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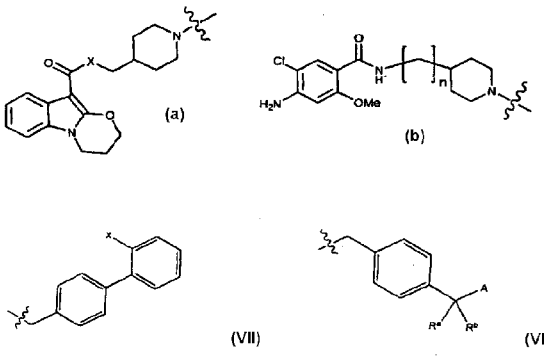
(54) **Title**: 5-HT RECEPTOR MODULATING COMPOUNDS



(57) **Abstract**: The present invention relates to compounds having 5-hydroxytryptamine receptor modulating activity, in particular compounds having an acidic moiety held distant from the 5-HT pharmacophore by a rigid linker group, to compositions containing such compounds and methods of treatment using them. Such compounds have an increased affinity for the 5-HT receptor and a reduced hERG effect. Certain compounds of the invention further exhibit an angiotensin II receptor modulating activity. Claimed are compounds of formula (I): HT - L - A. HT is a 5-HT receptor modulating moiety containing a basic nitrogen atom; A is an acid moiety; L is a linker moiety. Examples of particular preterred HT groups are: (a) (b). Examples of particular preferred L groups comprise formula (Vl) and (VII) moieties: Examples of acid moieties are: -C(O)OR I. -OP(O)(OR2)2, -P(O)(OR2)2, -SO2OR2, -S03H, -0S03H, -P(O)(OH)2.

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5-HT receptor modulating compounds

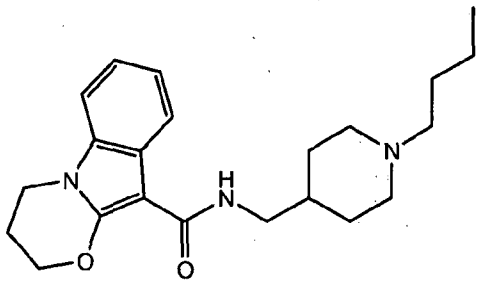
This invention relates to compounds having 5-hydroxytryptamine (hereinafter "5-HT") receptor modulating activity, in particular compounds having an acidic moiety held distant from the 5-HT pharmacophore by a linker group so as to prevent the acidic moiety and the 5-HT pharmacophore on the same molecule from interacting. The invention also relates to prodrugs and salts of the modulator compounds and to compositions comprising these compounds, salts and prodrugs.

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter. Serotonin is active in the central nervous system (CNS), demonstrating a broad activity in the brain in particular, and also in the gastrointestinal tract where it stimulates vomiting.

A number of receptor families and sub-families have been identified which are modulated by serotonin, these being known as 5-HT or 5-HT_x receptors. Certain 5-HT_x receptor subtypes are found within the CNS, e.g. 5-HT_{1A}, 5-HT_{5A} and 5-HT_6, whereas others are found outside the CNS, e.g. 5-HT_{2B}. Some receptor subtypes are found on both sides of the blood-brain barrier, e.g. 5-HT_4, where they potentiate different effects in the different locations.

Modulators (i.e. agonists or antagonists) of 5-HT receptors have been shown to be useful in the treatment of a wide range of conditions and are used as antidepressants, anxiolytics, antiemetics, antipsychotics and anti-migraine agents.

Many naturally-occurring and synthetic compounds are known which have a modulatory activity towards the 5-HT receptors. In particular, both agonists and antagonists of most receptors are known. For example, agonists of the 5-HT_4 receptor include cisapride, metoclopramide, renzapride and tegaserod, whereas one antagonist of the 5-HT_4 receptor is piboserod. Piboserod is a selective 5-HT_4 receptor antagonist used for the management of atrial fibrillation and irritable bowel syndrome, and has the following molecular structure:



In this structure, the 5-HT pharmacophore includes a basic nitrogen atom (in the piperidine ring) which is substituted by an n-butyl chain.

WO 2007/007072 describes how the specificity of action of 5-HT receptor modulators may be enhanced by attaching an acid moiety to the 5-HT pharmacophore via a linking group. This modification hinders passage of the modulator across the blood-brain barrier and thus restricts the effects of an administered modulator to the side of the barrier on which it is administered. Examples of acid:5-HT pharmacophore constructs are given in WO 2007/007072, as well as in WO 2007/149929 and WO 2005/061483.

The majority of the acid:5-HT pharmacophore constructs disclosed in these publications involve a readily flexible linker between the acid group and the basic nitrogen atom within the pharmacophore, for example a pentamethylene group as in Example 50 in WO 2007/007072 or a dimethyleneaminomethyl-p-phenylene group as in Compound 23 in WO 2007/149929.

The present inventors, however, have found that the overall performance of such acid:5-HT pharmacophore constructs is improved if the linker between the acid group (or its precursor if in prodrug form) and the basic nitrogen atom in the pharmacophore serves to maintain a distance between the two of several Å (0.1 nm; 10^{-10}m). In particular, the resultant compounds display increased binding affinities for their receptors. This distancing of the basic nitrogen and the acid group may readily be achieved by the use of linkers which, in part at least, are rigid, or which are substituted by bulky substituents preventing rotation. Rigidity can be achieved by, for example, incorporation of cyclic groups, especially unsaturated groups, of fused rings, bridged rings or bonds which on rotation do not bring the nitrogen and acid close together. WO 2007/007072, WO 2005/061483 and WO 2007/149929 make no suggestion that low flexibility in the groups linking the basic nitrogen and the acid group is important or desirable; however WO 2005/061483 and WO 2007/007072 do describe some compounds which utilise a methylene-p-phenylene linker.

The compounds of the present invention are particularly and surprisingly advantageous over the compounds of the prior art. Particular advantages include one or more of the following: increased affinity for the 5-HT receptor, believed to be because the acidic proton cannot interfere with the active basic nitrogen atom of the pharmacophore; and a reduced blocking effect on the human ether-a-go-go related

gene (hERG) channels. This reduced hERG effect is a critical parameter for consideration of the toxicological effects of the compounds of the invention; hERG blocking activity is linked to ventricular arrythmias and sudden death in the clinical setting. Further advantages of the preferred compounds of the invention include one or more of the following: a greater selectivity of modulation of the peripheral 5-HT receptors, especially the 5-HT_4 receptors; an antagonistic effect on angiotensin II receptors; little or no central nervous system toxicity effects when using clinically effective doses; high affinity for 5-HT receptors and thus a lowered clinical dose; and ease of preparation.

Thus viewed from one aspect the invention provides a 5-HT receptor modulator being a compound of formula I:

HT-L-A (I)

(wherein HT is a 5-HT receptor modulating moiety ("the 5-HT pharmacophore") containing a basic nitrogen atom;
A is an acid moiety; and
L is a linker moiety serving to maintain said basic nitrogen atom and said acid moiety at a separation of at least 0.4 nm, preferably at least 0.5 nm, more preferably at least 0.6 nm, especially at least 0.65 nm, e.g. up to 2 nm) or a prodrug form or salt thereof.

In one embodiment, the compounds of formula I are other than HT-CH_2-p-phenylene-A.

Preferred prodrugs of the acidic moiety include esters and amides of carboxylic acids, especially methyl esters thereof, and *N*-aryl derivatives of tetrazoles, especially *N*-triphenylmethyl derivatives thereof. Typical esters include alkyl esters, substituted alkyl esters, aryl esters, substituted aryl esters and acyloxyalkyl esters. Substituent groups which may be present include straight-chained, branched and cyclic alkyl groups. Such groups may be saturated or unsaturated and may further be interrupted by one or more heteroatoms selected from oxygen, sulphur and nitrogen. The substituent groups may further contain one or more carbonyl or thiocarbonyl groups. Preferred substituents include C_{1-6}-alkyl (e.g. methyl) groups. Other preferred substituents include heterocyclic rings containing one or more oxygen atoms, and optionally at least one carbonyl group. Examples of such groups include 1-3-dioxolane and 1,3-dioxol-2-one.

Preferred salts of the compounds of the invention are pharmaceutically acceptable salts, including sodium, potassium, magnesium and ammonium salts thereof as well as salts with anions such as chloride, sulphate and carbonate.

In a preferred embodiment, HT denotes a moiety having an affinity for the 5-HT_4 receptor subgroup, e.g. a 5-HT_4 receptor-specific moiety, especially preferably a moiety with 5-HT_4 antagonist activity.

Examples of suitable HT groups include those of formula II:

$$Ar\text{-}(C(O))_n\text{-}(E)_m\text{-}(G)_p\text{-}BN\text{-} \qquad (II)$$

(wherein Ar is an optionally substituted aryl ring optionally fused with one or more rings selected from: non-aromatic, optionally substituted, carbocylic rings; non-aromatic heterocyclic rings; carbocyclic aromatic rings; and heteroaromatic rings;
n is 0 or 1, preferably 1;
m is 0 or 1, preferably 1;
E is O or NH;
p is 0 or 1, preferably 1;
G is a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-6}-alkyl group; and
BN is a basic nitrogen moiety, preferably a moiety selected from an amine group, an amide group, a carbamate or a carbamate derivative, urea or a urea derivative, a carbazimidamide, a nitrogen-containing heterocyclic ring, a nitrogen-containing heteroarylic ring, and an azabicyclic ring).

As used herein, the term "aryl" is intended to mean a carbocyclic aromatic ring or ring system. Moreover, the term "aryl" includes fused ring systems wherein at least two aryl rings, or at least one aryl and at least one C_{3-8}-cycloalkyl share at least one chemical bond. Illustrative examples of "aryl" rings include optionally substituted phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl and indanyl. A preferred aryl group is phenyl. The term "aryl" relates to aromatic, preferably benzenoid groups connected via one of the ring-forming carbon atoms, and optionally carrying one or more substituents selected from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{1-6}-aminoalkyl, C_{1-6}-alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, or trifluoromethyl. As stated, preferred aryl groups are phenyl and, most suitably,

substituted phenyl groups carrying one or two of the substituents listed above which may be the same or different.

Other preferred examples of suitable aryl groups include optionally substituted benzyl, naphthalene, indoline, indole, oxazinoindoline, indolizine, isoindoline, indene, indane, indazole, azulene, benzimidazole, benzofuran, benzothiophene, benzthiazole, purine, 4H-quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,3-naphthyridine, pteridine, coumaran, benzodioxane, benzopyran, chroman, isochroman, carbazole, acridine, phenazine, phenothiazine, phenoxazine, thianthrene, phenanthrene, anthracene, tetralin, fluorene, and acenaphthylene, each of which may be optionally substituted. More preferably, the aryl group may be selected from benzyl, naphthalene, indole, benzodioxane, indazole and oxazinoindole.

The term "heterocyclic ring" is intended to mean three-, four-, five-, six-, seven- and eight-membered rings wherein carbon atoms together with from 1 to 3 heteroatoms constitute said ring. A heterocyclyl may optionally contain one or more unsaturated bonds situated in such a way, however, that an aromatic pi-electron system does not arise. The heteroatoms are independently selected from oxygen, sulphur and nitrogen. A heterocyclic ring may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, and the like. Heterocyclic rings may optionally also be fused to aryl rings, such that the definition includes bicyclic structures. Preferred such fused heterocyclyl groups share one bond with an optionally substituted benzene ring. Examples of benzo-fused heterocyclyl groups include, but are not limited to, benzimidazolidinone, tetrahydroquinoline, and methylenedioxybenzene ring structures.

Illustrative examples of "heterocyclic rings" are the heterocycles tetrahydrothiopyran, 4*H*-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2*H*-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, thiazoline, thiazolidine and 1,3-oxathiolane. Binding to the heterocycle

may be at the position of a heteroatom or via a carbon atom of the heterocycle, or, for benzo-fused derivatives, via a carbon of the benzenoid ring.

The basic nitrogen moiety (BN) may be any array of organic forms of nitrogen. Suitable forms of the basic nitrogen moiety may be selected from the group comprising an amine group, amide group, carbamates and urea derivatives, carbazimidamides, a nitrogen-containing heterocyclic or heteroarylic ring, including azabicycles. Amine groups can be primary, secondary or tertiary amines. Suitable nitrogen-containing heterocyclic or heteroaryl include pyridyl (pyridinyl), pyrimidinyl, thiazolyl, pyrazolyl, imidazolyl, tetrazolyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, phenoxathiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, lH-indazolyl, purinyl, 4H-quinolizinyl, isoquinolinyl, quinolinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a H-carbazole, carbazole, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, furazanyl, phenoxazinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl. Preferable heterocyclic groups include piperidino, morpholino, thiamorpholino, pyrrolidino, pyrazolino, pyrazolidino, pyrazoryl, piperazinyl, thienyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl, imidazolinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl and quinolyl, each of which may be optionally substituted. More preferably, the basic nitrogen moiety is selected from the group consisting of carbazimidamide and optionally substituted piperidinyl, e.g. unsubstituted piperidinyl.

Typically, the HT group may comprise a group of the formula III:

Ar-C(O)-E-G-BN- (III)

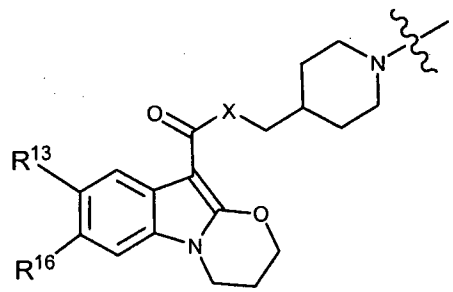
(wherein Ar is a monocyclic or polycyclic aromatic or heteroaromatic;
E is selected from the group consisting of O and NH;

G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl and C_{3-7}-cycloalkyl-C_{1-6}-alkyl; and

BN is a basic nitrogen moiety as herein defined;

or wherein G-BN together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl group).

Preferred HT groups are derivatives of piboserod having the formula IV:



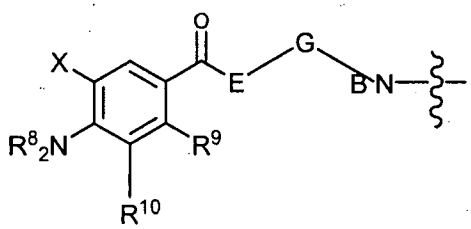
(IV)

(wherein R^{13} is selected from the group consisting of H, halogen (e.g. F, Cl, Br or I), NH_2 and C_{1-6}-alkyl; and

R^{16} is selected from the group consisting of H, halogen, OH, O-C_{1-6}-alkyl and C_{1-6}-alkyl).

Preferably, R^{13} and R^{16} are both H.

Other preferred HT groups are those of formula V:



(V)

(wherein E is selected from the group consisting of O and NH;

G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl and C_{3-7}-cycloalkyl-C_{1-6}-alkyl;

BN is a basic nitrogen moiety as herein defined;

or wherein G-BN together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl group;

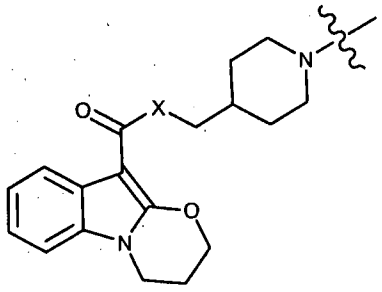
X is a halogen;

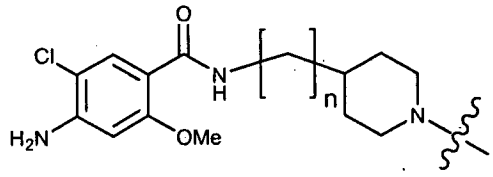
R^8 is independently selected from H and C_{1-6}-alkyl;
R^9 and R^{10} are independently selected from the group consisting of H, O-C_{1-6}-alkyl, C_{1-6}-alkyl, a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl;
or wherein together R^9 and R^{10} form a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl;
or wherein NR^8_2 and R^{10} together form a heterocycloalkyl group).

Compounds of the formula V may be, for instance, amino benzamide derivatives or amino benzoates.

Specific examples of suitable HT groups include the pharmacophores of the 5-HT modulators described in WO 2007/007072, WO 2007/149929 and WO 2005/061483, the contents of each of which documents are incorporated in their entirety herein. Indole derivatives and compounds comprising three condensed ring systems, i.e. tricyclic derivatives are preferred. Especially preferred are oxazino-indole derivatives, such as those shown in Example 1. Where the HT group comprises an oxazino-indole derivative, group L may be a benzyl derivative, e.g. a -CH_2-p-phenylene.

Particularly preferred HT groups are those set forth in the following Examples, in particular the groups:





wherein X denotes O or NH, preferably NH, and n=0 or 1.

In general, unless it contains a sufficiently elongate rigid section, any linker (e.g. a group L) having three or more bonds in its backbone which separate the acid and the nitrogen but allow a free rotation which can bring the two closer together is likely to allow the two to approach too closely. Desirably, between the attachment site of the acid group and the attachment site of the pharmacophore, the linker contains no more than two, more preferably no more than one, backbone bond, rotation about which would cause the nitrogen and acid to come closer. Where the nitrogen atom is not the attachment site of the linker, the intervening portion of the

pharmacophore desirably does not provide sufficient flexibility for the nitrogen and acid to approach too closely. Flexibility however may arise not just from rotations about bonds but from conformational changes and these too should be taken into account. Inter-group spacings may be assessed simply using conventional chemical modelling systems as bond angles and lengths may readily be calculated or determined from standard references.

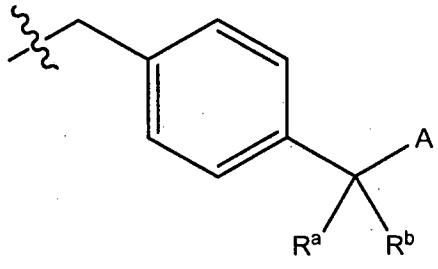
The linking group of the invention must be rigid and/or sterically hindered such that the acidic moiety and the basic nitrogen atom of the 5-HT modulating moiety do not come into close contact. Bulky substituents include highly substituted alkyl groups such as C_{1-12}-alkyl groups substituted with one or more alkyl or aryl substituents, e.g. isopropyl and tertiary butyl substituents. Other hindered linkers include hydrophobic cyclic groups, e.g. C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl and C_{6-10}-cycloaryl groups (e.g. benzyl). Rigid heterocyclic groups, e.g. 5- or 6-membered rings comprising 1 to 3 nitrogen, oxygen and/or sulphur atoms, may also be used as linkers according to the invention. Such heterocyclic groups can comprise unsaturated, saturated and polyunsaturated (e.g. aromatic) rings. Examples of heterocyclic linkers include piperidine, piperazine, pyrimidine, pyridine and benzothiazole groups.

Accordingly, in a preferred aspect of the invention, L comprises an optionally substituted mono- or bi-cyclic aryl or heteroaryl group; a linear C_{1-6}-alkyl group being substituted independently at each carbon atom by at least one optionally substituted C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-10}-cycloalkyl, aryl, heteroaryl, nitrile, hydroxy, amide, chloride or iodide group; an optionally substituted C_{3-10}-cycloalkyl or C_{4-10}-cycloalkenyl group; or an optionally substituted polycyclic alkyl or alkenyl group, e.g. a group having a steroid backbone. Preferably, L is other than -CH_2-p-phenylene, -CO-p-phenylene and -p-phenylene.

Especially preferred groups L are benzyl, e.g. an ortho- or meta-benzyl group, which may be optionally substituted by one or more substituents including alcohol (hydroxy), amine, halide (e.g. F, Cl, Br or I), alkyl (e.g. C_{1-6}-alkyl), alkenyl (e.g. C_{2-6}-alkenyl) or alkynyl (e.g. C_{2-6}-alkynyl) substituents. Where L is a benzyl group, it is preferably not a para-benzyl group, especially preferably not an unsubstituted para-benzyl group.

In another preferred embodiment, L includes an optionally substituted, aromatic carbocyclic or aromatic heterocyclic group. Such groups possess an inherent

rigidity which make them particularly well suited for use as rigid linkers according to the invention. Such linkers may, for example, comprise a group of the formula $-(CH_2)_n-Ar'-(CR^aR^b)_m-$ in which n is 0 or 1, preferably 1; Ar' is an optionally substituted aryl ring or heteroaromatic ring; R^a and R^b are each independently H or, more preferably, optionally substituted C_{1-6}- alkyl (preferably C_{1-4}-alkyl, e.g. methyl); and m is 0 or 1, preferably 1. Preferably, the points of attachment of the HT moiety and the acid moiety (A) (or, where present, the $-(CH_2)-$ and/or $-(CR^aR^b)-$ groups which in turn are linked to these moieties) on the aryl or heteroaromatic ring (Ar') will be meta- or para- to one another, most preferably para. Particularly preferred groups L are those of formula $-(CH_2)-Ar''-(CR^aR^b)-$ in which Ar'' is optionally substituted phenyl, preferably unsubstituted phenyl. In such linker groups, the $-(CH_2)-$ and $-(CR^aR^b)-$ groups are positioned either meta or para to one another. Where the phenyl group is *para*-substituted, the resulting linker and acid moieties may comprise a group of formula VI:



(VI)

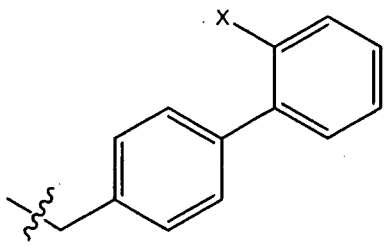
(wherein R^a and R^b are independently selected from H and optionally substituted C_{1-6}-alkyl; and A is an acid moiety as herein described). In a preferred embodiment of this aspect of the invention, at least one of R^a and R^b is C_{1-6}-alkyl (e.g. methyl) and especially preferably both R^a and R^b are C_{1-6}-alkyl groups (e.g. methyl).

In an alternative embodiment, L is an optionally substituted, optionally bridged C_4-C_{10}-cycloalkyl, preferably C_5-C_8-cycloalkyl, e.g. C_5-C_7-cycloalkyl, group. Optionally substituted, optionally bridged cyclopentyl and cyclohexyl groups are particularly preferred. In this embodiment, it is preferred that the points of attachment of the HT and A moieties on the cycloalkyl ring are not adjacent to one another. For example, where the cycloalkyl group is a cyclopentyl group, the HT and A moieties are preferably in a 1,3 relationship (i.e. meta to one another). This disposition of the groups on the cycloalkyl ring generally leads to a greater separation of the basic

nitrogen and acid functionalities, thereby achieving the desired object of the present invention. However, it will be appreciated there will be certain embodiments in which adjacent positioning of the HT and A moieties, i.e. in a 1,2 relationship, will maintain the basic nitrogen and acid moieties sufficiently far apart to avoid interaction. For example, two adjacent groups in axial disposition on a cyclohexane ring may be maintained in an essentially rigid "para" disposition by virtue of the presence of one or more bulky substituents in equatorial positions on the cyclohexane ring. In this aspect of the invention, the cycloalkyl ring may be substituted with one or more groups independently selected from straight chained or branched C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl groups, halogen (e.g. F, Cl, Br or I), oxo, hydroxy, C_1-C_6-alkoxy, cyano, amino, C_1-C_6-alkylamino and C_1-C_6-dialkylamino groups. Preferably the substituents are selected from groups which restrict the flexibility of the cycloalkyl ring, for example by steric or electronic interactions, such as one or more *tert*-butyl groups and/or halogen atoms. Up to three carbons of the cycloalkyl ring may be replaced by one or more heteroatoms selected from oxygen, sulphur and nitrogen. However, cycloalkyl groups without any heteroatom substitutions are preferred.

Bridging of a cycloalkyl group in the linker, L, introduces greater rigidity into the structure and so is a preferred aspect of the invention. A "bridging group" may represent a single bond which links two atoms of the cycloalkyl ring or may comprise one or more carbon, oxygen, sulphur or nitrogen atoms which bridge the cycloalkyl ring. Bridging groups consisting either of a bond or which comprise 1 or 2 atoms, especially 1 or 2 carbon atoms, are generally preferred. Bridging atoms may be independently substituted by one or more substituents as defined herein in respect of the cycloalkyl ring. Where one or more bridging groups are provided, linkage to the acid moiety (A) may either be via the main ring of the cycloalkyl group or, alternatively, via an atom which forms part of one of the bridging groups. Examples of suitable bridged cycloalkyl groups include bicyclo[2,2,1]heptane (norbornane), bicyclo[3,2,1]octane and adamantane. An especially preferred bridged cycloalkyl group is tricyclo[2,2,1,0^{2b}]heptane.

Another particularly preferred group L is biphenyl, especially methylene-para-biphenyl. In this embodiment, the group L-A is preferably a group of formula VII:



(VII)

(wherein X is -C(O)OH, optionally substituted -C(O)O-C_{1-6}-alkyl or an optionally substituted 5-tetrazolyl group) or a prodrug form or salt thereof.

In a preferred embodiment of the invention, A denotes an acid moiety which is a protic acidic moiety having a labile proton. In a preferred embodiment, the labile proton, when in said acid moiety, is kept distanced from the basic nitrogen atom of the HT moiety by at least 0.6 nm by the linker moiety.

Preferred groups A include those described in WO 2005/061483, e.g. wherein A is selected from the group consisting of -C(O)-OR^1, -OP(O)OR^2OR^2, -P(O)OR^2OR^2, -SO_2OR^2, -SO_3H, -OSO_3H and -PO_3H; wherein R^1 and R^2 are independently selected from the group consisting of H, M (wherein M is a counter-ion), C_{1-15}-alkyl, C_{3-8}-cycloalkyl, aryl, and $R^{1,2}$ wherein $R^{1,2}$ is R'-O-C(O)R", R'-O-C(O)-O-R", R'-C(O)-O-R", wherein R' and R" are independently selected from the group consisting of C_{1-15}-alkyl, C_{3-8}-cycloalkyl and aryl.

Particularly preferably, A denotes an oxyacid or a tetrazole group, or an ester or salt thereof, e.g. a carboxylic acid or an optionally substituted tetrazole group. By "oxyacid" is meant herein a group which in its protonated form contains oxygen, hydrogen and an atom selected from C, S and P linked by a double bond to at least one oxygen or, less preferably, sulphur. Thus, for example, carboxyl (COOH) and its sulphur analogues (CSSH, CSOH and COSH) are covered, although carboxyl is preferred. The preferred S oxyacids are SO_3H and OSO_3H, while the preferred P oxyacids are $OP(O)(OH)_2$ and PO_3H.

In addition to the "rigid linker" aspect of the present invention, the inventors have also determined that certain 5-HT modulators may be beneficially provided with an acidic group having a renin-angiotensin system modulating activity. In particular, compounds having a 5-HT_4 modulatory activity and an angiotensin II receptor modulatory activity are described herein. Such dual-action modulators are new and form a further aspect of the invention.

Angiotensin II is a vasoactive peptide hormone produced from angiotensin I by the peptidase angiotensin converting enzyme (ACE). Drugs which interfere with the activity of this enzyme (so-called "ACE inhibitors") can block the biosynthesis of angiotensin II and are widely used as cardiovascular drugs, e.g. as anti-hypertensives. Examples of such drugs include enalapril and captopril. Another class of cardiovascular drugs are the angiotensin II receptor antagonists, examples of which include the "sartans", e.g. telmisartan, losartan, valsartan, candesartan and irbesartan.

In view of the effects of the 5-HT receptor modulators, especially 5-HT_4 receptor modulators, on the cardiovascular system, compounds which combine 5-HT modulatory activity with angiotensin receptor modulatory function are uniquely placed for use in the treatment of cardiovascular diseases, especially congestive heart failure.

According to this aspect, the present invention provides compounds of formula Ib:

$$HT\text{-}L_b\text{-}A_b \qquad (Ib)$$

as well as the prodrugs and salts thereof, wherein HT is as hereinbefore defined and L_b is absent or is any linker which enables the pharmacophores of HT (5-HT receptor modulation) and A_b (renin-angiotensin system modulating activity) to function.

L_b is preferably a rigid linker L as hereinbefore defined, but may also be a non-rigid linker as described in WO 2007/007072, WO 2007/149929 and WO 2005/061483. Examples of linkers L_b according to the invention include, in addition to those defined above for L, straight chain or branched, optionally substituted C_{1-10}-alkyl, optionally substituted C_{2-10}-alkenyl, optionally substituted C_{2-10}-alkynyl, C_{1-10}-alkylamine, C_{1-10}-alkoxy, C_{2-10}-alkenyloxy, C_{2-10}-alkynyloxy, C_{1-10}-alkoxycarbonyl, C_{2-10}-alkenyloxycarbonyl and C_{2-10}-alkynyloxycarbonyl groups.

In a preferred embodiment, A_b denotes the pharmacophore of an ACE inhibitor or an angiotensin II receptor antagonist. Preferably, A_b denotes the pharmacophore of an angiotensin II receptor antagonist. The definition and scope of the term "pharmacophore" in this context would be clear to the person skilled in the art.

A_b preferably denotes an acidic pharmacophore, particularly preferably denoting a pharmacophore comprising a biphenyl, especially a methylene-para-

biphenyl group. Groups of formula VII as herein defined wherein X is -C(O)OH, optionally substituted -C(O)O-C_{1-6}-alkyl or an optionally substituted 5-tetrazolyl group, or a prodrug form or salt thereof, are especially preferred. Preferred groups of formula VII are those wherein X is -C(O)OH, -$C(O)OCH_3$ or optionally substituted tetrazole, e.g. *N*-trityl-tetrazole.

The compounds of the invention are 5-HT receptor modulators, typically 5-HT_4 receptor modulators. The compounds may be 5-HT (e.g. 5-HT_4) agonists or antagonists. Alternatively, these may be partial agonists.

By "5-HT receptor modulator" is meant any compound having 5-HT receptor modulatory activity described herein. Examples of such compounds include those of formula I and Ib. Especially preferred 5-HT receptor modulators include compounds 1-9, 11-15, 17-21, 22a-f and 23-30 as described in the Examples.

The conditions which may be treated using the compounds herein described include any which may be responsive to 5-HT receptor agonism or antagonism. Such conditions may be associated, for example, with diseases of the urinary system, the gastrointestinal system, or the cardiovascular system. Examples of particular conditions which may be treated using the compounds of the invention include gastroesophageal reflux, diarrhoea, abdominal cramps, dyspepsia, gastroparesis, constipation, post-operative ileus, intestinal pseudo-obstruction, irritable bowel syndrome, bladder diseases (e.g. hyperactive bladder, etc.), hypertension, pulmonary hypertension, portal hypertension, cardia hypertrophy and cardiac valve disease.

Viewed from a further aspect the invention provides a pharmaceutical composition comprising the 5-HT receptor modulator, e.g. a compound of formula I or Ib, or a physiologically tolerable prodrug form or salt thereof, together with at least one pharmaceutical carrier or excipient.

The carriers or excipients used in the compositions may be any of the materials commonly used in pharmaceutical compositions, e.g. solvents (such as water), pH modifiers, viscosity modifiers, fillers, diluents, binders, aromas, skin penetration enhancers, antioxidants and other preservatives, etc. The choice will depend on the dosage administration route and form. Typically, the compositions will be sterile.

The compositions of the invention may be in any convenient dosage administration form, e.g. solutions, dispersions, suspensions, syrups, tablets, coated

tablets, powders, sprays, suppositories, etc. Solutions, dispersions and tablets are preferred. These may be prepared in conventional fashion.

The administration route for the compounds and compositions of the invention may be enteral, e.g. oral, rectal or by tube, nasal, sub-lingual, by injection or infusion.

Viewed from another aspect the invention provides a 5-HT receptor modulator as herein described, e.g. compound of formula I, or a physiologically tolerable prodrug form or salt thereof for use in medicine.

Viewed from a still further aspect the invention provides the use of a 5-HT receptor modulator as herein described, such as a compound of formula I, or a physiologically tolerable prodrug form or salt thereof for use in the treatment of a 5-HT associated condition, e.g. for the manufacture of a medicament for use in a method of treatment of a 5-HT associated condition. Examples of 5-HT associated condition are known to the skilled person and include diseases of the cardiovascular system, diseases of the gastrointestinal system and diseases of the urinary system, especially cardiac failure.

Viewed from another aspect the invention provides a method of treatment of diseases of the cardiovascular system, the gastrointestinal system and the urinary system, said method comprising the step of administering a therapeutically effective amount of a 5-HT receptor modulator as herein described. In a preferred embodiment, the invention provides a method of treatment of cardiac failure.

Diseases of the urinary system which may be treated particularly readily using the compounds of the invention are diseases of the lower urinary tract.

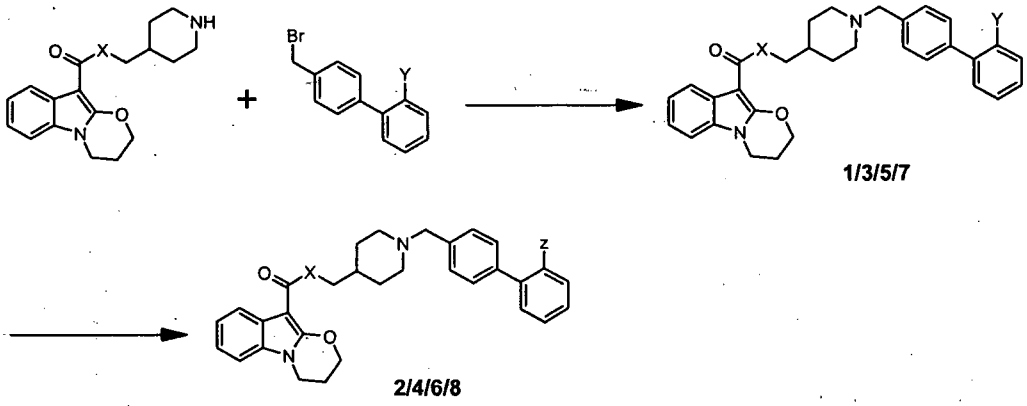
In the methods of the invention, the compounds may typically be administered at dosages of from about 0.1 mg to about 200 mg in single or divided doses. Preferably a daily dose should be between about 1 mg to about 100 mg, more preferably between about 2 mg and 75 mg. It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art.

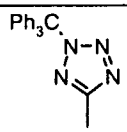
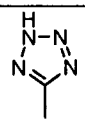
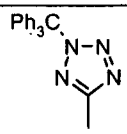
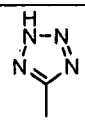
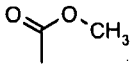
The synthesis of the 5-HT modulators of the invention may be performed using synthetic methodology well known in organic chemistry. Typical methods include alkylation of the basic nitrogen of the HT moiety with an alkylating agent comprising the acidic group or prodrug of the acidic group. For example, the HT moiety may be alkylated with a bromomethyl biphenyl derivative comprising a protected acid group. An alternative method would involve alkylation of nitrogen using an alkylating agent which comprises an aromatic cyano group, followed by

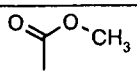
reaction with an azide to yield a tetrazole. The inventors also contemplate building a 5-HT pharmacophore on to an acidic hydrophobic scaffold using known methodology.

The preparation of representative compounds of the invention is illustrated by way of the following non-limiting examples:

Example 1 - Compounds 1-8



Compound	X	Y	Z	Molecular formula
1	NH			$C_{51}H_{47}N_7O_2$
2	NH			$C_{32}H_{33}N_7O_2$
3	O			$C_{51}H_{46}N6O_3$
4	O			$C_{32}H_{32}N_6O_3$
5	NH			$C_{33}H_{35}N_3O_4$

6	NH			$C_{32}H_{33}N_3O_4$
7	O			$C_{33}H_{34}N_2O_5$
8	O			$C_{32}H_{32}N_2O_5$

Compound 1

N-Trityl-5-[(4'-bromomethyl)-biphenyl-2-yl] tetrazole (1.05 g, 3.0 mmol) was added to a stirred suspension of N-(4-piperidylmethyl) 3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxamide (1.05 g, 3.0 mmol) and K_2CO_3 (1.65 g, 12.0 mmol) in acetone (30 ml) and heated to reflux for 24 h. The mixture was cooled to room temperature and filtered. The filtrate was evaporated *in vacuo* and the residue added CH_2Cl_2 (50 ml) and washed with H_20 (3 x 25 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was separated with flash chromatography (CH_2Cl_2/MeOH (9 : 1) to leave the intermediate **1** as a yellow oil (0.60 g, 25.3 %). ^{1}H NMR ($CDCl_3$): δ 8.32 (d, 1 H), 7.87 (d, 1 H), 7.41-7.17 (m, 16 H), 7.10-7.08 (m, 6 H), 6.89-6.84 (m, 6 H), 6.54 (t, 1 H), 4.51 (t, 2 H), 4.06 (t, 2 H), 3.40 (br s, 2 H), 3.30 (t, 2 H), 2.90-2.82 (m, 2 H), 2.37-2.26 (p, 2 H), 2.02-1.88 (m, 2 H) 1.71-1.50 (m, 2 H), 1.35-1.24 (m, 2 H). MS (ES): 790.1 $[M + H]^+$

Compound 2

Compound 1 (0.50 g, 0.63 mmol) was stirred in a mixture of CH_2Cl_2/TFA/H_2O (97:2:1, 25 ml) at room temperature overnight and evaporated *in vacuo*. The residue was separated with flash chromatography (CH_2Cl_2, MeOH, 9:1) to leave the free tetrazol compound **2** as a white solid (0.31, 90.1 %). ^{1}H NMR (DMSO-d_6): δ 11.07 (br s, 1 H), 8.61 (br s, 1 H), 8.01 (d, 1 H), 7.87-7.04 (m, 12 H), 6.91 (t, 1 H), 4.49 (t, 2 H), 4.27 (br s, 2 H), 4.13 (t, 2 H), 3.34-3.24 (m, 2 H), 2.95-2.85 (m, 2 H), 2.28-2.23 (m, 2 H), 1.89-1.60 (m, 5 H). MS (ES): 548.1 $[M + H]^+$

Compound 3

Following the procedure outlined for compound 1, N-(4-piperidylmethyl) 3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxylate (0.31 g, 0.88 mmol) and N-Trityl-5-[(4'-bromomethyl)-biphenyl-2-yl] tetrazole (0.49 g, 0.88 mmol) was

converted to intermediate **3** as a white solid (0.34 g, 48.7 %). ^{1}H NMR ($CDCl_3$): δ 7.93-7.88 (m, 2 H), 7.29-7.06 (m, 18 H), 6.89-6.84 (m, 6 H), 4.51 (t, 2 H), 4.17-4.05 (m, 4 H), 3.38 (br s, 2 H), 2.85-2.80 (m, 2 H), 2.37-2.26 (p, 2 H), 2.02-1.72 (m, 6 H) 1.71-1.50 (m, 2 H). MS (ES): 791.1 $[M + H]^+$

Compound 4

Following the procedure outlined for compound 2, the trityl group of compound 3 (0.24 g, 0.30 mmol) was cleaved to leave the free tetrazol compound **4** as a white solid (0.14 g, 85.3 %). ^{1}H NMR (DMSO-$_{d6}$): δ 9.70 (br s, 1 H), 7.75 (d, 1 H), 7.69-7.67 (m, 2 H), 7.62-7.57 (m, 2 H), 7.44 (d, 2 H), 7.31 (d, 2 H), 7.19-7.08 (m, 4 H), 4.49 (t, 2 H), 4.27 (br s, 2 H), 4.13-3.94 (m, 4 H), 3.40-3.37 (m, 2 H), 2.96 (t, 2 H), 2.28-2.23 (m, 2 H), 2.02.1.90 (m, 3 H), 1.52-1.40 (m, 2 H). MS (ES): 549.1 $[M + H]^+$

Compound 5

Following the procedure outlined for compound 1, N-(4-piperidylmethyl) 3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxamide (1.05 g, 3.0 mmol) and 4-bromomethyl-(1,1-biphenyl)-2-carboxylic acid methyl ester (0.91 g, 3.0 mmol) was converted to compound **5** as a white solid (0.65 g, 40.3 %). ^{1}H NMR ($CDCl_3$): δ 8.31 (d, 1 H), 7.82 (d, 1 H), 7.53-7.10 (m, 16 H), 7.10-7.08 (m, 6 H), 6.89-6.84 (m, 6 H), 6.54 (t, 1 H), 4.51 (t, 2 H), 4.06 (t, 2 H), 3.40 (br s, 2 H), 3.30 (t, 2 H), 2.90-2.82 (m, 2 H), 2.37-2.26 (p, 2 H), 2.02-1.88 (m, 2 H) 1.71-1.50 (m, 2 H), 1.35-1.24 (m, 2 H). MS (ES): 538.1 $[M + H]^+$

Compound 6

Compound 5 (0.40 g, 0.74 mmol) was stirred in a mixture of 2 M aqueous NaOH solution (1 ml) and MeOH (4 ml) and heated to reflux for 12 h, cooled to room temperature and evaporated *in vacuo*. The residue was redissolved in H_2O (5 ml) and the solution acidified to pH 2 with 2 M aqueous HCl. The free carboxylic acid **6** precipitated out of the solution, the precipitate filtered off and the residue recrystallized from acetone (0.20 g, 51.6 %). ^{1}H NMR (DMSO-$_{d6}$): δ 8.04 (d, 1 H), 7.71 (d, 1 H), 7.58-7.34 (m, 7 H), 7.27 (d, 1 H), 7.08-7.03 (m, 2 H), 6.87 (t, 1 H), 4.54 (t, 2 H), 4.10 (t, 2 H), 3.96 (br s, 2 H), 3.20 (t, 2 H), 3.10 (d, 2 H), 2.52-2.48 (m, 2 H), 2.30-2.25 (m, 2 H), 1.77-1.70 (m, 3 H), 1.50-1.42 (m, 2 H). MS (ES): 524.1 $[M + H]^+$

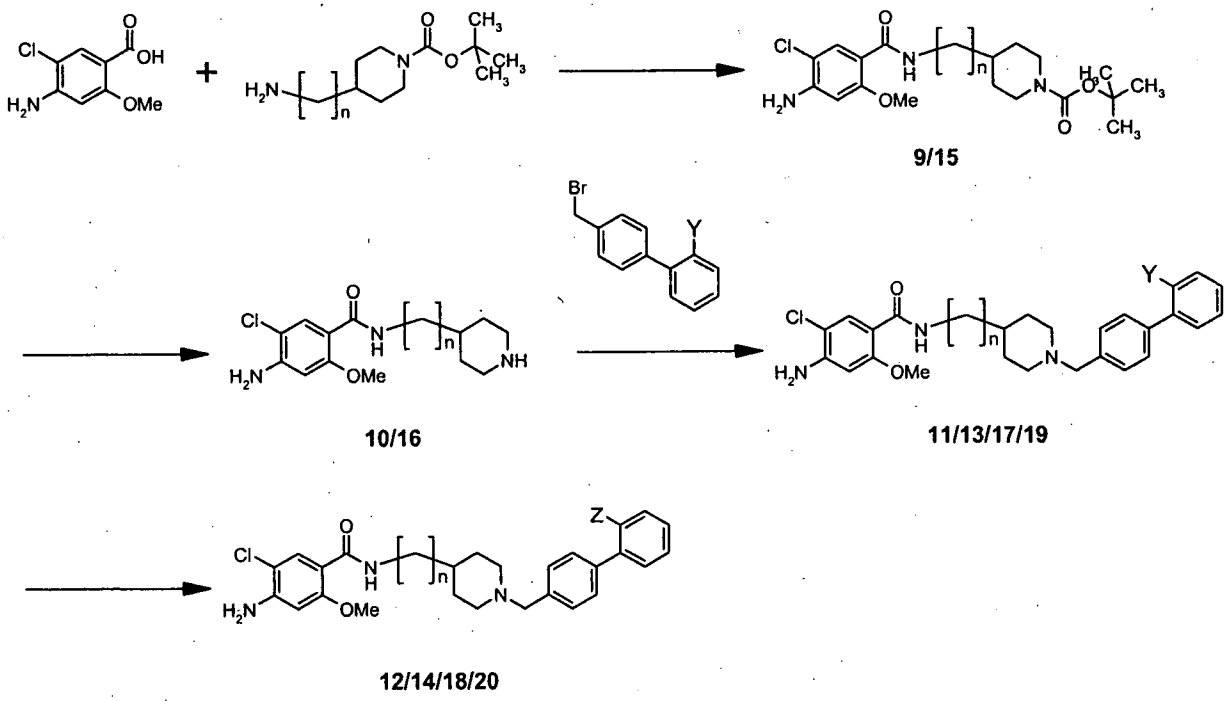
Compound 7

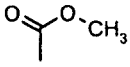
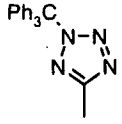
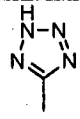
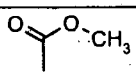
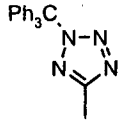
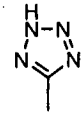
Following the procedure outlined for compound 1, N-(4-piperidylmethyl) 3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxylate (1.05 g, 3.0 mmol) and 4-bromomethyl-(1,1-biphenyl)-2-carboxylic acid methyl ester (0.91 g, 3.0 mmol) was converted to compound **7** as a white solid (0.86 g, 53.0 %). ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1 H), 7.77 (d, 1 H), 7.49-7.10 (m, 10 H), 4.50 (t, 2 H), 4.17 (d, 2 H), 4.06 (t, 2 H), 3.59 (s, 2 H), 3.52 (s, 2 H), 2.95-2.84 (m, 2 H), 2.37-2.27 (m, 2 H), 2.06-1.79 (m, 5 H) 1.71-1.50 (m, 2 H), 1.49-1.41 (m, 2 H). MS (ES): 539.1 $[M + H]^+$

Compound 8

Following the procedure outlined for compound 6, the compound from example 7 (1.51 g, 2.80 mmol) was converted to the free acid **8** as a white solid (1.04, 71.5 %). ^{1}H NMR (DMSO-$_{d6}$): δ 7.81 (d, 1 H), 7.60 (d, 1 H), 7.42-7.28 (m, 8 H), 7.13-7.07 (m, 2 H), 4.49 (t, 2 H), 4.10 (t, 2 H), 4.04 (d, 2 H), 3.66 (s, 2 H), 2.84 (d, 2 H), 2.28-2.22 (m, 2 H), 2.01 (t, 2 H), 1.74-1.70 (m, 3 H), 1.37-1.31 (m, 2 H). MS (ES): 525.1 $[M + H]^+$

Example 2 - Compounds 9-20



Compound	n	Y	Z	Molecular formula
9	0	//	//	//
10	0	//	//	//
11	0			$C_{28}H_{30}ClN_3O_4$
12	0			$C_{27}H_{28}ClN_3O_4$
13	0			$C_{46}H_{42}ClN_7O_2$
14	0			$C_{27}H_{28}ClN_7O_2$
15	1	//	//	//
16	1	//	//	//
17	1			$C_{29}H_{32}ClN_3O_4$
18	1			$C_{28}H_{30}ClN_3O_4$
19	1			$C_{47}H_{44}ClN_7O_2$
20	1			$C_{28}H_{30}ClN_7O_2$

Compound 9

A mixture of 4-amino-1-Boc-piperidine (2.0g, 10.0 mmol), 4-amino-5-chloro-2-methoxybenzoic acid (2.01 g, 10.0 mmol) and NEt_3 (1.01 g, 10.0 mmol) in DMF (40 ml) were added 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) (1.91 g, 10.0 mmol) and 1-hydroxybenzotriazole (HOBT) (1.35 g, 10.0 mmol) at 0 °C. The reaction mixture was stirred to room temperature overnight and concentrated *in vacuo*. The resulting residue was redissolved in CH_2Cl_2 (100 ml) and

extracted with aqueous K_2CO_3 (3 x 50 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo to leave the intermediate 4-Amino-5-chloro-2-methoxy-*N*-(1-Boc-4-piperidyl)benzamide **9** as a white solid. (3.93, 98.4 %) ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1 H), 7.60 (d, 1 H), 6.26 (s, 1 H), 4.40 (s, 2 H), 4.10-4.08 (m, 1 H), 3.94 (d, 2 H), 3.85 (s, 3 H), 2.96 (t, 2 H), 1.98-1.93 (m, 2 H), 1.43 (s, 9 H), 1.40-1.36 (m, 2 H).

Compound 10

A solution of 4-amino-5-chloro-2-methoxy-N-(1-Boc-4-piperidyl)benzamide (3.93 g, 9.84 mmol) in dioxane (25 ml) was cooled to 0 °C and added 4M HCl in dioxane (2.0 ml) and stirred to room temperature for 4 h. The mixture was evaporated *in vacuo*, added MeOH (20 ml) and heated under reflux for 1 h. The reaction mixture was evaporated *in vacuo* and the residue recrystallized from EtOH to leave the intermediate 4-Amino-5-chloro-2-methoxy-*N*-(4-piperidyl) benzamide hydrochloride **10** as a white crystalline solid (2.01 g, 62.8 %). ^{1}H NMR (DMSO-d_6): δ 9.19-9.13 (m, 2 H), 7.76 (d, 1 H), 7.60 (s, 1 H), 6.52 (s, 1 H), 6.16 (br s, 3 H), 4.99 (br s, 2 H), 3.81 (s, 3 H), 3.23-3.19 (m, 2 H), 2.99-2.95 (m, 2 H), 2.01-1.97 (m, 2 H),. 1.78-1.67 (m, 2 H).

Compound 11

Following the procedure outlined for compound 5, 4-amino-5-chloro-2-methoxy-*N*-(4-piperidyl) benzamide hydrochloride(1.60 g, 5.0 mmol) and 4-bromomethyl-(1,1-biphenyl)-2-carboxylic acid methyl ester (1.52 g, 5.0 mmol) was converted to compound **11** as a yellow solid (0.59 g, 23.2 %). ^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1 H), 7.81-7.76 (m, 1 H), 7.62 (d, 1 H), 7.54-7.34 (m, 5 H), 7.31-7.22 (m, 3 H), 6.26 (s, 1 H), 4.33 (s, 2 H), 4.11-3.97 (m, 1 H), 3.84 (s, 3 H), 3.60 (s, 3 H), 3.54 (s, 2 H), 2.85-2.74 (m, 2 H), 2.28-2.18 (m, 2 H), 2.02-1.97 (m, 2 H), 1.63-1.48 (m, 4 H). MS (ES): 508.2 $[M + H]^+$

Compound 12

Following the procedure outlined for compound 6, the compound from example 11 (0.51 g, 1.00 mmol) was converted to the free acid **12** as a white solid (0.34 g, 69.3 %). ^{1}H NMR (DMSO-d_6): δ 7.68-7.54 (m, 3 H), 7.52-7.25 (m, 7 H), 6.49 (s, 1 H),

5.94 (s, 2 H), 3.83 (s, 3 H), 3.60 (s, 2 H), 2.75-2.82 (m, 2 H), 2.30-2.20 (m, 2 H), 1.90-1.80 (m, 2 H), 1.67-1.55 (m, 2 H). MS (ES): 494.2 $[M + H]^+$

Compound 13

Following the procedure outlined for compound 1, 4-Amino-5-chloro-2-methoxy-*N*-(4-piperidyl)benzamide hydrochloride (0.80 g, 2.50 mmol) and N-trityl-5-[(4'-bromomethyl)-biphenyl-2-yl] tetrazole (1.39 g, 2.5 mmol) was converted to intermediate **13** as a white solid (98 mg, 6.4 %). ^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1 H), 7.85-7.80 (m, 1 H), 7.6 (d, 1 H), 7.51-7.30 (m, 4 H), 7.30-7.15 (m, 7 H), 7.06 (s, 4 H), 6.89-6.84 (m, 6 H), 6.26 (s, 1 H), 4.34 (s, 2 H), 4.12-4.04 (m, 1 H), 3.84 (s, 3 H), 3.37 (s, 2 H), 2.77-2.66 (m, 2 H), 2.17-2.07 (m, 2 H), 1.94-1.90 (m, 2 H), 1.61-1.43 (m, 5 H).

Compound 14

Following the procedure outlined for compound 2, the compound from example 13 (1.05 g, 1.38 mmol) was converted to free tetrazaol **14** as a white solid (0.43 g, 56.3 %). ^{1}H NMR (DMSO-$_{d6}$): δ10.8 (br s, 1 H), 7.71-7.45 (m, 7 H), 7.16-7.12 (m, 2 H), 6.46 (s, 1 H), 4.34-4.21 (m, 2 H), 3.95-3.80 (m, 1 H), 3.77 (s, 3 H), 3.31-3.20 (m, 2 H), 3.10-2.97 (m, 2 H), 2.04-1.80 (m, 4 H). MS (ES): 518.2 $[M + H]^+$

Compound 15

Following the procedure outlined for compound 9, 4-amino-5-chloro-2-methoxybenzoic acid (2.01 g, 10.0 mmol) and 1-Boc-4-(aminomethyl)piperidine was converted to 4-amino-5-chloro-2-methoxy-*N*-(1-Boc-4-methylpiperidyl)benzamide **15** as a white solid (3.90 g. 94.8 %). ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1 H), 7.28 (s, 5 H), 6.31 (s, 1 H), 4.12 (d, 2 H), 3.91 (s, 3 H), 3.33 (d, 2 H), 2.70 (t, 2 H), 1.81-1.66 (m, 3 H), 1.46 (s, 9 H), 1.26-1.12 (m, 2 H).

Compound 16

Following the procedure outlined for compound 10, 4-amino-5-chloro-2-methoxy-*N*-(1-Boc-4-methylpiperidyl)benzamide (3.90 g, 9.46 mmol) was converted to intermediate 4-amino-5-chloro-2-methoxy-*N*-(4-methylpiperidyl)benzamide hydrochloride **16** as a white solid (2.35 g, 74.6 %). ^{1}H NMR (DMSO-d_6): δ 9.24 (d, 1

H), 9.03-8.96 (m, 1 H), 7.99 (t, 1 H), 7.65 (s, 1 H), 6.55 (s, 1 H), 3.82 (s, 3 H), 3.22-3.14 (m, 4 H), 2.83-2.72 (m, 2 H), 1.79-1.71 (m, 3 H), 1.45-1.33 (m, 2 H).

Compound 17

Following the procedure outlined for compound 5, 4-amino-5-chloro-2-methoxy-*N*-(4-methylpiperidyl)benzamide hydrochloride (1.67 g, 5.0 mmol) and 4-bromomethyl-(1,1-biphenyl)-2-carboxylic acid methyl ester (1.52 g, 5.0 mmol) was converted to compound **17** as a white solid (0.67 g, 25.6 %). ^{1}H NMR ($CDCl_3$): δ 8.08 (s, 1 H), 7.80-7.72 (m, 2 H), 7.53-7.20 (m, 8 H), 6.26 (s, 1 H), 4.35 (s, 2 H), 3.86 (s, 3 H), 3.60 (s, 3 H), 3.51 (s, 2 H), 3.31 (t, 2 H), 2.94-2.85 (m, 2 H), 2.02-1.92 (m, 2 H), 1.73-1.56 (m, 4 H), 1.43-1.20 (m, 2 H).

Compound 18

Following the procedure outlined for compound 6, compound 17 (0.52 g, 1.00 mmol) was converted to the free acid 18 as a white solid (0.29 g, 57.1 %). MS (ES): 508.1 $[M + H]^+$

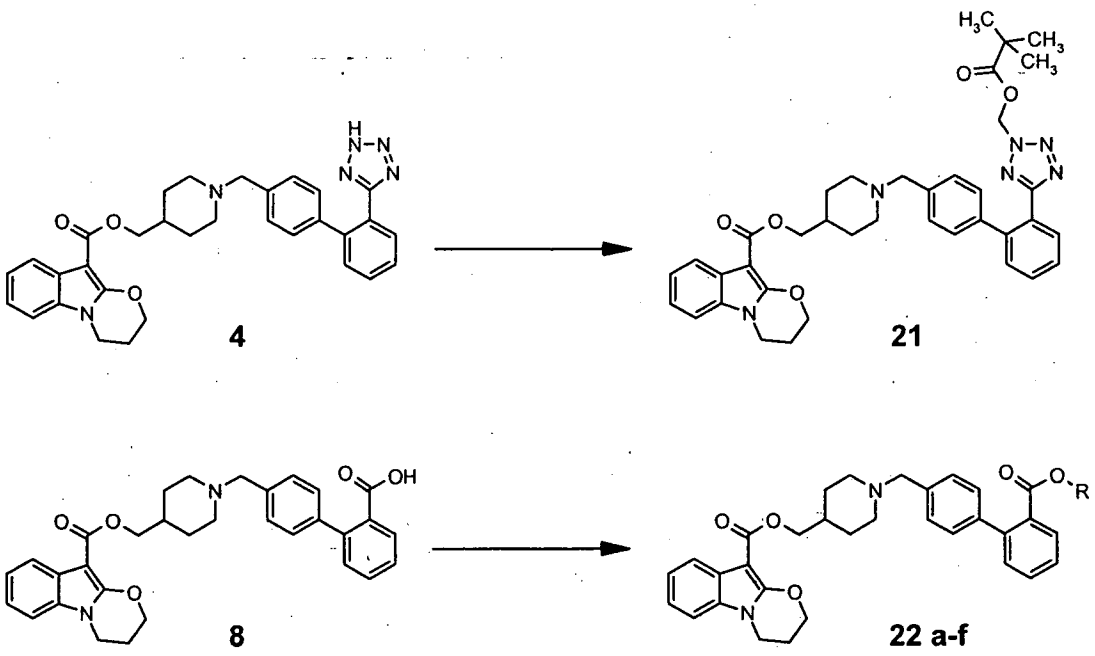
Compound 19

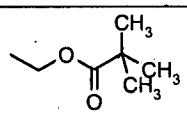
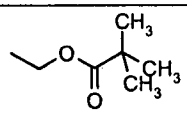
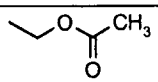
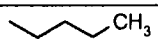
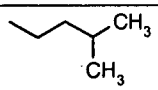
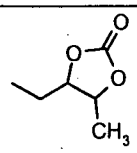
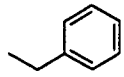
Following the procedure outlined for compound 1, 4-Amino-5-chloro-2-methoxy-*N*-(4-methylpiperidyl)benzamide hydrochloride (1.67 g, 5.00 mmol) and N-trityl-5-[(4'-bromomethyl)-biphenyl-2-yl] tetrazole (2.78 g, 5.0 mmol) was converted to intermediate **19** as a white solid (1.05 g, 29.1 %). ^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1 H), 7.98 (s, 1 H), 8.00-7.98 (m, 1 H), 7.90-7.85 (m, 1 H), 7.77 (t, 1 H), 7.44-7.16 (m, 11 H), 7.04 (s, 4 H), 6.89-6.84 (s, 6 H), 6.27 (s, 1 H), 4.24 (s, 2 H), 3.82 (s, 3 H), 3.34 (s, 2 H), 3.28 (t, 2 H), 2.85-2.77 (m, 2 H), 1.92-1.81 (m, 3 H), 1.64-1.54 (m, 3 H), 1.35-1.23 (m, 2 H).

Compound 20

Following the procedure outlined for compound 2, compound 19 (1.03 g, 1.33 mmol) was converted to the free tetrazol compound **20** as a white solid (0.49 g, 64.9 %). ^{1}H NMR (DMSO-$_{d6}$): δ10.59 (br s, 1 H), 7.95 (t, 1 H), 7.80-7.49 (m, 6 H), 7.15-7.11 (m, 2 H), 6.44 (s, 1 H), 4.29-4.18 (m, 2 H), 3.78 (s, 3 H), 3.47-3.23 (m, 2 H), 3.20-3.01 (m, 3 H), 2.90-2.69 (m, 2 H), 1.80-1.43 (m, 4 H). MS (ES): 532.2 $[M + H]^+$

Example 3 - Prodrugs of compound 4 and 8



Compound	X	R	Molecular formula
21	O		$C_{38}H_{42}N_6O_5$
22a	O		$C_{38}H_{42}N_2O_7$
22b	O		$C_{35}H_{36}N_2O_7$
22c	O		$C_{36}H_{40}N_2O_5$
22d	O		$C_{37}H_{42}N_2O_5$ CH_3SO_3H
22e	O		$C_{37}H_{36}N_2O_8$
22f	O		$C_{39}H_{38}N_2O_5$ CH_3SO_3H

Compound 21

Chloromethyl pivalate (0.054 g, 0.36 mmol) was added to a mixture of tetrazole compound **4** (0.158 g, 0.29 mmol) and caesium carbonate (0.094 g, 0.29 mmol) in DMF (1.0 ml). The mixture was heated to 60 °C for 12 hours, cooled to room temperature and evaporated *in vacuo*. The residue was separated with flash chromatography (SiO_2, CH_2Cl_2: MeOH 9:1) to leave the prodrug **21** as a white solid (0.030 g, 15.6 %). ^1H NMR ($CDCl_3$): δ 7.97 (d, 1 H), 7.80 (d, 1 H), 7.55-7.45 (m, 3 H), 7.26-7.10 (m, 7 H), 6.36 (s, 2 H), 4.54 (t, 2 H), 4.20 (d, 2 H), 4.11 (t, 2 H), 3.49 (br s, 2 H), 2.95-2.88 (m, 2 H), 2.37-2.32 (m, 2 H), 2.04-1.82 (m, 5 H), 1.60-1.45 (m, 2 H), 1.17 (s, 9 H)

Compound 22a

Following the procedure outlined for compound 21, compound **8** (0.20 g, 0.38 mmol) and chloromethyl pivalate (0.057 g, 0.38 mmol) was converted to the prodrug **22a** as a white solid. ^1H NMR ($CDCl_3$): δ 7.94 (d, 1 H), 7.82 (d, 1 H), 7.53-7.10 (m, 10 H), 5.74 (s, 2 H), 4.51 (t, 2 H), 4.18 (d, 2 H), 4.08 (t, 2 H), 3.55 (br s, 2 H), 2.99-2-92 (m, 2 H), 2.37-2.25 (m, 2 H), 2.10-1.86 (m, 5 H), 1.49-1.44 (m, 2 H), 1.16 (s, 9 H).

Compound 22b

Following the procedure outlined for compound 21, compound **8** (0.20 g, 0.38 mmol) and chloromethyl acetate (0.041 g, 0.38 mmol) was converted to the prodrug **22b** as a white solid (0.040 g, 16.7 %). ^1H NMR ($CDCl_3$): δ 7.94 (d, 1 H), 7.82 (d, 1 H), 7.53-7.11 (m, 10 H), 5.71 (s, 2 H), 4.52 (t, 2 H), 4.18 (d, 2 H), 4.09 (t, 2 H), 3.53 (br s, 2 H), 2.97-2.93 (m, 2 H), 2.38-2.26 (m, 2 H), 2.07-1.97 (m, 5 H), 1.86-1.80 (m, 3 H), 1.53-1.41 (m, 2 H).

Compound 22c

Following the procedure outlined for compound 21, compound **8** (0.10 g, 0.19 mmol) and *n*-butyl bromide (0.035 g, 0.19 mmol) was converted to the prodrug **22c** as a white solid (0.028 g, 25.4 %). ^1H NMR ($CDCl_3$): δ 7.94 (d, 1 H), 7.80 (d, 1 H), 7.52-7.11 (m, 10 H), 4.50 (t, 2 H), 4.18 (d, 2 H), 4.10-3.98 (m, 4 H), 3.52 (br s, 2 H), 2.97-2.92 (m, 2 H), 2.36-2.25 (m, 2 H), 2.07-1.96 (m, 2 H), 1.85-1.80 (m, 3 H), 1.53-1.25 (m, 4 H), 1.14-1.02 (m, 2 H), 0.77 (t, 2 H).

Compound 22d

Following the procedure outlined for compound 21, compound **8** (0.20 g, 0.38 mmol) and 3-methyl-1-bromobutane (0.057 g, 0.38 mmol) was converted to the prodrug **22d** as a white solid (0.049 g, 21.7 %). The corresponding mesylate salt was prepared. ^{1}H NMR (DMSO-$_{d6}$): δ 9.46 (br s, 1 H), 7.76-7.74 (m, 2 H), 7.63-7.57 (m, 4 H), 7.54-7.36 (m, 3 H), 7.29 (d, 1 H), 7.12-7.10 (m, 2 H), 4.51-4.47 (m, 2H), 4.35-4.33 (m, 2 H), 4.11-4.07 (m, 4 H), 4.01 (t, 2 H), 3.51-3.47 (m, 2 H), 3.33-3.30 (m, 1 H), 3.14-3.11 (m, 2 H), 2.35 (s, 3 H), 2,27-2.23 (m, 2 H), 2.01-1.98 (m, 2 H), 1.55-1.52 (m, 2 H), 1.31-1.29 (m, 1 H), 1.25-1.22 (m, 2 H), 0.74 (d, 6 H).

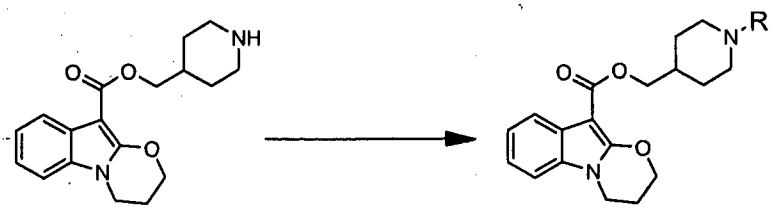
Compound 22e

Following the procedure outlined for compound 21, compound **8** (0.20 g, 0.38 mmol) and 4-chloromethyl-5-methyl-1,3-dioxol-2-one (0.056 g, 0.38 mmol))was converted to the prodrug **22e** as a white solid (0.039 g, 16.2 %). ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1 H), 7.78 (d, 1 H), 7.53-7.11 (m, 10 H), 4.78 (s, 2 H), 4.52 (t, 2 H), 4.18 (d, 2 H), 4.08 (t, 2 H), 3.57 (br s, 2 H), 2.94-2.90 (m, 2 H), 2.35-2.29 (m, 2 H), 2.07-2.04 (m, 5 H), 1.86-1.81 (m, 3 H), 1.53-1.39 (m, 3 H).

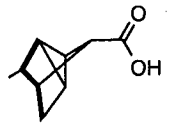
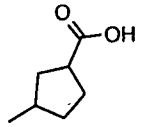
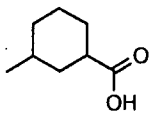
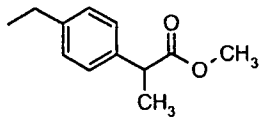
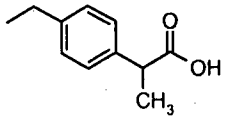
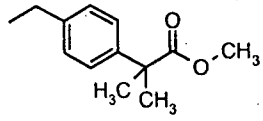
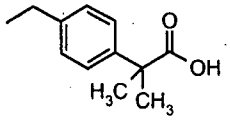
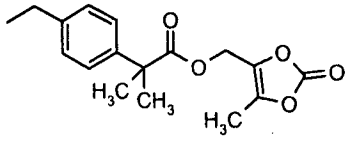
Compound 22 f

Following the procedure outlined for compound 21, compound **8** (0.20 g, 0.38 mmol) and benzyl bromide (0.065 g, 0.38 mmol) was converted to the prodrug **22f** as a white solid (0.044 g, 21.0 %). ^{1}H NMR ($CDCl_3$): δ 10.09 (br s, 1 H), 7.92 (d, 2 H), 7.45-7.43 (m, 1 H), 7.37-7.28 (m, 6 H), 7.17-7.12 (m, 8 H), 5.12 (s, 2 H), 4.55 (t, 2 H), 4.28-4.24 (m, 4 H), 4.10 (t, 2 H), 3.65-3.61 (m, 2 H), 2.95 (s, 3 H), 2.71-2.69 (m, 2 H), 2.36-2.33 (m, 2 H), 2.00-1.95 (m, 4 H).. The corresponding hydrochloride salt was prepared.

<u>Example 4</u> - Compounds 23-30



23/24/25/26/27/28/29/30

Compound	R	Molecular formula
23		$C_{26}H_{30}N_2O_5$
24		$C_{24}H_{30}N_2O_5$
25		$C_{25}H_{32}N_2O_5$
26		$C_{29}H_{34}N_2O_5$
27		$C_{28}H_{32}N_2O_5$
28		$C_{30}H_{36}N_2O_5$
29		$C_{29}H_{34}N_2O_5$
30		$C_{34}H_{38}N_2O_8$

Compound 23

Anti-3-oxotricyclo[2,2,1,0^{2b}]-heptane-7-carboxylic acid (0.12 g, 0.76 mmol) was added to a suspension of *N*-(4-piperidylmethyl)-3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxylate (0.20 g, 0.64 mmol), $NaCNBH_3$ (1.65 g, 12.0 mmol) and molecular sieves (4Å) in anhydrous MeOH (2.0 ml) and stirred at room temperature for 24 h. The reaction mixture was filtered, evaporated *in vacuo* and the residue separated with flash chromatography (CH_2Cl_2/MeOH - 9:1) to leave compound **23** as

a white solid (0.17 g, 49.5%). ^{1}H NMR (DMSO-d_6): δ 12.1 (br s, 1 H), 7.81 (d, 1 H), 7.29 (d, 1 H), 7.14-7.07 (m, 2 H), 4.51 (t, 2 H), 4.10 (t, 2 H), 4.01 (d, 2 H), 3.06 (br d, 2 H), 2.91-2.85 (m, 2 H), 2.26-2.23 (p, 2 H), 2.13-2.02 (m, 2 H), 1.90-1.63 (m, 5 H), 1.39-1.13 (m, 6 H). MS (ES): 451.1 $[M + H]^+$

Compound 24

Following the procedure outlined for compound **23**, *N*-(4-piperidylmethyl)-3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxylate (0.20 g, 0.64 mmol) and 3-oxo-1-cyclopentane carboxylic acid (0.090 g, 0.69 mmol) was converted to compound **24** as a white solid (0.12 g, 44.1 %). ^{1}H NMR (DMSO-d_6): δ 12.1 (br s, 1 H), 7.81 (d, 1 H), 7.29 (d, 1 H), 7.15-7.06 (m, 2 H), 4.49 (t, 2 H), 4.11 (t, 2 H), 4.01 (d, 2 H), 2.96 (br d, 2 H), 2.64-2.48 (m, 2 H), 2.28-2.23 (p, 2 H), 2.00-1.87 (m, 3 H), 1.78-1.58 (m, 8 H), 1.29-1.25 (m, 2 H). MS (ES): 427.5 $[M + H]^+$

Compound 25

Following the procedure outlined for compound **23**, *N*-(4-piperidylmethyl)-3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxylate (0.20 g, 0.64 mmol) and 3-oxo-1-cyclohexane carboxylic acid (0.099 g, 0.69 mmol) was converted to compound **25** as a white solid (0.11 g, 39.4 %). ^{1}H NMR (DMSO-d_6): δ 12.1 (br s, 1 H), 7.83 (d, 1 H), 7.28 (d, 1 H), 7.16-7.06 (m, 2 H), 4.50 (t, 2 H), 4.11 (t, 2 H), 4.02 (d, 2 H), 2.89-2.83 (m, 2 H), 2.61-2.12 (m, 5 H),1.97-1.36 (m, 8 H), 1.28-1.11 (m, 6 H). MS (ES): 441.5 $[M + H]^+$

Compound 26

Following the procedure outlined for compound **1**, *N*-(4-piperidylmethyl)-3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxylate (0.31 g, 0.88 mmol) and methyl 2-[4-(bromomethyl)phenyl]propanoate (0.23 g, 0.88 mmol) was converted to compound **26** as a white solid (0.26 g, 61.2 %). ^{1}H NMR ($CDCl_3$): δ 7.99 (d, 1 H), 7.30-7.15 (m, 7 H), 4.55 (t, 2 H), 4.21 (d, 2 H), 4.12 (t, 2 H), 3.76-3.69 (q, 1 H), 3.67 (s, 3 H), 3.49 (br s, 2 H), 2.92 (br d, 2 H), 2.39-2.34 (p, 2 H), 2.05-1.67 (m, 6 H), 1.51 (d, 3 H), 1.47-1.14 (m, 2 H).

Compound 27

Following the procedure outlined for compound **6**, compound **26** (1.10 g, 2.24 mmol) was converted to the free acid **27** as a white solid (0.57, 53.5 %). ^{1}H NMR (DMSO-$_{d6}$): δ 12.38 (br s, 1 H), 7.79 (d, 1 H), 7.55 (d, 2 H), 7.33-7.14 (m, 3 H), 7.13-7.08 (m, 2 H), 4.50 (t, 2 H), 4.20-4.03 (m, 6 H), 3.76-3.70 (m 1 H), 3.12-3.01 (m, 3 H), 2.27-2.24 (m, 2 H), 2.05- 2.00 (m, 3 H), 1.93-1.87 (m, 2 H), 1.36 (d, 3 H).

Compound 28

Following the procedure outlined for compound **1**, *N*-(4-piperidylmethyl)-3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]indole-10-carboxylate (0.47 g, 1.5 mmol) and methyl 2-[4-(bromomethyl)phenyl]-2-methylpropanoate (0.40 g, 1.5 mmol) was converted to compound **28** as a white solid (0.34 g, 44.9%). ^{1}H NMR ($CDCl_3$): δ 7.97-7.92 (m, 1 H), 7.25-7.10 (m, 7 H), 4.51 (t, 2 H), 4.17 (d, 2 H), 4.08 (t, 2 H), 3.63 (s, 3 H), 3.47 (s, 2 H), 2.92-2.86 (m, 2 H), 2.37-2.29 (p, 2 H), 2.02-1.92 (m, 2 H), 1.91-1.66 (m, 3 H). 1,55 (s, 6 H), 1.43-1.38 (m, 2 H).

Compound 29

Following the procedure outlined for compound **6**, compound **27** (0.34 g, 0.67 mmol) was converted to the free acid **28** as a white solid (0.15 g, 45.4 %). ^{1}H NMR (DMSO-$_{d6}$): δ 12.10 (br s, 1 H), 7.83-7.78 (m, 1 H), 7.31-7.13 (m, 5 H), 7.12-7.06 (m, 2 H), 4.48 (t, 2 H), 4.13-4.01 (m, 4 H), 3.70 (br s, 2 H), 2.84-2.80 (m, 2 H), 2.26- 2.21 (p, 2 H), 1.96 (t, 2 H), 1.91-1.72 (m, 3 H), 1.44 (s, 6 H), 1.32-1.22 (m, 2 H).

Compound 30

4-chloromethyl-5-methyl-1,3-dioxol-2-one (0.078 g, 0.53 mmol) was added to a mixture of free acid compound **24** (0.20 g, 0.40 mmol) and K_2CO_3 (0.16 g, 1.22 mmol) in DMA (1.0 ml). The mixture was stirred at room temperature for 12 hours and the mixture evaporated *in vacuo*. The residue was separated by flash chromatography (SiO_2, CH_2Cl_2: MeOH - 9:1) to leave the prodrug **30** as a white solid (0.12 g, 50.0 %). The corresponding hydrochloride salt was prepared. ^{1}H NMR (DMSO-$_{d6}$): δ 10.30 (br s, 1 H), 7.80 (d, 1 H), 7.58-7.52 (m, 2 H), 7.37-7.28 (m, 2 H), 7.15-7.06 (m, 2 H), 4.97 (s, 2 H), 4.50 (t, 2 H), 4.21 (d, 2 H), 4.11 (t, 2 H), 4.04 (d, 2 H), 3.31 (br s, 2 H), 2.94-2.91 (m, 2 H), 2.26-2.22 (m, 2 H), 2.11 (s, 3 H), 1.93-1.89 (m, 3 H), 1.63-1.55 (m, 2 H), 1.51 (s, 6 H).

Example 5 - *In vitro* biological testing of hydrophilic 5-HT$_4$ ligands in binding assays and adenylyl cyclase assays

Materials and methods

Establishment of HEK293 cell lines stably expressing human 5-HT$_{4(b)}$ receptors

The development of HEK293 cell lines stably expressing human 5-HT$_{4(b)}$ receptors was described and published previously (Bach et al. 2001). Briefly, HEK293 cells (ATCC) were grown in Dulbecco's modified Eagle's medium with 10% foetal calf serum and penicillin (100 U/ml) and streptomycin (100 µg/ml). Cells were transfected with plasmid DNA (pcDNA3.1(-) containing human 5-HT$_{4(b)}$ receptor cDNA) using SuperFect Transfection Reagent (QIAGEN) according to the manufacturers protocol. Serial dilutions of transfected cells were plated in 96 well plates containing G418 (geneticin; Amersham) at 0.4 mg/ml, and isolated single colonies of cells transformed to the neomycin-resistant phenotype were expanded and tested for expression of serotonin receptors by measuring serotonin-stimulated adenylyl cyclase activity (Themmen et al. 1993). Transformed cells were always grown in the presence of G418 (0.4 mg/ml). For binding and adenylyl cyclase analysis, stable cell lines were grown and maintained in UltraCULTURE™ general purpose serum-free medium (BioWhittaker, Walkersville, MD, USA), supplemented with L-glutamine (2 mM), penicillin (100 U/ml) and streptomycin (100 µg/ml).

Membrane preparation for radioligand binding and adenylyl cyclase assay

Membranes were prepared from stably transfected HEK293 cells cultured on 150-mm cell culture dishes and grown to 80% confluence in serum-free medium (UltraCULTURE™, BioWhittaker) with penicillin (10 U/ml) and 2 mM L-Glutamine (BioWhittaker). Cells were washed twice with 10 ml ice-cold HBSS, scraped with a rubber policeman in 10 ml ice-cold HBSS and collected by centrifugation at 800 g for 5 min at 4 °C. The cell pellet was resuspended in 1 ml/dish ice-cold STE buffer (27% (w/v) sucrose, 50 mM Tris-HCl, pH 7.5 at 20 °C, 5 mM EDTA) and homogenized with an Ultra-Turrax (IKA) homogenizer, using five 10 s bursts with 30 s cooling in ice-water between bursts. To remove nuclei, the homogenate was centrifuged at 300 g for 5 min at 4 °C and the supernatant was further centrifuged at 17000 g for 20 min at 4 °C and the supernatant removed. The crude membrane pellet was resuspended

with ten strokes of tight fitting pestle B in a Dounce glass-glass homogenizer in 1 ml/dish ice-cold TE (50 mM Tris-HCl, pH 7.5 at RT, 5 mM EDTA). This procedure was repeated twice and the resuspended membranes were finally aliquotted and flash frozen in liquid nitrogen and stored at -70 °C until use.

Radioligand binding assay

Binding assays were performed on membranes of HEK293 cells stably expressing the human 5-$HT_{4(b)}$ receptor (refs.) in 96-well, round-bottom microtiter plates with total reaction volumes of 50-200 µl, containing the indicated concentration of [^{3}H]GR113808 with or without competing unlabelled ligand in a binding buffer containing 50 mM Tris-HCl (pH 7.5 at RT), 1 mM EDTA, 5 mM EGTA, 2 mM $MgCl_2$, 1 mM ascorbate, 0.1 % BSA and 100 µM GTP. The plates were incubated at 23 EC for 60 min and harvested onto UniFilter™-96 GF/C™ (Packard Instrument Co., Meriden, CT, USA), presoaked in 0.3% polyethyleneimine (Sigma), using a Packard FilterMate Universal Harvester with 96-well format, and washed 4-6 times with approximately 0.25 ml/well of ice-cold buffer, containing 50 mM Tris-HCl (pH 7.0 at RT) and 2 mM $MgCl_2$. The filters were dried and counted at approximately 40% efficiency in a Top-Count liquid scintillation counter (Packard), using 20 µl per filter well of Micro-Scint liquid scintillation cocktail (Packard).

Adenylyl cyclase assay

Adenylyl cyclase activity was measured in membranes of HEK293 cells stably expressing the human 5-$HT_{4(b)}$ receptor (refs.) by determining conversion of [α-^{32}P]ATP to [^{32}P]cAMP in membranes prepared in STE by homogenization of cells grown and washed as described above in a Dounce glass-glass homogenizer by 10 strokes with the tight-fitting pestle. Membranes were kept on ice prior to assay. Adenylyl cyclase activities were measured in 10-µl aliquots in a final volume of 50 µl in the presence of 0.1 mM [α-^{32}P]ATP (1-2 x 10^6 cpm/assay), 4 mM $MgCl_2$, 20 µM GTP, 1 mM EDTA, 1 mM [^{3}H]cAMP (ca. 10,000 cpm/assay), 1 µM 3-isobutyl-1-methyl xanthine (IBMX; Sigma), a nucleoside triphosphate regenerating system consisting of 20 mM creatine phosphate (Sigma), 0.2 mg/ml creatine phosphokinase (Sigma) and 40 U/ml myokinase (Sigma) and additives described in the text and figures. When forskolin (Calbiochem, La Jolla, CA, USA) was used the

concentration was 100 μM. Incubations were for 20 min at 32 °C. Cyclic AMP formed was quantified by the double column chromatography system of Salomon et al. (1974) as modified by Bockaert et al. (1976).

Analysis of binding and adenylyl cyclase data

Binding and adenylyl cyclase data were analyzed by non-linear regression using Microsoft Excel with the Solver add-in, using the below equations.

Competitive binding assays - The data were fit to the equation

$$Y=a+(b-a)/(1+x/c) \quad [1]$$

where a is non-specific binding, b is total binding in the absence of competitor, c is IC_{50}, and x is the concentration of competitor. Where relevant, relative binding data were obtained by recalculating the data using a=0 and b=100.

Activation of adenylyl cyclase - The data were fit to the equation

$$Y=a+(b-a)x/(c+x) \quad [2]$$

where a is basal adenylyl cyclase activity, b is maximal adenylyl cyclase activity stimulated by the agonist, c is EC_{50}, and x is the concentration of agonist.

IC_{50} values from competitive binding assays were converted to K_b values by the method of Cheng and Prusoff (1973).

Protein measurements

The protein concentrations in the membrane preparations were measured with the Micro BCA Protein Assay Reagent Kit (Pierce, Rockford, IL, USA) using bovine serum albumin (BSA) as standard.

Radiochemicals

[^{3}H]GR113808 (84 Ci/mmol), [α-^{32}P]ATP (400 Ci/mmol) and [^{3}H]cAMP (30-50 Ci/mmol) were from Amersham (Buckinghamshire, England).

Compounds

5-Hydroxytryptamine hydrochloride (5-HT, serotonin) was from Sigma (St. Louis, MO, USA). GR113808 (1-methyl-1H-indole-3-carboxylic acid, [1-[2-[(methylsulfonyl)amino]ethyl]-4-piperidinyl]methyl ester) maleate was from Tocris (Avonmouth, UK). The other compounds tested were synthesized by Drug Discovery Laboratories AS (DDL) (Oslo, Norway).

Results of *in vitro* biological testing of 5-HT_4 ligands in adenylyl cyclase and binding assays, organised by compound (Table 1)

Compound	Antagonist pK_b value		Agonist/ Antagonist properties	Binding affinity (pK_d value)	
	pK_b	N		pK_d	n
GR113808	10.05	1	Antagonist	9.95 – 10.41	2
SB207266 (piboserod)	10.27 - 10.43 – 9.57	3	Antagonist	9.58 – 9.68 – 9.78 – 10.45 – 10.39	5
2	10.37 – 9.08	2	Antagonist	8.41 – 8.38 – 8.36	3
4	11.35	1	Antagonist	ND	
5	ND			ND	
6	ND			ND	
7	10.88 – 10.32	2	Antagonist, Inverse agonist	*11.60 – 12.69*	2
8	10.20 – 9.48	2	Antagonist, Inverse agonist	10.44 -*10.11*	2
11			ND	6.96-7.26	3
12			ND	5.47	2
14			ND	6.59-6.81	3
17			ND	8.43-8.30	2
18			ND	6.76-6.90	2
20			ND	7.73-7.56	3
23	8.44	2	Antagonist	8.82	2
24	8.60	4	Antagonist	8.94	5
25	8.60	3	Antagonist	8.92	2
27	8.79	2	Antagonist	9.29	2
29	8.78	8	Antagonist	9.45	9

ND = not determined

<u>Example 6</u> - Effects of compounds 2, 7, 8, 24 and 27 on hERG (Huntigdon)

The purpose of this study was to assess the effects of the above compounds on hERG (human ether-a-go-go related gene) tail current by examining the acute effect of the test compounds on the hERG ion channel in an appropriate *in vitro* test system. The

human embryonic kidney cell (HEK-293), which has been stably transfected with hERG ion channel cDNA, is a preparation that is considered suitable for this purpose.

Four concentrations of each test compound were tested in a screening assay to determine the liability to block hERG channels. Using the patch-clamp technique, peak hERG tail current amplitude was measured prior to and following exposure to the compounds at the following nominal concentrations:

Compound 2 - 10 nM, 1 μM, 10 μM, 30 μM and 50 μM;

Compound 7 - 100 nM, 1 μM and 10 μM;

Compound 8 - 100 nM, 1 μM, 10 μM and 100 μM;

Compound 24 -100 nM, 1 μM, 10 μM and 100 μM; and

Compound 27 -100 nM, 1 μM, 10 μM and 100 μM

for approximately 7 to 32 minutes (n=3 cells for each concentration). In addition, peak hERG tail current amplitude was measured in a separate group of 3 cells, prior to and following exposure to vehicle (0.1% DMSO) for time-matched vehicle data correction. Terfenadine (at the submaximally effective concentration of 50 nM, n=3), a known inhibitor of the I_{Kr} current, was used as a positive control compound.

The test compound data were corrected for the mean effect of vehicle and rundown and the concentration-response data were plotted and fitted with a sigmoidal function, from which the IC_{50} values for each compound were calculated.

The IC_{50} values for compounds 2, 7, 8, 24 and 27 were calculated to be 27.5μM, 131nM, 47.5μM, 209μM and 25μM respectively.

Claims:

1. A 5-hydroxytryptamine (5-HT) receptor modulating compound of formula I:

HT-L-A (I)

(wherein HT is a 5-HT receptor modulating moiety containing a basic nitrogen atom; A is an acid moiety; and
L is a linker moiety serving to maintain said basic nitrogen atom and said acid moiety at a separation of at least 0.4 nm, preferably at least 0.5 nm, more preferably at least 0.6 nm, especially at least 0.65 nm, e.g. up to 2 nm) or a prodrug form or salt thereof.

2. A compound as claimed in claim 1, wherein said acid moiety is a protic acidic moiety having a labile proton which, when in said acid moiety, is kept distanced from said basic nitrogen atom by said linker moiety by at least 0.6 nm.

3. A compound as claimed in claim 1, wherein the acid moiety A is selected from the group consisting of $-C(O)-OR^1$, $-OP(O)OR^2OR^2$, $-P(O)OR^2OR^2$, $-SO_2OR^2$, $-SO_3H$, $-OSO_3H$ and $-PO_3H$; wherein R^1 and R^2 are independently selected from the group consisting of H, M (wherein M is a counter-ion), C_{1-15}-alkyl, C_{3-8}-cycloalkyl, aryl, and $R^{1,2}$ wherein $R^{1,2}$ is R'-O-C(O)R", R'-O-C(O)-O-R", R'-C(O)-O-R", wherein R' and R" are independently selected from the group consisting of C_{1-15}-alkyl, C_{3-8}-cycloalkyl and aryl.

4. A compound as claimed in any one of claims 1 to 3, wherein L comprises: an optionally substituted mono- or bi-cyclic aryl or heteroaryl group; a linear C_{1-6}-alkyl group being substituted independently at each carbon atom by at least one optionally substituted C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-10}-cycloalkyl, aryl, heteroaryl, nitrile, hydroxy, amide, chloride or iodide group; an optionally substituted C_{3-10}-cycloalkyl or C_{4-10}-cycloalkenyl group; or an optionally substituted polycyclic alkyl or alkenyl group, e.g. a group having a steroid backbone.

5. A compound as claimed in any one of claims 1 to 4 wherein L is other than $-CH_2$-p-phenylene and -CO-p-phenylene.

6. A compound as claimed in any one of claims 1 to 5, wherein L comprises a group of the formula $-(CH_2)_n-Ar'-(CR^aR^b)_m-$ in which n is 0 or 1, preferably 1; Ar' is an optionally substituted aryl ring or heteroaromatic ring; R^a and R^b are each independently H or, more preferably, optionally substituted C_{1-6}- alkyl (preferably C_{1-4}-alkyl, e.g. methyl); and m is 0 or 1, preferably 1.

7. A compound as claimed in any one of claims 1 to 4, wherein L is an optionally substituted, optionally bridged C_4-C_{10}-cycloalkyl, preferably C_5-C_8-cycloalkyl, e.g. C_5-C_7-cycloalkyl, group.

8. A compound of formula I as claimed in any preceding claim, wherein A is an oxyacid or a tetrazole group, or an acid or ester or salt thereof.

9. A compound as claimed in any one of claims 1 to 8, wherein HT is a group of formula II:

$$Ar-(C(O))_n-(E)_m-(G)_p-BN- \qquad (II)$$

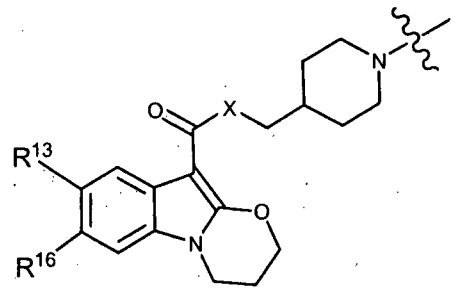
(wherein Ar is an optionally substituted aryl ring optionally fused with one or more rings selected from: non-aromatic, optionally substituted, carbocylic rings; non-aromatic heterocyclic rings; carbocyclic aromatic rings; and heteroaromatic rings;
n is 0 or 1;
m is 0 or 1;
E is O or NH;
p is 0 or 1;
G is a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-6}-alkyl group; and
BN is a basic nitrogen moiety, preferably a basic nitrogen atom-containing moiety selected from an amine group, an amide group, a carbamate or a carbamate derivative, urea or a urea derivative, a carbazimidamide, a nitrogen-containing heterocyclic ring, a nitrogen-containing heteroarylic ring, and an azabicyclic ring).

10. A compound as claimed in any one of claims 1 to 9, wherein HT is a group of the formula III:

Ar-C(O)-E-G-BN- (III)

(wherein Ar is a monocyclic or polycyclic aromatic or heteroaromatic;
E is selected from the group consisting of O and NH;
G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl and C_{3-7}-cycloalkyl-C_{1-6}-alkyl; and
BN is a basic nitrogen moiety;
or wherein G-BN together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl group).

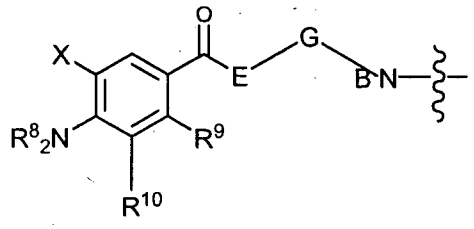
11. A compound as claimed in any preceding claim, wherein HT is a group having the formula IV:



(IV)

(wherein R^{13} is selected from the group consisting of H, halogen, NH_2 and C_{1-6}-alkyl; and
R^{16} is selected from the group consisting of H, halogen, OH, O-C_{1-6}-alkyl and C_{1-6}-alkyl).

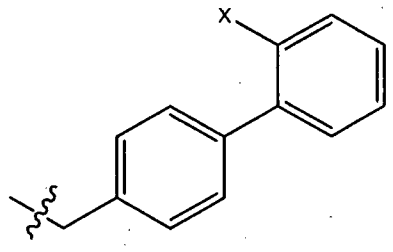
12. A compound as claimed in any one of claims 1 to 10, wherein HT is a group of formula V:



(V)

(wherein E is selected from the group consisting of O and NH;
G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl and C_{3-7}-cycloalkyl-C_{1-6}-alkyl;
BN is a basic nitrogen moiety;
or wherein G-BN together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl group;
X is a halogen;
R^8 is independently selected from H and C_{1-6}-alkyl;
R^9 and R^{10} are independently selected from the group consisting of H, O-C_{1-6}-alkyl, C_{1-6}-alkyl, a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl;
or wherein together R^9 and R^{10} form a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl;
or wherein NR^8_2 and R^{10} together form a heterocycloalkyl group).

13. A compound of formula I as claimed in any preceding claim, wherein L-A is a group of formula VII



(VII)

(wherein X is -C(O)OH, optionally substituted -C(O)O-C_{1-6}-alkyl or an optionally substituted 5-tetrazolyl group) or a prodrug form or salt thereof.

14. A compound of formula Ib:

$$HT\text{-}L_b\text{-}A_b \qquad (Ib)$$

(wherein HT is a group having 5-HT receptor modulating activity and is as defined in claim 1;
A_b is a group having renin-angiotensin system modulating activity; and
L_b is absent or is a linker which enables the pharmacophores of HT and A_b to function) or a prodrug and/or salt thereof.

15. The compound of claim 14, wherein A_b denotes a group of formula VII as defined in claim 13.

16. A pharmaceutical composition comprising a 5-HT receptor modulating compound as claimed in any one of claims 1 to 15, or a physiologically tolerable prodrug form or salt thereof, together with at least one pharmaceutical carrier or excipient.

17. A 5-HT receptor modulating compound as claimed in any one of claims 1 to 15, or a physiologically tolerable prodrug form or salt thereof for use in medicine.

18. A 5-HT receptor modulating compound as claimed in any one of claims 1 to 15, or a physiologically tolerable prodrug form or salt thereof for use in the treatment of a 5-HT associated condition, e.g. for the treatment of a disease of the cardiovascular system, the gastrointestinal system or the urinary system.

19. Use of a 5-HT receptor modulating compound as claimed in any one of claims 1 to 15, or a physiologically tolerable prodrug form or salt thereof in the manufacture of a medicament for the treatment of a 5-HT associated condition, e.g. for the treatment of a disease of the cardiovascular system, the gastrointestinal system or the urinary system.

20. A method of treatment of a disease of the cardiovascular system, the gastrointestinal system or the urinary system comprising administration of an

effective amount of a 5-HT receptor modulating compound as claimed in any one of claims 1 to 15, or a physiologically tolerable prodrug form or salt thereof, to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000656

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/34 C07D498/04 A61K31/5365 A61K31/445 A61P1/00
A61P9/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/061483 A2 (BIO MEDISINSK INNOVASJON AS [NO]; KLAVENESS JO [NO]; LEVY FINN OLAV [N) 7 July 2005 (2005-07-07) examples 31-32, 38, 40-44 Formula II inclaim 1 Use of compounds in cardiovascular and gastrointestinal disorders:claims 13-16 Mechanism of action is 5-HT modulation:claim 17 ----- -/--	1-5, 8-12,14, 16-20

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2010	02/07/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000656

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/007072 A1 (BIO MEDISINSK INNOVASJON AS [NO]; COCKBAIN JULIAN [GB]; KLAVENESS JO [) 18 January 2007 (2007-01-18) examples 40-41, 49-53 Piboserod derivative with Benzyl-group at piperidine nitrogenexample 47 Use in therapy of cardiovascular and gastrointestinal diseases:; page 2, line 21 - line 22 disclosure of formula: 5-HT-spacer-oxyacid:claim 8 Mode of action: 5-HT receptor modulation:claims 2-5	1-5, 8-12,14, 16-20
X Y	US 5 998 409 A (GASTER LARAMIE MARY [GB] ET AL) 7 December 1999 (1999-12-07) column 16; example 25 Use in therapy of stroke, arrythmia: claims 16,20-21 Mode of action: 5-HT antagonist:; column 1, line 31 - line 32	1,2, 16-20 3
X Y	US 5 852 014 A (GASTER LARAMIE MARY [GB] ET AL) 22 December 1998 (1998-12-22) column 16; example 25 Mode of action is 5-HT modulation: ; column 1, line 26 - line 27 Use in therapy of diseases such as IBS, arrythmia, stroke: claims 4-6	1,2, 16-20 3
Y	CRAIG JAMIESON, ELIZABETH M. MOIR, ZORAN RANKOVIC, GRANT WISHART: "Medicinal Chemistry of hERG Optimizations: Highlights and Hang-Ups" JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 17, 27 July 2006 (2006-07-27), pages 5029-5046, XP007913541 DOI: 10.1021/jm0603791 CCC Formation of Zwitterions as a strategy to reduce hERG liability: ; paragraph [02.2] Introduction of carboxyl group into otherwise basic drugs optimises hERG profile: examples 32,34,36,40; table 3	3

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000656

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/149929 A1 (ARYX THERAPEUTICS INC [US]; BECKER CYRUS [US]; RUBENS COURTNEY [US]; P) 27 December 2007 (2007-12-27) Markush formula in: claim 1 page 31; compounds ATI-7507, ATI-7505 use for gastrointestinal disorders:claim 21 Markush-formula XI-3 on page 23 disclosing an alkyl-aryl spacer between the piperidin-moiety and the acid moiety and example: ; page 60; compound 66	1,6, 16-20
X	ES 2 103 675 A1 (ALMIRALL LAB [ES]) 16 September 1997 (1997-09-16) page 9; table 2; compound 1 Mode of action: 5-HT antagonist:claim 8 Use in therapy of irritable bowel syndrome:; page 1, line 16	1,16-20
A	EP 0 884 319 A2 (SMITHKLINE BEECHAM PLC [GB]) 16 December 1998 (1998-12-16) Piboserod as 5-HT modulator:claims 1,9	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2010/000656

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005061483 A2	07-07-2005	AT 457309 T	15-02-2010
		AU 2004303722 A1	07-07-2005
		CA 2551171 A1	07-07-2005
		DK 1701951 T3	07-06-2010
		EP 1701951 A2	20-09-2006
		ES 2340855 T3	10-06-2010
		HK 1089177 A1	16-04-2010
		JP 2007516278 T	21-06-2007
		US 2007254874 A1	01-11-2007
WO 2007007072 A1	18-01-2007	EP 1902044 A1	26-03-2008
		US 2009029979 A1	29-01-2009
US 5998409 A	07-12-1999	NONE	
US 5852014 A	22-12-1998	NONE	
WO 2007149929 A1	27-12-2007	US 2008085915 A1	10-04-2008
ES 2103675 A1	16-09-1997	NONE	
EP 0884319 A2	16-12-1998	DK 884319 T3	30-08-2004