Abstract:

Title: N-OXIDE-CONTAINING PHARMACEUTICAL COMPOUNDS

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 November 2008 (20.11.2008)

(10) International Publication Number
WO 2008/139152 A1

(51) International Patent Classification:
C07C 291/04 (2006.01)
C07C 311/32 (2006.01)
C07D 401/12 (2006.01)
C07D 403/14 (2006.01)
C07D 417/14 (2006.01)

(21) International Application Number:
PCT/GB2008/001595

(22) International Filing Date: 09 May 2008 (09.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0709150.7 11 May 2007 (11.05.2007) GB
0724379.3 13 December 2007 (13.12.2007) GB

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(54) Title: N-OXIDE-CONTAINING PHARMACEUTICAL COMPOUNDS

(57) Abstract: The invention provides a method of preparing a therapeutically active compound having reduced hERG activity, which method comprises: (a) selecting a non-N-oxide drug compound containing a basic tertiary amino group, wherein said non-N-oxide compound is known to have or is suspected of having a therapeutically unacceptable level of hERG inhibitory activity; (b) testing the non-N-oxide drug compound for hERG inhibitory activity; (c) reacting the non-N-oxide drug compound with an oxidising agent to form an N-oxide drug compound having an N-oxide at the basic tertiary amino group; (d) testing the N-oxide drug compound for hERG inhibitory activity; (e) testing the N-oxide drug compound for therapeutically useful activity; (f) comparing the hERG inhibitory activity of the N-oxide drug compound and non-N-oxide drug compound; and (g) when the N-oxide drug compound has therapeutically useful activity and has hERG activity which is at least ten fold less than the hERG inhibitory activity of the non-N-oxide drug compound, formulating the N-oxide drug compound for use in medicine. Also provided by the invention are novel compounds prepared by the aforementioned method and the use of the novel compounds in medicine.
N-OXIDE-CONTAINING PHARMACEUTICAL COMPOUNDS

This invention relates to therapeutically useful compounds having reduced hERG affinity and to methods for diminishing HERG affinity. More particularly, the invention provides compounds that have been modified in order to remove unwanted hERG potassium channel activity while at the same time, retaining their desired pharmacological activity.

Background


The unwanted binding of pharmacological agents and drugs to the hERG channel can cause prolongation of the cardiac action potential between the Q and T phases (QT prolongation) and this has been cause for concern within the pharmaceutical industry for many years (B Fermini & A Fossa, Pre-clinical assessment of drug-induced QT prolongation. Current issues and impact on drug discovery, Annual reports in Medicinal Chemistry vol. 39, 323-334, 2004).

The initial phase of depolarization in cardiac muscle tissue (phase 0) is mediated primarily by the activation of voltage-dependent Na+ channels. Na+ channel activity is also the main determinant of ventricular depolarization as represented by the QRS wave of the ECG. The shape of the remainder of the action potential, including the initial repolarization phase (phase 1), the plateau phase (phase 2), and the later phases of repolarization (phases 3 and 4), results from the flow of Ca2+ into the cell through voltage-dependent Ca2+ channels, balanced by the efflux of K+ out of the cell through voltage-dependent K+ channels. The activity of these channels also helps to determine the QT interval measured on the ECG. Several K+ channels exist in the
human ventricular myocardium each carrying a distinct K+ current (/). The HERG K+ channel carries the delayed rectifier current known as /Kr. Inhibition of HERG channel activity can lead to a prolongation of the action potential duration and the QT interval.

Many drugs have either been withdrawn or carry "black box" warnings due to unwanted hERG activity and many deaths have been attributed to QT prolongation leading to the fatal arrhythmia, Torsades du Pointes in patients receiving these drugs.

Examples of compounds that have either been removed from the market or are known to be associated with a significant risk of Torsades du Pointes are set out in Table 1 below.

Table 1

<table>
<thead>
<tr>
<th>Structure</th>
<th>Generic Name</th>
<th>Class/Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Amiodarone</td>
<td>Anti-arrhythmic</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Bepridil</td>
<td>Anti-anginal</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>Chloroquine</td>
<td>Anti-malarial</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>Cisapride</td>
<td>GI stimulant</td>
</tr>
</tbody>
</table>
Disopyramide Anti-arrhythmic

Dofetilide Anti-arrhythmic

Domperidone Anti-nausea Sedative; Anti-nausea

Droperidol Sedative; Anti-nausea

Halofantrine Anti-malarial

Haloperidol Anti-psychotic
lbutilide Anti-arrhythmic
Levomethadyl Opiate agonist
Mesoridazine Anti-psychotic
Methadone Opiate agonist
Pimozide Anti-psychotic
Procainamide Anti-arrhythmic
The separation of hERG blocking activity and therapeutically useful effects such as kinase inhibition, GPCR agonism or antagonism and therapeutically useful ion channel blockade is currently considered to be of substantial importance in the development of any new drug. Typically there should be at least a tenfold difference between the level of activity against the therapeutic target and the level of hERG blocking activity for a particular compound to be considered worthy of further development as a drug candidate.


A structural feature common to the majority of the drug compounds listed in Table 1 is the presence of a basic tertiary amino group of the formula:

\[
\text{CH}_2\text{N}^+\text{CH}_2\text{r}^2\text{CH}_2\text{r}\text{CH}_2\text{r}^2
\]

and it is believed that this structural fragment may be involved in binding to the hERG channel and hence may be at least partially responsible for the deleterious hERG activity.
Summary of the invention

An object of the present invention is to provide a means for the removal of hERG activity in compounds which have been shown to bind at the hERG ion channel whilst not eliminating or reducing substantially the pharmacological activity of the compound..

As indicated above, many compounds bearing a basic nitrogen functionality have been found to have unacceptable safety profiles due to their ability to block the hERG potassium channel and thus prolong the QT interval in humans and animals. It has now been found that by forming an N-oxide with the basic amine functional group on such molecules, the hERG activity is dramatically reduced whilst potency against the intended pharmacological target is maintained.

Accordingly, in a first aspect, the invention provides a method of modifying a drug compound known to have deleterious hERG activity, wherein the drug compound contains a basic tertiary amino group; which method comprises reacting the drug compound with an oxidising agent to form an N-oxide at the said basic tertiary amino group so as to give an N-oxide drug compound, whereby the N-oxide drug compound has reduced hERG activity relative to its parent non-N-oxide drug compound.

Preferably, the N-oxide drug compound has a hERG inhibitory activity which is at least ten fold less than the hERG inhibitory activity of the non-N-oxide drug compound, and more preferably is at least twenty fold less active, and most preferably is at least thirty fold less active than the non-N-oxide drug compound.

In another aspect, the invention provides a method of preparing a therapeutically active compound having reduced hERG activity, which method comprises:

(a) selecting a non-N-oxide drug compound containing a basic tertiary amino group, wherein said non-N-oxide compound is known to have or is suspected of having a therapeutically unacceptable level of hERG inhibitory activity;
(b) testing the non-N-oxide drug compound for hERG inhibitory activity;
(c) reacting the non-N-oxide drug compound with an oxidising agent to form an N-oxide drug compound having an N-oxide at the basic tertiary amino group;
(d) testing the N-oxide drug compound for hERG inhibitory activity;
(e) testing the N-oxide drug compound for therapeutically useful activity;
(f) comparing the hERG inhibitory activity of the N-oxide drug compound and non-N-oxide drug compound; and

(g) when the N-oxide drug compound has therapeutically useful activity and has hERG activity which is at least ten fold less than the hERG inhibitory activity of the non-N-oxide drug compound, formulating the N-oxide drug compound for use in medicine.

In a further aspect, the invention provides a method of preparing a therapeutically active compound having reduced hERG activity, which method comprises:

(a) selecting a non-N-oxide compound containing a basic tertiary amino group, wherein said non-N-oxide compound is known to have or is suspected of having a therapeutically unacceptable level of hERG inhibitory activity;

(b) testing the non-N-oxide compound for hERG inhibitory activity;

(c) reacting the non-N-oxide compound with an oxidising agent to form an N-oxide compound having an N-oxide at the basic tertiary amino group;

(d) testing the N-oxide compound for hERG inhibitory activity;

(e) testing the N-oxide compound for therapeutically useful activity;

(f) comparing the hERG inhibitory activity of the N-oxide compound and non-N-oxide compound; and

(g) when the N-oxide compound has therapeutically useful activity and has hERG activity which is at least ten fold less than the hERG inhibitory activity of the non-N-oxide compound, formulating the N-oxide compound for use in medicine.

In each of the above aspects of the invention, it will be appreciated that the steps (a) to (g) do not necessarily need to be carried out in the order (a) to (g) and the order of the steps may be varied.

The nitrogen atom of the basic tertiary amino group does not form part of an aromatic ring; i.e. the N-oxide is not formed at a nitrogen atom of a heteroaryl group such as a pyridine, pyrimidine or pyrazine ring. However, the nitrogen atom can form part of a cyclic non-aromatic amine group such as the nitrogen atom in an N-substituted pyrrolidine or piperidine group. Alternatively, the basic tertiary amino group can form part of an acyclic amine function.
The basic tertiary amino group is preferably a non-aromatic amino group; i.e. it is not attached to an aromatic ring (e.g. as in the case of an aniline or aminopyridine).

The term "drug compound" (e.g. as used *perse* or as part of the term "N-oxide drug compound") refers to a compound that has a therapeutic use. The term does not cover compounds that have no therapeutic use. The therapeutic use may be any one of a wide range of uses, and examples include antibiotic, anti-arrhythmic, anti-nausea, anti-psychotic, anti-malarial, anti-anginal and anti-cancer uses. The therapeutic use may be one which has been demonstrated through clinical studies in patients or one which is predictable on the basis of *in vivo* studies carried out in animals, or studies comprising cell based assays or *in vitro* assays for activity against a biological target such as an enzyme or a receptor.

The term "therapeutically active compound" as used herein refers to a compound that has an actual or potential therapeutic use and which displays biological activity that either demonstrates a therapeutic use or is indicative of a therapeutic use. The biological activity can be activity which has been demonstrated through clinical studies in patients or can be activity in one or more *in vivo* or *in vitro* assays that is predictive of therapeutic utility. For example, the therapeutically active compound may act as a modulator (e.g. inhibitor) of an enzyme such as a kinase or may act as an agonist or antagonist at a receptor, where such modulatory or agonist or antagonist activity is indicative of a therapeutic use.

The therapeutic use or biological activity of the N-oxide drug compound or therapeutically active compound may be of the same type as the therapeutic use or biological activity of the non-N-oxide compound, or the N-oxide compound may have a different therapeutic use or biological activity to the non-N-oxide compound.

The N-oxide drug compound or therapeutically active compound typically contains the structural fragment A:

![Structural Fragment A]

\[ \text{(A)} \]
wherein the asterisks indicate points of attachment either to a hydrogen atom or an organic residue.

It is preferred that the nitrogen atom of the N-oxide is attached to three methylene (CH₂) groups and hence a preferred structural fragment is fragment (B):

\[
\begin{align*}
&\text{I} \\
&\text{CH}_2 \\
&\text{*-CH—} \\
&\text{N-CHj-*} \\
&\text{°} \\
\end{align*}
\]

(B)

In a more preferred embodiment, the N-oxide drug compound or therapeutically active compound contains the structural fragment (C):

\[
\begin{align*}
&\text{I} \\
&\text{CH}_2 \\
&\text{*-CH—} \\
&\text{N—-CH}_2(\text{CH}_2)_n-* \\
&\text{O} \\
\end{align*}
\]

where \( n \) is 1, 2 or 3.

In a further aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an N-oxide drug compound or therapeutically active compound containing structural fragment (A), (B) or (C) as defined herein.

In each of the embodiments and aspects of the invention as hereinbefore defined and as set out below and in the claims, the N-oxide drug compound or therapeutically active compound may be other than:

- \( \{2-[4-(1,2-diphenyl-but-1-enyl)-phenoxy]-ethyl\text{-dimethyl-amine} \) N-oxide;
- clozapine N-oxide;
- amitriptyline N-oxide; and
- scopolamine N-oxide.

The drug compound or therapeutically active compound may also be other than a compound as disclosed in our earlier applications GB 061 1565.3 and PCT/GB2007/002123, the contents of each of which are incorporated herein by reference.
Thus, the N-oxide drug compound or therapeutically active compound may be other than a compound of formula \( W_1^\text{NH-C(O)-NH-W}_2^\text{ where } W_1^\text{ and } W_2^\text{ are the same or different and each is an optionally substituted aryl or optionally substituted heteroaryl group.}

The N-oxide drug compound or therapeutically active compound may be other than a compound of the formula (X):

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{X}_1^1 & \quad \text{N} \\
\text{X}_2^1 & \quad \text{X}_3^1 \\
\text{G} & \quad \text{A}_N^+ \\
\text{R}_3^R & \quad \text{O}^- \\
\text{X}_4^3 & \quad \text{X}_5^4
\end{align*}
\]

or a salt, solvate or tautomer thereof, wherein:

- \( G \) is \( \text{CH}_2, \text{O}, \text{NH}, \text{NHCO} \) or \( \text{CONH} \);
- \( A \) is a group \((\text{CH}_2)_n\), where \( n \) is 1 to 4 provided that when \( G \) is \( \text{O} \) or \( \text{NH} \), \( n \) is at least 2;
- \( X_1^1 \) is nitrogen or \( \text{CH} \);
- \( X_2^2 \) is nitrogen or a group \( \text{CR}_5 \);
- \( X_3^3 \) is nitrogen or a group \( \text{CR}_5 \);
- \( X_4^4 \) is nitrogen or \( \text{CH} \); provided that no more than two of \( X_2^2, X_3^3 \) and \( X_4^4 \) are nitrogen;
- \( R_1^R \) is hydrogen, cyano, \( \text{C}_{1-4} \) alkyl, trifluoromethyl or a 5-6 membered monocyclic aryl or heteroaryl group containing up to 3 heteroatom ring members selected from \( \text{O}, \text{N} \) and \( \text{S} \) and being optionally substituted by one or two \( \text{C}_{1-4} \) alkyl groups;
- \( R_2^R \) is hydrogen, cyano, \( \text{C}_{1-4} \) alkyl, trifluoromethyl or a 5-6 membered monocyclic aryl or heteroaryl group containing up to 3 heteroatom ring members selected from \( \text{O}, \text{N} \) and \( \text{S} \) and being optionally substituted by one or two \( \text{C}_{1-4} \) alkyl groups; provided that no more than one of \( R_1^R \) and \( R_2^R \) can be an aryl or heteroaryl group;
or \( R_1^R \) and \( R_2^R \) together with the carbon atoms to which they are attached form a benzene ring;
R₃ and R₄ are the same or different and each is C₁₋₄ alkyl; or R₃ and R₄ together with the nitrogen atom to which they are attached form an azetidine, pyrrolidine, piperidine, piperazine, M-methylpiperazine or morpholine group; or R₃ together with the nitrogen atom to which it is attached and the moiety A together form a saturated 5 to 7 membered heterocyclic ring optionally containing a second heteroatom ring member selected from O and S, wherein the heterocyclic ring is optionally substituted by 1 to 4 methyl groups, and R₄ is C₁₋₄ alkyl;

R⁵ is hydrogen or a substituent R⁶;
R⁶ is halogen; hydroxy; trifluoromethyl; cyano; nitro; amino; mono- or di-C₁₋₄ hydrocarbylamino; a carbocyclic or heterocyclic group having from 3 to 12 ring members and optionally substituted by one or more substituents R⁷; or a group Rᵇ=NRᶜ;
Rᵇ is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹, S, SO, SO₂, NR, SO₂NRᶜ or NR²SO₂;
R⁸ is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members and being optionally substituted by one or more substituents R⁷;
- a C₁₋₁₂ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di-C₁₋₄ non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members optionally substituted by one or more substituents R⁷; wherein one or more carbon atoms of the C₁₋₁₂ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR⁰, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹;

R⁶ is R⁰, hydrogen or C₁₋₄ hydrocarbyl;
X¹ is O, S or NR⁰; and
X² is =O, =S or =NR⁰;

wherein R⁷ is selected from R⁶ provided that when the substituents R⁷ contain a carbocyclic or heterocyclic group having from 3 to 12 ring members, the said carbocyclic or heterocyclic group can be unsubstituted or substituted by one or more substituents R⁸; and
R⁸ is selected from R⁶ except that any carbocyclic or heterocyclic groups constituting or forming part of R⁸ may not bear a substituent containing or consisting of a carbocyclic or heterocyclic group but may optionally bear one or more substituents selected from halogen; hydroxy; trifluoromethyl; cyano; nitro; amino; mono- or di-C₁₋₄...
hydrocarbylamino; or a group $R^a-R^b$; where $R^a$ is as hereinbefore defined and $R^b$ is hydrogen or a $C_{1-6}$ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-$C_{1-4}$ saturated hydrocarbylamino and wherein one or more carbon atoms of the

$C_{1-6}$ hydrocarbyl group may optionally be replaced by $O$, $S$, $SO$, $SO_2$, $NR^C$, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$.

The compound (or N-oxide drug compound) may also be other than a compound selected from:

- 4-amino-5-chloro-$N$-{(3R,4S)-1-[3-(4-fluoro-phenoxy)-propyl]-3-methoxy-1-oxy-piperidin-4-yl}-2-methoxy-benzamide;
- 4-[4-(4-chloro-phenyl)-4-hydroxy-1-oxy-piperidin-1-yl]-1-(4-fluoro-phenyl)-butan-1-one;
- 1-{1-[4,4-bis-(4-fluoro-phenyl)-butyl]-1-oxy-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;
- 1-(4-tert-butyl-phenyl)-4-[4-(hydroxy-diphenyl-methyl)-1-oxy-piperidin-1-yl]-butan-1-ol;

and

- 2-(3,4-dimethoxy-phenyl)-5-[(2-(3,4-dimethoxy-phenyl)-ethyl]-oxy-methyl-amino]-2-isopropyl-pentanenitrile.

In another aspect, the invention provides a compound of the formula (1):

$$
\begin{align*}
\text{Ar}^1 & \\
R^1 & \\
\text{Ar}^2 & \\
\text{R}^3 & \\
\text{Q}^1 & \\
\text{Q}^2 & \\
\text{N} & \\
\text{O} & \\
\text{(CH}_2\text{n)} & \\
\text{Q}^2 & \\
\text{Ar}^2 & \\
\end{align*}
$$

or a salt, solvate or tautomer thereof, wherein:

- $n$ is 2 or 3;
- $R^1$ is hydrogen, hydroxy, $C_{1-4}$ alkoxy or together with $R^2$ forms a second bond between the two carbon atoms marked “q”;
- $R^2$ is hydrogen, hydroxy, $C_{1-4}$ alkoxy or together with $R^1$ forms a second bond between the two carbon atoms marked “q”;
- $Q^1$ is a bond, $NR^3$ or $C(O)NR^3$ or $NR^3CO$;
- $R^3$ is hydrogen or $C_{1-4}$ alkyl;
Ar\textsuperscript{1} is a monocyclic or bicyclic aryl or heteroaryl group of 5 to 10 ring members of which up to four ring members are heteroatoms selected from O, N and S, the monocyclic or bicyclic aryl or heteroaryl group being optionally substituted by one or more substituents selected from a group R\textsuperscript{10} consisting of halogen, hydroxy, amino, mono-or di- C\textsubscript{1-4} alkylamino, C\textsubscript{1-4} acylamino, C\textsubscript{1-4} alkoxy, oxo, trifluoromethyl, difluoromethoxy, cyano, phenyl, benzyl, benzoyl, halobenzyl, halobenzoyl, C\textsubscript{1-4} alkylsulphonyl, C\textsubscript{1-4} alkylsulphinyl, C\textsubscript{1-4} alkysulphanyl, alkylsulphonylamino, C\textsubscript{1-4} acyl, C\textsubscript{1-4} alkoxycarbonyl, and carboxy; 

Q\textsuperscript{2} is a bond, O, S, SO, SO\textsubscript{2}, NR\textsuperscript{3}, CO or CH(Ar\textsuperscript{3});

Ar\textsuperscript{2} is a monocyclic or bicyclic aryl or heteroaryl group of 5 to 10 ring members of which up to four ring members are heteroatoms selected from O, N and S, the monocyclic or bicyclic aryl or heteroaryl group being optionally substituted by one or more substituents R\textsuperscript{10}; and

Ar\textsuperscript{3} is a monocyclic aryl or heteroaryl group of 5 or 6 ring members of which up to two ring members are heteroatoms selected from O, N and S, the aryl or heteroaryl group being optionally substituted by one or more substituents R\textsuperscript{10}.

In formula (1), Ar\textsuperscript{1} is an optionally substituted monocyclic or bicyclic aryl or heteroaryl group of 5 to 10 ring members of which up to four ring members are heteroatoms selected from O, N and S. Preferably up to two ring members are heteroatoms selected from O, N and S. More Preferably, Ar\textsuperscript{1} is an optionally substituted phenyl group or an optionally substituted benzimidazole or 1,3-dihydrobenzimidazol-2-one group.

The optional substituents for Ar\textsuperscript{1} are preferably selected from a group R\textsuperscript{10a} consisting of fluorine, chlorine, bromine, methoxy, amino, fluoro benzyl (e.g. 4-fluorobenzyl), mono-or di-methylamino, acetylamino, oxo, trifluoromethyl, difluoromethoxy, cyano, methylsulphonyl, acetyl, methoxycarbonyl and ethoxycarbonyl.

More preferably, the optional substituents for Ar\textsuperscript{1} are preferably selected from a group R\textsuperscript{10b} consisting of chlorine, methoxy, amino, fluoro benzyl (e.g. 4-fluorobenzyl) and oxo.

The moiety R\textsuperscript{1} is hydrogen, hydroxy, C\textsubscript{1-4} alkoxy or together with R\textsuperscript{2} forms a second bond between the two carbon atoms marked "q". More preferably, R\textsuperscript{1} is hydrogen, hydroxy, or together with R\textsuperscript{2} forms a second bond between the two carbon atoms marked "q".
In one embodiment, R\textsubscript{1} is hydrogen.

In another embodiment, R\textsubscript{1} is hydroxy.

In a further embodiment, R\textsubscript{1} together with R\textsubscript{2} forms a second bond between the two carbon atoms marked "q".

The moiety R\textsubscript{2} is hydrogen, hydroxy, C\textsubscript{i-4} alkoxy or together with R\textsubscript{1} forms a second bond between the two carbon atoms marked "q". More preferably, R\textsubscript{2} is hydrogen, methoxy or together with R\textsubscript{1} forms a second bond between the two carbon atoms marked "q".

In one embodiment, R\textsubscript{2} is hydrogen.

In another embodiment, R\textsubscript{2} is methoxy.

The moiety Q\textsubscript{1} is a bond, NR\textsubscript{3}, C(O)NR\textsubscript{3} or NR\textsubscript{3}CO.

More preferably, Q\textsubscript{1} is a bond, NH, C(O)NH or NHCO.

In one embodiment, Q\textsubscript{1} is a bond.

In another embodiment, Q\textsubscript{1} is NH.

In another embodiment, Q\textsubscript{1} is C(O)NH.

In another embodiment, Q\textsubscript{1} is NHCO.

The group (CH\textsubscript{2})\textsubscript{n} can be either an ethylene group (n=2) or a propylene group (n=3).

In one embodiment, n is 2.

In another embodiment, n is 3.

The moiety Q\textsubscript{2} is a bond, O, S, SO, SO\textsubscript{2}, NR\textsubscript{3}, CO or CH(Ar\textsubscript{3}).

More preferably, Q\textsubscript{2} is a bond, O, CO or CH(Ar\textsubscript{3}).

In one embodiment, Q\textsubscript{2} is a bond.

In another embodiment, Q\textsubscript{2} is O.
In another embodiment, $Q^2$ is CO.

In a further embodiment, $Q^2$ is CH(Ar$^3$).

Ar$^3$ is a monocyclic aryl or heteroaryl group of 5 or 6 ring members of which up to two ring members are heteroatoms selected from O, N and S, the aryl or heteroaryl group being optionally substituted by one or more substituents $R^{10}$.

More preferably, Ar$^3$ is a phenyl group optionally substituted by one to three (e.g. 0, 1 or 2) substituents $R^{10}$.

In one embodiment, Ar$^3$ is a phenyl group substituted by one or two halogen atoms selected from fluorine and chlorine.

Ar$^2$ is a monocyclic or bicyclic aryl or heteroaryl group of 5 to 10 ring members of which up to four ring members are heteroatoms selected from O, N and S, the monocyclic or bicyclic aryl or heteroaryl group being optionally substituted by one or more substituents $R^{10}$.

Preferably, Ar$^2$ is a monocyclic aryl or heteroaryl group of 5 or 6 ring members of which up to two (and more preferably up to one) ring members are heteroatoms selected from O, N and S, or a bicyclic heteroaryl group of 9 ring members of which one or two ring members are nitrogen atoms, the monocyclic and bicyclic groups being optionally substituted by one or more substituents $R^{10}$.

More preferably, Ar$^2$ is a phenyl group or a benzimidazolyl or 1,3-dihydrobenzimidazol-2-one group optionally substituted by one or more substituents $R^{10c}$ wherein $R^{10c}$ is selected from fluorine, chlorine, bromine, methoxy, amino, fluorobenzyl (e.g. 4-fluorobenzyl), mono- or di-methylamino, acetylamino, oxo, trifluoromethyl, difluoromethoxy, cyano, methylsulphonyl, methylsulphonlamino, acetyl, methoxycarbonyl and ethoxycarbonyl.

In one embodiment, Ar$^2$ is a phenyl group optionally substituted by one to three substituents $R^{10d}$ selected from fluorine, chlorine, amino and methoxy.

In another embodiment, Ar$^2$ is a 1,3-dihydrobenzimidazol-2-one group group.

The compound of formula (1) may be other than;
4-amino-5-chloro-N-{(3R,4S)-1-[3-(4-fluoro-phenoxy)-propyl]-3-methoxy-1-oxy-piperidin-4-yl}-2-methoxy-benzamide; and
4-[4-(4-chloro-phenyl)-4-hydroxy-1-oxy-piperidin-1-yl]-1-(4-fluoro-phenyl)-butan-1-one;
1-{[4,4-bis-(4-fluoro-phenyl)-butyl]-1-oxy-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one.

The invention also provides a compound of the formula (2):

\[
\begin{align*}
\text{R}^4 & \quad \text{R}^5 \\
\text{R}^6 & \quad \text{R}^7 \\
\text{R}^8 & \quad \text{R}^9 \\
\end{align*}
\]

or a salt, solvate or tautomer thereof, wherein;

R^4 is hydrogen or methyl;
R^5 is hydrogen or methyl;
R^6 is hydrogen, methyl or C\text{1-4} alkoxyethyl;
or R^4 together with R^5 and the intervening nitrogen and carbon atoms forms a pyrrolidine or piperidine ring;
or R^5 together with R^6 and the intervening nitrogen and carbon atoms forms a piperidine ring;
R^7 is hydrogen, C\text{1-8} alkyl, or an optionally substituted benzyl group wherein the optional substituents for the benzyl group are selected from a group R^{10} consisting of halogen, hydroxy, amino, mono-or di- C\text{1-4} alkylamino, C\text{1-4} acylamino, C\text{1-4} alkoxy, oxo, trifluoromethyl, difluoromethoxy, cyano, phenyl, benzyl, benzoyl, halobenzyl, halobenzoyl, C\text{1-4} alkylsulphonyl, C\text{1-4} alkylsulphinyl, C\text{1-4} alkylsulphanyl, alkylsulphonlamino, C\text{1-4} acyl, C\text{1-4} alkoxy carbonyl, and carboxy;
R^8 is hydrogen or C\text{1-4} alkyl;
or the moiety

\[
\begin{align*}
\text{R}^4 & \quad \text{R}^5 \\
\text{R}^6 & \quad \text{R}^7 \\
\text{R}^8 & \quad \text{R}^9 \\
\end{align*}
\]

forms a group:

R^9 is hydrogen, hydroxy or C\text{1-4} alkyl;
Q³ is a bond, O or CH₂ or is selected from:
- CH(OH);
- CH₂CH(OH);
- HNC(O);
- C(O)NH;
- CH₂CH(CH₃)NH;
- C(CONH₂)(phenyl) wherein the phenyl group is optionally substituted with 1 to 3 substituents R¹⁰;
- C(1-acetoxy propyl)(phenyl) wherein the phenyl group is optionally substituted with 1 to 3 substituents R¹⁰;
- N(R¹¹) where R¹¹ is hydrogen, C₁₋₄ alkyl or a benzyl group wherein the aromatic ring of the benzyl group is optionally substituted with 1 to 3 substituents R¹⁰;

q is O or 1 provided that when q is o, Q³ is other than O; and

Ar⁴ is selected from:
- quinoliny (e.g. 4-quinoliny) optionally substituted with 1 to 3 substituents R¹⁰;
- pyridyl optionally substituted with 1 to 3 substituents R¹⁰;
- phenothiaziny (e.g. 10-phenothiaziny) optionally substituted with 1 to 3 substituents R¹⁰;
- phenanthrenyl optionally substituted with 1 to 3 substituents R¹⁰;
- phenyl optionally substituted with 1 to 3 substituents R¹⁰;
- phenyl substituted with R¹₂ and optionally with Oto 2 further substituents R¹⁰;
- indolyl (e.g. 1-indolyl) substituted by a group R¹³; and
- pyridyl (e.g. 4-pyridyl) substituted by a group R¹⁴;

R¹² is a group:

![Diagram](image1.png)

wherein the asterisk indicates the point of attachment to the phenyl ring; and

R¹³ is a group:

![Diagram](image2.png)
wherein the asterisk indicates the point of attachment to the indolyl ring, e.g. the 3-position of the indolyl ring; and

R\textsuperscript{14} is a group:

\begin{center}
\includegraphics[width=0.8\textwidth]{indolyl_attachment.png}
\end{center}

wherein the asterisk indicates the point of attachment to the pyridyl ring, e.g. the 3-position of the pyridyl ring; Q\textsuperscript{1} is O or S and R\textsuperscript{15} is phenyl or cyano.

In one embodiment, R\textsuperscript{14} is a group:

\begin{center}
\includegraphics[width=0.8\textwidth]{pyridyl_attachment.png}
\end{center}

In one sub-group of compounds within formula (2), R\textsuperscript{4} is hydrogen or methyl; R\textsuperscript{5} is hydrogen or methyl; and R\textsuperscript{6} is hydrogen, methyl or C\textsubscript{14} alkoxyethyl.

More preferably, R\textsuperscript{6} is hydrogen, methyl or 2-methylpropyloxyethyl.

In one embodiment, R\textsuperscript{6} is hydrogen.

In another embodiment, R\textsuperscript{6} is methyl.

In one embodiment, R\textsuperscript{6} is 2-methylpropyloxyethyl.

In another sub-group of compounds within formula (2), R\textsuperscript{4} together with R\textsuperscript{5} and the intervening nitrogen and carbon atoms forms a pyrrolidine or piperidine ring.

In one embodiment, R\textsuperscript{4} together with R\textsuperscript{5} and the intervening nitrogen and carbon atoms forms a pyrrolidine ring.

In a further sub-group of compounds within formula (2), R\textsuperscript{5} together with R\textsuperscript{6} and the intervening nitrogen and carbon atoms forms a piperidine ring.
In another sub-group of compounds within formula (2), the moiety

\[ \text{forms a group:} \]

The moiety \( R^7 \) is hydrogen, \( C_{1-8} \) alkyl, or an optionally substituted benzyl group wherein the optional substituents for the benzyl group are selected from a group \( R^{10} \).

In one embodiment, \( R^7 \) is hydrogen or \( C_{1-8} \) alkyl.

In another embodiment, moiety \( R^7 \) an optionally substituted benzyl group wherein the optional substituents for the benzyl group are selected from a group \( R^{10} \).

The optional substituents for the benzyl group are more typically selected from a group \( R^{10c} \) as hereinbefore defined. More preferably, the benzyl group is substituted by a methylsulphonylamino group, for example at the 4-position of the benzene ring thereof.

\( R^8 \) is hydrogen or \( C_{1-4} \) alkyl. In one embodiment, \( R^8 \) is hydrogen. In another embodiment, \( R^8 \) is \( C_{1-4} \) alkyl such as methyl.

In the moiety \((CHR^9)_q\), \( q \) can be 0 or 1. In one embodiment, \( q \) is 1. In another embodiment, \( q \) is 0.

The moiety \( R^9 \) is hydrogen, hydroxy or \( C_{1-4} \) alkyl.

In one embodiment, \( R^9 \) is hydrogen.

In another embodiment, \( R^9 \) is hydroxy.

In a further embodiment, \( R^9 \) is \( C_{1-4} \) alkyl, e.g. methyl.

Further sub-groups of formula (2) are those wherein:

- \( Q^3 \) is a bond.
- \( Q^3 \) is O.
- \( Q^3 \) is \( CH_2 \).
- $Q^3$ is CH(OH).
- $Q^3$ is CH$_2$CH(OH).
- $Q^3$ is HNC(O).
- $Q^3$ is CO(NH).
- $Q^3$ is C(H$_2$CH(CH$_3$)NH.
- $Q^3$ is C(1-acetoxypropyl)(phenyl) wherein the phenyl group is optionally substituted with 1 to 3 substituents R$^{10}$.
- $Q^3$ is C(CONH$_2$)(phenyl) wherein the phenyl group is optionally substituted with 1 to 3 substituents R$^{10}$.
- $Q^3$ is N(R$^{11}$) where R$^{11}$ is hydrogen, C$_{1-4}$ alkyl or a benzyl group wherein the aromatic ring of the benzyl group is optionally substituted with 1 to 3 substituents R$^{10}$.

When $Q^3$ is C(CONH$_2$)(phenyl), it may be represented by the formula:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{C} & \\
\text{ phenyl} & \quad \text{(R$^{10}$)}_p
\end{align*}
\]

wherein p is 0, 1, 2 or 3.

The substituents R$^{10}$ may be selected from any of the groups R$^{10a}$, R$^{10b}$ and R$^{10c}$ as defined herein. In one embodiment, however, p is 0; i.e. the phenyl ring is unsubstituted.

When $Q^3$ is C(1-acetoxypropyl)(phenyl), it may be represented by the formula:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{C} & \\
\text{ phenyl} & \quad \text{(R$^{10}$)}_r
\end{align*}
\]

wherein r is 0, 1, 2 or 3.

The substituents R$^{10}$ may be selected from any of the groups R$^{10a}$, R$^{10b}$ and R$^{10c}$ as defined herein. In one embodiment, however, r is 0; i.e. the phenyl ring is unsubstituted.
When $Q^3$ is $N(R^{11})$, $R^{11}$ is hydrogen, C$_{1-4}$ alkyl or a benzyl group wherein the aromatic ring of the benzyl group is optionally substituted with 1 to 3 substituents $R^{10}$.

Preferably, $R^{11}$ is hydrogen, or a benzyl group wherein the aromatic ring of the benzyl group is optionally substituted with 1 to 3 substituents $R^{10}$, $R^{10a}$, $R^{10b}$ and $R^{10c}$ as defined herein. In one embodiment, $R^{11}$ is hydrogen. In another embodiment, $R^{11}$ is an unsubstituted benzyl group.

Further sub-groups of formula (2) are those wherein:

- $Ar^4$ is quinolinyl (e.g. 4-quinolinyl) optionally substituted with 1 to 3 substituents $R^{10}$.
- $Ar^4$ is pyridyl optionally substituted with 1 to 3 substituents $R^{10}$.
- $Ar^4$ is phenothiazinyl (e.g. 10-phenothiazinyl) optionally substituted with 1 to 3 substituents $R^{10}$.
- $Ar^4$ is phenanthrenyl optionally substituted with 1 to 3 substituents $R^{10}$.
- $Ar^4$ is phenyl optionally substituted with 1 to 3 substituents $R^{10}$.
- $Ar^4$ is phenyl substituted with $R^{12}$ and optionally with 0 to 2 further substituents $R^{10}$.
- $Ar^4$ is indolyl (e.g. 1-indolyl) substituted by a group $R^{13}$.
- pyridyl (e.g. 4-pyridyl) substituted by a group $R^{14}$.

When $Ar^4$ is phenyl substituted with $R^{12}$, $R^{12}$ is a group:

![Image of a phenyl group with an asterisk indicating the point of attachment to the phenyl ring.]

wherein the asterisk indicates the point of attachment to the phenyl ring.

When $Ar^4$ is indolyl (e.g. 1-indolyl) substituted by a group $R^{13}$, $R^{13}$ is a group:

![Image of an indolyl group with an asterisk indicating the point of attachment to the indolyl ring.]

wherein the asterisk indicates the point of attachment to the indolyl ring, e.g. the 3-position of the indolyl ring.
When Ar⁴ is pyridyl (e.g. 4-pyridyl) substituted by a group R¹⁴; R¹⁴ is a group:

![Chemical Structure](image)

wherein the asterisk indicates the point of attachment to the pyridyl ring, e.g. the 3-position of the pyridyl ring.

In each of the above sub-groups, the group Ar⁴ is optionally substituted by 1 to 3 substituents R¹⁰.

The substituents R¹⁰ may be as defined above or may be chosen from any of groups R¹⁰a, R¹⁰b and R¹⁰c as defined herein.

One preferred group of substituents R¹⁰ consists of fluorine, chlorine, bromine, iodine, trifluoromethyl, methoxy, methylthio, methylsulphonyl, amino and methylsulphonylamino.

One particular preferred group of compounds within formula (2) may be represented by formula (3):

![Chemical Structure](image)

or salts, solvates or tautomers thereof wherein Q¹ is O or S; R¹⁵ is cyano or phenyl; and R¹⁶ and R¹⁷ are each methyl or NR¹⁶R¹⁷ forms a pyrrolidine or piperidine ring.

One sub-group of compounds within formula (3) can be represented by formula (3A):

![Chemical Structure](image)

or salts, solvates or tautomers thereof.
Particular compounds within formula (3) are compounds 24 to 28 below.

<table>
<thead>
<tr>
<th>Compound 24</th>
<th>Compound 25</th>
<th>Compound 26</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound 27</th>
<th>Compound 28</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Further specific compounds of the invention are set out in Table 2 below.

**Table 2**

<table>
<thead>
<tr>
<th>Compound 1</th>
<th>Compound 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound 4</th>
<th>Compound 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Further examples of compounds of the invention are set out in Table 3 below.

Table 3

<table>
<thead>
<tr>
<th>Compound 10</th>
<th>Compound 11</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Compound 10" /></td>
<td><img src="image2.png" alt="Compound 11" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound 12</th>
<th>Compound 13</th>
<th>Compound 14</th>
<th>Compound 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Compound 12" /></td>
<td><img src="image4.png" alt="Compound 13" /></td>
<td><img src="image5.png" alt="Compound 14" /></td>
<td><img src="image6.png" alt="Compound 15" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound 16</th>
<th>Compound 17</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image7.png" alt="Compound 16" /></td>
<td><img src="image8.png" alt="Compound 17" /></td>
</tr>
</tbody>
</table>
Another compound of the invention is the compound (4):

or a salt, solvate or tautomer thereof.

The various functional groups and substituents making up the compounds of the formulae (1), (2) and (3) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular
weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

In a further aspect, the compound of the invention containing a fragment A, B or C as defined above may be an N-oxide (formed at a non-aromatic basic tertiary amino group) of any one or more compounds selected from acecainide, aceperone, acepromazine, acetophenazine, acranil, adiphenine, ahistan, ajmaline, alfentanil, allylproline, almitrine, alverine, aminopentamide, aminopromazine, amisulpride, amodiaquin, amorolfine, amoxapine, amperozide, anileride, apocodine, apomorphine, aripiprazole, atevirdine, azaperone, azatadine, azelastine, bamifylline, bamipine, barndipine, benactyzine, bencyclane, benidipine, benperidol, benproperine, benzetimide, benzphetamine, benzpiperylon, benzquinamide, benztropine, bepotastine, bepridil, bezitramide, biperiden, biphendrine, bromhexine, bromperidol, buclizine, budipine, buflomedil, buprenorphine, buspirone, butalamine, butamirate, butaperazine, butaverine, butethamate, buzepide, carboxamine, carpipramine, cetirizine, chlorcyclizine, chloropyramine, chlorpheniramime, chlorphenoxyamine, chlorproethazine, chlorpromazine, cinepazide, cinitapride, cinnarizine, citalopram, cloboamide, clobenzepam, clocapramine, clomiphenes, clomipramine, clopenthixol, cloperastine, cloricromen, clospirazine, cyproheptadine, dapiprazole, deoptpine, dextemizine, dibenzepin, diethazine, difloxacin, dihexyverine, diisopromine, dilazep, dimetacrine, dimethasoquin, diphenoxylate, dolasetron, donepezil, dotehepin, dropropizine, emedastine, eprazinone, etafenone, ethopropazine, etidocaine, etodroxizine, etymemazine, fenbutrazate, fexofenadine, fipexide, fluacizine, flunarizine, flupentixol, fluphenazine, flurazepam, fonazine, gallopamil, hexestrol bis(β-diethylaminomethyl ether), homochlorcyclizine, hycanthone, hydroxychloroquine, hydroxyzine, ifenprodil, indoramin, irinotecan, isopromethazine, isothipendyl, ketanserin, ketobemidone, lefetamine, lidocaine, lobeline, lofepramine, lomefloxacine, lomerizine, loperamide, loprazolam, lorcanide, loxapine, lumefantrine, manidipine, mebeverine, mehydroseline, meclizine, melperone, mepazine, mepixanonx, mequetazine, methapyrilene, methdilazine, methixene, methotrimeprazine, methoxypromazine, p-methyldiphenhydramine, N-methylpiperazine, metofenazine, mianserin, molindone, morazone, morcizine, mosapramine, naftopidil, niaprazine, nizofenone, nomifensine, noxiptilin, olanzapine, opromazine, oxememazine, oxypendyl, oxytetrine, pamaquine, perazine, pericyazine, perlapine, perphenazine,
phenindamine, pheniramine, phenoperidine, picoperine, picumast, pipacycline, pipamazine, pipamperone, pipazethate, piperidolate, piperilate, piperoxan, piperylone, pipotiazine, pipradol, piprozolin, pirbuterol, pirenzepine, piribedil, piridocaine, pirirramide, pizotyline, pridinol, prochlorperazine, promethazine, propacetamol, propiomazine, propipocaine, propiverine, propizepine, propoxycaine, propoxyphene, prothipendyl, quinine, risperidone, roxatidine, setastine, spiperone, sufentanil, sulforidazine, sulpiride, thiambutene, thiethylperazine, thiopropazate, thioproperazine, thiothixene, thiphenamil, thonzylamine, ticlopidine, timiperone, timoridine, trihexyphenidyl, trimetazidine, trimetazidine, trimipramine, tripolidine, urapidil, veralipride, verapamil, vетrabutine, viminol, zimeldine and zipeprol.

The properties and preparations of each of the foregoing compounds are disclosed in *The Merck Index*, Thirteenth Edition, ISBN Number 091 1910-1 3-1 and references therein.

Salts, Solvates, Tautomers, Isomers, Prodrugs and Isotopes

A reference to a compound of the formulae (1) and (2) and sub-groups thereof also includes ionic forms, salts, solvates, isomers, tautomers, prodrugs, isotopes and protected forms thereof, for example, as discussed below.

Many compounds of the formulae (1) and (2) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as phenolate, carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formulae (1) and (2) include the salt forms of the compounds.

The salts can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.
Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulphonic, (+)-(1S)-camphor-10-sulphonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecysulphuric, ethane-1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, (+)-L-lactic, (±)-DL-lactic, lactobionic, maleic, malic, (-)-L-malic, malonic, (±)-DL-mandelic, methanesulphonic, naphthalene-2-sulphonic, naphthalene-1,5-disulphonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, (+)-L-tartaric, thiocyanic, tannic, undecylenic and valeric acids, as well as acetylated amino acids and cation exchange resins.

If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO⁻), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na⁺ and K⁺, alkaline earth metal cations such as Ca²⁺ and Mg²⁺, and other cations such as Al³⁺. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH₄⁺) and substituted ammonium ions (e.g., NH₃R⁺, NH₂R₂⁺, NHR₃⁺, NR₄⁺). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is N(CH₃)₄⁺.

The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. ScL, Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms, which may be useful, for
example, in the purification or separation of the compounds of the invention, also form part of the invention.

Compounds of the formulae (1) and (2) may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formulae (1) and (2) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formulae (1) and (2).

Examples of tautomeric forms include, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thio-ketone/enethiol, and nitro/aci-nitro.

Where compounds of the formulae (1) and (2) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formulae (1) and (2) include all optical isomeric forms thereof (e.g. enantiomers, epimers and diastereoisomers), either as individual optical isomers, or mixtures (e.g. racemic mixtures) or two or more optical isomers, unless the context requires otherwise.

The optical isomers may be characterised and identified by their optical activity (i.e. as + and - isomers, or \(d\) and \(l\) isomers) or they may be characterised in terms of their absolute stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see Advanced Organic Chemistry by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, Angew. Chem. Int. Ed. Engl., 1966, 5, 385-415.

Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art.

As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-
pyroglutamic acid, (-)-di-toluoyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)
camphorsulphonic, separating the diastereoisomers by preferential crystallisation, and then
dissociating the salts to give the individual enantiomer of the free base.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one
enantiomer in a pair of enantiomers may exhibit advantages over the other
enantiomer, for example, in terms of biological activity. Thus, in certain circumstances,
it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or
only one of a plurality of diastereoisomers. Accordingly, the invention provides
compositions containing a compound of the formula (I) having one or more chiral
centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or
95%) of the compound of the formula (I) is present as a single optical isomer (e.g.
enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g.
substantially all) of the total amount of the compound of the formula (I) may be present
as a single optical isomer (e.g. enantiomer or diastereoisomer).

The compounds of the invention include compounds with one or more isotopic
substitutions, and a reference to a particular element includes within its scope all
isotopes of the element. For example, a reference to hydrogen includes within its
scope ¹H, ²H (D), and ³H (T). Similarly, references to carbon and oxygen include
within their scope respectively ¹²C, ¹³C and ¹⁴C and ¹⁶O and ¹⁸O.

The isotopes may be radioactive or non-radioactive. In one embodiment of the
invention, the compounds contain no radioactive isotopes. Such compounds are
preferred for therapeutic use. In another embodiment, however, the compound may
contain one or more radioisotopes. Compounds containing such radioisotopes may be
useful in a diagnostic context.

Also encompassed by formula (I) are any polymorphic forms of the compounds,
solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with
compounds such as cyclodextrins, or complexes with metals) of the compounds, and
pro-drugs of the compounds. By "prodrugs" is meant for example any compound that
is converted in vivo into a biologically active compound of the formula (I).

**Biological Activity**
The N-oxide drug compounds of the invention have a wide range of different therapeutic uses including for example anti-biotic, anti-arrhythmic, anti- nauseas, anti-psychotic, anti-histamine, anti-anginal and anti-cancer uses.

The N-oxide drug compounds of the invention have substantially lower hERG activity than their corresponding non-N-oxide analogues. Preferred N-oxide drug compounds of the invention are those that have at least a tenfold lower hERG channel inhibiting activity than their corresponding non-N-oxide forms.

The hERG channel inhibiting activity of the compounds can be determined using the method of Zhou Z, Gong Q, Ye B, Fan Z, Makielski JC, Robertson GA, January CT. *Biophys J.* 1998 Jan;74(1):230-41, as described in more detail below.

**Methods for the Preparation of Compounds of the Invention**

The N-oxide drug compounds of the invention can be prepared by the oxidation of the corresponding non-N-oxide compounds. Thus, for example, the N-oxide drug compounds of formulae (1), (2), (3) and (4) can be prepared by the N-oxidation of compounds of the formulae (10), (11), (9) and (8) respectively:

Where the compounds of formulae (10) and (11) contain a number of oxidisable nitrogen atoms, for example nitrogen atoms forming part of heteroaryl ring systems.
such as pyridine and quinolizine, the N-oxidation may be carried out using an oxidising agent that selectively or preferentially oxidises non-aromatic nitrogen atoms.

Examples of reagents capable of oxidizing a non-aromatic amine to an N-oxide in the presence of a basic heteroaromatic nitrogen atom are arylsulphonyloxaziridines such as 2-benzenesulphonyl-3-phenyl-oxaziridine which has the structure (12):

![Structure of 2-Benzenesulphonyl-3-phenyl-oxaziridine](image)

2-Benzenesulphonyl-3-phenyl-oxaziridine can be prepared by the methods set out in the examples.

The compound of formula (8) is known by the code number VX-680 and is described in the articles by (1) Elizabeth A Harrington et al., Nature Medicine 10, 262 - 267 (2004); and (2) Farid Gizatullin et al., Cancer Res. 2006 Aug 1;66 (15):7668-77 16885368. The compound can be made using the methods described in WO 02/068415 or methods analogous thereto.

Compounds of the formula (9) can be prepared by the methods described in WO 01/17995 or methods analogous thereto.


Amiodarone and analogues thereof can be prepared by the methods described in US 3248401 or methods analogous thereto.

Bepridil and analogues thereof can be prepared by the methods described in US 3962238, DE 2310918 or methods analogous thereto.
Chloroquine and analogues thereof can be prepared by the methods described in US 2233970 or methods analogous thereto.

Cisapride and analogues thereof can be prepared by the methods described in US 49621 15, EP 76530 or methods analogous thereto.

Disopyramide and analogues thereof can be prepared by the methods described in US 225054 or methods analogous thereto.

Dofetilide and analogues thereof can be prepared by the methods described in US 4959366, EP 245997 or methods analogous thereto.

Domperidone and analogues thereof can be prepared by the methods described in US 4066772 or methods analogous thereto.

Droperidol and analogues thereof can be prepared by the methods described in US 3161645 or methods analogous thereto.

Halofantrine and analogues thereof can be prepared by the methods described in US 4507288, EP 138374 or methods analogous thereto.

Haloperidol and analogues thereof can be prepared by the methods described in US 3438991, GB 895309 or methods analogous thereto.

Ibutilide and analogues thereof can be prepared by the methods described in US 5155268, EP 164865 or methods analogous thereto.

Levomethadyl and analogues thereof can be prepared by the methods described in A. Pohland et al., J. Amer. Chem. Soc, 71, 460, (1949) or methods analogous thereto.

Mesoridazine and analogues thereof can be prepared by the methods described in US 3084161 or methods analogous thereto.

Methadone and analogues thereof can be prepared by the methods described in US 2644010, US 2983757 or methods analogous thereto.

Pimozide and analogues thereof can be prepared by the methods described in FR M3695 or methods analogous thereto.
Procainamide and analogues thereof can be prepared by the methods described in M. Yamazaki et al., *J. Pharm Soc. Jap.*, 73, 294 (1953) and Y. Tashika et al., *ibid*, 1069 or methods analogous thereto.

Sotalol and analogues thereof can be prepared by the methods described in Uloth et al., *J. Med. Chem.*, 9, 88 (1966) or methods analogous thereto.

Thioridazine and analogues thereof can be prepared by the methods described in Bourquin et al., *Helv. Chim. Acta*, 41, 1072 (1958) or methods analogous thereto.

**Pharmaceutical Formulations**

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound of the invention together with a pharmaceutically acceptable carrier, and optionally one or more additional excipients.

Accordingly, in another aspect, the invention provides a pharmaceutical composition comprising a compound of the formula (I) and a pharmaceutically acceptable carrier.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short term infusion or longer term infusion and can be via passive delivery or through the utilisation of a suitable infusion pump.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, co-solvents, organic solvent mixtures, cyclodextrin complexation agents, emulsifying agents (for forming and stabilizing emulsion formulations), liposome components for forming liposomes, gellable polymers for forming polymeric gels, lyophilisation protectants and combinations of agents for, *inter alia*, stabilising the active ingredient in a soluble form and rendering the formulation isotonic with the blood of the intended recipient. Pharmaceutical formulations for parenteral administration
may also take the form of aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents (R. G. Strickly, Solubilizing Excipients in oral and injectable formulations, Pharmaceutical Research, Vol 21(2) 2004, p 201-230).

A drug molecule that is ionizable can be solubilized to the desired concentration by pH adjustment if the drug's $pK_a$ is sufficiently away from the formulation pH value. The acceptable range is pH 2-12 for intravenous and intramuscular administration, but subcutaneously the range is pH 2.7-9.0. The solution pH is controlled by either the salt form of the drug, strong acids/bases such as hydrochloric acid or sodium hydroxide, or by solutions of buffers which include but are not limited to buffering solutions formed from glycine, citrate, acetate, maleate, succinate, histidine, phosphate, tris(hydroxymethyl)-aminomethane (TRIS), or carbonate.

The combination of an aqueous solution and a water-soluble organic solvent/surfactant (i.e., a cosolvent) is often used in injectable formulations. The water-soluble organic solvents and surfactants used in injectable formulations include but are not limited to propylene glycol, ethanol, polyethylene glycol 300, polyethylene glycol 400, glycerin, dimethylacetamide (DMA), N-methyl-2-pyrrolidone (NMP; Pharmasolve), dimethylsulphoxide (DMSO), Solutol HS 15, Cremophor EL, Cremophor RH 60, and polysorbate 80. Such formulations can usually be, but are not always, diluted prior to injection.

Propylene glycol, PEG 300, ethanol, Cremophor EL, Cremophor RH 60, and polysorbate 80 are the entirely organic water-miscible solvents and surfactants used in commercially available injectable formulations and can be used in combinations with each other. The resulting organic formulations are usually diluted at least 2-fold prior to IV bolus or IV infusion.

Alternatively increased water solubility can be achieved through molecular complexation with cyclodextrins.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.
The pharmaceutical formulation can be prepared by lyophilising a compound of Formula (I) or acid addition salt thereof. Lyophilisation refers to the procedure of freeze-drying a composition. Freeze-drying and lyophilisation are therefore used herein as synonyms. A typical process is to solubilise the compound and the resulting formulation is clarified, sterile filtered and aseptically transferred to containers appropriate for lyophilisation (e.g. vials). In the case of vials, they are partially stoppered with lyo-stoppers. The formulation can be cooled to freezing and subjected to lyopholisation under standard conditions and then hermetically capped forming a stable, dry lyophile formulation. The composition will typically have a low residual water content, e.g. less than 5% e.g. less than 1% by weight based on weight of the lyophile.

The lyophilisation formulation may contain other excipients for example, thickening agents, dispersing agents, buffers, antioxidants, preservatives, and tonicity adjusters. Typical buffers include phosphate, acetate, citrate and glycine. Examples of antioxidants include ascorbic acid, sodium bisulphite, sodium metabisulphite, monothioglycerol, thiourea, butylated hydroxytoluene, butylated hydroxyl anisole, and ethylenediaminetetraacetic acid salts. Preservatives may include benzoic acid and its salts, sorbic acid and its salts, alkyl esters of para-hydroxybenzoic acid, phenol, chlorobutanol, benzyl alcohol, thimerosal, benzalkonium chloride and cetylpyridinium chloride. The buffers mentioned previously, as well as dextrose and sodium chloride, can be used for tonicity adjustment if necessary.

Bulking agents are generally used in lyophilisation technology for facilitating the process and/or providing bulk and/or mechanical integrity to the lyophilized cake. Bulking agent means a freely water soluble, solid particulate diluent that when co-lyophilised with the compound or salt thereof, provides a physically stable lyophilized cake, a more optimal freeze-drying process and rapid and complete reconstitution. The bulking agent may also be utilised to make the solution isotonic.

The water-soluble bulking agent can be any of the pharmaceutically acceptable inert solid materials typically used for lyophilisation. Such bulking agents include, for example, sugars such as glucose, maltose, sucrose, and lactose; polyalcohols such as sorbitol or mannitol; amino acids such as glycine; polymers such as polyvinylpyrrolidine; and polysaccharides such as dextran.
The ratio of the weight of the bulking agent to the weight of active compound is typically within the range from about 1 to about 5, for example of about 1 to about 3, e.g. in the range of about 1 to 2.

Alternatively they can be provided in a solution form which may be concentrated and sealed in a suitable vial. Sterilisation of dosage forms may be via filtration or by autoclaving of the vials and their contents at appropriate stages of the formulation process. The supplied formulation may require further dilution or preparation before delivery for example dilution into suitable sterile infusion packs.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

In one preferred embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion.

In another preferred embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, e.g. lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as...
citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (e.g. tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit™ type polymer) can be designed to release the active component at a desired location within the gastrointestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in patient prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.
Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the formula (I) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within this range, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic.

EXAMPLES

The following examples illustrate the invention.
Preparation of 2-Benzensulphonyl-3-phenyl-oxaziridine

A. N-Benzylidene-benzenesulphonamide

A solution of benzenesulphonyl chloride (10 g) in methanol (150 ml) was cooled to 0°C and ammonia gas was bubbled into the reaction mixture over a period of 15 minutes. The reaction mixture was further stirred overnight at RT. On completion, the methanol was removed under reduced pressure and water (100 ml) was added. The reaction mixture was extracted with ethyl acetate (2*100 ml). The combined organic extracts were dried over sodium sulphate. The solvent was removed under reduced pressure to give 8.6 grams of benzenesulphonamide (96%). The benzene-sulphonamide (2 g) was taken together with benzaldehyde (1.34 g), Amberlyst resin (0.2 g) and molecular sieves (2 g) in dry toluene (20 ml) and refluxed (110°C) for 30 minutes (till evolution of water ceases). The reaction mixture cooled to RT (without stirring) filtered through a Celite® bed and washed with toluene (40 ml). Finally, the toluene was removed under reduced pressure and the obtained a residue that when kept in the refrigerator for 30 minutes yielded a solid that was triturated with n-pentane (20 ml) filtered and dried for 15-20 min to give the desired product (2.5g, 89%).

B. 2-Benzensulphonyl-3-phenyl-oxaziridine

N-Benzylidene-benzenesulphonamide was taken together with a saturated solution of sodium bicarbonate (12.5 ml) and N-benzyl-N,N-diethylethanaminium chloride (0.25 g) and cooled to 0°C. 3-Chloroperbenzoic acid (3 g) in chloroform (22.5 ml) was added dropwise to the reaction mixture over a period of 15 min at 0°C and stirring maintained for 1 hour. On completion, the organic layer was separated and washed with water (20 ml), 10% Na₂SO₃ solution (20 ml), sat. NaHCO₃ (20 ml) and sat. NaCl (20 ml). The organic layer was dried over potassium carbonate, filtered and the chloroform removed under reduced pressure (below 40°C). The crude product was treated with n-pentane (5 ml) and the resulting solid filtered. This solid was further
triturated with ethyl acetate (14 ml) and then aged with n-Pentane (14 ml) overnight in the refrigerator. The resulting mixture was filtered and dried to yield the title compound (1.4g, 48%).

EXAMPLE 1

**ri-(4-Fluoro-benzyl)-1H-benzoimidazol-2-vn-(1-r2-(4-methoxy-phenyl)-ethyl1-oxy-piperidin-4-yl)-amine**

![Chemical Structure]

[1-(4-Fluoro-benzyl)-1H-benzoimidazol-2-yl]-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl]-amine (149 mg) was dissolved in 3 ml dry DCM and 1.1 eq of 2-benzene-sulphonyl-3-phenyl-oxaziridine was added at room temperature. The reaction mixture was stirred for additional 30 minutes and the mixture was loaded on to silica gel column and eluted with 10% saturated NH$_3$ZMeOH in DCM to yield the title compound.

N.M.R. (DMSO) δ 7.24-7.07 (m, 8H), 6.95-6.81 (m, 5H), 5.30 (2, 2H), 3.99-3.88 (m, 1H), 3.73 (s, 3H), 3.41-3.28 (m, 4H), 3.1 1-3.05 (m, 4H), 2.40-2.29 (m, 2H), 1.86 (d, 2H). LC/MS rt 2.75 ES+ 475

EXAMPLE 2

**N-f4-(2-(f2-(4-Methanesulfonylamino-phenyl)-ethyl-methyl-amino>-ethoxy)-phenvn-methanesulfonamide N-oxide**
N-[4-(2-[[2-(4-Methanesulfonylamino-phenyl)-ethyl]-methyl-amino]-ethoxy)-phenyl]-methanesulfonamide (115 mg) was dissolved in 3 ml dry DCM and 1.1 eq of 2-benzenesulphonyl-3-phenyl-oxaziridine was added at room temperature. The reaction mixture was stirred for overnight. The precipitate was filtered and washed with DCM and dried to yield the title compound. N.M.R. (DMSO) δ 9.81 (br s, 2H), 7.22-7.14 (m, 6H), 6.96 (d, 2H), 4.59-4.41 (m, 2H), 3.66-3.29 (m, 4H), 3.14-3.04 (m, 5H), 2.95 (s, 3H), 2.88 (s, 3H). LC/MS rt 2.52 ES+ 456

EXAMPLE 3

{2-r4-(1,2-Diphenyl-but-1-enyl)-phenoxy1-ethyl)-dimethyl-amine N-oxide

is commercially available.

EXAMPLE 4

r4-(1-Oxy-pyrrolidin-1-ylmethyl)-pyridin-2-yl1-(5-phenyl-thiazol-2-yl)-amine
The starting material was prepared according to the route described in Bilodeau M. T., *Bioorg. Med. Chem. Lett.* (2004), 14, 2941-2945 and was then reacted with 2-benzenesulphonyl-3-phenyl-oxaziridine as described in Example 1 to give the title compound. N.M.R. (DMSO) $\delta$ 8.37 (d, 1H), 7.80 (s, 1H), 7.59 (d, 3H), 7.39 (t, 2H), 7.25-7.27 (m, 2H), 7.10 (d, 1H), 4.62 (br s, 2H), 3.65-3.59 (m, 3H), 2.12-1.98 (m, 4H). LC/MS rt 2.19 ES+ 353

**Example 5**

3-(indol-3-yl)-4-f1-(N-oxydimethylaminopropyl)-indol-3-vn-maleimide

The title compound was prepared from commercially available 3-(indol-3-yl)-4-[1-(N-dimethylaminopropyl)]-indol-3-yl]-maleimide by following the method of Example 1. N.M.R. (DMSO) $\delta$ 11.78 (br s, 1H), 11.21 (br s, 1H), 7.79-7.76 (m, 2H), 7.53 (d, 1H), 7.38 (d, 1H), 7.05 (t, 1H), 6.97 (t, 1H), 6.89 (d, 1H), 6.77 (d, 1H), 6.71-6.63 (m, 2H), 5.76 (s, 1H), 4.36 (t, 2H), 3.15 (t, 2H), 3.00 (s, 6H), 2.28-2.22 (m, 2H). LC/MS rt 1.86 ES+ 429.

**COMPARATIVE EXAMPLES A, B, C, D & E**

Examples A to E are presented as comparative examples. In these examples, which are specifically excluded from formulae (1) and (2) herein, the formation of an N-oxide
at the tertiary amino nitrogen atom has been found to have a deleterious effect on biological activity that is not compensated for by the reduced hERG activity.

**COMPARATIVE EXAMPLE A**

4-Amino-5-chloro-N-((3R,4S)-1-r3-(4-fluoro-phenoxy)-propyl)-3-methoxy-1-oxy-piperidin-4-yl)-2-methoxy-benzamide

The title compound was prepared from commercially available 4-amino-5-chloro-N-((3R,4S)-1-[3-(4-fluoro-phenoxy)-propyl]-3-methoxy-piperidin-4-yl)-2-methoxy-benzamide by following the method of Example 1.

N.M.R. (DMSO) $\delta$ 7.92 (d, 1H), 7.65 (s, 1H), 7.12 (t, 2H), 6.98-6.93 (m, 2H), 6.51 (s, 1H), 5.99 (s, 2H), 4.31 (br s, 1H), 4.06 (t, 2H), 4.00 (br s, 1H), 3.83 (2, 3H), 3.20-3.15 (m, 2H), 2.92 (br s, 1H), 2.66 (t, 2H), 2.01 (br s, 1H). LC/MS $t$ 3.13 ES+ 482.

**COMPARATIVE EXAMPLE B**

4-[4-(4-Chloro-phenyl)-4-hydroxy-1-oxy-piperidin-1-yl]-1-(4-fluoro-phenyl)-butan-1-one

The title compound was prepared from commercially available 4-[4-(4-chloro-phenyl)-4-hydroxy-piperidin-1-yl]-1-(4-fluoro-phenyl)-butan-1-one by following the method of Example 1.

N.M.R. (DMSO) $\delta$ 8.08-8.04 (m, 2H), 7.42-7.30 (m, 6H), 5.39 (s, 1H), 3.52-3.48 (m, 2H), 3.26-3.17 (m, 4H), 2.95-2.91 (m, 2H), 2.68-2.60 (m, 2H), 2.19-2.15 (m, 2H), 1.53-1.48 (m, 2H) LC/MS $t$ 2.07 ES+ 392.

**COMPARATIVE EXAMPLE C**
1-(1-r4,4-Bis-(4-fluoro-phenyl)-butyll-1-oxy-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

The title compound was prepared from commercially available 1-[1-[4,4-bis-(4-fluoro-phenyl)-butyl]-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one by following the method of Example 1.

N.M.R. (DMSO) δ 10.92 (2, 1H), 7.37-7.33 (m, 5H), 7.14-7.09 (m, 4H), 6.97-6.95 (m, 3H), 4.44-4.36 (m, 1H), 4.05-4.00 (m, 1H), 3.24-3.20 (m, 2H), 3.05-2.98 (m, 2H), 2.21-2.00 (m, 6H), 1.77-1.48 (m, 6H) LC/MS rt 3.43 ES+ 477.

COMPARATIVE EXAMPLE D

1-(4-tert-Butyl-phenyl)-4-r4-(hydroxy-diphenyl-methyl)-1-oxy-piperidin-1-yl-butanol

The title compound was prepared from commercially available 1-(4-tert-butyl-phenyl)-4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butanol by following the method of Example 1.

N.M.R. (DMSO) δ 7.49 (d, 4H), 7.29-7.21 (m, 8H), 7.12 (t, 2H), 6.38 (2, 1H), 4.51 (t, 1H), 3.2-3.1 (m, 4H), 2.95 (d, 2H), 2.64 (t, 1H), 2.17 (q, 2H), 1.85-1.79 (m, 2H), 1.61 (t, 2H), 1.23 (s, 9H), 1.07 (d, 2H). LC/MS rt 3.65 ES+ 488.

COMPARATIVE EXAMPLE E

2-(3,4-Dimethoxy-phenyl)-5-U2-(3,4-dimethoxy-phenvn-ethyll-oxy-methyl-aminoV2-isopropyl-pentan enitrile
The title compound was prepared from commercially available 2-(3,4-dimethoxy-phenyl)-5-[[2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-amino]-2-isopropyl-pentanenitrile by following the method of Example 1.

5 EXAMPLES 6 TO 11

By following the method of Example 1, the compounds of Examples 6 to 11 may be prepared. The precursor compounds in Examples 6 to 11 can be prepared by the synthetic routes described in Bilodeau M. T., *Bioorg. Med. Chem. Lett.* (2004), J4, 2941-2945, the methods described in WO 01/17995 (PCT/US00/24432) and methods analogous thereto.

<table>
<thead>
<tr>
<th>Example</th>
<th>Precursor</th>
<th>N-Oxide</th>
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<tbody>
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<tr>
<td>8</td>
<td><img src="attachment" alt="Image5" /></td>
<td><img src="attachment" alt="Image6" /></td>
</tr>
</tbody>
</table>
EXAMPLE 12

BIOLOGICAL ASSAYS

A. Functional hERG Assay

The compounds of Examples 1 to 5 were each tested for hERG inhibiting activity using the method of Zhou Z, Gong Q, Ye B, Fan Z, Makielski JC, Robertson GA, January CT. Biophys J. 1998 Jan;74(1):230-41.

Test compounds are tested in triplicate in a 5-point dose response curve on HEK-293 cells stably expressing the hERG potassium channel. Potassium current is measured using the patch clamp technique on a Molecular Devices Patch Express 7000. hERG channels are activated by 2 second pulses to +20 mV from a holding potential of -80 mV, and peak tail currents are recorded upon repolarization to -50 mV. This voltage-clamp pulse protocol is performed continuously during the experiment (vehicle control,
test compound, washout, and positive control additions. An interpulse interval of 15 seconds allows recovery from any residual inactivation. Test compounds are incubated with cells between 3-8 minutes until the current reaches a steady state level, defined by a Standard Deviation of 0.01. After the final test compound concentration is tested, test compound is washed out with continuous perfusion of extracellular solution for 3 minutes, followed by application of positive control (10 µM Cisapride). If the positive control fails to achieve 100% inhibition the experiment is discarded.

Test compounds are diluted in 100% DMSO at 1000X the highest concentration to be tested, vortexed, and sonicated. Visual inspection will determine that compounds are completely solubilized. Test compounds are then diluted into glass vials in 100% DMSO for all test concentrations at 1000X the final concentration to be tested and vortexed. Test compounds are then diluted 1:1000 into extracellular solution and vortexed to achieve final concentration for testing. Final DMSO concentration is 0.1% for all concentrations of test compounds, Vehicle (negative) control, and Cisapride (positive) control in extracellular solution. The compositions of the solutions used are as follows:

Intracellular Soln (mM): KCl 130, EDTA 5, MgCl₂ 5, HEPES 10, Na-ATP 5, pH=7.2
Extracellular Soln (mM): NaCl 137, KCl 4, CaCl₂ 1.8, MgCl₂ 1, Dextrose 11, HEPES 10, pH=7.4
Vehicle: 0.1% DMSO

B. Target Assays

The N-oxides of the invention and their non-N-oxide precursors were tested in receptor or enzyme binding assays relevant to the biological activities of the precursor compounds and, where appropriate, IC₅₀ values were measured.

The assays used were as follows:

(i) Histamine H₁ receptor binding assay

Histamine H₁ receptor binding ability was determined by MDS Pharmaceutical Services by means of a GTPγS binding assay using [³⁵S]GTPγS, human recombinant CHO cells, and 3 µM histamine as a control. Test compounds were incubated for 30 minutes.
(ii) Estrogen α receptor binding assay

The ability of the compounds of Example 3 to bind to estrogen receptors was measured by means of an assay using human recombinant estrogen α (ER α) receptors expressed in Sf9 insect cells. A 4.5 ng aliquot of the receptor proteins in modified Tris-HCl buffer pH 7.5 was incubated with 0.5 nM [3H]Estradiol for 2 hours at 25°C in the presence or absence of test compound. Non-specific binding was estimated in the presence of 1 mM diethylstilbestrol. The receptor proteins were filtered and washed and the filters were then counted to determine [3H]Estradiol specifically bound. From the results obtained, the IC₅₀ values of the compounds of Example 3 were determined.

(iii) Protein Kinase Ca (PKCa) activity assay

In a final reaction volume of 25 μL, PKCα (h) (5-10 mil) was incubated with 20 mM HEPES pH 7.4, 0.03% Triton X-100, 0.1 mM, 0.1 mg/mL phosphatidylinerine, 10 μg/mL diacylglycerol, 0.1 mg/mL histone H1, 10 mM MgAcetate and [γ-33P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required) and either no test compound (control) or varying concentrations of test compound. The reaction was initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of 5 μL of a 3% phosphoric acid solution. 10 μL of the reaction was then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting. From the results, the IC₅₀ values of the test compounds were obtained.

(iv) VEGF induced HUVEC growth inhibition assay protocol (Cellular KDR assay)

The activity of a compound against endothelial growth factor (VEGF) and its receptor tyrosine kinase KDR provides a good indicator of the compound's potential to inhibit angiogenesis and thereby prevent or slow down tumour vascularization. The following test protocol was used to test for activity against VEGF2 and KDR in a cell based assay.

Human Umbilical Vein Endothelial Cells (HUVEC cells) (Lonza # CC-2519) were seeded in 96-well plates at a concentration of 5000 cells per well in complete EGM-2 endothelial media and allowed to adhere overnight. The cells were washed and the complete media was replaced with basal media containing 10ng/ml VEGF. Test compounds were prepared from 10mM DMSO stocks to give a final concentration.
range from 3µM to 1mM and vehicle control. The DMSO content was constant at 0.4%. Test compounds were incubated with the cells for 48h at 37°C 5% CO₂ in a humidified atmosphere. Alamar blue 10% (v/v) was then added and incubated for a further 6h, and fluorescent product detected using the BMG FLUOstar plate reader. Data were analysed using a 4-parameter logistic equation in GraphPad Prism.

The results obtained from testing the compounds of Examples 1 to 5, and Comparative Examples A, B, C, D and E in assays (i) to (iv) are set out in Table 4 below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity @ Target</th>
<th>hERG Binding IC₅₀ (µM)</th>
<th>Ratio</th>
<th>Functional hERG (HEK-293 cells) IC₅₀ (µM)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astemazole (Example 1 precursor)</td>
<td>0.0017</td>
<td>Histamine H1</td>
<td>0.007</td>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>Astemazole N-oxide (Example 1)</td>
<td>2.51</td>
<td>Histamine H1</td>
<td>0.044</td>
<td></td>
<td>1.94</td>
</tr>
<tr>
<td>Dofetilide</td>
<td></td>
<td></td>
<td>0.026</td>
<td>38</td>
<td>0.016</td>
</tr>
<tr>
<td>Dofetilide N-oxide (Example 2)</td>
<td></td>
<td></td>
<td>0.998</td>
<td></td>
<td>2.490</td>
</tr>
<tr>
<td>Tamoxifen (Example 3 precursor)</td>
<td>0.003</td>
<td>Estrogen α</td>
<td>0.49</td>
<td>37</td>
<td>16.83</td>
</tr>
<tr>
<td>Tamoxifen N-oxide (Example 3)</td>
<td>0.006</td>
<td>Estrogen α</td>
<td>18.2</td>
<td></td>
<td>60.75</td>
</tr>
<tr>
<td>Example 4 precursor</td>
<td>0.06</td>
<td>KDR(h)</td>
<td>0.546</td>
<td>20</td>
<td>3.67</td>
</tr>
<tr>
<td>Example 4</td>
<td>0.085</td>
<td>KDR(h)</td>
<td>11.1</td>
<td></td>
<td>11.48</td>
</tr>
<tr>
<td>Example 5 precursor</td>
<td>0.017</td>
<td>PKCα</td>
<td>1.43</td>
<td>18</td>
<td>0.37</td>
</tr>
<tr>
<td>Compound</td>
<td>Activity @ Target</td>
<td>hERG Binding ICₕ₀ (µM)</td>
<td>Ratio Compound: precursor</td>
<td>Functional hERG (HEK-293 cells) ICₕ₀ (µM)</td>
<td>Ratio Compound: precursor</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>---------------------------</td>
<td>--------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Example 5</td>
<td>0.198</td>
<td>PKCδ</td>
<td>25.4</td>
<td>14.22</td>
<td></td>
</tr>
<tr>
<td>Comparative Example A Precursor</td>
<td>0.017</td>
<td>5-HT₄</td>
<td>0.23</td>
<td>28</td>
<td>0.03</td>
</tr>
<tr>
<td>Comparative Example A N-Oxide</td>
<td>2.4</td>
<td>5-HT₄</td>
<td>6.39</td>
<td>28</td>
<td>3.2</td>
</tr>
<tr>
<td>Comparative Example B Precursor</td>
<td>0.001</td>
<td>Dopamine D2</td>
<td>0.313</td>
<td>70</td>
<td>0.04</td>
</tr>
<tr>
<td>Comparative Example B N-oxide</td>
<td>0.325</td>
<td>Dopamine D2</td>
<td>21.9</td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Comparative Example C Precursor</td>
<td>0.002</td>
<td>Dopamine D2</td>
<td>0.03</td>
<td>14</td>
<td>0.07</td>
</tr>
<tr>
<td>Comparative Example C N-oxide</td>
<td>0.031</td>
<td>Dopamine D2</td>
<td>0.423</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Comparative Example D Precursor</td>
<td>0.009</td>
<td>Histamine H1</td>
<td>0.065</td>
<td>11</td>
<td>0.34</td>
</tr>
<tr>
<td>Comparative Example D N-oxide</td>
<td>2.73</td>
<td>Histamine H1</td>
<td>0.698</td>
<td></td>
<td>3.00</td>
</tr>
<tr>
<td>Comparative Example E Precursor</td>
<td>0.024</td>
<td>Calcium L-type</td>
<td>4.38</td>
<td>&gt;23</td>
<td>0.42</td>
</tr>
<tr>
<td>Comparative Example E N-oxide</td>
<td>2.91</td>
<td>Calcium L-type</td>
<td>&gt;100</td>
<td></td>
<td>&gt;30</td>
</tr>
</tbody>
</table>
Activity of 3-(indol-3-yl)-4-ri-(N-oxydimethylaminopropyl)-indol-3-yll-maleimide against Protein Kinase C Isoforms

The activities of the compound of Example 5 (3-(indol-3-yl)-4-[1-(N-oxydimethylaminopropyl)-indol-3-yl]-maleimide) and its precursor (3-(indol-3-yl)-4-[1-(N-dimethylaminopropyl)-indol-3-yl]-maleimide) against various Protein Kinase C isoforms were determined (assays carried out by Millipore, Dundee Technology Park, Dundee, UK) and the results are shown in the Table below.

<table>
<thead>
<tr>
<th>Protein Kinase C Isoform</th>
<th>Compound of Example 5</th>
<th>Precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Inhibition @ 0.1uM</td>
<td></td>
</tr>
<tr>
<td>PKCα(h)</td>
<td>23</td>
<td>82</td>
</tr>
<tr>
<td>PKCβ(h)</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>PKCβ(h)</td>
<td>60</td>
<td>81</td>
</tr>
<tr>
<td>PKCβIΙ(h)</td>
<td>27</td>
<td>56</td>
</tr>
<tr>
<td>PKCγ(h)</td>
<td>65</td>
<td>88</td>
</tr>
<tr>
<td>PKCδ(h)</td>
<td>58</td>
<td>84</td>
</tr>
<tr>
<td>PKCε(h)</td>
<td>51</td>
<td>82</td>
</tr>
<tr>
<td>PKCη(h)</td>
<td>24</td>
<td>58</td>
</tr>
<tr>
<td>PKCζ(h)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PKCμ(h)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>PKCζ(h)</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

The results demonstrate that a small decrease in potency occurs when the basic nitrogen atom is converted to an N-oxide but, in all cases, the loss of activity is less than 4-fold and, in many cases, the activity of the N-oxides is in excess of 50% of the activity of the basic precursor compound, and in some cases the precursor and the N-oxide are nearly equipotent. These results may be contrasted with the 38 fold difference in functional hERG activity between the precursor compound and the N-oxide and further illustrate how forming an N-oxide can have the effect of reducing toxicity due to hERG effects and widening the therapeutic window of a tertiary amine drug substance.
EXAMPLE 14

**Activity of Astemazole and Astemazole N-oxide (Example 1) against Plasmodium falciparum:** *in vitro screening model (asynchronous)*

The compounds of Example 1 were tested for activity against Plasmodium falciparum, the parasite responsible for malaria.

Two strains of *P. falciparum* were used: (a) the 3D7 clone of NF54 isolate which is sensitive to all anti-malarials, (b) the K1 strain originating from Thailand that is resistant to chloroquine and pyrimethamine, but sensitive to mefloquine. The cultures are naturally asynchronous (65-75% ring stage) and were maintained in RPMI 1640 medium supplemented with 5% washed human A+ erythrocytes, 25 mM Hepes, 32 mM NaHCO₃, and 0.5% Albumax II® (lipid-rich bovine serum albumin) (Invitrogen), 0.2% w/v glucose, 0.03% L-glutamine and 150 μM cold hypoxanthine). All cultures and assays were conducted at 37°C under 5% CO₂, 95% air mixture.

**Drug sensitivity assays:**

Assays were performed in sterile 96-well microtitre plates in assay medium (culture medium containing only 5uM cold hypoxanthine). Stock drug solutions were prepared in 100% DMSO (dimethylsulfoxide) at 20 mg/ml unless otherwise suggested by the supplier. The compound was further diluted in 96-well plates to the appropriate concentration using complete medium RPMI 1640 supplemented with 5uM cold hypoxanthine and AlbuMAXII.

Parasite cultures were washed three times with RPMI 1640 to remove excess cold hypoxanthine and diluted to a 0.5% parasitemia. Fifty µl of culture were added to the plates containing the drugs to give a final volume of 100 µl/well (0.5% parasitemia, 2.5% hematocrit). Each drug was tested in triplicate and parasite growth compared to control and blank (uninfected erythrocytes) wells. Plates were incubated for 24 h, at which point 20 µl (0.1-0.2 uCi/well) of [³H] hypoxanthine (Perkin Elmer, Hounslow, United Kingdom) was added to each well. Cultures were incubated for a further 24 h and the assay terminated by freezing the plates at -80oC. Plates were thawed and harvested onto glass fibre filter mats using a 96-well cell harvester (Harvester 96™, Tomtec, Oxon, UK) and left to dry. After the addition of MultiLex™ solid scintillant (PerkinElmer, Hounslow, United Kingdom) the incorporated radioactivity was counted using a Wallac® 1450 Betalux scintillation counter (Wallac®). The results were...
recorded as counts per minute (CPM) per well at each drug concentration, control and blank wells. Data acquired by the Wallac® BetaLux scintillation counter were exported into a MICROSOFT® EXCEL spreadsheet (Microsoft Corp.), and the IC50/IC90 values of each drug were calculated by using XLFit® (ID Business Solutions Ltd., UK) line fitting software.

Primary screen:
The preliminary screen uses the 3D7 strain. The compounds were usually tested at 6 concentrations (30, 10, 3, 1, 0.3, and 0.1 µg/ml) unless otherwise indicated. If the compound does not affect parasite growth at 10 µg/ml it is classified as inactive, between 10 and 1 µg/ml, the compound is designated as partially active, and if <1 µg/ml, the compound is classified as active and is further evaluated by three-fold serial dilutions in a repeat test.

Secondary screen:
Both the 3D7 clone and the K1 line were used. The compound was diluted three-fold over at 12 different concentrations with an appropriate starting concentration based on the preliminary screen. The IC50 was determined by a sigmoidal dose response analysis using Microsoft x/Fit™ (IDBS, UK). For each assay, the IC50 and IC90 values for each parasite line were determined against the known anti-malarials chloroquine and artemesunate, plus other standard compounds appropriate for the assay.

Activity criteria:
IC50 µg/ml:
> 10 µg/ml - Inactive
1 - 10 µg/ml - Moderately active
< 1 µg/ml - Active

Activity of standard drugs:

<table>
<thead>
<tr>
<th></th>
<th>IC50 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D7 (CQ-S)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>1 - 4 ng/ml</td>
</tr>
<tr>
<td>Artesunate</td>
<td>2 - 8 ng/ml</td>
</tr>
</tbody>
</table>

Results
EXAMPLE 15

Cellular Toxicity of Astemazole and Astemazole N-oxide (Example 1) in an in vitro test using KB cells.

The toxicity of drugs towards cells can be determined by means of an in vitro test method that makes use of KB cells, a cell line derived from a human carcinoma of the nasopharynx. The protocol for the test method and the results thereby obtained are set out below.

On day 1, the KB cells were harvested, counted and washed in serum-free medium (2000 rpm, 10 mins, 4°C) and re-suspended in fresh medium (RPMI 1640 +10% HIFC) at a concentration of 4x10^4/ml. 100µl was added to wells on a 96-well plate (4x10^3/well). The plate was incubated overnight at 37°C, 5%CO₂/air mix to allow the cells to adhere.

On day 2, test compounds were prepared in 100% DMSO 20mg/ml (with ball milling or sonicating if necessary) and diluted down to a starting concentration of 600µg/ml (2X top concentration) with RPMI + 10% HIFCS, unless otherwise indicated. The control wells have no drug.

A 10-fold serial dilution was performed across the plate - 300, 30, 3 etc etc. Podophyllotoxin was used as the control drug. The plate was incubated for 72 hours at 37°C, 5%CO₂/air.

On day 5 of the protocol, each well was assessed by microscope observation. 20µl Alamar Blue™ was then added to each well. Plates were incubated for a further 2-4 hours before reading (Gemini), EX/EM 530/580, cut-off 550nm. IC₅₀ (IC₉₀) values were calculated using sigmoidal regression analysis (MS x/fit™)

Stock drug solutions were prepared in 100% DMSO (dimethylsulfoxide) unless otherwise suggested by the supplier at 20 mg/ml, and ball milled or sonicated if necessary. For the assays, the compound was further diluted to the appropriate concentration using complete medium.
Results

<table>
<thead>
<tr>
<th></th>
<th>KB cells 3D7 CC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1 precursor</td>
<td>4.20</td>
</tr>
<tr>
<td>Example 1</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Biological Data - Conclusions

The data from the Examples illustrate that forming an N-oxide at the basic tertiary amino group leads to a substantial reduction in hERG inhibiting activity across all of the compounds tested including the Comparative Examples. Therefore, forming an N-oxide in a compound having a tertiary amino group represents an effective means of substantially reducing hERG activity. In some compounds (Comparative Compounds A to E), and in particular those where the presence of the tertiary amino group is important to the therapeutic activity of the compound, the reduction in hERG activity was accompanied by a substantial loss of the biological activity upon which the therapeutic use of the compound is based. In other compounds (Examples 2 to 5), the hERG activity was substantially reduced but the biological activity upon which the therapeutic activity of the compound is based is affected to a much lesser extent. In these compounds, therefore, the formation of an N-oxide is highly beneficial in a therapeutic context. Any small reduction in biological activity at a relevant target can be compensated for by small increases in concentration of the compound without increasing the hERG activity to a level at which it may cause problems.

Compounds of the invention in which formation of an N-oxide has been found to be particularly beneficial are compounds having kinase inhibiting activity, for example tyrosine kinase inhibiting or serine kinase inhibiting activity, and compounds having estrogen receptor binding activity. Compounds having kinase inhibiting activity or estrogen receptor binding activity represent preferred embodiments of the present invention.

In the case of astemazole and its N-oxide (Example 1), the data show that the activity of the compound as a histamine H1 receptor blocking agent is adversely affected by N-oxide formation, to an extent that is not compensated for by the reduction in hERG activity. However, the activity of the compound against the malarial parasite *P. falciparum* is reduced by a much lesser extent (approximately 10 fold) than the hERG
activity as measured in the functional hERG cell based assay (32 fold), thereby indicating that the formation of the N-oxide has the effect of widening the therapeutic window for astemizole in the treatment of malaria.

A further and most unexpected result of the formation of the N-oxide of astemazole is that it dramatically reduces the cellular toxicity of the compound as demonstrated by the relative activities of astemazole per se and astemazole N-oxide against KB cells (see Example 8).

**Equivalents**

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.
CLAIMS

1. A method of modifying a drug compound known to have deleterious hERG activity, wherein the drug compound contains a basic tertiary amino group; which method comprises reacting the drug compound with an oxidising agent to form an N-oxide at the said basic tertiary amino group so as to give an N-oxide drug compound, whereby the N-oxide drug compound has reduced hERG activity relative to its parent non-N-oxide drug compound;

2. A method of preparing a therapeutically active compound having reduced hERG activity, which method comprises:
   (a) selecting a non-N-oxide drug compound containing a basic tertiary amino group, wherein said non-N-oxide compound is known to have or is suspected of having a therapeutically unacceptable level of hERG inhibitory activity;
   (b) testing the non-N-oxide drug compound for hERG inhibitory activity;
   (c) reacting the non-N-oxide drug compound with an oxidising agent to form an N-oxide drug compound having an N-oxide at the basic tertiary amino group;
   (d) testing the N-oxide drug compound for hERG inhibitory activity;
   (e) testing the N-oxide drug compound for therapeutically useful activity;
   (f) comparing the hERG inhibitory activity of the N-oxide drug compound and non-N-oxide drug compound; and
   (g) when the N-oxide drug compound has therapeutically useful activity and has hERG activity which is at least ten fold less than the hERG inhibitory activity of the non-N-oxide drug compound, formulating the N-oxide drug compound for use in medicine.

3. A method of preparing a therapeutically active compound having reduced hERG activity, which method comprises:
   (a) selecting a non-N-oxide compound containing a basic tertiary amino group, wherein said non-N-oxide compound is known to have or is suspected of having a therapeutically unacceptable level of hERG inhibitory activity;
(b) testing the non-N-oxide compound for hERG inhibitory activity;
(c) reacting the non-N-oxide compound with an oxidising agent to form an N-oxide compound having an N-oxide at the basic tertiary amino group;
(d) testing the N-oxide compound for hERG inhibitory activity;
(e) testing the N-oxide compound for therapeutically useful activity;
(f) comparing the hERG inhibitory activity of the N-oxide compound and non-N-oxide compound; and
(g) when the N-oxide compound has therapeutically useful activity and has hERG activity which is at least ten fold less than the hERG inhibitory activity of the non-N-oxide compound, formulating the N-oxide compound for use in medicine.

4. A method according to claim 2 or claim 3 wherein the non-N-oxide drug compound or non-N-oxide compound has kinase inhibiting activity.

5. A method according to claim 2 or claim 3 wherein the non-N-oxide drug compound or non-N-oxide compound has tyrosine kinase inhibiting activity.

6. A method according to claim 2 or claim 3 wherein the non-N-oxide drug compound or non-N-oxide compound has serine kinase inhibiting activity.

7. A method according to any one of claims 2 to 6 wherein the therapeutically active compound has kinase inhibiting activity.

8. A method according to claim 7 wherein the therapeutically active compound has tyrosine kinase inhibiting activity.

9. A method according to claim 7 wherein the therapeutically active compound has serine kinase inhibiting activity.

10. A method according to any one of claims 2 to 9 wherein the therapeutically useful activity is kinase inhibitory activity.

11. A method according to any one of claims 2 to 10 wherein the therapeutically useful activity is anti-cancer activity.
12. A method according to any one of claims 2 to 10 wherein the therapeutically useful activity is anti-malarial activity.

13. A method according to any one of claims 2 to 12 wherein the N-oxide drug compound or therapeutically active compound contains the structural fragment A:

\[
\begin{align*}
\text{CH}_2 & \quad \text{*} \\
\text{CH}_2 & \quad \text{N}^+ \quad \text{C} \quad \text{*} \\
\text{*} & \quad \text{O} \quad \text{*}
\end{align*}
\]

(A)

wherein the asterisks indicate points of attachment either to a hydrogen atom or an organic residue.

14. A method according to claim 13 wherein the nitrogen atom of the N-oxide is attached to three methylene (\(\text{CH}_2\)) groups and the structural fragment is fragment (B):

\[
\begin{align*}
\text{CH}_2 & \quad \text{*} \\
\text{CH}_2 & \quad \text{N}^+ \quad \text{CH}_2 \quad \text{*} \\
\text{*} & \quad \text{O} \quad \text{*}
\end{align*}
\]

(B)

15. A method according to claim 14 wherein the the N-oxide drug compound contains the structural fragment (C):

\[
\begin{align*}
\text{CH}_2 & \quad \text{*} \\
\text{CH}_2 & \quad \text{N}^+ \quad \text{CH}_2 \quad \text{CH}_2 \quad (\text{CH}_2)_n \quad \text{*} \\
\text{*} & \quad \text{O} \quad \text{*}
\end{align*}
\]

(C)

wherein \(n\) is 1, 2 or 3.

16. A method according to any one of the preceding claims wherein the N-oxide drug compound or therapeutically active compound is other than:

\(\{2-[4-(1,2-diphenyl-but-1-enyl)-phenoxy]-ethyl\}-\text{dimethyl-amine} \quad \text{N-oxide};\)

\(\text{amitriptyline} \quad \text{N-oxide};\)
4-amino-5-chloro-N-((3R,4S)-1-[3-(4-fluoro-phenoxy)-propyl]-3-methoxy-1-oxy-piperidin-4-yl)-2-methoxy-benzamide;
4-[4-(4-chloro-phenyl)-4-hydroxy-1-oxy-piperidin-1-yl]-1-(4-fluoro-phenyl)-butan-1-one;
5 1-[(4,4-bis-(4-fluoro-phenyl)-butyl]-1-oxy-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;
1-(4-tert-butyl-phenyl)-4-[4-(hydroxy-diphenyl-methyl)-1-oxy-piperidin-1-yl]-butan-1-ol;
2-(3,4-dimethoxy-phenyl)-5-[[2-(3,4-dimethoxy-phenyl)-ethyl]-oxy-methyl-amino]-2-isopropyl-pentanenitrile;
clozapine N-oxide;
scopolamine N-oxide;
and is other than a compound of formula $W_1^1$-$NH$-$C(O)$-$NH$-$W_2^2$ where $W_1^1$ and $W_2^2$ are the same or different and each is an optionally substituted aryl or optionally substituted heteroaryl group.

17. A method according to any one of the preceding claims wherein the N-oxide drug compound or therapeutically active compound is other than:

{2-[4-(1,2-diphenyl-but-1-enyl)-phenoxy]-ethyl}dimethyl-amine N-oxide;
amitriptyline N-oxide;

4-amino-5-chloro-N-((3R,4S)-1-[3-(4-fluoro-phenoxy)-propyl]-3-methoxy-1-oxy-piperidin-4-yl)-2-methoxy-benzamide;
4-[4-(4-chloro-phenyl)-4-hydroxy-1-oxy-piperidin-1-yl]-1-(4-fluoro-phenyl)-butan-1-one;
1-[(4,4-bis-(4-fluoro-phenyl)-butyl]-1-oxy-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;
1-(4-tert-butyl-phenyl)-4-[4-(hydroxy-diphenyl-methyl)-1-oxy-piperidin-1-yl]-butan-1-ol;
2-(3,4-dimethoxy-phenyl)-5-[[2-(3,4-dimethoxy-phenyl)-ethyl]-oxy-methyl-amino]-2-isopropyl-pentanenitrile;
clozapine N-oxide;
scopolamine N-oxide;
and is other than a compound of the formula (X):
or a salt, solvate or tautomer thereof, wherein:

G is CH$_2$, O, NH, NHCO or CONH;

A is a group ($\text{CH}_2$)$_n$ where n is 1 to 4 provided that when G is O or NH,

n is at least 2;

X$^1$ is nitrogen or CH;

X$^2$ is nitrogen or a group CR$_5$;

X$^3$ is nitrogen or a group CR$_5$;

X$^4$ is nitrogen or CH; provided that no more than two of X$^2$, X$^3$ and X$^4$

are nitrogen;

R$^1$ is hydrogen, cyano, C$_{1-4}$ alkyl, trifluoromethyl or a 5-6 membered monocyclic aryl or heteroaryl group containing up to 3 heteroatom ring members selected from O, N and S and being optionally substituted by one or two C$_{1-4}$ alkyl groups;

R$^2$ is hydrogen, cyano, C$_{1-4}$ alkyl, trifluoromethyl or a 5-6 membered monocyclic aryl or heteroaryl group containing up to 3 heteroatom ring members selected from O, N and S and being optionally substituted by one or two C$_{1-4}$ alkyl groups; provided that no more than one of R$^1$ and R$^2$ can be an aryl or heteroaryl group;

or R$^1$ and R$^2$ together with the carbon atoms to which they are attached form a benzene ring;

R$^3$ and R$^4$ are the same or different and each is C$_{1-4}$ alkyl; or R$^3$ and R$^4$ together with the nitrogen atom to which they are attached form an azetidine, pyrrolidine, piperidine, piperazine, M-methylpiperazine or morpholine group; or

R$^3$ together with the nitrogen atom to which it is attached and the moiety A together form a saturated 5 to 7 membered heterocyclic ring optionally containing a second heteroatom ring member selected from O and S, wherein
the heterocyclic ring is optionally substituted by 1 to 4 methyl groups, and $R^4$ is 
C$_{1-4}$ alkyl;

$R^5$ is hydrogen or a substituent $R^6$;

$R^6$ is halogen; hydroxy; trifluoromethyl; cyano; nitro; amino; mono- or di-C$_{1-4}$
hydrocarbylamino; a carbocyclic or heterocyclic group having from 3 to 12 ring 
members and optionally substituted by one or more substituents $R^7$; or a group $R^8$-$R^9$;

$R^8$ is a bond, O, CO, X' C(X)$^2$, C(X)$^2$X$^1$, X' C(X)$^2$X$^1$, S, SO, SO$_2$, NR$^C$, SO$_2$NR$^0$ or 
NR$^C$SO$_2$;

$R^b$ is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members 
and being optionally substituted by one or more substituents $R^7$;
- a C$_{1-12}$ hydrocarbyl group optionally substituted by one or more 
substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy;
ami no; mono- or di-C$_{1-8}$ non-aromatic hydrocarbylamino; and 
carbocyclic and heterocyclic groups having from 3 to 12 ring members 
optionally substituted by one or more substituents $R^7$; wherein one or 
more carbon atoms of the C$_{1-12}$ hydrocarbyl group may optionally be 
replaced by O, S, SO, SO$_2$, NR$^C$, X'$ C(X)$$^2$, C(X)$^2$X$^1$ or X'$ C(X)$$^2$X$^1$;

$R^7$ is $R^b$, hydrogen or C$_{1-4}$ hydrocarbyl;

$X^1$ is O, S or NR$^C$; and

$X^2$ is =O, =S or =NR$^C$;

wherein $R^7$ is selected from $R^6$ provided that when the substituents $R^7$
contain a carbocyclic or heterocyclic group having from 3 to 12 ring members,
the said carbocyclic or heterocyclic group can be unsubstituted or substituted 
by one or more substituents $R^b$; and

$R^8$ is selected from $R^6$ except that any carbocyclic or heterocyclic groups 
constituting or forming part of $R^8$ may not bear a substituent containing or 
consisting of a carbocyclic or heterocyclic group but may optionally bear one or 
more substituents selected from halogen; hydroxy; trifluoromethyl; cyano; nitro;
amino; mono- or di-C$_{1-4}$ hydrocarbylamino; or a group $R^a$-$R^{bb}$; where $R^a$ is as 
hereinbefore defined and $R^{bb}$ is hydrogen or a C$_{1-6}$ hydrocarbyl group optionally 
substituted by one or more substituents selected from hydroxy, oxo, halogen,
cyano, nitro, carboxy, amino, mono- or di-C$_{1-4}$ saturated hydrocarbylamino and
wherein one or more carbon atoms of the C\textsubscript{1-6} hydrocarbyl group may optionally be replaced by O, S, SO, SO\textsubscript{2}, \textit{X}1\textit{C}(\textit{X}2), \textit{C}(\textit{X}2)\textit{X}1 or \textit{X}1\textit{C}(\textit{X}2)\textit{X}1.

18. A compound of the formula (1):

![Diagram](image)

or a salt, solvate or tautomer thereof, wherein:

- \textit{n} is 2 or 3;
- \textit{R}1 is hydrogen, hydroxy, C\textsubscript{1-6} alkoxy or together with \textit{R}2 forms a second bond between the two carbon atoms marked "q";
- \textit{R}2 is hydrogen, hydroxy, C\textsubscript{1-6} alkoxy or together with \textit{R}1 forms a second bond between the two carbon atoms marked "q";
- \textit{Q}1 is a bond, NR\textsubscript{3} or C(O)NR\textsubscript{3} or NR\textsubscript{3}CO;
- \textit{R}3 is hydrogen or C\textsubscript{1-4} alkyl;
- \textit{Ar}1 is a monocyclic or bicyclic aryl or heteroaryl group of 5 to 10 ring members of which up to four ring members are heteroatoms selected from O, N and S, the monocyclic or bicyclic aryl or heteroaryl group being optionally substituted by one or more substituents selected from a group \textit{R}1\textsubscript{0} consisting of halogen, hydroxy, amino, mono-or di- C\textsubscript{1-4} alkylamino, C\textsubscript{1-4} acylamino, C\textsubscript{1-4} alkoxy, oxo, trifluoromethyl, difluoromethoxy, cyano, phenyl, benzyl, benzyloxy, haloalkyl, haloalkylamino, haloalkylsulphonyl, C\textsubscript{1-4} alkoxy, haloalkylsulphonyl, C\textsubscript{1-4} alkoxy and haloalkylsulphonyl amino, C\textsubscript{1-4} acyl, C\textsubscript{1-4} alkoxy, and carboxy;
- \textit{Q}2 is a bond, O, S, SO, SO\textsubscript{2}, NR\textsubscript{3}, CO or CH(Ar\textsubscript{3})
- \textit{Ar}2 is a monocyclic or bicyclic aryl or heteroaryl group of 5 to 10 ring members of which up to four ring members are heteroatoms selected from O, N and S, the monocyclic or bicyclic aryl or heteroaryl group being optionally substituted by one or more substituents \textit{R}1\textsubscript{0}; and
- \textit{Ar}3 is a monocyclic aryl or heteroaryl group of 5 or 6 ring members of which up to two ring members are heteroatoms selected from O, N and S, the aryl or heteroaryl group being optionally substituted by one or more substituents \textit{R}1\textsubscript{0}.
19. A compound of the formula (2):

![Chemical structure](image)

or a salt, solvate or tautomer thereof, wherein;

- $R^4$ is hydrogen or methyl;
- $R^5$ is hydrogen or methyl;
- $R^6$ is hydrogen, methyl or C$_{1-4}$ alkoxy methyl;
- or $R^4$ together with $R^5$ and the intervening nitrogen and carbon atoms forms a pyrrolidine or piperidine ring;
- or $R^5$ together with $R^6$ and the intervening nitrogen and carbon atoms forms a piperidine ring;
- $R^7$ is hydrogen, C$_{1-8}$ alkyl, or an optionally substituted benzyl group wherein the optional substituents for the benzyl group are selected from a group $R^{10}$ consisting of halogen, hydroxy, amino, mono- or di- C$_{1-4}$ alkylamino, C$_{1-4}$ acylamino, C$_{1-4}$ alkoxy, oxo, trifluoromethyl, difluoromethoxy, cyano, phenyl, benzyl, benzoyl, halobenzyl, halobenzoyl, C$_{1-4}$ alkylsulphonyl, C$_{1-4}$ alkylsulphinyl, C$_{1-4}$ alkylsulphanilyl, alkylsulphonylamino, C$_{1-4}$ acyl, C$_{1-4}$ alkoxy carbonyl, and carboxy;
- $R^8$ is hydrogen or C$_{1-4}$ alkyl;
- or the moiety

![Chemical structure](image)

$R^9$ is hydrogen, hydroxy or C$_{1-4}$ alkyl;

- $Q^3$ is a bond, O or CH$_2$ or is selected from:
  - CH(OH);
  - CH$_2$CH(OH);
  - HNC(O);
• C(O)NH;
• CH$_2$CH(CH$_3$)NH;
• C(CONH$_2$)(phenyl) wherein the phenyl group is optionally substituted with 1 to 3 substituents R$_{10}$;
• C(1-acetoxypropyl)(phenyl) wherein the phenyl group is optionally substituted with 1 to 3 substituents R$_{10}$;
• N(R$_{11}$) where R$_{11}$ is hydrogen, C$_{1-4}$ alkyl or a benzyl group wherein the aromatic ring of the benzyl group is optionally substituted with 1 to 3 substituents R$_{10}$;

q is 0 or 1 provided that when q is 0, Q$_3$ is other than O; and

Ar$_4$ is selected from:
• quinolinyl (e.g. 4-quinolinyl) optionally substituted with 1 to 3 substituents R$_{10}$;
• pyridyl optionally substituted with 1 to 3 substituents R$_{10}$;
• phenothiazinyl (e.g. 10-phenothiazinyl) optionally substituted with 1 to 3 substituents R$_{10}$;
• phenanthrenyl optionally substituted with 1 to 3 substituents R$_{10}$;
• phenyl optionally substituted with 1 to 3 substituents R$_{10}$;
• phenyl substituted with R$_{12}$ and optionally with 0 to 2 further substituents R$_{10}$;
• indolyl (e.g. 1-indolyl) substituted by a group R$_{13}$; and
• pyridyl (e.g. 4-pyridyl) substituted by a group R$_{14}$;

R$_{12}$ is a group:

\[
\text{wherein the asterisk indicates the point of attachment to the phenyl ring; and}
\]

R$_{13}$ is a group:
wherein the asterisk indicates the point of attachment to the indolyl ring, e.g. the 3-position of the indolyl ring; and
R₁⁴ is a group:

```
  N
 / \  
O   N
```

or a group

wherein the asterisk indicates the point of attachment to the pyridyl ring, e.g. the 3-position of the pyridyl ring; Q₁ is O or S and R₁⁵ is phenyl or cyano.

20. A compound according to claim 19 of the formula (3):

```
  O
  N
```

or salts, solvates or tautomers thereof wherein Q₁ is O or S; R₁⁵ is cyano or phenyl; and R₁⁶ and R₁⁷ are each methyl or NR₁⁶R₁⁷ forms a pyrrolidine or piperidine ring.

21. A compound according to claim 20 of the formula (3A):

```
  O
  N
```

or salts, solvates or tautomers thereof.

22. A compound according to claim 20 which is selected from compounds 24 to 28 below.
23. A compound of the formula:

or a salt, solvate or tautomer thereof.

24. A compound selected from:
- [1-(4-fluoro-benzyl)-1H-benzoimidazol-2-yl]-{1-[2-(4-methoxy-phenyl)-ethyl]-1-oxy-piperidin-4-yl}-amine;
- [4-(1-oxy-pyrrolidin-1-ylmethyl)-pyridin-2-yl]-[5-phenyl-thiazol-2-yl]-amine; and
- 3-(indol-3-yl)-4-[1-(N-oxydimethylaminopropyl)-indol-3-yl]-maleimide.

25. A pharmaceutical composition comprising a compound according to any one of claims 18 to 24 and a pharmaceutically acceptable carrier.

26. A compound according to any one of claims 18 to 24 for use in medicine.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07C291/04 C07C311/32 C07D401/12 C07D403/14 C07D417/14
A61K31/13 A61P35/00 C07D413/14 C07D417/12

According to International Patent Classification (IPC) into both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
C07C 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, CHEN ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim</th>
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<td>X</td>
<td>G. CARON ET AL.: &quot;Structure-property relationships in the basicity and lipophilicity of aryalkyl amine oxides.&quot; HELVETICA CHIMICA ACTA, vol. 82, 1999, pages 1630-1639, XP002488873 See compounds 2a-4a, figure 1, page 1631.</td>
<td>19</td>
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<td>A</td>
<td>WO 2006/136823 A (ASTEX THERAPEUTICS LTD [GB]; INST OF CANCER RES ROYAL CANCE [GB]; CANC) 28 December 2006 (2006-12-28) See examples; lines 13-14, page 95.</td>
<td>1-26</td>
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<tr>
<td>F. X</td>
<td>WO 2007/144579 A (SENTINEL ONCOLOGY LTD [GB]; BOYLE ROBERT GEORGE [GB]; TRAVERS STUART [ ] 21 December 2007 (2007-12-21) cited in the application the whole document</td>
<td>1-26</td>
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**D. Further documents are listed in the continuation of Box C**

- Special categories of cited documents:
  - IA* document defining the general state of the art which is not considered to be of particular relevance
  - IE* earlier document but published on or after the international filing date
  - IL* 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)
  - IO* document referring to an oral disclosure, use, exhibition or other means
  - IP* document published prior to the international filing date but later than the priority date claimed

- V later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- S* document Member of the same patent family

**Date of international search**

21 August 2008

**Date of mailing of the international search report**

29/08/2008

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Paleisstraat 2 ML - 2280 HV Rijswijk Tel (+31-70) 340.2040, Te. 31 651 epo nl, Fax (+31-70) 340.3015

**Authorized officer**

Menchaca, Roberto
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<tr>
<td>WO 2006136823 A</td>
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