂—CH=CH—; —C(CH₃)=CH— or when X is CH or N, A may be —(CH₂)₂—CH=O or —CH=CH—CH=. Other examples of A are as described in the examples hereinafter.

R₁ and R₂ are often hydrogen or R₁ and R₂ are gem-dimethyl.

r is often 1.

R_3 is preferably hydrogen.

R_4 is preferably hydrogen or halo, such as fluoro.

Y is preferably O or NH.

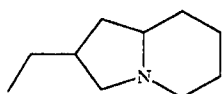
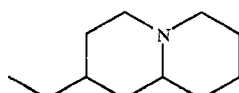
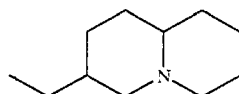
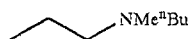
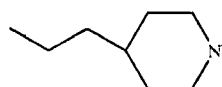
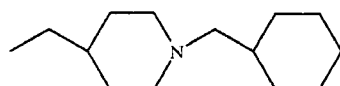
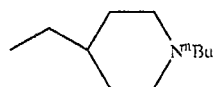
When Z is of sub-formula (a), n^1 is preferably 2, 3 or 4 when the azacycle is attached at the nitrogen atom and n^1 is preferably 1 when the azacycle is attached at a carbon atom, such as the 4-position when q is 2.

When Z is of sub-formula (b), n^2 is preferably such that the number of carbon atoms between the ester or amide linkage is from 2 to 4 carbon atoms.

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

When Z is of sub-formula (c), n^3 is preferably 2, 3 or 4. R_8 and R_9 are preferably both alkyl, especially one of R_8 and R_9 is C_4 or larger alkyl.

Specific values of Z of particular interest are as follows:



The invention also provides novel compounds within formula (I) with side chains (i), (ii), (iii), (iv), (v), (vi) or (vii). In a further aspect, the piperidine ring in (i), (ii) or (iii) may be replaced by pyrrolidinyl or azetidiny, and/or the N-substituent in (i) or (ii) may be replaced by C_3 or larger alkyl or optionally substituted benzyl.

The present invention provides a compound of formula (I) wherein R_5 is 3-phenoxypropyl, in particular a compound of formula analogous to E3 described hereafter wherein the n-butyl R_5 substituent is replaced by phenoxypropyl.

In an alternative aspect, the N-substituent in formula (i) or (ii) may be replaced by $(CH_2)_nR^1$ as defined in formula (1) of EP-A-501322 and in relation to the specific examples of EP-A-501322.

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, malic, citric, succinic, benzoic, ascorbic, methanesulphonic, α -keto glutaric, α -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.

It will also be realised that the $(CH_2)_2$ moiety in compounds of formula (I) wherein Z is (b), may adopt an α or β configuration with respect to the fused azabicyclic moiety.

The compounds of formula (I) may be prepared by conventional coupling of the indole moiety with Z. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A and EP-A-36269 (Beecham Group p.l.c.), EP-A-429984 (Nisshin Flour Milling Co.) and EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited). It will be appreciated that the $(CH_2)_r-O$ containing ring or R_3/R_4 introduction/modification may be carried out before or after coupling.

Aza(bi)cyclic side chain intermediates are known compounds or may be prepared according to the methods described in WO 93/03725 and WO 93/05040 (SmithKline Beecham p.l.c.).

The compounds of the present invention are 5-HT₄ 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-HT₄ receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT₄ 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).

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis et al 1988, Mol Pharmacol., 34, 880-887). Activity can 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 prodromal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT₄ receptors, and hence that administration of a 5-HT₄ antagonist is of potential benefit in relieving a migraine attack.

Other CNS disorders of interest include schizophrenia, Parkinson's disease and Huntingdon's chorea.

The invention also provides a pharmaceutical composition comprising a compound of formula (IA), 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 infusible solutions or suspensions. 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, tableting 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, polyvinylpyrrolidone and starch derivatives such as sodium starch glycolate. 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 tableting. 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 or prophylaxis of irritable bowel syndrome, 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.

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-oesophageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine.

The following Example illustrates the preparation of compounds of formula (I), the following Descriptions relate to the preparation of intermediates.

Examples								
	R ₁	R ₂	r	R ₃	R ₄	X	Y	Z
E1	H	H	1	H	H	O	O	(i)
E2	H	H	1	H	H	O	O	(vi)
E3	H	H	1	H	H	O	NH	(i)
E4	H	H	1	H	H	O	O	(iii)
E5	H	H	1	H	H	O	NH	(iii)
E6	H	H	0	H	H	O	O	(i)
E7	H	3-(CH ₃) ₂	1	H	H	O	O	(i)
E8	H	H	1	H	H	S	O	(i)
E9	H	H	2	H	H	O	O	(i)
E10	H	H	1	H	H	CH ₂	O	(i)
E11	H	H	0	H	H	CH ₂	O	(i)
E12	H	H	2	H	H	CH ₂	O	(i)
E13	H	H	0	H	H	CH ₂	NH	(i)
E14	H	H	0	H	H	O	NH	(i)
E15	H	H	1	H	H	O	O	Bzppm
E16	H	H	1	H	H	SO	O	(i)
E17	—	Δ	—	H	H	CH	O	(i)

-continued

Examples								
	R ₁	R ₂	r	R ₃	R ₄	X	Y	Z
E18	—	Γ	—	H	H	CH	O	(i)
E19	H	H	1	H	H	S	NH	(i)
E20	H	H	1	H	H	O	NH	Bzppm
E21	H	H	1	H	H	O	NH	ppm
E22	H	H	1	H	H	O	NH	nC ₆ H ₁₃ ppm
E23	H	H	1	H	H	O	NH	(ii)
E24	H	H	1	H	H	O	NH	Etppm
E25	H	H	1	H	H	O	NH	MeSO ₂ aEtppm
E26	H	H	1	H	H	O	NH	(vi)
E27	H	H	1	8-F	H	O	O	(i)
E28	H	H	1	8-F	H	O	NH	(i)
E29	H	H	1	H	H	NMe	O	(i)
E30	—	π	—	H	H	S	O	(i)
E31	H	H	0	H	H	S	O	(i)
E32	—	θ	—	H	H	S	O	(i)
E33	—	Λ	—	H	H	N	O	(i)
E34	H	H	0	H	H	S	NH	(i)
E35	—	θ	—	H	H	S	NH	(i)
E36	H	H	1	H	H	NH	O	(i)
E37	H	H	0	H	H	O	O	(vi)
E38	H	H	2	H	H	O	NH	(i)
E39	H	H	Γ	H	H	N	O	(i)
E40	H	H	0	H	H	S	O	(vi)
E41	H	H	0	H	H	S	NH	(vi)
E42	—	θ	—	H	H	S	O	(vi)
E43	—	θ	—	H	H	S	NH	(vi)
E44	H	H	1	H	H	S	O	(vi)
E45	—	Γ	—	H	H	N	NH	(i)
E46	H	H	1	H	H	NH	NH	(i)
E47	H	H	1	H	H	O	NH	Phpppm
E48	H	H	1	H	H	O	NH	Meppm

Δ - AR₁R₂ is —(CH₂)₂—CH=

Γ - AR₁R₂ is —CH=CH—CH=

π - AR₁R₂ is —C(CH₃)=CH—

θ - AR₁R₂ is —CH=CH—

Δ - AR₁R₂ is —C(CH₃)=CH—C(CH₃)=

Bz - benzyl

ppm - 4-piperidylmethyl

aEt - aminoethyl

Phr - 3-phenoxypropyl

EXAMPLE 1

(1-"Butyl-4-piperidyl)methyl-3,4-dihydro-2H-[1,3]
oxazino[3,2-a]indole-10-carboxylate (E1)

a) A suspension of indole-3-carboxylic acid (500 mg, 0.003 mole) in dichloromethane (50 ml) was treated with oxalyl chloride (0.635 g, 0.005 mole) and two drops of dimethylformamide. The mixture was stirred at room temperature for one and a half hours then the solvent was removed in vacuo to leave the acid chloride.

A solution of 1-butyl-4-piperidinemethanol, D6, (513 mg, 0.003 mole) in dry THF (10 ml) under an atmosphere of nitrogen, was cooled in an ice bath. n-Butyllithium (1.88 ml of 1.6M solution in hexane, 0.003 mole) was added dropwise and the resulting solution stirred at 0° C. for 15 minutes.

The acid chloride was dissolved in dry THF (20 ml) and the solution added dropwise to the solution of the lithium alkoxide at 0° C.

The reaction mixture was allowed to warm to room temperature and was stirred for 3 hours. The solvent was removed in vacuo and the residue partitioned between chloroform and water. The chloroform was separated, washed several times with water, dried and concentrated to give (1-butyl-4-piperidyl)methyl-1H-indole-3-carboxylate as a pale brown gum.

¹H NMR (250 MHz) CDCl₃; δ: 9.90 (br s, 1H), 8.10–8.18 (m, 1H), 7.78 (d, 1H), 7.37–7.46 (m, 1H), 7.16–7.28 (m,

2H), 4.19 (d, 2H), 3.05–3.15 (br d, 2H), 2.40–2.49 (m, 2H), 0.90 (t, 3H), 1.20–2.18 (m, 11H).

b) A suspension of N-chlorosuccinimide (57 mg, 0.48 mmole) in chloroform (2 ml) was treated with a solution of (1-"butyl-4-piperidyl)methyl indole-3-carboxylate (100 mg, 0.32 mmole) in chloroform (2 ml) and the mixture stirred at room temperature for 2 h. The pale yellow solution was treated with 3-bromo-1-propanol (0.03 ml, 0.32 mmole), stirred at room temperature for 16 h; then basified with 10% Na₂CO₃ solution and extracted with chloroform. The extract was dried and concentrated to leave a yellow gum, which was dissolved in acetone (6 ml), treated with anhydrous potassium carbonate (130 mg, 0.94 mmole) and stirred at room temperature for 18 h. The mixture was treated with 10% Na₂CO₃ solution and extracted with ethyl acetate. The extract was dried and concentrated to leave a brown oil, which was chromatographed, first on silica gel eluting with chloroform/methanol (97:3), then on basic alumina eluting with ethyl acetate to give a colourless oil. This was crystallised from ether/pentane to afford the title compound (E1) as a white solid (11 mg) mp 117–119° C.

¹H NMR (CDCl₃); δ: 7.97 (d, 1H), 7.10–7.30 (m, 3H), 4.55 (t, 2H), 4.20 (d, 2H), 4.11 (t, 2H), 2.90–3.03 (m, 2H), 2.25–2.40 (m, 4H), 1.75–2.00 (m, 5H), 1.22–1.55 (m, 6H), 0.91 (t, 3H); MS (EI) M⁺ 370

EXAMPLE 2

eq-Quinolizidin-2-ylmethyl-3,4-dihydro-2H-[1,3]
oxazino[3,2-a]indole-10-carboxylate (E2)

a) eq-2-Hydroxymethylquinolizidine (N. J. Leonard et al., J. Org. Chem., 1957, 22, 1445) was reacted with indole-3-carboxylic acid chloride using the method described in Example 1 a to afford eq-quinolizidin-2-ylmethyl 1H-indole-3-carboxylate mp 154–157° C.

¹H NMR (CDCl₃); 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).

b) eq-Quinolizidin-2-ylmethyl 1H-indole-3-carboxylate was treated initially with N-chlorosuccinimide (1.5 equivalents) for 2 h, then with 3-bromo-1-propanol (2 equivalents) for 16 h, followed by anhydrous potassium carbonate in acetone, using the method described in Example 1b. The crude product was purified using the same chromatography conditions as in Example 1b to afford the title compound as a colourless oil (51%). This was converted to its hydrochloride salt and crystallised from acetone mp 164–167° C.

¹H NMR (HCl salt) (d⁶DMSO); δ: 10.35 (br.s, 1H), 7.85 (d, 1H), 7.32 (d, 1H), 7.07–7.20 (m, 2H), 4.54 (t, 2H), 4.13 (t, 2H), 4.05 (d, 2H), 3.25–3.43 (m, 2H), 2.74–3.15 (m, 3H), 2.20–2.33 (m, 2H), 2.00–2.15 (m, 1H), 1.35–1.95 (m, 10H).

EXAMPLE 3

N-[(1-"Butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (E3, SB 207266)

Method 1:

A stirred solution of N-chlorosuccinimide (57 mg, 0.48 mmole) in chloroform (3 ml) was treated with a solution of N-[(1-"butyl-4-piperidyl)methyl] indole-3-carboxamide, D1, (100 mg, 0.32 mmole) in chloroform (8 ml) and kept at room temperature for 2 h, then treated with 3-bromo-1-propanol (0.03 ml, 0.32 mmole). After stirring for 16 h, more 3-bromo-1-propanol (0.03 ml, 0.32 mmole) was added. The mixture was stirred at room temperature for a further 3 h, then treated with excess, 10% Na₂CO₃ solution and

-continued

	R ₁	R ₂	r	R ₃	R ₄	X	Y	Z
E45	—	Γ	—	H	H	NH	NH	(i)
E46	H	H	1	H	H	N	NH	(i)
E47	H	H	1	H	H	O	NH	Phprppm

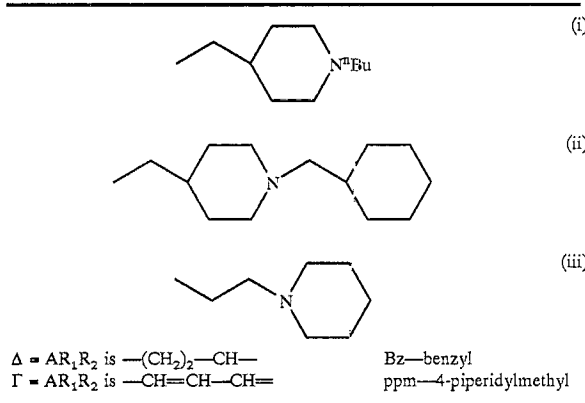
and where r is such that A is —CH₂—(CH₂)_r—CH₂—, and the point of attachment of Z when containing 4-piperidylmethyl is through the methnyl.

11. A compound which is: N-3,4-dihydro-2H-oxazino indole-10-carboxamide.

12. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.

13. A pharmaceutical formulation comprising a compound according to claim 11 and a pharmaceutically acceptable carrier.

wherein the variables are defined as follows:



-continued

π = AR ₁ R ₂ is —C(CH ₃)=CH—	aEt—aminoethyl
υ = AR ₁ R ₂ is —CH=CH—	Phpr—3-phenoxypropyl
Λ = AR ₁ R ₂ is —C(CH ₃)=CH—C(CH ₃)=	

and wherein r is such that A is —CH₂—(CH₂)_r—CH₂—, and the point of attachment of Z when containing 4-piperidylmethyl is through the methyl.

14. A method of treating irritable bowel syndrome which comprises administering an effective amount of a compound according to claim 1.

15. A method of treating urinary incontinence which comprises administering an effective amount of a compound according to claim 1.

16. A method of treating atrial arrhythmia which comprises administering an effective amount of a compound according to claim 1.

17. A method of treating stroke which comprises administering an effective amount of a compound according to claim 1.

18. A method of treating irritable bowel syndrome which comprises administering an effective amount of a compound according to claim 11.

19. A method of treating urinary incontinence which comprises administering an effective amount of a compound according to claim 11.

20. A method of treating atrial arrhythmia which comprises administering an effective amount of a compound according to claim 11.

21. A method of treating stroke which comprises administering an effective amount of a compound according to claim 11.

* * * * *