Title: NEW TRICYCLIC ANGIOTENSIN II AGONISTS

Abstract: There is provided compounds of formula (I), wherein the dotted line, X1, X2, X3, A, Y1, Y2, Y3, Y4, Z1, Z2, R1 and R² have meanings given in the description, and pharmaceutically-acceptable salts thereof, which compounds are useful as selective agonists of the AT2 receptor, and thus, in particular, in the treatment of inter alia gastrointestinal conditions, such as dyspepsia, IBS and MCF, and cardiovascular disorders.
NEW TRICYCLIC ANGIOTENSIN II AGONISTS

Field of the Invention

This invention relates to novel pharmaceutically-useful compounds, in particular compounds that are angiotensin II (AngII) agonists, more particularly agonists of the AngII type 2 receptor (hereinafter the AT2 receptor), and especially agonists that bind selectively to that receptor. The invention further relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to synthetic routes to their production.

Background and Prior Art

The endogenous hormone AngII is a linear octapeptide (Asp$^1$-Arg$^2$-Val$^3$-Tyr$^4$-Ile$^5$-His$^6$-Pro$^7$-Phe$^8$), and is the active component of the renin-angiotensin system (RAS). It is produced by the sequential processing of the pro-hormone angiotensinogen by renin and angiotensin converting enzyme (ACE).

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, body fluid and electrolyte homeostasis. Ang II exerts these physiological actions in many organs including the kidneys, the adrenal glands, the heart, blood vessels, the brain, the gastrointestinal tract and the reproductive organs (de Gasparo et al, Pharmacol. Rev. (2000) 52, 415-472).

Two main classes of AngII receptors have been identified, and designated as the type 1 receptor (hereinafter the AT1 receptor) and the AT2 receptor. The AT1 receptor is expressed in most organs, and is believed to be
responsible for the majority of the biological effects of AngII. The AT2 receptor is more prevalent than the AT1 receptor in fetal tissues, the adult ovaries, the adrenal medulla and the pancreas. An equal distribution is reported in the brain and uterus (Ardaillou, *J. Am. Soc. Nephrol.*, 10, S30-39 (1999)).

Several studies in adult individuals appear to demonstrate that, in the modulation of the response following AngII stimulation, activation of the AT2 receptor has opposing effects to those mediated by the AT1 receptor.

The AT2 receptor has also been shown to be involved in apoptosis and inhibition of cell proliferation (see de Gasparo *et al.*, supra). Further, it seems to play a role in blood pressure control. For example, it has been shown in transgenic mice lacking AT2 receptors that their blood pressure was elevated. Furthermore, it has been concluded that the AT2 receptor is involved in exploratory behaviour, pain sensitivity and thermoregulation.

The expression of AT2 receptors has also been shown to increase during pathological circumstances, such as vascular injury, wound healing and heart failure (see de Gasparo *et al.*, supra).

The expected pharmacological effects of agonism of the AT2 receptor are described generally in de Gasparo *et al.*, supra.

More recently, AT2 receptor agonists have been shown to be of potential utility in the treatment and/or prophylaxis of disorders of the alimentary tract, such as dyspepsia and irritable bowel syndrome, as well as multiple organ failure (see international patent application WO 99/43339).
International patent application WO 00/68226 and US patent number 6,235,766 disclose compounds comprising substituted imidazolyl groups, which groups are attached, via a methylene bridge, to a phenylthiophene moiety, as agonists of angiotensin-(1-7) receptors. International patent application WO 02/072569 discloses similar compounds as agonists of the same receptors. International patent application WO 01/44239 discloses biphenylsulfonamide compounds as combined angiotensin and endothelin receptor antagonists. The use of the compounds as Ang II receptor agonists is neither mentioned nor suggested in any of these documents.

AngII antagonists (which bind to the AT1 and/or AT2 receptors) have been disclosed in *inter alia* European patent applications EP 409 332, EP 512 675, EP 516 392, EP 542 059 and EP 624 583; international patent applications WO 92/20662, WO 93/01177, WO 94/27597, WO 94/02142, WO 95/23792 and WO 94/03435; and US patent numbers 5,091,390, 5,177,074, 5,412,097, 5,250,521, 5,260,285, 5,376,666, 5,252,574, 5,262,412, 5,312,820, 5,330,987, 5,166,206, 5,932,575, 5,240,928 and 6,235,766. In particular, international patent applications WO 92/20662, WO 93/01177 and US patent number 5,252,574 disclose compounds comprising 5-alkyl-1,2,4-triazol-3-one groups attached via a methylene bridge to a 2'-substituted biphenyl moiety (the same/similar compounds being disclosed in GB 2263636 as neurotensin antagonists and in DE 196 01 189 as chemical curiosities). AngII agonists, and particularly AT2 receptor agonists, are not contemplated in any of these documents.

Peptide and non-peptide AT2 receptor agonists, unrelated structurally to those described herein, and potential uses thereof, have been disclosed in, for example, international patent applications WO 00/38676, WO 00/56345, WO 00/09144, WO 99/58140, WO 99/52540, WO 99/46285, WO 99/45945, WO 99/42122, WO 99/40107, WO 99/40106, WO 99/39743,

US patent number 5,444,067 discloses compounds comprising a 5,7-dimethyl-2-ethylpyridinoimidazolyl group attached, via a methylene bridge, to a phenylthiophene moiety, as AngII agonists. Further, international patent application WO 02/96883 discloses compounds comprising certain monocyclic heterocyclic groups attached, via a methylene bridge, to substituted phenylthiophene and biphenyl moieties. The compounds disclosed therein are indicated as AngII agonists and in particular as selective AT2 receptor agonists.

However, there remains a need for effective and/or selective AT2 receptor agonists, which are expected to find utility in *inter alia* the above-mentioned conditions.

**Disclosure of the Invention**

According to the invention there is provided a compound of formula I,

![Chemical Structure](image)

wherein
X₁ represents -C(R₁⁸)(R₁⁹)-, -N(R₁⁸)- or –O-;
the dotted line signifies an optional double bond; and
in the case when the dotted line does not signify a double bond, X₂ and X₃
independently represent -C(R₁⁶)(R₁⁷)-, -N(R₁⁶)-, –O-, -C(O)- or
\( -\text{C}(R_{1}^{15})(R_{1}^{18})-\text{C}(R_{1}^{19})(R_{1}^{20}) \) provided that:
(i) when X₁ represents –N(R₁⁸)-, then X₂ and X₃ do not both represent
\(-\text{N}(R_{1}^{16})-\);
(ii) when X₁ represents –O-, then X₂ and X₃ do not both represent
\(-\text{O}-.\)
(iii) when X₁ represents –O- and X₂ represents –N(R₁⁶)-, then X₃
represents –C(O)-; and
(iv) when X₁ represents –O- and X₃ represents –N(R₁⁶)-, then X₂ does not
represent –C(R₁⁵)(R₁⁷)-; or
in the case when the dotted line signifies a double bond, X₂ and X₃
independently represent –N- or –C(R₁⁵)-, provided that when X₁ represents
\(-\text{N}(R_{1}^{18})-\), one of X₂ or X₃ represents –N- and the other represents
\(-\text{C}(R_{1}^{16})-\), then R₁⁶ represents H;
R₁⁸, R₁⁹, R₁⁶, R₁⁷, R₁⁸, R₁⁹, R₁⁶, R₁⁷ and R₁⁸ independently represent H, C₁-₆
alkyl, C₁-₆ alkoxy-C₁-₆ alky, Ar¹, Het¹, C₁-₃ alkyl-Ar², C₁-₃ alkyl-Het², C₁-₃
alkoxy-Ar³ or C₁-₃ alkoxy-Het³;
Ar¹, Ar² and Ar³ each independently represent a C₆-₁₀ aryl group, which
group is optionally substituted by one or more substituents selected from
=O, -OH, cyano, halo, nitro, C₁-₆ alkyl (optionally terminated by
\(-\text{N}(\text{H})\text{C}(\text{O})\text{OR}_{1}^{11a}, \text{C}_{1-6} \text{ alkoxy, phenyl, -N}(\text{R}_{1}^{12a})\text{R}_{1}^{12b}, \text{ -C}(\text{O})\text{R}_{1}^{12c},
\text{-C}(\text{O})\text{OR}_{1}^{12d}, \text{-C}(\text{O})\text{N}(\text{R}_{1}^{12e})\text{R}_{1}^{12f}, \text{-N}(\text{R}_{1}^{12g})\text{C}(\text{O})\text{R}_{1}^{12h}, \text{-N}(\text{R}_{1}^{12i})\text{C}(\text{O})\text{N}(\text{R}_{1}^{12j})\text{R}_{1}^{12k},
\text{-N}(\text{R}_{1}^{12m})\text{S}(\text{O})_{2}\text{R}_{1}^{11b}, \text{-S}(\text{O})_{2}\text{R}_{1}^{11c}, \text{-OS}(\text{O})_{2}\text{R}_{1}^{11d} \text{ and -S}(\text{O})_{2}\text{N}(\text{R}_{1}^{12a})\text{R}_{1}^{12p};
\text{Het¹, Het² and Het³ each independently represent a four- to twelve-}
membered heterocyclic group containing one or more heteroatoms selected
from oxygen, nitrogen and/or sulfur, which heterocyclic group is optionally
substituted by one or more substituents selected from =O, -OH, cyano, halo,
nitro, C₁₋₆ alkyl (optionally terminated by -N(H)C(O)OR¹¹ₐ), C₁₋₆ alkoxy, phenyl, -N(R¹₂₈)R¹₂₉, -C(O)R¹₂₉, -C(O)OR¹₂₉, -C(O)N(R¹₂₉)R¹₂₉, -N(R¹₂₈)C(O)R¹₂₉, -N(R¹₂₉)C(O)N(R¹₂₉)R¹₂₉, -N(R¹₂₉)S(O)₂R¹₁₁₉, -S(O)ₚR¹₁₁₉, -OS(O)₂R¹₁₁₉ and -S(O)₂N(R¹₂₉)R¹₂₉;

R¹₁₁₉ to R¹₁₂₉ independently represent C₁₋₆ alkyl;
R¹₁₂₉ to R¹₁₂₉ independently represent H or C₁₋₆ alkyl;

p represents 0, 1 or 2;

A represents -C(O) or -CH₂-;

Y₁, Y₂, Y₃ and Y₄ independently represent -CH- or -CF-;

Z₁ represents -CH-, -O-, -S-, -N- or -CH=CH₂;

Z₂ represents -CH-, -O-, -S- or -N-;

provided that:

(a) Z₁ and Z₂ are not the same;
(b) when Z₁ represents -CH=CH₂, then Z₂ may only represent -CH- or -N-; and
(c) other than in the specific case in which Z₁ represents -CH=CH₂, and Z₂ represents -CH-, when one Z₁ and Z₂ represents -CH-, then the other represents -O- or -S-;

R² represents -S(O)₂N(H)C(O)R⁴, -S(O)₂N(H)S(O)₂R⁴, -C(O)N(H)S(O)₂R⁴, or, when Z₁ represents -CH=CH₂, R² may represent -N(H)S(O)₂N(H)C(O)R⁵ or -N(H)C(O)N(H)S(O)₂R⁵;

R³ represents C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkyl or di-C₁₋₃-alkylamino-C₁₋₆-alkyl;

R⁴ represents C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₆-alkyl, C₁₋₃ alkoxy-C₁₋₆-alkoxy, C₁₋₆ alkylamino or di-C₁₋₆ alkylamino; and

R⁵ represents C₁₋₆ alkyl,
or a pharmaceutically-acceptable salt thereof,

which compounds and salts are referred to together hereinafter as "the compounds of the invention".


Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Unless otherwise specified, alkyl groups, and the alkyl parts of alkoxy, alkoxyalkyl, alkoxyalkoxy, alkylamino, alkylaminoalkyl, alkyl-aryl, alkyl-heterocyclic groups, alkoxy-aryl and alkoxy-heterocyclic groups, as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic/acyclic. Such alkyl groups, and alkyl parts of alkoxy, alkoxyalkyl, alkoxyalkoxy, alkylamino, alkylaminoalkyl, alkyl-aryl, alkyl-heterocyclic, alkoxy-aryl and alkoxy-heterocyclic groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated. Unless otherwise specified, such groups may also be substituted by one or more halo, and especially fluoro, atoms.

For the avoidance of doubt, alkoxy and alkoxyalkoxy groups are attached to the rest of the molecule via the/an oxygen atom in that group, alkylamino groups are attached to the rest of the molecule via the nitrogen atom of the amino part of that group, alkoxyalkyl, alkylaminoalkyl, alkyl-aryl and alkyl-heterocyclic groups are attached to the rest of the molecule via the alkyl part
of that group, and alkoxy-aryl and alkoxy-heterocyclic groups are attached to the rest of the molecule via the alkyl part of the alkoxy part of that group.

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

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention (for example any two or more of the substituents R\textsuperscript{1a} to R\textsuperscript{1j}) may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in the situation in which two or more of R\textsuperscript{1a} to R\textsuperscript{1j} represent C\textsubscript{1-6} alkyl groups, the alkyl groups in question may be the same or different. Similarly, when aryl and heterocyclic groups are substituted by more than one substituent as defined herein, the identities of the individual substituents are not to be regarded as being interdependent.

C\textsubscript{6-10} aryl groups include phenyl, naphthyl and the like (preferably phenyl). Preferred optional substituents on aromatic groups include C\textsubscript{1-3} alkyl groups (such as methyl) or C\textsubscript{1-3} alkoxy groups.

Het (Het\textsuperscript{1} to Het\textsuperscript{3}) groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het (Het\textsuperscript{1} to Het\textsuperscript{3}) groups may be fully saturated, wholly aromatic, partly aromatic and/or bicyclic in character. Heterocyclic groups that may be mentioned include benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzimidazolyl, benzomorpholinyl, benzothiophenyl, chromanyl, cinnolinyl, dioxanyl, furanyl, hydantoinyl, imidazolyl, imidazo[1,2-a]pyridinyl, indolyl, isoquinolinyl, isoxazolyl, maleimido, morpholinyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl,
pyrimindinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiophenyl, thiochromanyl, triazolyl, tetrazolyl and the like. Values of Het¹ that may be mentioned include thiophenyl, furanyl, pyridinyl and thiazolyl. Values of Het² that may be mentioned include pyridinyl, furanyl, thiophenyl and thiazolyl. Values of Het³ that may be mentioned include pyridinyl.

Substituents on Het (Het¹ to Het³) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het (Het¹ to Het³) groups may be via any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system. Het (Het¹ to Het³) groups may also be in the N- or S-oxidised form.

Preferred ring systems comprising the substituents Y₁, Y₂, Y₃ and Y₄ include phenyl groups. For the avoidance of doubt, the ring systems in compounds of formula I that comprise the groups Z₁ and Z₂, are aromatic in nature. In some instances, for example in cases where one or more of Z₁ and Z₂ represent –CH- or –N- the skilled person will appreciate that an additional H atom may necessarily be bonded to that CH group or N atom, in order to ensure that the rules of valency are adhered to. Preferred ring systems comprising Z₁ and Z₂ include oxazole groups, thiazole groups, phenyl groups, pyridinyl groups, thiophenyl groups and furanyl groups.

In this respect, compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.
Compounds of the invention also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

Preferred compounds of the invention include those in which:

- $X_1$ represents $-C(R^{1a})(R^{1b})$- or $-N(R^{1b})$-;
- $X_2$ represents $-O$-, $-N(R^{1c})$- or, more preferably, $-C(R^{1c})(R^{1d})$-;
- $X_3$ represents $-O$-, $-C(R^{1c})(R^{1b})-C(R^{1b})(R^{1j})$- or, more preferably,
  $-C(R^{1c})(R^{1d})$- or $-C(O)$-;
- $R^{1a}$ represents H or C$_{1-3}$ alkyl, such as methyl;
- $R^{1b}$ represents C$_{1-3}$ alkyl, such as methyl, or, especially, H;
- $R^{1c}$ represents H or C$_{1-3}$ alkyl, such as methyl;
- $R^{1d}$ represents H or C$_{1-3}$ alkyl, such as methyl.

More preferred compounds of the invention include those in which:

- $X_1$ represents $-CH_2$- or $-N(CH_3)_2$-;
- $X_2$ represents $-CH_2$- or $-C(CH_3)_2$-;
- $X_3$ represents $-CH_2$- or $-C(O)$-;
- A represents $-CH_2$-;
\[ Y_1, Y_2, Y_3 \text{ and } Y_4 \text{ all represent } \text{CH}^{-}; \]
\[ Z_1 \text{ represents } \text{CH}=\text{CH}^{-} \text{ or, especially, } \text{-S-}; \]
\[ Z_2 \text{ represents } \text{CH}^{-}; \]
\[ R^2 \text{ represents } \text{S(O)}_2\text{N(H)}\text{C(O)}R^4; \]
\[ R^3 \text{ represents } \text{n-butyl or, particularly, } \text{iso-butyl; } \]
\[ R^4 \text{ represents } \text{n-butoxymethyl, iso-butoxy and especially, } \text{n-butoxy.} \]

Preferred ring systems comprising the groups \( X_1, X_2 \) and \( X_3 \) include optionally substituted 2-pyrroolidinon-1-yl groups, 2-imidazolidinon-1-yl and hydantoin-3-yl groups.

More preferred compounds of the invention include the compounds of the examples described hereinafter.

Compounds of formula I may be made in accordance with techniques well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

(i) for compounds of formula I in which \( R^2 \) represents \( \text{-S(O)}_2\text{N(H)}\text{C(O)}R^4 \) or \( \text{-S(O)}_2\text{N(H)}\text{S(O)}_2R^4 \), and \( R^4 \) is as hereinbefore defined, reaction of a compound of formula II,
wherein the dotted line, $X_1$, $X_2$, $X_3$, $A$, $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Z_1$, $Z_2$ and $R^3$ are as hereinbefore defined with a compound of formula III,

$$R^4L^1$$

wherein $G$ represents C(O) or S(O)$_2$ (as appropriate), $L^1$ represents a suitable leaving group, such as halo (e.g. chloro or bromo) and $R^4$ is as hereinbefore defined, for example at around room temperature or above (e.g. up to 60-70°C) in the presence of a suitable base (e.g. pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, di-iso-propylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, or mixtures thereof) and an appropriate solvent (e.g. pyridine, dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, trifluoromethylbenzene or triethylamine). Preferred base/solvent systems for compounds of formula III in which $G$ is C(O) include pyrrolidinopyridine/pyridine, pyrrolidinopyridine/triethylamine, dimethylaminopyridine/pyridine or dimethylaminopyridine/triethylamine. Preferred base/solvent systems for compounds of formula III in which $G$ is S(O)$_2$ include NaOH/THF;
(ii) for compounds of formula I in which $R^2$ represents $-\text{S(O)}_2\text{N(H)}\text{C(O)}R^4$ and $R^4$ represents $C_{1-6}$ alkoxy-$C_{1-6}$-alkyl, coupling of a compound of formula II as hereinbefore defined with a compound of formula IV,

\[
R^{4a}\text{CO}_2\text{H}
\]

wherein $R^{4a}$ represents $C_{1-6}$ alkoxy-$C_{1-6}$-alkyl, for example under similar conditions to those described under process step (i) above, in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyl-diimidazole, $N,N'$-dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, $N,N'$-disuccinimidyl carbonate, benzotriazole-1-yloxytris(dimethylamino)phosphoniumhexafluorophosphate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate, bromo-tris-pyrrolidinophosponium hexafluorophosphate or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate), a suitable base (as mentioned in process step (i) above) and an appropriate solvent (as mentioned in process step (i) above);

(iii) for compounds of formula I in which $R^2$ represents $-\text{C(O)}\text{N(H)}\text{S(O)}_2\text{R}^4$ and $R^4$ is as hereinbefore defined, coupling of a compound of formula V,
wherein the dotted line, $X_1$, $X_2$, $X_3$, $A$, $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Z_1$, $Z_2$ and $R^3$ are as hereinbefore defined with a compound of formula VI,

$$R^4S(O)_2NH_2$$

VI

wherein $R^4$ is as hereinbefore defined, for example in the presence of a suitable coupling reagent (such as those described in process step (ii) hereinbefore), and under similar reaction conditions to those described hereinbefore for preparation of compounds of formula I in which $R^4$ represents $C_{1-6}$ alkoxy-$C_{1-6}$-alkyl;

(iv) for compounds of formula I in which $R^2$ represents $-C(O)NH(S(O))_2R^4$ and $R^4$ is as hereinbefore defined, coupling of a compound of formula VII,

wherein the dotted line, $X_1$, $X_2$, $X_3$, $A$, $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Z_1$, $Z_2$ and $R^3$ are as hereinbefore defined with a compound of formula VIII,

$$R^4S(O)_2Cl$$

VIII
wherein $R^4$ is as hereinbefore defined, for example at around 50°C in the presence of a suitable base (e.g. sodium hydride) and an appropriate organic solvent (e.g. THF);

(v) for compounds of formula I in which $R^2$ represents $-\text{N(H)S(O)}_2\text{N(H)C(O)}R^5$ and $R^5$ is as hereinbefore defined, reaction of a compound of formula IX,

![Chemical Structure](image)

wherein the dotted line, $X_1$, $X_2$, $X_3$, $A$, $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Z_1$, $Z_2$ and $R^3$ are as hereinbefore defined with a compound of formula X,

\[R^5\text{C(O)N(H)S(O)}_2\text{Cl}\]  

wherein $R^5$ is as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or triethylamine) and a suitable organic solvent (e.g. benzene or dichloromethane);

(vi) for compounds of formula I in which $R^2$ represents $-\text{N(H)C(O)N(H)S(O)}_2R^5$ and $R^5$ is as hereinbefore defined, reaction of a
compound of formula IX as hereinbefore defined with a compound of formula XI,

\[ R^5\text{S(O)}_2\text{N(H)}\text{C(O)}\text{OR}^x \quad \text{XI} \]

wherein \( R^x \) represents \( C_{1-2} \) alkyl and \( R^5 \) is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane);

(vii) for compounds of formula I in which \( R^2 \) represents \(-\text{N(H)}\text{C(O)}\text{N(H)}\text{S(O)}_2\text{R}^5 \) and \( R^5 \) is as hereinbefore defined, reaction of a compound of formula IX as hereinbefore defined with an isocyanate compound of formula XII,

\[ R^5\text{S(O)}_2\text{NCO} \quad \text{XII} \]

wherein \( R^5 \) is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane);

(viii) for compounds of formula I in which \( R^2 \) represents \(-\text{S(O)}_2\text{N(H)}\text{C(O)}\text{R}^4 \) and \( R^4 \) represents \( C_{1-6} \) alkylamino, reaction of a compound of formula II as hereinbefore defined with an isocyanate compound of formula XIII,

\[ R^{4b}\text{NCO} \quad \text{XIII} \]

wherein \( R^{4b} \) is \( C_{1-6} \) alkyl, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or potassium hydroxide and an appropriate organic solvent (e.g. acetone or acetonitrile); or
(ix) for compounds of formula I in which R² represents \(-\text{S(O)}\text{O}_2\text{N(H)C(O)}\text{R}^4\) and \(\text{R}^4\) represents di-\(\text{C}_{1-6}\) alkylamino, reaction of a corresponding compound of formula I in which \(\text{R}^2\) represents \(-\text{S(O)}\text{O}_2\text{N(H)C(O)}\text{R}^4\) and \(\text{R}^4\) represents \(\text{C}_{1-6}\) alkoxy with an amine of formula XIV,

\[\text{R}^{4c}\text{N(H)}\text{R}^{4d}\]  

wherein \(\text{R}^{4c}\) and \(\text{R}^{4d}\) independently represent \(\text{C}_{1-6}\) alkyl, for example at above room temperature (e.g. at between 70°C and 100°C) in the presence of an appropriate organic solvent (e.g. toluene).

Compounds of formula V may be prepared by oxidation of a compound of formula XV,

\[
\begin{align*}
\text{XV}
\end{align*}
\]

wherein the dotted line, \(X_1, X_2, X_3, A, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2\) and \(R^3\) are as hereinbefore defined, for example under standard oxidation conditions in the presence of a suitable oxidising agent, such as potassium permanganate or chromium (VI) oxide.
Compounds of formulae II, VII, IX and XV may be prepared by reaction of a compound of formula XVI,

\[
\text{XVI}
\]

wherein \(R'\) represents \(-\text{SO}_2\text{NH}_2\) (in the case of a compound of formula II), \(-\text{CONH}_2\) (in the case of a compound of formula VII), \(-\text{NH}_2\) (in the case of a compound of formula IX), or \(-\text{CHO}\) (in the case of a compound of formula XV) and \(R^3, Z^1\) and \(Z^2\) are as hereinbefore defined, or a protected derivative thereof, with a compound of formula XVII,

\[
\text{XVII}
\]

wherein \(L^2\) represents a suitable leaving group, such as trimethylsulphonate, or halo, such as iodo or bromo, and the dotted line, \(X_1, X_2, X_3, A, Y_1, Y_2, Y_3\) and \(Y_4\) are as hereinbefore defined, for example in the presence of an appropriate coupling catalyst system (e.g. a palladium catalyst, such as \(\text{Pd(PPh}_3)_4\) or \(\text{Pd(OAc)}_2/\text{ligand}\) (wherein the ligand may be, for example, \(\text{PPh}_3, \text{P(o-Tol)}_3\) or \(1,1'-\text{bis(diphenylphosphino)ferrocene}\)) and a suitable base (e.g. sodium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, cesium fluoride, triethylamine or di-\text{-iso-}propylethylamine), as well as a suitable solvent system (e.g. toluene,
ethanol, dimethoxymethane, dimethylformamide, ethylene glycol dimethyl ether, water, dioxane or mixtures thereof). This reaction may be carried out at above room temperature (e.g. at a high temperature, such as the reflux temperature of the solvent system that is employed). Preferably, compounds of formula XVI are protected at the $R^y$ position prior to carrying out the reaction with the compound of formula XVII. Suitable protecting groups for different values of $R^y$ are described hereinafter. If a protected version of a compound of formula XVI is employed, this reaction may be followed by deprotection of the $R^y$ group under standard conditions, for example as described hereinafter.

Compounds of formulae II, VII, IX and XV may alternatively be prepared by reaction of a compound of formula XVIII,

![Chemical Structure XVIII](image)

wherein the dotted line, $X_1$, $X_2$ and $X_3$ are as hereinbefore defined with a compound of formula XIX,

![Chemical Structure XIX](image)

wherein $A$, $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Z_1$, $Z_2$, $R^y$, $R^3$ and $L^1$ are as hereinbefore defined ($L^1$, in particular, may represent bromo), or a protected (at the $R^y$ part)
derivative thereof, for example at around or below room temperature in the presence of a suitable base (e.g. potassium hydroxide, potassium tert-butoxide, triethylamine or di-iso-propylethylamine) and an appropriate organic solvent (e.g. DMSO, DMF, THF or CH₂Cl₂). When A represents –CH₂–, suitable bases include potassium hydroxide and potassium tert-butoxide and suitable solvents include DMSO, THF, DMF, dioxane or DCM. When A represents –C(O)–, suitable bases include triethylamine and di-iso-propylethylamine and suitable solvents include DMSO, DMF, THF and CH₂Cl₂. Suitable protecting groups for different values of R⁵ are described hereinafter. If a protected version of a compound of formula XIX is employed, this reaction may be followed by deprotection of the R⁵ group under standard conditions, for example as described hereinafter.

Compounds of formula XVI and protected derivatives thereof may be prepared by reaction of a corresponding compound of formula XX,

![Chemical Structure](image)

wherein R⁵, R³, Z₁ and Z₂ are as hereinbefore defined, or an appropriate protected derivative thereof, with a reagent system that will enable the introduction of the –B(OH)₂ into the appropriate ring system. Suitable reagent systems include trialkylborates (e.g. tri-iso-propylborate). Such reactions may be carried out, for example, at low temperature (e.g. between -100°C and 0°C, e.g. between -80°C (such as -78°C) and -10°C (such as -20°C)) in the presence of a suitable base (e.g. n-butyl lithium) and an appropriate organic solvent (e.g. THF), followed by acid hydrolysis (e.g. in the presence of dilute HCl).
Compounds of formula XVII may be prepared by standard techniques, for example by way of reaction of a compound of formula XVIII as hereinbefore defined with a compound of formula XXI,

![Chemical Structure](image)

wherein A, Y₁, Y₂, Y₃, Y₄, L¹ and L² are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formulae II, VII, IX and XV (second process).

Compounds of formula XIX are known in the art. For example, they may be prepared according, or analogously, to processes described in *inter alia* US patent number 5,312,820, UK patent application GB 2281298, and/or by reaction of a compound of formula XVI as hereinbefore defined with a compound of formula XXII,

![Chemical Structure](image)

wherein A, Y₁, Y₂, Y₃, Y₄ and L² are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formulae II, VII, IX and XV (first process), followed by conversion of the OH group in the resultant intermediate to an appropriate leaving group, L¹ (e.g., in the case where A is –CH₂– and L¹ is
bromo, conversion may be carried out by reaction with CBr$_4$, for example at or around room temperature in the presence of a base (e.g. triphenylphosphine) and a suitable organic solvent (e.g. DMF); similarly, when A represents −C(O)− and L$^1$ represents Cl, the intermediate acid may be reacted with SOCl$_2$ in benzene or toluene, or with oxalyl chloride in DCM).

Compounds of formula XX are available using known techniques. For example:

(a) Compounds of formula XX in which R$^y$ represents −S(O)$_2$NH$_2$, -C(O)NH$_2$ or −CHO, and protected derivatives thereof, may be prepared by reaction of a compound of formula XXIII,

\[
\text{XXIII}
\]

wherein R$^{ya}$ represents −S(O)$_2$NH$_2$, -C(O)NH$_2$ or −CHO and Z$_1$ and Z$_2$ are as hereinbefore defined, or a protected derivative thereof, with a compound of formula XXIV,

\[
\text{XXIV}
\]

wherein L$^3$ represents a suitable leaving group (such as toluenesulphonate, benzenesulphonate, methanesulphonate or halo, such as bromo or iodo) and R$^3$ is as hereinbefore defined, for example at below room temperature (e.g. between around −35°C and
around -85°C), in the presence of a suitable base (e.g. n-butyl lithium) and an appropriate solvent (e.g. THF).

(b) Compounds of formula XX in which \( R^y \) is \(-S(O)_2NH_2\) and N-protected derivatives thereof, may be prepared by reaction of an appropriate compound of formula XXV,

```
XXV
```

wherein \( R^3 \), \( Z_1 \) and \( Z_2 \) are as hereinbefore defined with an appropriate reagent for introduction of a \(-S(O)_2NH_2\) group into the appropriate ring system (for example chlorosulphonic acid, or thionyl chloride in the presence of a suitable strong base (e.g. butyl lithium)), followed by reaction of the resultant intermediate with ammonia, or a protected derivative thereof (e.g. tert-butylamine), under conditions that are well known to those skilled in the art.

(c) Certain protected derivatives (e.g. alkyl, such as \( C_{1-6} \) alkyl, for example tert-butyl, protected derivatives) of compounds of formula XX in which \( R^y \) represents \(-C(O)NH_2\) may be prepared by reaction of a compound of formula XXV as hereinbefore defined, with a compound of formula XXVI,

```
R^zN=O
XXVI
```

wherein \( R^z \) represents an appropriate protecting group, such as an alkyl group, including \( C_{1-6} \) alkyl, e.g. tert-butyl, for example at low
temperature (e.g. \(-78^\circ\text{C}\) to around \(0^\circ\text{C}\)), in the presence of a suitable base (e.g. \(n\)-butyl lithium) and an appropriate solvent (e.g. THF).

(d) Certain protected derivatives (e.g. alkyl, such as \(C_{1-6}\) alkyl, for example tert-butyl, protected derivatives) of compounds of formula XX in which \(R^y\) represents \(-\text{C(O)NH}_2\) may also be prepared by reaction of a compound of formula XXVII,

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{Z}_1 \\
\text{Z}_2 \\
\text{R}_3
\end{array}
\]

XXVII

wherein \(R^3\), \(Z_1\) and \(Z_2\) are as hereinbefore defined with a protected (e.g. an (e.g. \(C_{1-6}\)) alkyl, such as tert-butyl-protected) derivative of ammonia (e.g. tert-butylamine) under standard coupling conditions (see, for example, those described hereinbefore for preparation of compounds of formula I (process step (iii))). Compounds of formula XXVII are known in the art or may be prepared by way of standard techniques, for example oxidation of a corresponding compound of formula XX in which \(R^y\) is \(-\text{CHO}\) e.g. under those conditions described hereinbefore for preparation of compounds of formula V.

(e) Compounds of formula XX in which \(R^y\) is \(-\text{CHO}\), \(Z_1\) represents \(-\text{CH}=\text{CH}-\) and \(Z_2\) represents \(-\text{CH}_2-\), and protected derivatives thereof, may be prepared by reaction of a compound of formula XXV in which \(Z_1\) represents \(-\text{CH}=\text{CH}-\) and \(Z_2\) represents \(-\text{CH}_2-\) with an appropriate reagent system for the introduction of an aldehyde group into the benzene ring (e.g. TiCl_4/CHCl_3, SnCl_4/CH_2Cl_2 or 1,3,5,7-azaadamantane/TFA) under standard reaction conditions, followed
by (if appropriate) protection of the resultant benzaldehyde under standard conditions.

(f) Compounds of formula XX in which R² is –NH₂, Z₁ represents –CH=CH- and Z₂ represents –CH-, and N-protected derivatives thereof, may be prepared by nitration of a compound of formula XXV in which Z₁ represents –CH=CH- and Z₂ represents –CH-, followed by reduction of the resultant nitrobenzene and (if appropriate) protection of the resultant aminobenzene, all of which steps may be carried out under standard conditions.

Compounds of formulae III, IV, VI, VIII, X, XI, XII, XIII, XIV, XVIII, XXI, XXII, XXIII, XXIV, XXV and XXVI are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include sulphonamido, amido, amino and aldehyde. Suitable protecting groups for sulphonamido, amido and amino include tert-butyloxy carbonyl, benzyl oxycarbonyl, 2-trimethylsilyl ethoxy carbonyl (Teoc) or tert-butyl. Suitable protecting groups for aldehyde include alcohols, such as methanol or ethanol, and
diols, such as 1,3-propanediol or, preferably, 1,2-ethanediol (so forming a cyclic acetal).

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques (e.g. using trifluoroacetic acid, sulfuric acid, toluenesulfonic acid or boron trichloride).

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

Medical and Pharmaceutical Uses

Compounds of the invention are useful because they possess pharmacological activity. The compounds of the invention are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

In particular, compounds of the invention are agonists of AngII, more particularly, are agonists of the AT2 receptor, and, especially, are selective agonists of that sub-receptor, for example as may be demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in those conditions in which endogenous production of AngII is deficient and/or where an increase in the effect of AngII is desired or required.

The compounds of the invention are further expected to be useful in those conditions where AT2 receptors are expressed and their stimulation is desired or required.

The compounds of the invention are further indicated in the treatment of conditions characterised by vasoconstriction, increased cell growth and/or differentiation, increased cardiac contractility, increased cardiovascular hypertrophy, and/or increased fluid and electrolyte retention.

The compounds of the invention are further indicated in the treatment of stress-related disorders, and/or in the improvement of microcirculation and/or mucosa-protective mechanisms.
Thus, compounds of the invention are expected to be useful in the treatment of disorders, which may be characterised as indicated above, and which are of, for example, the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system and the central nervous system (CNS).

Disorders of the gastrointestinal tract that may be mentioned include oesophagitis, Barrett's oesophagus, gastric ulcers, duodenal ulcers, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pancreatitis, hepatic disorders (such as hepatitis), gall bladder disease, multiple organ failure (MOF) and sepsis. Other gastrointestinal disorders that may be mentioned include xerostomia, gastritis, gastroparesis, hyperacidity, disorders of the bilary tract, coeliac, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion and Sjögren's syndrome.

Disorders of the respiratory tract that may be mentioned include inflammatory disorders, such as asthma, obstructive lung diseases (such as chronic obstructive lung disease), pneumonitis, pulmonary hypertension and adult respiratory distress syndrome.

Disorders of the kidneys that may be mentioned include renal failure, nephritis and renal hypertension.

Disorders of the eyes that may be mentioned include diabetic retinopathy, premature retinopathy and retinal microvascularisation.

Disorders of the female reproductive system that may be mentioned include ovulatory dysfunction.
Cardiovascular disorders that may be mentioned include hypertension, cardiac hypertrophy, cardiac failure, atherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post-balloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, angina, cardiac arrhythmias, claudicatio intermittens, preeclampsia, myocardial infarction, reinfarction, ischaemic lesions, erectile dysfunction and neointima proliferation.

Disorders of the CNS that may be mentioned include cognitive dysfunctions, dysfunctions of food intake (hunger/satiety) and thirst, stroke, cerebral bleeding, cerebral embolus and cerebral infarction.

Compounds of the invention may also be useful in the modulation of growth metabolism and proliferation, for example in the treatment of hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, the healing of ulcers, inhibition of adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer (e.g. in the gastrointestinal tract, lung cancer, etc), apoptosis, tumours (generally) and hypertrophy, diabetes, neuronal lesions and organ rejection.

The compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a condition in which endogenous production of AngII is deficient, and/or a condition where an increase in the effect of AngII is desired or required, and/or a condition where AT2 receptors are expressed and their stimulation is desired or required, which method comprises administration of a therapeutically effective amount of a
compound of the invention to a person suffering from, or susceptible to, such a condition.

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or via inhalation, in a pharmaceutically acceptable dosage form.

When the condition to be treated is multiple organ failure, preferred routes of administration are parenteral (e.g. by injection). Otherwise, the preferred route of administration for compounds of the invention is oral.

The compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be administered in combination with other AT2 agonists that are known in the art, as well as in combination with AT1 receptor antagonists that are known in the art, such as losartan, or in combination with an inhibitor of angiotensin converting enzyme (ACE).
According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention; and

(B) an AT1 receptor antagonist, or an ACE inhibitor,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of compound of the invention in conjunction with an AT1 receptor antagonist, or an ACE inhibitor, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises compound of the invention, and at least one comprises AT1 receptor antagonist, or ACE inhibitor, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including compound of the invention and AT1 receptor antagonist or ACE inhibitor).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention and an AT1 receptor antagonist, or an ACE inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, or an ACE inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,
which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Depending upon the disorder and patient to be treated and the route of administration, the compounds of the invention may be administered at varying doses.

Although doses will vary from patient to patient, suitable daily doses are in the range of about 1 to 1000 mg per patient, administered in single or multiple doses. More preferred daily doses are in the range 2.5 to 250 mg per patient.

Individual doses of compounds of the invention may be in the range 1 to 100 mg.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention have the advantage that they bind selectively to, and exhibit agonist activity at, the AT2 receptor. By compounds which “bind selectively” to the AT2 receptor, we include that the affinity ratio for the relevant compound (AT2:AT1) is at least 5:1, preferably at least 10:1 and more preferably at least 20:1.
The compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art.

**Biological Tests**

The following test procedures may be employed.

10

**Test A**

**Receptor Binding Assay using Rat Liver Membrane AT₁ Receptor**

Rat liver membranes were prepared according to the method of Dudley et al *(Mol. Pharmacol. (1990) 38, 370)*. Binding of $^{125}$IAng II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM MgCl₂, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, $^{125}$IAng II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 4 × 2 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a gamma counter. The characteristics of the Ang II binding AT₁ receptor were determined by using six different concentrations (0.03-5 nmol/L) of the labeled $^{125}$IAngII. Non-specific binding was determined in the presence of 1 µM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound $^{125}$IAngII. The dissociation constant ($K_d = 1.7 \pm 0.1$ nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit.
(Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate.

Test B

Receptor Binding Assay using Porcine Myometrial Membrane AT2 Receptor

Myometrial membranes were prepared from porcine uteri according to the method by Nielsen et al (Clin. Exp. Pharm. Phys. (1997) 24, 309). Any possible interference that may be exhibited by binding of compound to AT1 receptors was blocked by addition of 1 μM of a selective AT1 inhibitor. Binding of $^{125}$IAng II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM MgCl₂, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, $^{125}$IAng II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured using a gamma counter. The characteristics of the Ang II binding AT₂ receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled $^{125}$IAng II. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound $^{125}$IAng II. The dissociation constant ($K_d = 0.7 \pm 0.1$ nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate.
Test C

Duodenal Mucosal Alkaline Secretion Assay

Compounds were exposed to the duodenal mucosa in barbiturate-
anaesthetised rats prepared for in situ titration of duodenal mucosal alkaline
secretion, according to the methodology described by Flemström et al in

The invention is illustrated by way of the following examples.

\textbf{Example 1}

\textit{N-Butyloxycarbonyl-3-[4-(2-oxopyrrolidin-1-ylmethyl)phenyl]-5-iso-
butylthiophene-2-sulfonamide}

\textit{(a) N-\textit{tert}-Butylthiophene-2-sulfonamide}

Thiophene-2-sulfonyl chloride (15 g, 0.082 mol) was dissolved in CHCl$_3$
(200 mL) under N$_2$ atmosphere and then cooled to 0°C. \textit{tert}-Butylamine
(25.9 mL, 0.246 mol) dissolved in CHCl$_3$ (50 mL) was then added dropwise
to the reaction mixture. The reaction mixture was stirred for 1 hour at room
temperature and then at reflux for 10 min. Toluene (700 mL) was added
and the organic phase was washed with water (3 x 50 mL), dried, and
concentrated \textit{in vacuo}. The sub-title product was used without further
purification in the next step.

$^1$H NMR $\delta$(CDCl$_3$): 7.60 (1H, dd, $J = 1.3$, 3.8 Hz), 7.53 (1H, dd, $J = 1.3$, 5.0
Hz), 7.02 (1H, dd, $J = 5.0$, 3.8 Hz), 5.13 (1H, m), 1.24 (9H, m).

$^{13}$C NMR $\delta$(CDCl$_3$): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

\textit{(b) 5-\textit{iso}-Butyl-\textit{N-tert}-butylthiophene-2-sulfonamide}

\textit{N-\textit{tert}-Butylthiophene-2-sulfonamide} (10 g, 0.046 mol; see step (a) above)
was dissolved in THF (85 mL) under N$_2$ and then cooled to $-78^\circ$C. \textit{n-BuLi}
(1.6 M, 76.9 mL, 0.12 mol) was added \textit{via} a syringe. The reaction mixture
was stirred at $-78^\circ$C for 30 min. and then at $-40^\circ$C for 2 hours. Iodo-2-methylpropane (10.5 mL, 0.09 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with NH$_4$Cl (aq.) and extracted with EtOAc. The combined organic phase was washed with brine and dried and concentrated \textit{in vacuo}. The crude product was purified on column chromatography (hexanes:EtOAc (10:1)) to give the sub-title compound in 55% yield (7.0 g, 0.025 mol).

$^1$H NMR $\delta$(CDCl$_3$): 7.43 (1H, d, $J = 3.6$ Hz), 6.67 (1H, d, $J = 3.8$ Hz), 4.83 (1H, m), 2.67 (2H, d, $J = 7$ Hz), 1.88 (1H, m), 1.26 (9H, m), 0.93 (6H, $J = 6.6$ Hz). $^{13}$C NMR $\delta$(CDCl$_3$): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(c) \textit{5-iso-Butyl-2-(N-tert-butyliaminosulfonyl)thiophene-3-boronic acid}

5-\textit{iso-Butyl-N-tert-butylthiophene-2-sulfonamide} (10.6 g, 0.039 mol; see step (b) above) was dissolved in THF (165 mL) under N$_2$ and then cooled to $-78^\circ$C. n-BuLi (1.6 M, 60.19 mL, 0.096 mol) was added \textit{via} a syringe. The reaction mixture was stirred at $-20^\circ$C for 4 hours. Tri-\textit{iso-propyl}borate (13.3 mL, 0.058 mol) was then added \textit{via} a syringe and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 2 M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine, dried and concentrated \textit{in vacuo}. The product may be used without further purification.

MS(ESI$^+$) m/z: 236.8

(d) 1-(4-Bromobenzyl)pyrrolidin-2-one

DMSO (20 mL, dried over 4Å molecular sieve) was added to ground potassium hydroxide (2.24 g, 40 mmol) and the mixture was stirred for 5 minutes. 2-Pyrrolidinone (850 mg, 10.0 mmol) was then added and the mixture was stirred for 2 hours. 4-Bromobenzylbromide (5.0 g, 20 mmol)
was added and the mixture was cooled briefly and stirred for a further hour before water (20 mL) was added. The mixture was extracted with ether (3 × 100 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over CaCl₂ and the solvent was removed in vacuo. The residue was chromatographed on silica gel using hexane:acetone (2:1) as eluent to obtain the desired product as a colourless solid in 64% yield (1.63 g, 6.41 mmol).

MS (ESI⁺) m/z: 253.7, 255.7 (M⁺)

¹H NMR (CDCl₃, 270 MHz): δ 7.46 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.40 (s, 2H), 3.26 (t, J = 7.1 Hz, 2H), 2.44 (t, J = 7.1 Hz, 2H), 2.00 (qn, J = 7.1 Hz, 2H)

¹³C NMR (CDCl₃, 67.5 MHz): δ 174, 136.6, 131.7, 129.8, 121.4, 46.5, 45.9, 30.8, 17.7

IR (neat): 3405, 3059, 2923, 1678, 1482 cm⁻¹

Anal. Calcd for C₁₁H₁₂BrNO: C, 51.99; H, 4.76; N, 5.51. Found: C, 52.0; H, 4.8; N, 5.5

(e) 3-[4-(2-Oxopyrrolidin-1-ylmethyl)phenyl]-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide

5-iso-Butyl-2-(N-tert-butylaminosulfonyl)thiophene-3-boronic acid (200 mg, 0.626 mmol; see step (c) above), 1-(4-bromobenzyl)pyrrolidin-2-one (106 mg, 0.418 mmol; see step (d) above), toluene (20 mL), ethanol (1.5 mL), NaOH (2.5 mL, 1.0M, 2.5 mmol) and Pd(PPh₃)₄ (15 mg, 13 μmol) were mixed together under N₂. The mixture was warmed to reflux for 2 hours, diluted with EtOAc (50 mL), washed with water and then brine, and dried over MgSO₄. The solvent was evaporated and the residue was purified by flash chromatography using hexane:acetone (2:1) as eluent to give the sub-title compound in 84% yield (157 mg, 0.350 mmol).

MS (ESI⁺) m/z: 449.4 (M⁺)
$^1$H NMR (CDCl$_3$, 270 MHz): δ 7.60 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 6.74 (s, 1H), 4.50 (s, 2H), 3.31 (t, $J = 7.3$ Hz, 2H), 2.69 (d, $J = 7.1$ Hz, 2H), 2.50 (t, $J = 8.4$ Hz, 2H), 2.05 (m, 2H), 1.91 (m, 1H), 0.98 (s, 9H), 0.96 (d, $J = 6.9$ Hz, 6H)

$^{13}$C NMR (CDCl$_3$, 67.5 MHz): δ 175.2, 148.4, 142.6, 136.8, 134.3, 132.2, 129.4, 128.9, 128.1, 54.5, 46.8, 46.3, 39.1, 30.8, 30.5, 29.4, 22.1, 17.7

IR (neat): 3281, 2955, 1686, 1465 cm$^{-1}$

Anal. Calcd for C$_{23}$H$_{32}$N$_2$O$_3$S$_2$: C, 61.57; H, 7.19; N, 6.24. Found: C, 61.7; H, 7.1; N, 6.0

(f) 3-[4-(2-Oxopyrrolidin-1-ylmethyl)phenyl]-5-iso-butylthiophene-2-sulfonamide

BCl$_3$ (2 mL, 1M in hexane) was added to a solution of 3-[4-(2-oxopyrrolidin-1-ylmethyl)phenyl]-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide (100 mg, 0.223 mmol; see step (e) above) in CH$_2$Cl$_2$ and the mixture was stirred under a N$_2$ atmosphere for 40 minutes at ambient temperature. The reaction mixture was then diluted with EtOAc (50 mL) and washed with water and then brine, dried over MgSO$_4$ and concentrated to give crude sub-title product.

(g) N-Butyloxycarbonyl-3-[4-(2-oxopyrrolidin-1-ylmethyl)phenyl]-5-iso-butylthiophene-2-sulfonamide

The crude product from step (f) above was dissolved in pyridine (2 mL). Pyrrolidinopyridine (64 mg, 0.35 mmol) followed by n-butyl chloroformate (414 µL, 6.41 mmol) were added. The reaction mixture was stirred overnight at room temperature under a N$_2$ atmosphere. The reaction mixture was evaporated and co-evaporated. The residue was purified by flash chromatography using MeOH:CHCl$_3$ (1:30) as eluent to give the title compound in 84% yield (92 mg, 0.19 mmol).

MS (EI) m/z: 493.3 (M$^+$)
Example 2

N-Butyloxycarbonyl-3-[4-(3-methyl-2-oxoimidazolidin-1-ylmethyl)-phenyl]-5-iso-butylthiophene-2-sulfonamide

(a) 1-(4-Bromobenzyl)-3-methylimidazolidin-2-one

Potassium tert-butoxide (0.282 g, 2.51 mmol) was added to a stirred solution of 1-methylimidazolidinone (0.21 g, 2.09 mmol; Acros Organics) in THF (5 mL) at room temperature. After 30 minutes, 4-bromobenzylbromide (0.63 g, 2.51 mmol) in THF (3 mL) was added slowly and the mixture was stirred for 3 hours. The reaction was quenched with aqueous NH₄Cl (satd.) and extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with brine, dried over MgSO₄ and evaporated under reduced pressure. The crude product was purified by flash chromatography using acetone:petroleum ether (1: 4) as eluent to afford 0.493 g of the sub-title compound in 87% yield.

MS (ESI⁺) m/z: 270 (M⁺+1)

1H NMR (CDCl₃, 270 MHz): δ 7.43 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.30 (s, 2H), 3.27 (m, 2H), 3.13 (m, 2H), 2.81 (s, 3H)

13C NMR (CDCl₃, 67.5 MHz): δ 161.3, 136.3, 131.6, 129.8, 121.2
IR (neat): 2981, 2934, 1701, 1450, 1156 cm\(^{-1}\)

(b) \(\text{3-}[4-(3-\text{Methyl}-2-\text{oxoimidazolidin-1-ylmethyl})\text{phenyl}]5\text{-iso-butyl-N-}\text{tert}-\text{butylthiophene-2-sulfonamide}\)

\(\text{5-isobutyl-2-(N-tert-butylaminosulfonyl)}\text{thiophene-3-boronic acid (0.444 g, 1.39 mmol; see Example 1(c) above), 1-(4-bromobenzyl)-3-methyl-imidazolidin-2-one (0.25 g, 0.93 mmol; see step (a) above), toluene (3.5 mL), ethanol (1 mL), NaOH (1.0 M, 1.5 mL, 3.70 mmol) and Pd(PPh\(_3\))\(_4\) (0.032 g, 0.026 mmol) were mixed together under N\(_2\). The mixture was heated at 100°C for 6 hours and then diluted with EtOAc (20 mL), washed with water and then brine, and dried over MgSO\(_4\). The solvent was evaporated and the residue was purified by flash chromatography using petroleum ether:acetone (2:1) as eluent to give 0.255 g of sub-title compound in 59% yield.}

\(\text{MS (ESI\(^+\)) m/z: 464 (M\(^+\))}\)

\(^1\text{H NMR (CDCl\(_3\), 270 MHz): \(\delta 7.56 (d, J = 8.3\text{ Hz}, 2\text{H}), 7.32 (d, J = 8.3\text{ Hz}, 2\text{H}), 6.73 (s, 1\text{H}), 4.39 (s, 2\text{H}), 4.16 (s, 1\text{H}), 3.27 (m, 2\text{H}), 3.17 (m, 2\text{H}), 2.82 (s, 3\text{H}), 2.66 (d, J = 6.9\text{ Hz}, 2\text{H}), 1.90 (m, 1\text{H}), 0.95 (m, 15\text{H})}\)

\(^{13}\text{C NMR (CDCl\(_3\), 67.5 MHz): \(\delta 161.4, 148.2, 142.7, 137.7, 136.2, 133.9, 129.1, 128.8, 128.1, 54.4, 48.1, 44.9, 42.1, 39.1, 31.4, 30.4, 29.3, 22.1\}\)

IR (neat): 3302, 3049, 2869, 1700, 1512 cm\(^{-1}\)

(c) \(\text{3-}[4-(3-\text{Methyl}-2-\text{oxoimidazolidin-1-ylmethyl})\text{phenyl}]5\text{-iso-butylthiophene-2-sulfonamide}\)

Trifluoroacetic acid (10 mL) was added to 3-[4-(3-methyl-2-oxoimidazolidin-1-ylmethyl)phenyl]-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide (0.235 g, 0.50 mmol; see step (b) above). Two drops (ca. 0.05 mL) of anisole were also added and the mixture was stirred under a N\(_2\) atmosphere for 18 hours at ambient temperature. The reaction mixture was
evaporated and co-evaporated with acetonitrile to give crude sub-title compound.

(d) \textit{N}-Butyloxycarbonyl-3-[4-(3-methyl-2-oximidazolidin-1-ylmethyl)-phenyl]-5-iso-butylthiophene-2-sulfonamide

The crude product from step (c) above was dissolved in pyridine (5 mL). Pyrrolidinopyridine (0.075 g, 0.50 mmol) and \textit{n}-butyl chloroformate (0.69 g, 5.06 mmol) were added and the reaction mixture was stirred overnight at room temperature under a N\textsubscript{2} atmosphere. The mixture was evaporated and co-evaporated with acetonitrile and the residue was taken up in chloroform (25 mL), washed with 10\% aqueous citric acid, followed by water and then brine, and dried over MgSO\textsubscript{4}. The residue was purified by flash chromatography using CHCl\textsubscript{3}:MeOH as eluent to give 0.183 g of the title compound in 71\% yield.

MS (ES\textsuperscript{+}) m/z: 508 (M\textsuperscript{+})

\begin{itemize}
\item \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 270 MHz): \textit{s} 8.70 (brs, 1H), 7.43 (d, \textit{J} = 8.6 Hz, 2H), 7.25 (d, \textit{J} = 8.6 Hz, 2H), 6.71 (s, 1H), 4.26 (s, 2H), 4.03 (t, \textit{J} = 6.6 Hz, 2H), 3.27 (s, 2H), 3.17 (s, 2H), 2.80 (s, 3H), 2.67 (d, \textit{J} = 6.9 Hz, 2H), 1.94 (m, 1H), 1.49 (m, 2H), 1.25 (m, 2H), 0.96 (d, \textit{J} = 6.6 Hz, 6H), 0.88 (t, \textit{J} = 7.3 Hz, 3H)
\end{itemize}

\begin{itemize}
\item \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 67.5 MHz): \textit{s} 161.4, 148.2, 142.7, 137.7, 133.9, 129.1, 128.8, 128.1, 54.4, 48.1, 44.9, 42.1, 39.1, 31.4, 30.4, 29.4, 22.1
\end{itemize}

IR (neat): 2956, 1747, 1696, 1156 cm\textsuperscript{-1}
Example 3

$N$-Butyloxycarbonyl-3-[4-(3-methyl-2,5-dioxoimidazolidin-1-ylmethyl)-phenyl]-5-iso-butylthiophene-2-sulfonamide

(a) 3-(4-Bromobenzyl)-1-methylimidazolidin-2,4-dione

Potassium tert-butoxide (0.27 g, 2.41 mmol) was added to a stirred solution of 1-methylhydantoin (0.25 g, 2.19 mmol; Acros Organics) in THF (5 mL) at room temperature and, after 30 minutes, 4-bromobenzylbromide (0.575 g, 2.30 mmol) in THF (3 mL) was added slowly. The mixture was stirred at 50°C for 6 hours. The reaction was quenched with aqueous NH$_4$Cl (satd.) and extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine, dried over MgSO$_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography using acetone:petroleum ether (1:3) as eluent to afford 0.354 g of the sub-title compound in 57% yield.

MS (ESI$^+$) m/z: 284 (M$^+$+1)

$^1$H NMR (CDCl$_3$, 270 MHz): δ 7.40 (d, $J = 8.6$ Hz, 2H), 7.27 (d, $J = 8.6$ Hz, 2H), 4.55 (s, 2H), 3.82 (m, 2H), 2.95 (s, 3H)

$^{13}$C NMR (CDCl$_3$, 67.5 MHz): δ 169.3, 155.7, 134.9, 131.7, 130.5, 122.0, 51.6, 41.9, 29.6

IR (neat): 2987, 2956, 1738, 1705, 1450, 1131 cm$^{-1}$

(b) 3-[4-(3-Methyl-2,5-dioxoimidazolidin-1-ylmethyl)phenyl]-5-iso-butyl-$N$-tert-butylthiophene-2-sulfonamide

5-iso-Butyl-2-($N$-tert-butylaminosulfonyl)thiophene-3-boronic acid (0.147 g, 0.459 mmol; see Example 1(c) above), 3-(4-bromobenzyl)-1-methylimidazolidin-2,4-dione (0.1 g, 0.353 mmol; see step (a) above), CsF (0.139 g, 0.918 mmol), DME (5 mL) and Pd(PPh$_3$)$_4$ (0.012 g, 0.01 mmol) were mixed under N$_2$. The mixture was heated at 100°C for 2 hours and then diluted with EtOAc (15 mL), washed with water and then brine, and dried
over MgSO₄. The solvent was evaporated and the residue was purified by flash chromatography using petroleum ether:acetone as eluent to give 0.129 g of the sub-title compound in 76% yield.

MS (ESI⁺) m/z: 478 (M⁺)

¹H NMR (CDCl₃, 270 MHz): δ 7.54 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 6.71 (s, 1H), 4.68 (s, 2H), 4.08 (s, 1H), 3.88 (s, 2H), 3.00 (s, 3H), 2.66 (d, J = 6.6 Hz, 2H), 1.90 (m, 1H), 0.96 (s, 9H), 0.93 (d, J = 6.6 Hz, 6H)

¹³C NMR (CDCl₃, 67.5 MHz): δ 169.3, 156.4, 148.3, 142.6, 136.3, 134.5, 129.2, 128.8, 128.5, 54.4, 51.7, 42.1, 39.1, 30.4, 29.6, 29.4, 22.1

IR (neat): 3272, 2981, 1756, 1712, 1442, 1142 cm⁻¹

(c) 3-[(4-(3-Methyl-2,5-dioxoimidazolidin-1-ylmethyl)phenyl]-5-iso-butyli thiophene-2-sulfonamide

Trifluoroacetic acid (5 mL) was added to 3-[(4-(3-methyl-2,5-dioxoimidazolidin-1-ylmethyl)phenyl]-5-iso-butyli-N-tert-butylthiophene-2-sulfonamide (0.1 g, 0.24 mmol; see step (b) above). Two drops (ca. 0.05 mL) of anisole were then added and the mixture was stirred under a N₂ atmosphere for 18 hours at ambient temperature. The reaction mixture was evaporated and co-evaporated with acetonitrile (5 mL x 3) to give crude sub-title compound.

(d) N-Butyloxycarbonyl-3-[(4-(3-methyl-2,5-dioxoimidazolidin-1-ylmeth yl)phenyl]-5-iso-butyli thiophene-2-sulfonamide

The crude product from step (c) above was dissolved in pyridine (3 mL). Pyrrolidinopyridine (0.036 g, 0.24 mmol) and n-butyl chloroformate (0.328 g, 2.41 mmol) were added. The reaction mixture was stirred overnight at room temperature under a N₂ atmosphere. The mixture was evaporated and co-evaporated with acetonitrile and the residue was taken up in chloroform (20 mL), washed with 10% aqueous citric acid, followed by water and then brine, and dried over MgSO₄. The residue was purified by flash
chromatography using petroleum ether:acetone as eluent to give 0.07 g of the title compound in 56% yield.

MS (ESI\(^+\)) m/z: 522 (M\(^+\))

\(^1\)H NMR (CDCl\(_3\), 270 MHz): \(\delta\) 7.40 (s, 4H), 6.71 (s, 1H), 4.64 (s, 2H), 4.03 (t, \(J = 6.6\) Hz, 2H), 3.87 (s, 2H), 2.98 (s, 3H), 2.68 (d, \(J = 7.3\) Hz, 2H), 1.92 (m, 1H), 1.50 (m, 2H), 1.23 (m, 2H), 0.96 (d, \(J = 6.3\) Hz, 6H), 0.87 (t, \(J = 7.3\) Hz, 3H)

\(^{13}\)C NMR (CDCl\(_3\), 67.5 MHz): \(\delta\) 169.6, 156.5, 151.3, 150.2, 145.9, 136.3, 133.6, 129.4, 129.1, 128.5, 66.7, 51.6, 42.1, 39.2, 30.4, 29.6, 29.1, 22.1, 18.7, 13.5

IR (neat): 2959, 1747, 1715, 1450, 1157 cm\(^{-1}\)

Example 4

\(\text{N-Butyloxycarbonyl-3-[4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-ylmethyl)phenyl]-5-iso-butylthiophene-2-sulfonamide}\)

(a) 3-(4-Bromobenzyl)-1,5,5-trimethylimidazolidin-2,4-dione

Potassium tert-butoxide (0.237 g, 2.11 mmol) was added to a stirred solution of 1,5,5-trimethylhydantoin (0.25 g, 1.76 mmol) in THF (5 mL) at room temperature. After 30 minutes, 4-bromobenzylbromide (0.483 g, 1.93 mmol) in THF (3 mL) was added slowly and the mixture was stirred at 50°C for 6 hours. The reaction mixture was quenched with aqueous NH\(_4\)Cl (satd.) and extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with brine, dried over MgSO\(_4\) and evaporated under reduced pressure. The crude product was purified by flash chromatography using acetone:petroleum ether (1:3) as eluent to afford 0.218 g of the subtitle compound in 40% yield.

MS (ESI\(^+\)) m/z: 312 (M\(^+\)+1)

\(^1\)H NMR (CDCl\(_3\), 270 MHz): \(\delta\) 7.24 (d, \(J = 8.6\) Hz, 2H), 7.07 (d, \(J = 8.6\) Hz, 2H), 4.41 (s, 2H), 2.69 (s, 3H), 1.17 (s, 6H)
\[^13\text{C}\] NMR (CDCl\textsubscript{3}, 67.5 MHz): δ 138.7, 131.7, 130.0, 129.0, 128.3, 105.9, 105.6, 54.8, 52.2, 13.5, 11.0
IR (neat): 2981, 2934, 1761, 1714, 1450, 1133 cm\(^{-1}\)

5 (b) 3-[4-(3,4,4-Trimethyl-2,5-dioxoimidazolidin-1-ylmethyl)phenyl]-5-iso-
butyl-N-\textit{tert}-butylthiophene-2-sulfonamide

5-iso-Butyl-2-(\textit{N-tert}-butylaminosulfanyl)thiophene-3-boronic acid (0.16 g, 0.50 mmol; see Example 1(c) above), 3-(4-bromobenzyl)-1,5,5-
trimethylimidazolidin-2,4-dione (0.12 g, 0.385 mmol; see step (a) above),
CsF (0.152 g, 1.00 mmol), DME (5 mL) and Pd(PPh\textsubscript{3})\textsubscript{4} (0.017 g, 0.015 mmol) were mixed under N\textsubscript{2}. The mixture was heated at 100°C for 3 hours and then diluted with EtOAc (15 mL), washed with water and then brine, and dried over MgSO\textsubscript{4}. The solvent was evaporated and the residue was purified by flash chromatography using petroleum ether:acetone as eluent to give 0.132 g of sub-title compound in 68% yield.

MS (ESI\textsuperscript{+}) m/z: 506 (M\textsuperscript{+})

\[^1\text{H}\] NMR (CDCl\textsubscript{3}, 270 MHz): δ 7.53 (d, \(J = 8.3\) Hz, 2H), 7.39 (d, \(J = 8.3\) Hz, 2H), 6.70 (s, 1H), 4.66 (s, 2H), 4.03 (s, 1H), 2.86 (s, 3H), 2.64 (d, \(J = 6.6\) Hz, 2H), 1.88 (m, 1H), 1.34 (s, 6H), 0.94 (d, \(J = 6.9\) Hz, 6H), 0.91 (s, 9H)

\[^13\text{C}\] NMR (CDCl\textsubscript{3}, 67.5 MHz): δ 176.3, 155.1, 148.3, 142.5, 136.6, 134.4, 129.2, 128.7, 128.2, 61.2, 54.4, 41.8, 39.1, 30.4, 29.4, 24.4, 22.1, 22.0
IR (neat): 3317, 2973, 1765, 1708, 1442, 1136 cm\(^{-1}\)

(c) 3-[4-(3,4,4-Trimethyl-2,5-dioxoimidazolin-1-ylmethyl)phenyl]-5-iso-
butylthiophene-2-sulfonamide

Trifluoroacetic acid (5 mL) was added to 3-[4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-ylmethyl)phenyl]-5-iso-butyl-N-\textit{tert}-butylthiophene-2-sulfonamide (0.12 g, 0.237 mmol; see step (b) above). Two drops (ca. 0.05 mL) of anisole were also added and the mixture was stirred under a N\textsubscript{2} atmosphere for 18 hours at ambient temperature. The reaction mixture was
evaporated and co-evaporated with acetonitrile (5 mL x 3) to give crude sub-title compound.

(d) \( N \)-Butyloxy carbonyl-3-[4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl-methyl)phenyl]-5-iso-butylthiophene-2-sulfonamide

The crude product from step (c) above was dissolved in pyridine (3 mL). Pyrrolidinopyridine (0.035 g, 0.237 mmol) and \( n \)-butyl chloroformate (0.324 g, 2.37 mmol) were added. The reaction mixture was stirred overnight at room temperature under a \( \text{N}_2 \) atmosphere. The mixture was evaporated and co-evaporated with acetonitrile and the residue was taken up in chloroform (20 mL), washed with 10% aqueous citric acid, followed by water and then brine, and dried over \( \text{MgSO}_4 \). The residue was purified by flash chromatography using \( \text{CHCl}_3: \text{MeOH} \) (10:1) as eluent to give 0.092 g of the title compound in 71% yield.

\[
\text{MS (ESI}^+\text{)} \quad \text{m/z: 550 (M}^+\text{)}
\]

\(^{1}\text{H NMR (CDCl}_3, \text{ 270 MHz):} \quad \delta \ 7.40-7.33 \ (m, 4H), \ 6.70 \ (s, 1H), \ 4.61 \ (s, 2H), \ 3.99 \ (t, \ J = 6.6 \text{ Hz, 2H}), \ 2.85 \ (s, 3H), \ 2.66 \ (d, \ J = 6.9 \text{ Hz, 2H}), \ 1.89 \ (m, 1H), \ 1.46 \ (m, 2H), \ 1.35 \ (s, 6H), \ 1.21 \ (m, 2H), \ 0.94 \ (d, \ J = 6.6 \text{ Hz, 6H}), \ 0.84 \ (t, \ J = 7.3 \text{ Hz, 3H})
\]

\(^{13}\text{C NMR (CDCl}_3, \text{ 67.5 MHz):} \quad \delta \ 176.4, \ 154.9, \ 151.2, \ 145.8, \ 136.6, \ 133.5, \ 129.3, \ 129.1, \ 128.0, \ 66.8, \ 61.3, \ 41.8, \ 39.2, \ 30.3, \ 29.1, \ 24.3, \ 22.1, \ 21.9, \ 18.6, \ 13.5
\]

IR (neat): 2960, 1749, 1708, 1460, 1156 cm\(^{-1}\)

Example 5

Title compounds of the Examples were tested in Tests A and B above and were found to exhibit an affinity for AT2 receptors of less than \( \text{Ki} = 100 \) nM (e.g. less than 50 nM). The title compounds of the Examples were found to exhibit an affinity to AT1 receptors of more than \( \text{Ki} = 500 \) nM (e.g. more than 1 \( \mu \text{M} \)).
Example 6

Title compounds of the Examples are tested in Test C above and are found to stimulate markedly mucosal alkalisation. This effect is blocked by co-administration of the selective AT2 receptor antagonist PD123319 (Sigma Chemical Company).
Claims

1. A compound of formula I,

\[
\begin{align*}
X_1 & \quad X_2 \quad X_3 \\
\text{O} & \quad \text{N} & \quad \text{A} \\
\text{Y}_1 & \quad \text{Y}_2 & \quad \text{Z}_1 & \quad \text{Z}_2 & \quad \text{R}^2 \\
\text{Y}_3 & \quad \text{Y}_4 & \quad \text{Z}_2 & \quad \text{Z}_1 & \quad \text{R}^3
\end{align*}
\]

wherein

\(X_1\) represents \(-\text{C}(\text{R}^{1a})(\text{R}^{1b})\), \(-\text{N}(\text{R}^{1a})\) or \(-\text{O}\);

the dotted line signifies an optional double bond; and

in the case when the dotted line does not signify a double bond, \(X_2\) and \(X_3\) independently represent \(-\text{C}(\text{R}^{1c})(\text{R}^{1d})\), \(-\text{N}(\text{R}^{1e})\), \(-\text{O}\), \(-\text{C}(\text{O})\) or \(-\text{C}(\text{R}^{1f})(\text{R}^{1g})\) provided that:

(i) when \(X_1\) represents \(-\text{N}(\text{R}^{1a})\), then \(X_2\) and \(X_3\) do not both represent \(-\text{N}(\text{R}^{1e})\);

(ii) when \(X_1\) represents \(-\text{O}\), then \(X_2\) and \(X_3\) do not both represent \(-\text{O}\);

(iii) when \(X_1\) represents \(-\text{O}\) and \(X_2\) represents \(-\text{N}(\text{R}^{1e})\), then \(X_3\) represents \(-\text{C}(\text{O})\); and

(iv) when \(X_1\) represents \(-\text{O}\) and \(X_3\) represents \(-\text{N}(\text{R}^{1e})\), then \(X_2\) does not represent \(-\text{C}(\text{R}^{1c})(\text{R}^{1d})\); or

in the case when the dotted line signifies a double bond, \(X_2\) and \(X_3\) independently represent \(-\text{N}\) or \(-\text{C}(\text{R}^{1c})\), provided that when \(X_1\) represents
-N(R^{1a})-, one of X_2 or X_3 represents \(-N-\) and the other represents -C(R^{1c})-, then R^{1e} represents H;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g}, R^{1h} \text{ and } R^{1i} \text{ independently represent } H, \ C_{1-6} \text{ alkyl, } \ C_{1-6} \text{ alkoxy-} \ C_{1-6} \text{ alkyl, } \text{Ar}^1, \text{Het}^1, \ C_{1-3} \text{ alkyl-} \text{Ar}^2, \ C_{1-3} \text{ alkyl-} \text{Het}^2, \ C_{1-3} \text{ alkoxy-} \text{Ar}^3 \text{ or } \ C_{1-3} \text{ alkoxy-} \text{Het}^3; \\
\text{Ar}^1, \text{Ar}^2 \text{ and } \text{Ar}^3 \text{ each independently represent a } C_{6-10} \text{ aryl group, which group is optionally substituted by one or more substituents selected from } =O, \ -OH, \text{cyano, halo, nitro, } \ C_{1-6} \text{ alkyl (optionally terminated by } -N(H)C(O)OR^{11a}, \ C_{1-6} \text{ alkoxy, phenyl, } -N(R^{12a})R^{12b}, \ -C(O)R^{12c}, \ -C(O)OR^{12d}, \ -C(O)N(R^{12b})R^{12f}, -N(R^{12b})C(O)R^{12h}, -N(R^{12b})C(O)N(R^{12j})R^{12k}, -N(R^{12m})S(O)_{2}R^{11b}, -S(O)_{2}R^{11c}, -OS(O)_{2}R^{11d} \text{ and } -S(O)_{2}N(R^{12n})R^{12p}; \\
\text{Het}^1, \text{Het}^2 \text{ and } \text{Het}^3 \text{ each independently represent a four- to twelve-membered heterocyclic group containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic group is optionally substituted by one or more substituents selected from } =O, \ -OH, \text{cyano, halo, nitro, } \ C_{1-6} \text{ alkyl (optionally terminated by } -N(H)C(O)OR^{11a}, \ C_{1-6} \text{ alkoxy, phenyl, } -N(R^{12a})R^{12b}, \ -C(O)R^{12c}, \ -C(O)OR^{12d}, -C(O)N(R^{12b})R^{12f}, -N(R^{12b})C(O)R^{12h}, -N(R^{12b})C(O)N(R^{12j})R^{12k}, -N(R^{12m})S(O)_{2}R^{11b}, -S(O)_{2}R^{11c}, -OS(O)_{2}R^{11d} \text{ and } -S(O)_{2}N(R^{12n})R^{12p}; \\
R^{11a} \text{ to } R^{11d} \text{ independently represent } C_{1-6} \text{ alkyl; } R^{12a} \text{ to } R^{12p} \text{ independently represent } H \text{ or } C_{1-6} \text{ alkyl; } \\
p \text{ represents } 0, \ 1 \text{ or } 2; \\
A \text{ represents } -C(O) \text{ or } -CH_2-; \\
Y_1, Y_2, Y_3 \text{ and } Y_4 \text{ independently represent } -CH- \text{ or } -CF-; \\
Z_1 \text{ represents } -CH-, -O-, -S-, -N- \text{ or } -CH=CH-; \\
Z_2 \text{ represents } -CH-, -O-, -S- \text{ or } -N-; \\
\text{provided that: } \\
(a) \ \ Z_1 \text{ and } Z_2 \text{ are not the same; } \\
b) \ \text{when } Z_1 \text{ represents } -CH=CH-, \text{ then } Z_2 \text{ may only represent } -CH- \text{ or } \\
-N- \text{; and}
(c) other than in the specific case in which \(Z_1\) represents \(-\text{CH}=\text{CH}_2\), and \(Z_2\) represents \(-\text{CH}_2\), when one \(Z_1\) and \(Z_2\) represents \(-\text{CH}_2\), then the other represents \(-\text{O-}\) or \(-\text{S-}\);

\(R^2\) represents \(-\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^4\), \(-\text{S}(\text{O})_2\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^4\), \(-\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^4\), or, when \(Z_1\) represents \(-\text{CH}=\text{CH}_2\), \(R^2\) may represent \(-\text{N}(\text{H})\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^5\) or \(-\text{N}(\text{H})\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^5\);

\(R^3\) represents \(\text{C}_{1-6}\) alkyl, \(\text{C}_{1-6}\) alkoxy, \(\text{C}_{1-6}\) alkoxy-\(\text{C}_{1-6}\)-alkyl or \(\text{di-C}_{1-3}\)-alkylamino-\(\text{C}_{1-4}\)-alkyl;

\(R^4\) represents \(\text{C}_{1-6}\) alkyl, \(\text{C}_{1-6}\) alkoxy, \(\text{C}_{1-6}\) alkoxy-\(\text{C}_{1-6}\)-alkyl,

\(\text{C}_{1-3}\) alkoxy-\(\text{C}_{1-6}\)-alkoxy, \(\text{C}_{1-6}\) alkylamino or \(\text{di-C}_{1-6}\) alkylamino; and

\(R^5\) represents \(\text{C}_{1-6}\) alkyl,

or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein the dotted line does not signify a double bond.

3. A compound as claimed in Claim 1 or Claim 2 wherein \(X_1\) represents \(-\text{C}(\text{R}^{1\text{a}})(\text{R}^{1\text{b}})\)- or \(-\text{N}(\text{R}^{1\text{a}})\)-.

4. A compound as claimed in Claim 3 wherein \(X_1\) represents \(-\text{CH}_2\)- or \(-\text{N}(\text{CH}_3)\)-.

5. A compound as claimed in any one of the preceding claims wherein \(X_2\) represents \(-\text{C}(\text{R}^{1\text{c}})(\text{R}^{1\text{d}})\)-.

6. A compound as claimed in Claim 5 wherein \(X_2\) represents \(-\text{CH}_2\)- or \(-\text{C}(\text{CH}_3)_2\)-.

7. A compound as claimed in any one of the preceding claims wherein \(X_3\) represents \(-\text{C}(\text{R}^{1\text{c}})(\text{R}^{1\text{d}})\)- or \(-\text{C}(\text{O})\)-.
8. A compound as claimed in Claim 7 wherein X₃ represents –CH₂- or –C(O)–.

9. A compound as claimed in any one of the preceding claims wherein A represents –CH₂–.

10. A compound as claimed in any one of the preceding claims wherein Y₁, Y₂, Y₃ and Y₄ all represent –CH–.

11. A compound as claimed in any one of the preceding claims wherein Z₁ represents -S- or –CH=CH–.

12. A compound as claimed in Claim 11 wherein Z₁ represents -S-.

13. A compound as claimed in any one of the preceding claims wherein Z₂ represents –CH–.

14. A compound as claimed in any one of the preceding claims wherein R³ represents n-butyl or iso-butyl.

15. A compound as claimed in Claim 14 wherein R³ represents iso-butyl.

16. A compound as claimed in any one of the preceding claims wherein, when R² represents -S(O)₂N(H)C(O)R⁴, -S(O)₂N(H)S(O)₂R⁴ or -C(O)N(H)S(O)₂R⁴, R⁴ represents n-butyl, n-butoxymethyl, iso-butoxy or n-butoxy.

17. A compound as claimed in any one of the preceding claims wherein R² represents -S(O)₂N(H)C(O)R⁴.
18. A compound as claimed in Claim 17 wherein \( R^d \) represents \( n \)-butoxymethyl, \( iso \)-butoxy or \( n \)-butoxy.

19. A compound as claimed in any one of Claims 16 to 18 wherein \( R^d \) represents \( n \)-butoxy.

20. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

21. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

22. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

23. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which endogenous production of AngII is deficient.

24. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which an increase in the effect of AngII is desired or required.

25. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.
26. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

27. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which endogenous production of AngII is deficient.

28. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which an increase in the effect of AngII is desired or required.

29. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

30. The use as claimed in any one of Claims 26 to 29, wherein the condition is of the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system, or the central nervous system.

31. The use as claimed in Claim 30, wherein the condition is oesophagitis, Barrett’s oesophagus, a gastric ulcer, a duodenal ulcer, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, hepatic disorders (including hepatitis), gall bladder disease, multiple organ failure, sepsis, xerostomia,
gastritis, gastroparesis, hyperacidity, a disorder of the biliary tract, coeliacia, Crohn’s disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion, Sjögren’s syndrome, inflammatory disorders, asthma, an obstructive lung disease (including chronic obstructive lung disease), pneumonitis, pulmonary hypertension, adult respiratory distress syndrome, renal failure, nephritis, renal hypertension, diabetic retinopathy, premature retinopathy, retinal microvascularisation, ovulatory dysfunction, hypertension, cardiac hypertrophy, cardiac failure, atherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post balloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, angina, cardiac arrhythmias, claudicatio intermittens, preeclampsia, myocardial infarction, reinfarction, ischaemic lesions, erectile dysfunction, neointima proliferation, cognitive dysfunctions, dysfunctions of food intake (hunger/satiety), thirst, stroke, cerebral bleeding, cerebral embolus, cerebral infarction, hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, an ulcer, adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer, apoptosis, tumours, hypertrophy diabetes, neuronal lesions or organ rejection.

32. The use as claimed in Claim 31, wherein the condition is non-ulcer dyspepsia, irritable bowel syndrome, multiple organ failure, hypertension or cardiac failure.

33. A method of treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.
34. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

35. A kit of parts comprising components:
(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and
(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

36. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, and an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

37. A kit of parts comprising components:
(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and
(b) a pharmaceutical formulation including an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,
which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

38. A process for the preparation of a compound as defined in Claim 1, which comprises:

(i) for compounds of formula I in which \( R^2 \) represents \(-S(O)_2N(H)C(O)R^4 \) or \(-S(O)_2N(H)S(O)_2R^4 \), and \( R^4 \) is as defined in Claim 1, reaction of a compound of formula II,

\[
\begin{align*}
&\text{II} \\
&X_1 X_2 X_3 X_4 Y_1 Y_2 Y_3 Y_4 Z_1 Z_2 Z_3 R^3
\end{align*}
\]

wherein the dotted line, \( X_1, X_2, X_3, A, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 \) and \( R^3 \) are as defined in Claim 1 with a compound of formula III,

\[
\begin{align*}
&\text{III} \\
&R^4G L^1
\end{align*}
\]

wherein \( G \) represents \( C(O) \) or \( S(O)_2 \) (as appropriate), \( L^1 \) represents a suitable leaving group and \( R^4 \) is as defined in Claim 1;

(ii) for compounds of formula I in which \( R^2 \) represents \(-S(O)_2N(H)C(O)R^4 \) and \( R^4 \) represents \( C_{1-6} \) alkoxy-\( C_{1-6} \)-alkyl, coupling of a compound of formula II as defined above with a compound of formula IV,

\[
\begin{align*}
&\text{IV} \\
&R^{4a}CO_2H
\end{align*}
\]

wherein \( R^{4a} \) represents \( C_{1-6} \) alkoxy-\( C_{1-6} \)-alkyl;

(iii) for compounds of formula I in which \( R^2 \) represents \(-C(O)N(H)S(O)_2R^4 \) and \( R^4 \) is as defined in Claim 1, coupling of a compound of formula V,
wherein the dotted line, $X_1$, $X_2$, $X_3$, $A$, $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Z_1$, $Z_2$ and $R^3$ are as defined in Claim 1 with a compound of formula VI,

$$R^4S(O)_2NH_2$$

wherein $R^4$ is as defined in Claim 1;

(iv) for compounds of formula I in which $R^2$ represents $-C(O)N(H)S(O)_2R^4$ and $R^4$ is as defined in Claim 1, coupling of a compound of formula VII,

$$\text{VII}$$

wherein the dotted line, $X_1$, $X_2$, $X_3$, $A$, $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Z_1$, $Z_2$ and $R^3$ are as defined in Claim 1 with a compound of formula VIII,

$$R^4S(O)_2Cl$$

wherein $R^4$ is as defined in Claim 1;

(v) for compounds of formula I in which $R^2$ represents $-N(H)S(O)_2N(H)C(O)R^2$ and $R^5$ is as defined in Claim 1, reaction of a compound of formula IX,
wherein the dotted line, X₁, X₂, X₃, A, Y₁, Y₂, Y₃, Y₄, Z₁, Z₂ and R³ are as defined in Claim 1 with a compound of formula X,

\[ R^5C(O)N(H)S(O)_2Cl \]  

X

wherein \( R^5 \) is as defined in Claim 1;

(vi) for compounds of formula I in which \( R^2 \) represents \(-N(H)C(O)N(H)S(O)_2R^5 \) and \( R^5 \) is as defined in Claim 1, reaction of a compound of formula IX as defined above with a compound of formula XI,

\[ R^5S(O)_2N(H)C(O)OR^x \]  

XI

wherein \( R^x \) represents C₁₋₂ alkyl and \( R^5 \) is as defined in Claim 1;

(vii) for compounds of formula I in which \( R^2 \) represents \(-N(H)C(O)N(H)S(O)_2R^5 \) and \( R^5 \) is as defined in Claim 1, reaction of a compound of formula IX as defined above with a compound of formula XII,

\[ R^5S(O)_2NCO \]  

XII

wherein \( R^5 \) is as defined in Claim 1;

(viii) for compounds of formula I in which \( R^2 \) represents \(-S(O)_2N(H)C(O)R^4 \) and \( R^4 \) represents C₁₋₆ alkylamino, reaction of a compound of formula II as defined above with a compound of formula XIII,

\[ R^{4b}NCO \]  

XIII

wherein \( R^{4b} \) is C₁₋₆ alkyl; or

(ix) for compounds of formula I in which \( R^2 \) represents \(-S(O)_2N(H)C(O)R^4 \) and \( R^4 \) represents di-C₁₋₆ alkylamino, reaction of a corresponding compound of formula I in which \( R^2 \) represents
59

-S(O)₂N(H)C(O)R⁴ and R⁴ represents C₁-₅ alkoxy with a compound of formula XIV,

\[ R^{4c}N(H)R^{4d} \]

wherein R⁴c and R⁴d independently represent C₁-₅ alkyl.

39. A compound of formula II as defined in Claim 38 or a protected derivative thereof.

40. A compound of formula V as defined in Claim 38 or a protected derivative thereof.

41. A compound of formula VII as defined in Claim 38 or a protected derivative thereof.

42. A compound of formula IX as defined in Claim 38 or a protected derivative thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/10 A61K31/4025 A61K31/4178 A61P1/00

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)
IPC 7 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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 00 68226 A (AVENTIS PHARMA DEUTSCHLAND GMBH) 16 November 2000 (2000-11-16) cited in the application whole document</td>
<td>1,22</td>
</tr>
<tr>
<td>A</td>
<td>WO 02 07569 A (AVENTIS PHARMA DEUTSCHLAND GMBH) 31 January 2002 (2002-01-31) cited in the application whole document</td>
<td>1,22</td>
</tr>
<tr>
<td>A</td>
<td>US 5 252 574 A (ALLEN E E ET AL) 12 October 1993 (1993-10-12) cited in the application * the whole document, particularly columns 113-116, table V *</td>
<td>1</td>
</tr>
</tbody>
</table>

X Further documents are listed in the continuation of box C. X Patent family members are listed in 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
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

*T* later document published after the international filing date or priority data 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

*Z* document member of the same patent family

Date of the actual completion of the international search
1 April 2004

Date of mailing of the international search report
13/04/2004

Name and mailing address of the ISA
European Patent Office, P.B. 5816 Patentiffian 2 NL - 3330 HU Driebergen
Tel. (+31-70) 340-2040, Tx. 31 651 xpo nl
Fax: (+31-70) 340-3016

Form PCT/ISA/210 (second sheet) (January 2004)

Authorized officer
Allard, M

page 1 of 2
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 92 20662 A (MERCK &amp; CO., INC.) 26 November 1992 (1992-11-26) cited in the application the whole document</td>
<td>1</td>
</tr>
</tbody>
</table>
# INTERNATIONAL SEARCH REPORT

**Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claim 33 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DE 19961686 A1</td>
<td>28-06-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 4753600 A</td>
<td>21-11-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0010248 A</td>
<td>13-02-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2373010 A1</td>
<td>16-11-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1349530 T</td>
<td>15-05-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CZ 20013907 A3</td>
<td>13-02-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 200100572 A</td>
<td>17-02-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 0068226 A1</td>
<td>16-11-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1185527 A1</td>
<td>13-03-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 20010814 A1</td>
<td>28-02-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0201311 A2</td>
<td>28-10-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2002544130 T</td>
<td>24-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 20015309 A</td>
<td>28-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 515242 A</td>
<td>28-11-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 351609 A1</td>
<td>05-05-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SK 15942001 A3</td>
<td>04-04-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TR 200103171 T2</td>
<td>21-06-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2002077344 A1</td>
<td>20-06-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6235766 B1</td>
<td>22-05-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2001018449 A1</td>
<td>30-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200108801 A</td>
<td>22-08-2002</td>
</tr>
</tbody>
</table>

|                                       |                  | DE 20020782 U1          | 22-02-2001       |
|                                       |                  | WO 0207569 A1           | 31-01-2002       |
|                                       |                  | EP 1304946 A1           | 02-05-2003       |

|                                       |                  | JP 1999257 C            | 08-12-1995       |
|                                       |                  | JP 5194500 A            | 03-08-1993       |
|                                       |                  | JP 7017636 B            | 01-03-1995       |

|                                       |                  | EP 0586513 A1           | 16-03-1994       |
|                                       |                  | JP 3290657 B2           | 10-06-2002       |
|                                       |                  | JP 6507642 T            | 01-09-1994       |
|                                       |                  | WO 9220662 A1           | 26-11-1992       |
|                                       |                  | US 5436259 A            | 25-07-1995       |
|                                       |                  | US 5281614 A            | 25-01-1994       |