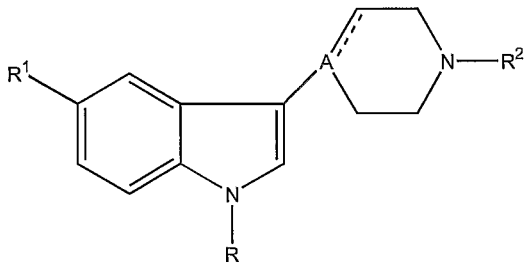
5-Heteroaryl substituted indoles

The present invention relates to novel 5-heteroaryl substituted indoles having high affinity for α_1-adrenoceptors. Accordingly, the compounds of the invention are considered useful for the treatment of diseases or disorders responsive to α_1-adrenoceptor antagonists. Further, as some of the compounds are selective α_1-adrenoceptor ligands they may be particularly useful as PET or SPECT ligands.

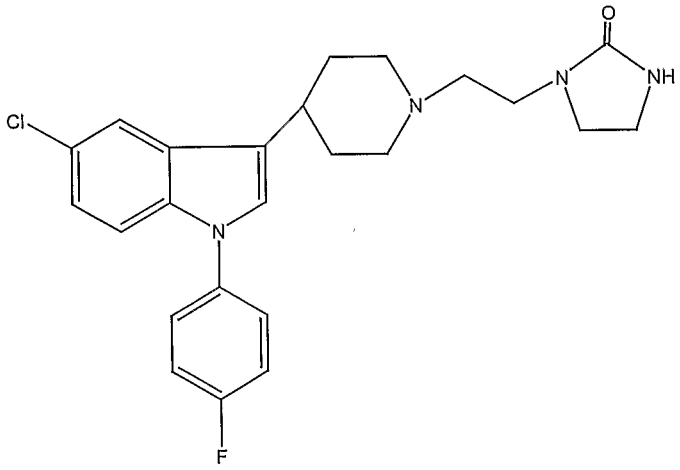
Background

US patent No. 4,710,500 discloses, in general, optionally 5-substituted indole derivatives having the general formula:



The compounds may be substituted in position 5 with a substituent selected from halogen, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, lower alkylthio, CF_3, lower alkylsulphonyl, amino, lower alkylamino and lower di-alkyamino. The compounds are claimed to be potent and long-lasting dopamine antagonists, and accordingly useful for the treatment of psychoses, and additionally to be strong 5-HT antagonists indicating effects in the treatment of negative symptoms of schizophrenia and depression and for the treatment of cardiovascular diseases.

The use of sertindole having the formula



as an antipsychotic is specifically claimed in EP-A2-0 392 959.

This type of compounds has also been shown to be useful for the treatment of a range of other disorders including anxiety (WO 92/00070), cognitive disorders (WO 92/15303), abuse (WO 92/15302) and hypertension (WO 92/15301).

WO 92/15301 discloses compounds having affinity for the α_1-adrenoceptor, however, the compounds disclosed herein are not selective for the α_1-adrenoceptor.

WO 99/46259 and WO 01/21614 relate to α_1-adrenoceptor antagonists related to the compounds of the invention which, however, have very different substituents on the piperazine, piperidine and tetrahydropyridine ring. The compounds of WO 01/21614 are not substituted in position 5 of the indole ring with a heteroaryl group.

Interest in the development of α_1-adrenoceptor antagonists has primarily focused on therapeutics for the treatment of cardiovascular diseases (Hieble et al., *Exp. Opin. Invest. Drugs,* **1997**, 6, 3657). Prazosin is the prototype of an α_1-adrenoceptor antagonist which has very potent peripherally effects. Prazosin has also in some animal models indicated effects in the central nervous system, although prazosin is considered to have poor CNS penetration.

Evidence exists indicating that blockade of α_1-adrenoceptor neurotransmission could be beneficial in the treatment of psychoses. Most classical antipsychotics including clozapine bind potently to α_1-adrenoceptors labelled with [^{3}H]prazosin or [^{3}H]WB-4101. Some studies seem to indicate a central role of the α_1-component for the atypical profile of clozapine. (Baldessarini, et al., *Br. J. Psychiatry*, **1992**, 160, 12-16 and Prinssen, et al., *Eur. J. Pharmacol.*, **1994**, 262, 167-170).

Several lines of evidence indicate that blockade of α_1-adrenoceptor neurotransmission alone could be beneficial in the treatment of schizophrenia. Metabolic and post-mortem studies indicate hyperactivity of the noradrenergic system in psychotic patients (R.J. Baldessarini, D. Huston-Lyons, A. Campbell, E. Marsh, B.M. Cohen, *Br J Psychiatry Suppl* 12 (1992)). The firing pattern of midbrain dopamine neurons in rats is modulated by prazosin administration (J. Grenhoff, T.H. Svensson, *Eur J Pharmacol* **233**, 79 (1993)) and by electrical stimulation of noradrenergic neurons in the locus coeruleus (J. Grenhoff, M. Nisell, S. Ferre, G. Aston-Jones, T.H. Svensson, *J Neural Transm Gen Sect* **93**, 11 (1993)). In addition, prazosin reversed the disruption of prepulse inhibition of acoustic startle response in rats induced by phencyclidine (PCP) (V.P. Bakshi, M.A. Geyer, *J Pharmacol Exp Ther* **283**, 666 (1997) and B.S. Carasso, V.P. Bakshi, M.A. Geyer, *Neuropharmacology* **37**, 401 (1998)).

Further, repeated co-administration of prazosin and haloperidol was found to reduce the effect of haloperidol on the firing of dopamine neurons in nigrostriatal areas, suggesting that the combination would be effective as antipsychotic treatment without producing extrapyramidal side effects (EPS) (Chiodo, et al., *J. Neurosci.* **1985**, 3, 2539-2544).

Co-administration of sub-threshold doses of the dopamine D_2 antagonist raclopride and the α_1-adrenoceptor antagonist prazosin caused significantly enhanced suppression of conditioned avoidance behaviour in rats without inducing catalepsy (M.L. Wadenberg, *et al, J Neural Transm* **107**, 1229 (2000)). It was suggested that α_1 adrenoceptor blockade in the presence of a low D_2 receptor occupancy might improve antipsychotic efficacy and thereby improve the therapeutic window with regard to extrapyramidal side effects.

It has also been suggested that centrally acting α_1-adrenoceptor antagonists will have antimanic effects while corresponding agonists would be beneficial for the treatment of depression (Lipinsky, et al., *Life Sciences*, **1987**, 40, 1947-1963).

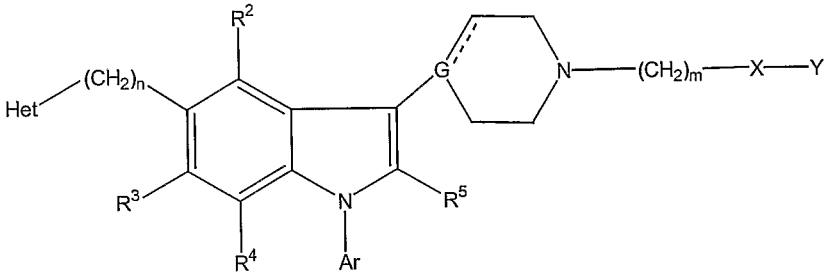
Centrally acting α_1-adrenoceptor antagonists may also have effect against Post Traumatic Stress Disorder (Raskind, M.A.; Dobie, D.J.; Kanter, E.D.; Petrie, E.C.; Thompson, C.E.; Peskind, E.R., J. Clin. Psychiatry, 2000, 61, 129-133 and Taylor, F.; Raskind, M.A., J. Clin Psychopharmacol. 2002, 22, 82-85)

Labelled compounds of the present invention are considered to be valuable PET (positron emission tomography) ligands and SPECT ligands due to their selectivity for α_1-adrenoceptors.

Finally, it is well established that α_1-adrenoceptor antagonists acting peripherally are useful for the treatment of benign prostatic hyperplacia, hypertension and cardiac arrhytmias and for the reduction of intra ocular pressure.

The invention

According to the present invention novel compounds having the formula



(I)

wherein

Het is a five- or six-membered aromatic, heterocyclic ring containing at least one nitrogen atom as a ring member, and optionally substituted with C_{1-6}-alkyl;

n is 0 or 1;

G is N, C or CH; the dotted line meaning a bond when G is C, and the dotted line meaning no bond when G is CH or N;

Ar is phenyl optionally substituted with one or more substituents independently selected from halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl and cyano, or Ar is 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, C_{1-6}-alkylamino and C_{1-6}-dialkylamino;

m is 1, 2 or 3;

X is a bond, $-CH_2-$, -O-, -S-, -NH-, -NHCO- or -CONH-; and

Y is cyano, C_{1-6}-alkyloxy, C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkoxy, or C_{1-6}-alkylcarbonyloxy or Y is phenyl which may optionally be substituted one or more times with substituents selected from halogen, C_{1-6}-alkyl, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyloxy, nitro, cyano, amino, C_{1-6}-alkylamino, C_{1-6}-dialkylamino, methylenedioxy and ethylenedioxy, or Y is an aromatic mono- or bicyclic heterocyclic ring containing only one heteroatom which may optionally be substituted one or more times with substituents selected from halogen, C_{1-6}-alkyl, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyloxy, nitro, cyano, amino, C_{1-6}-alkylamino and C_{1-6}-dialkylamino; provided Y is not cyano when X is O, S, NH, NHCO or CONH; and Y is not C_{1-6}-alkoxy when X is O, S or NH;

or pharmaceutically acceptable acid addition salts thereof, is provided.

In a particular embodiment of the invention, Het is optionally substituted triazolyl, pyrazolyl, pyrimidyl, pyridinyl or imidazolyl. Suitably, Het is 1-methyl-1*H*-1,2,4-triazol-3-yl, 2-methyl-2*H*-1,2,4-triazol-3-yl, 3-methyl-3*H*-1,2,3-triazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, 2-methyl-2*H*-pyrazol-3-yl, 1-methyl-1*H*-imidazol-2-yl, pyrimidin-2-yl or pyridin-3-yl.

In another embodiment, the invention relates to compounds of formula (I) wherein Y is cyano, C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkoxy, or C_{1-6}-alkylcarbonyloxy or Y is optionally substituted phenyl, in particular the group of compounds wherein Y is C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkoxy, or C_{1-6}-alkylcarbonyloxy or Y is optionally substituted phenyl

In a third embodiment, X is a bond , $-CH_2-$, O or S, preferably O or S.

In a fourth embodiment, Y is an optionally substituted, aromatic bicyclic heterocyclic ring containing only one heteroatom, such as for example optionally substituted indolyl, benzofuranyl or dihydro-1,4-benzodioxinyl.

In a fifth embodiment, X is -NHCO- or -CONH-.

In a sixth embodiment, Y is optionally substituted phenyl.

In a seventh embodiment, the invention relates to compounds wherein Y is C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkoxy or C_{1-6}-alkylcarbonyloxy

Finally, the invention relates to the group of compounds wherein Y is cyano.

The compounds of the invention are potent α_1-adrenoceptor antagonists and the compounds are therefore useful for the treatment of disorders or diseases responsive to antagonism of the α_1-adrenoceptor.

Some of the compounds of the invention have stronger affinity to the α_{1a}-adrenoceptor than the α_{1b}-adrenoceptor and the α_{1d}-adrenoceptor.

Thus, in another aspect, the present invention relates to a pharmaceutical composition comprising at least one compound of formula I as defined above or a pharmaceutically acceptable acid addition salt thereof and optionally a second pharmaceutically active ingredient in combination with one or more pharmaceutically acceptable carriers or diluents.

In a further aspect, the present invention relates to the use of a compound of formula I as defined above or an acid addition salt thereof and optionally a second pharmaceutically active ingredient for the manufacture of a pharmaceutical medicament for the treatment of a disorder or disease responsive to antagonism of α_1-adrenoceptor.

Thus, in still another aspect, the present invention relates to the use of a compound of formula I as above and optionally a second agent having antipsychotic activity for the preparation of a medicament for the treatment of psychosis.

Diseases and disorders responsive to antagonism of α_1-adrenoceptors includes psychosis, mania, benign prostatic hyperplacia, hypertension, post traumatic stress disorder and cardiac arrhytmias. Antagonists of α_1-adrenoceptors are also useful for the reduction of intra ocular pressure.

In a further aspect, the invention relates to a method for the treatment of a disorder or disease responsive to antagonism of $\alpha 1$-adrenoceptors in a mammal comprising administering a compound of formula I as above and optionally a second pharmaceutically active ingredient to said mammal.

In still another aspect, the present invention relates to a method for the treatment of psychosis in a mammal comprising administering a compound of formula I as above and optionally a second agent having antipsychotic activity to said mammal.

The above mentioned second pharmaceutically active ingredient may be another agent having antipsychotic activity, for example an agent having dopamine D_2 antagonistic effect. As

mentioned above, evidence exists which indicate that such combinations may be advantageous for treatment of psychoses without causing extrapyramidal effects.

Finally, the present invention relates to radio-labelled compounds of formula I and the use thereof in various biological assays and PET- or SPECT studies.

Detailed Description of the Invention

When used herein halogen means fluoro, chloro, bromo or iodo.

The term C_{1-6} alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including groups such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

The terms C_{1-6}-alkoxy, C_{1-6}-alkylamino, C_{1-6}-dialkylamino etc. designate such groups in which C_{1-6} alkyl is as defined above.

Het meaning a five-membered aromatic heterocyclic ring containing at least one nitrogen as a ring member, includes, but are not limited to, heterocyclic rings selected from pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, tetrazol-1-yl, tetrazol-2-yl, tetrazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, , thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,3,4-oxadiazol-5-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-thiadiazol-3-yl, oxatriazol-4-yl and thiatriazol-4-yl.

Het meaning a six-membered aromatic heterocyclic ring containing at least one nitrogen as a ring member, includes, but are not limited to, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl and pyrimidin-5-yl.

Y meaning an aromatic mono- or bicyclic heterocyclic ring containing only one heteroatom includes, but are not limited to, rings such as pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, furan-2-yl, furan-3-yl, 2-thienyl, 3-thienyl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl, indol-7-yl, benzofuran-2-yl, benzofuran-3-yl, benzofuran-

4-yl, benzofuran-5-yl, benzofuran-6-yl, benzofuran-7-yl, isobenzofuran-1-yl, isobenzofuran-3-yl, isobenzofuran-4-yl, isobenzofuran-5-yl, isobenzofuran-6-yl, isobenzofuran-7-yl, benzothien-2-yl, benzothien-3-yl, benzothien-4-yl, benzothien-5-yl, benzothien-6-yl, benzothien-7-yl, isobenzothien-1-yl, isobenzothien-3-yl, isobenzothien-4-yl, isobenzothien-5-yl, isobensothien-6-yl, isobenzothien-7-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, quinolin-8-yl, isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl and isoquinolin-8-yl.

The acid addition salts of the compounds of the invention are pharmaceutically acceptable salts formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids.

The selectivity of the compounds of the invention for the α_1-adrenoceptor makes them particularly useful for the development of radiolabelled ligands useful in various biological assays and in PET and SPECT studies.

The compounds of the invention "can be labelled by reacting the unlabelled precursor molecules with [^{11}C] methyl iodide, [^{11}C] methyl triflate, or other [^{11}C] labelled reagents derived from [^{11}C] carbon dioxide. The compounds may also be labelled with ^{18}F, ^{123}I or ^{125}I.

Radiolabeling of compounds of the present invention may be performed according to radiolabeling methods known and used in the prior art. For example, as stated in the specification, compounds can be labelled by reaction of the appropriate precursors with radio-labelled reagents, including ^{11}C-labelled reagents such as [^{11}C]methyl iodide and [^{11}C]methyl triflate.

It is also within the knowledge of a person skilled in the art of radiopharmaceuticals to label compounds with ^{18}F or ^{123}I. Compounds of the present invention radiolabelled with ^{18}F may be prepared by aromatic nucleophilic substitution of a precursor molecule containing an appropriate leaving group (such as nitro, bromo, iodo or triflate) by reaction with [^{18}F]F$^-$. For example, compounds of the present invention may be radiolabelled with ^{18}F in the 4-position of the phenyl

group attached to the indole N-1. The compounds may be prepared by aromatic nucleophilic substitution of a precursor molecule containing an appropriate leaving group (such as nitro, bromo, iodo or triflate) by reaction with [^{18}F]F-. After appropriate activation of the aromatic ring with one or two electron withdrawing groups, such as formyl group(s). The formyl groups may easily be removed after radioflourination by reaction with Wilkinson's catalyst in dioxane at elevated temperature (Sobrio, F.; Amokhtari, M.; Gourand, F.; Dhilly, M.; Dauphin, F.; Barré, L., *Bioorg. Med. Chem.* **2000**, 8, 2511-2518).

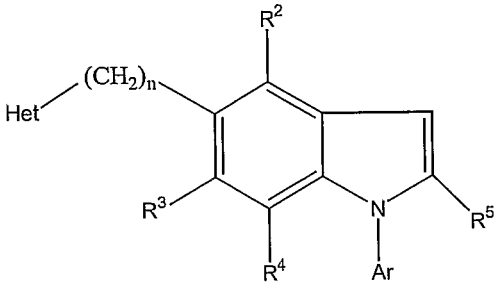
Radiolabelling with ^{125}I or ^{123}I may be performed by halodemetalation of the corresponding tin substituted (organotin) precursors, for example by treatment of an ethanolic solution of the organotin precursor with Na^{123}I or Na^{125}I in the presence of chloramine-T and aqueous hydrochloric acid analogously to the procedure described by Foged et al (Foged, C.; Halldin, C.; Hiltunen, J.; Braestrup, C.; Thomsen, C.; Hansen, H.C.; Suhara, T.; Pauli, S.; Swahn, C.-G.; Karlsson, P.; Larsson, S. and Farde, L., *Nucl. Med. Biol.* **1996**, 23, 201-209).

The organotin precursors of the compounds of the invention can be readily prepared from 1-(4-bromophenyl) or 1-(4-iodophenyl) substituted 5-heteroaryl-indoles by reaction with n-butyllithium or tert-butyllithium in THF at low temperature, followed by reaction with a trialkyltin halide such as trimethyltin chloride or tributyltin chloride. Magnesium metalated intermediates may also be used in place of lithium. Alternatively, palladium catalyzed reaction with hexaalkyldistannanes may also give the corresponding organotin precursors. (Ali, H.; Johan, and van Lier, J.E., *Synthesis* **1996**, 423-445)

Alternatively, 4-[^{18}F]flouroiodobenzene may be prepared as described in the literature (Shah, A.; Widdowson, D. A.; Pike, V. W., *J.Labelled Compd.Radiopharm.* **1997**, 40, 65-67), and reacted with N-unsubstituted indole to give the final radiolabelled compounds.

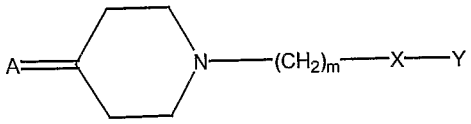
The compounds of the present invention can be prepared according to the procedures described below:

a) Reacting an indole derivative of the following formula



(II)

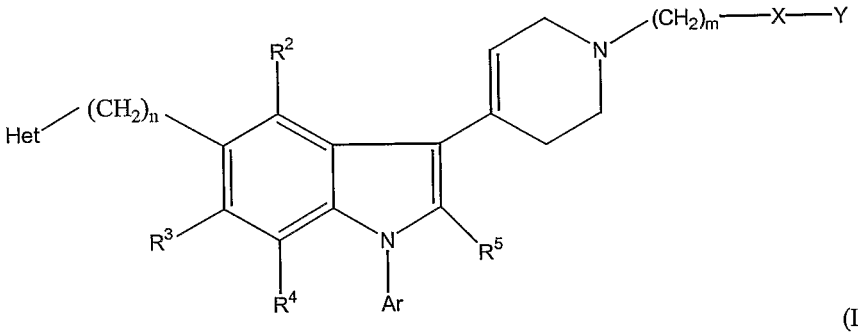
wherein R^2, R^3, R^4, R^5, Ar, Het and n are as defined above, with a 4-piperidone of the formula



(III)

wherein m, X and Y are as defined above, A is an oxygen atom or a $-O-(CH_2)_q-O-$ chain, wherein q is 2 or 3;

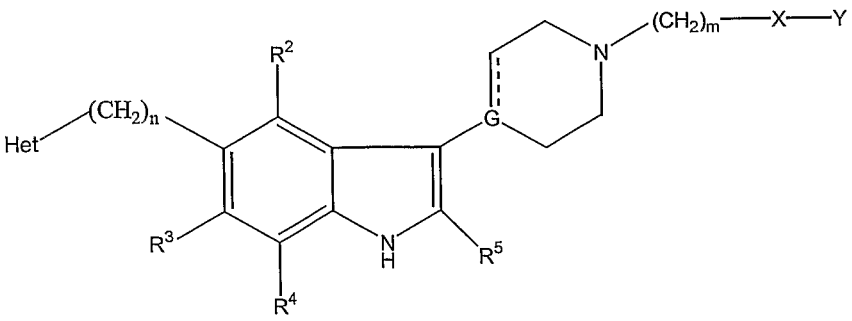
b) reducing the tetrahydropyridine double bond in a compound of the formula



(IV)

wherein R^2, R^3, R^4, R^5, m, X, Y, Ar, Het and n are as defined above;

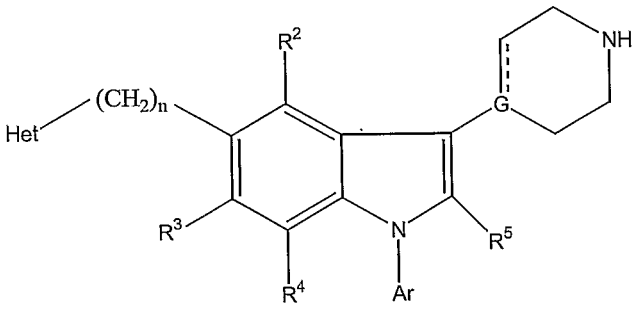
c) reacting a compound of the formula



(V)

wherein R^2, R^3, R^4, R^5, m, X, Y, G, the dotted line, Het and n are as defined above, with a compound of the formula Ar-hal wherein Ar is as defined above and "hal" is halogen, in the presence of a metal catalyst,

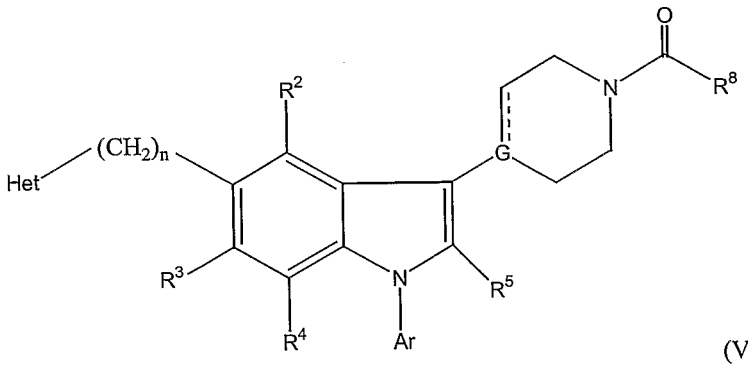
d) reacting a compound of the formula



(VI)

wherein R^2, R^3, R^4, R^5, G, the dotted line, Ar, Het and n are as defined above, with a reagent of formula L-$(CH_2)_m$-X-Y wherein m, X, and Y are defined above and L is halogen, mesylate or tosylate

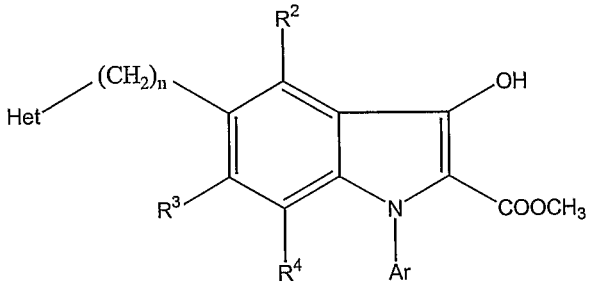
e) reducing the carbonyl group of a compound of the formula



(VII)

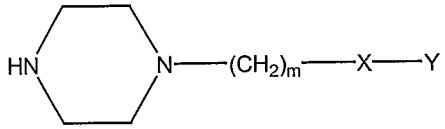
wherein R^2, R^3, R^4, R^5, G, the dotted line, Ar, Het and n are as defined above and R^8 is $(CH_2)_{(m-1)}$-X-Y, wherein m, X, and Y are defined above

f) decarboxylating a compound of the formula



(VIII)

wherein R^2, R^3, R^4, Ar, Het and n are as defined above, followed by reaction with a piperazine of the formula



(IX)

wherein m, X and Y is as defined above;

g) alkylating the group Het in a compound of formula I wherein Het is unsubstituted on at least one pyrrole-like nitrogen atom with an alkylating reagent, such as C_{1-6}-alkyl-L, wherein L is chloro, bromo, iodo, mesylate or tosylate.

Method g) may accordingly be used to introduce radiolabelled alkyl groups, such as [^{11}C]methyl iodide, [^{11}C]methyl triflate, etc.

Methods for the preparation of the starting materials used in the above processes are described in US patent No. 4,710,500, WO 92/00070, WO 99/46259 and in Perregaard et al., *J.Med.Chem.* **1992** (35), 1092-1101, or can be prepared analogously to the procedures described herein.

Starting materials wherein the group Het is tetrazol-5-yl may be prepared by reacting the corresponding 5-cyano-indole with azide.

Starting materials wherein the group Het-$(CH_2)_n$- is tetrazol-5-ylmethyl may likewise be prepared from the corresponding indole containing a 5-cyanomethyl group by reaction with azide. The 5-cyanomethyl-indoles may be prepared by hydrolysis of the corresponding 5-cyano-indole, reduction of the carboxylic acid functionality obtained to hydroxymethyl, reaction with methanesulphonyl chloride to form the corresponding 5-chloromethyl-indoles followed by reaction with a cyanide to form the 5-cyanomethyl-indole.

N-Boc-protected 5-bromo-1-Ar-3-piperidinyl-1*H*-indole is prepared in three steps from 5-bromo-1-Ar-1*H*-indole. Reaction of 4-piperidin-2-one hydrochloride, hydrate with 5-bromo-Ar-fluorophenyl)-1*H*-indole using acidic conditions followed by catalytic hydrogenation analogously to published procedures (Perregaard, et al. *J Med Chem* **1992,** *35,* 1092) results in the unsubstituted piperidyl compound. Finally, reaction with boc-anhydride affords the desired starting material.

Introduction of heteroaryl groups in the 5-positions in the *N*-Boc-protected 5-bromo-1-Ar-3-piperidinyl-1*H*-indole is accomplished by two alternative methods A and B.

In Method A, the *N*-boc-protected 5-bromo-1-Ar-3-piperidinyl-1*H*-indole is treated with *n*-butyllithium followed by transmetalation to the corresponding zinc chloride. Addition of the appropriate heteroaryl halide and 5 mol% tetrakis(triphenylphosphine)palladium(0) affords the corresponding heteroaryl substituted intermediates. In the reverse method B deprotonation of the heteroaryl derivatives or halogen/metal exchange of heteroaryl halides followed by transmetalation to the corresponding zinc chlorides and tetrakis(triphenylphosphine)palladium(0) catalysed cross-coupling with the *N*-boc-protected 5-bromo-1-Ar-3-piperidinyl-1*H*-indole results in the corresponding 5-heteroaryl-indoles.

The boc-protected derivatives obtained by Methods A and B is deprotected and used as starting materials for method d) described below.

Starting materials for methods a), b), c) and e) may be prepared analogously using properly protected starting materials.

In method a), the reaction is performed under strong acidic conditions by heating. Trifluoroacetic acid or HCl in ethanol are preferred as acidic catalysts.

In method b), the reduction is preferably carried out at low hydrogen pressures (3 Ato.) in the presence of platinum or palladium on carbon black.

In method c), the arylation is preferably carried out at about 160-210 °C in aprotic polar solvents such as N-methyl-2-pyrrolodine or hexamethylphosphoric triamide with K_2CO_3 as base and copper as a catalyst.

In method d), the alkylations are performed in a an aprotic solvent such as dimethylformamide or acetonitrile using an appropriate base such as potassium carbonate or diisopropyl ethyl amine at elevated temperatures (50-120 °C).

In method e), the reduction is preferably carried out with $LiALH_4$ in THF or diethylether or with diborane in THF.

Method f), is a two step procedure in which compound VIII is first decarboxylated in the presence of an inorganic salt as e.g. LiCl or $MgCl_2$ in a polar solvent as e.g. diglyme, hexamethylphosphoric triamide or N-methyl-2-pyrolidone at elevated temperatures (120-150 °C). Finally, the appropriate piperazine is added and the temperature raised to about 200 °C and kept there until the corresponding indoxyle has disappeared according to TCL analysis. The compounds of Formula VIII are conveniently prepared according to the procedures reported by Unangst et al., *J. Heterocyclic Chem.* **1984**, 21, 709.

In method g), the alkylation with alkyl iodides or bromides is performed by in aprotic solvents such as acetone or dimethylformamide using an appropriate base such as potassium carbonate or diisopropyl ethyl amine at elevated temperatures (40-90 °C).

In the following, the invention is further illustrated by way of examples that, however, may not be construed as limiting.

Examples

General. All reactions were carried out under a positive pressure of nitrogen or argon. Glassware for water sensitive reactions was dried in an oven at 150 °C over night. THF was freshly distilled from sodium/benzophenone. DMF was sequentially dried and stored over 3 Å molecular sieves. $ZnCl_2$ was flame dried in vacuo and dissolved to 1.0 M in dry THF after cooling to room temperature. Acetone and CH_3CN for alkylation reactions were HPLC-grade. Saturated HCl/MeOH solutions were prepared by saturation of MeOH with HCl gas. For flash chromatography either silica gel of type Kieselgel 60, 230-400 mesh ASTM or Biotage Flash40 (50 or 100 g columns) were used. ^1H NMR spectra were recorded of all novel compounds at 250 MHz on a Bruker AC 250 or at 500 MHz on a Bruker Avance DRX500 instrument. Deuterated chloroform (99.8%D) or DMSO-d_6 (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet,

dd=double doublet, dt=double triplet, tt=triplet of triplets, m=multiplet. NMR signals corresponding to acidic protons are generally omitted. Melting points are reported uncorrected. Solvent residuals in elemental analysis samples were measured by Karl Fisher titration (H_2O) or by Thermo Gravimetric Analysis (TGA) on a TA-instruments TGA 2950 with heating rate 10 °C per min. The nature of the solvent was identified by ^{1}H-NMR. Solvent residuals are not reported in the NMR data. Analytical and preparative HPLC were run on a Shimadzu HPLC system with two Shimadzu LC-8A pumps. The UV trace was obtained using a Shimadzu SPD-10A detector operating at 254 nm. ELSD trace was obtained using a Sedere Sedex 55 detector operating at 42 °C and 2.3 bar. For analytical HPLC-MS a Perkin Elmer API 150EX mass spectrometer equipped with a Perkin Elmer SCIEX Heated Nebulizer (APCI) ion source. The total ion current (TIC) was recorded in positive mode for m/z 100-1000 amu. Analytical HPLC was run injecting 10 µL to a Waters Symmetry C-18 (4.6x30 mm, 3.5 µm) column. The sample was eluted with a gradient of the following solvent mixtures: A: water/TFA 100/0.05 and B: Acetonitrile/water/TFA 95/5/0.035. Gradient: A/B 90/10 → 0/100 during 4 minutes, then isocratic A/B 90/10 during 1 minute. Flow was 2 mL/min throughout. Preparative HPLC-MS was run with 190 µL injections on a YMC RP18 (50x20 mm) column with a gradient of A/B 80/20 → 0/100 during 7 minutes, then isocratic 80/20 during one minute. The flow was 22.7 mL/min throughout and detection was performed using the MS (TIC) signal in a split system. The reported purities are based on integration of the peaks in the UV and ELSD spectrum.

Reagents:

The following reagents were prepared according to published procedures: 3-(2-Chloroethyl)imidazolidin-2-one (Perregaard, et al. *Med Chem* **1992**, *35*, 1092 and Johnston, et al., *J Med Chem* **1963**, *6*, 669), 3-(2-chloroethyl)-oxazolidin-2-one (Robinson, et al., *J Am Chem Soc* **1972**, *94*, 7883), 3-(2-chloroethyl)-1-methyl-2-pyrrolidin-2-one (Sucrow, et al., *Chem. Ber.* **1972**, *105*, 1621), 1-methyl-1,2,3-triazole (Begtrup, et al., *Acta Chem Scand* **1990**, *44*, 1050), 4-bromo-1-methyl-1,2,3-triazole (Hüttel, et al., *Liebigs Ann Chem* **1955**, *593*, 207), 2-bromo-1-methyl-1,3,4-triazole (Bernardini, et al., *Soc Chim* **1975**, *5*, 647), 5-bromo-1-methyl-1,2,4-triazole (Bernardini, et al., *Soc Chim* **1975**, *5*, 647) and 3-bromo-1-methyl-1,2,4-triazole,[7] 3-Iodo-1-methylpyrazole (Balle, et al. *Synthesis* **2002**, 1509-1512).

Preparation of Starting Material

4-(5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (1). A solution of 5-Bromo-1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indole (125 g, 0.33 mol) (Prepared as described by Perregaard et al *J Med Chem* **1992**, *35*, 1092) and di-*tert*-butyl

dicarbonate (260 g, 1.2 mol) in 1:1 THF/H_2O mixture (1 L) was stirred over night with K_2CO_3 (300 g, 2.2 mol) at 60 °C. EtOAc (1 L) was added. After separation of the two phases, the aqueous phase was extracted with EtOAc (3 × 0.5 L). The combined organic phases were washed with brine and dried over $MgSO_4$. The crude product (115 g) was washed with cold MeOH to yield 97 g of **1** as white crystals: Mp 160-162 °C (heptane); ^{1}H-NMR ($CDCl_3$): 1.49 (s, 9H), 1.65 (q, 2H), 2.04 (d, 2H), 2.85-3.00 (m, 3H), 4.25 (d, 2H), 7.03 (s, 1H), 7.15-7.35 (m, 4H), 7.39-7.43 (m, 2H), 7.78 (s, 1H); MS m/z (relative intensity): 473 + 475 (MH+, 1%), 417+419 (40%), 373+375(100%); Anal. ($C_{24}H_{26}BrFN_2O_2$): C, H, N.

Preparation of Intermediates (Method A)

Cross-coupling of 4-(5-bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (1) with a heteroaryl halide

4-(5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester **(1)** (10 g, 21.1 mmol) in THF (20 mL) was added during 2 minutes to a solution of *n*-butyllithium (39.6 mL, 63.4 mmol) in THF (210 mL) at –78 °C. After stirring for 3 minutes $ZnCl_2$ in THF (105.6 mL, 105.6 mmol) was added. The solution was stirred for further 30 minutes at –78 °C. The heteroaryl halide (amount specified below) was added together with $Pd(PPh_3)_4$ (1.2 g, 5 mol %) and DMF (60 mL). The reaction mixture was stirred at 80 °C for 8 h. After cooling to room temperature, H_2O (300 mL) and EtOAc (500 mL) were added and the phases were separated. The organic phase was washed with H_2O (200 mL) and saturated aqueous $CaCl_2$ (3 × 100 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography. The amount of reagents and solvents were scaled according to the actual amount of **1** used.

The following derivatives were prepared according to Method A

4-(1-(4-Fluorophenyl)-5-(1-methylpyrazol-3-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2a). A solution of **1** (6.8 g, 14.4 mmol) in THF was reacted with 1-methyl-3-iodopyrazole (3.0 g, 14.4 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 20/80 → 50/50) to yield 4.31 g (63%) of **2a** as white crystals: Mp. 145.3-145.6 °C (EtOAc/heptane); ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.68 (q, 2H), 2.10 (d, 2H), 2.93 (t, 2H), 3.11 (t, 1H), 3.98 (s, 3H), 4.26 (s, broad, 2H), 6.57 (d, J = 2.0 Hz, 1H), 7.04 (s, 1H), 7.17-7.24 (m, 2H), 7.39 (d, J = 2.1 Hz, 1H), 7.42-7.52 (m, 3H), 7.65 (d, J = 8.6 Hz, 1H), 8.08 (s, 1H); MS m/z: 475 (7%, MH^+), 419 (100%), 375 (73%); Anal. ($C_{28}H_{31}N_4FO_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(1-methylpyrazol-4-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2b). A solution of **1** (10 g, 21.1 mmol) in THF was reacted with 1-methyl-4-

bromopyrazole (4.2 g, 31.7 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 20/80 → 30/70) to yield 2.8 g (28%) of **2b** as white crystals: Mp 133-136 °C (EtOAc/heptane); ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.71 (q, 2H), 2.10 (d, 2H), 2.94 (t, 2H), 3.05 (t, 1H), 3.96 (s, 3H), 4.27 (s, broad, 2H), 7.04 (s, 1H), 7.20-7.25 (m, 2H), 7.34 (d, 1H), 7.41-7.50 (m, 3H), 7.63 (s, 1H), 7.71 (s, 1H), 7.79 (s, 1H); MS m/z: 475 (5%, MH^+), 419 (86%), 375 (100%); Anal. ($C_{28}H_{31}N_4FO_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2c). A solution of **1** (20 g, 42 mmol) in THF was reacted with 3-bromo-1-methyl-1,2,4-triazole (8.8 g, 55 mmol). The crude product was purified by flash chromatography (EtOAc/heptane/MeOH 50/50/0 → 100/0/0 → 90/0/10) and crystallised from Et_2O to yield 8 g (40%) of **2c** as white crystals: Mp 189-191 °C (Et_2O); ^{1}H-NMR ($CDCl_3$) 1.50 (s, 9H), 1.70 (q, 2H), 2.12 (d, 2H), 2.95 (t, 2H), 3.13 (t, 1H), 4.00 (s, 3H), 4.28 (s, broad, 2H), 7.06 (s, 1H), 7.15-7.28 (m, 2H), 7.40-7.52 (m, 3H), 8.00 (d, 1H), 8.08 (s, 1H), 8.42 (s, 1H); MS m/z: 476 (72%, MH^+), 420 (66%), 376 (100%); Anal. ($C_{27}H_{30}N_5FO_2 \cdot 2.17$ % Et_2O): C, H, N.

4-(1-(4-Fluorophenyl)-5-(1-methyl-1,3,4-triazol-2-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2d). A solution of **1** (10 g, 21.1 mmol) in THF was reacted with 2-bromo-1-methyl-1,3,4-triazole (2.8 g, 17.3 mmol). The crude product was purified by flash chromatography (EtOAc/heptane/MeOH 30/70/0 → 100/0/0 → 90/0/10) to yield 2.5 g (31%) of **2d** as white crystals: Mp 156-158 °C (toluene/heptane 1:1); ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.70 (q, 2H), 2.08 (d, 2H), 2.90 (t, 2H), 3.07 (t, 1H), 3.78 (s, 3H), 4.26 (s, broad, 2H), 7.13 (s, 1H), 7.20-7.28 (m, 2H), 7.41- 7.50 (m, 3H), 7.53 (d, 1H), 8.05 (s, 1H), 8.21 (s, 1H); MS m/z: 476 (100%, MH^+), 420 (51 %), 376 (83%); Anal. ($C_{27}H_{30}N_5FO_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-5-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2e). A solution of **1** (7.5 g, 15.8 mmol) in THF was reacted with 5-bromo-1-methyl-1,2,4-triazole (2.1 g, 13 mmol). The crude product was purified by flash chromatography (EtOAc/heptane/MeOH 30/70/0 → 100/0/0 → 90/0/10) to yield 2.8 g (45%) of **2e** as a pale yellow foam: ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.70 (q, 2H), 2.09 (d, 2H), 2.91 (t, 2H), 3.07 (t, 1H), 4.03 (s, 3H), 4.28 (s, broad, 2H), 7.13 (s, 1H), 7.20-7.30 (m, 2H), 7.42-7.50 (m, 3H), 7.52 (d, 1H), 7.96 (s, 1H), 8.02 (s, 1H); MS m/z: 476 (100%, MH^+), 420 (33%), 376 (41%); Anal. ($C_{27}H_{30}N_5FO_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2f). A solution of **1** (18 g, 38 mmol mmol) in THF was reacted with 2-

bromopyrimidine (10 g, 75 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 10/90 → EtOAc/MeOH 90/10) and crystallised from Et_2O to yield 12 g (67%) of **2f** as white crystals: Mp. 164-166 °C (Et_2O); ^{1}H-NMR ($CDCl_3$) 1.50 (s, 9H), 1.71 (q, 2H), 2.14 (d, 2H), 2.96 (t, 2H), 3.16 (t, 1H), 4.27 (s, broad, 2H), 7.08 (s, 1H), 7.13 (t, 1H), 7.20-7.25 (m, 2H), 7.43-7.49 (m, 2H), 7.51 (d, 1H), 8.36 (d, 1H), 8.77-8.81 (m, 3H); MS m/z: 473 (11%, MH^+), 417 (100%), 373 (84%); Anal. ($C_{28}H_{29}N_4FO_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(pyrimidin-5-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2g). A solution of **1** (10 g, 21.1 mmol) in THF was reacted with 5-bromopyrimidine (5g, 31.6 mmol). Flash chromatography (EtOAc/heptane/NEt_3 30/70/4 → 70/30/4) gave 8.2 g which was recrystallised form toluene/heptane 1:1 to yield 5.0 g (50%) of **2g**: Mp 144-146 °C (toluene/heptane 1:1); MS m/z: 473 (MH+, 3%), 417 (100%), 373 (33%); ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.75 (q, 2H), 2.13 (d, 2H), 2.95 (t, 2H), 3.08 (t, 1H), 4.28 (s, broad, 2H), 7.13 (s, 1H), 7.20-7.30 (m, 2H), 7.42 (dd, 1H), 7.43-7.50 (m, 2H) 7.57 (d, 1H), 7.85 (d, 1H), 9.02 (s, 2H), 9.19 (s, 1H); Anal. ($C_{28}H_{29}FN_4O_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(1-methyl-1,2,3-triazol-4-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (2h). A solution of **1** (4.7 g, 10 mmol) in THF was reacted with 4-bromo-1-methyl-1,2,3-triazole (1.1 g, 6.8 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 20/80 → 100/0) to yield 900 mg (28%) of **2h** as a white foam: ^{1}H-NMR ($CDCl_3$) 1.50 (s, 9H), 1.69 (q, 2H), 2.12 (d, 2H), 2.94 (t, 2H), 3.09 (t, 1H), 4.18 (s, 3H), 4.28 (s, broad, 1H), 7.06 (s, 1H), 7.17-7.24 (m, 2H), 7.40-7.55 (m, 3H), 7.61 (d, 1H), 7.78 (s, 1H), 8.23 (s, 1H); MS m/z: 476 (4%, MH^+), 420 (46%), 376 (100%); Anal.($C_{27}H_{30}N_5FO_2 \cdot 2.70$ % EtOAc): C, H, N.

Preparation of Intermediates (Method B)

Cross-coupling of a heteroarylzinc chloride with 4-(5-bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (1)

4-(5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester **(1)** (8.3 g, 16.9 mmol) was added to a solution of heteroarylzinc chloride in THF (amount and preparation specified below) with $Pd(PPh_3)_4$ (5 mol%) and DMF (30% of the amount of THF). The solution was stirred at 80 °C for 8 h. Work up was performed as described in method A. The amounts of reagents and solvents were scaled according to the actual amount of **1** used.

The following derivatives were prepared according to Method B:

4-(1-(4-Fluorophenyl)-5-(1-methylpyrazol-5-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (3a). 1-Methylpyrazole (3.2 g, 39 mmol) in THF (200 mL) was cooled to – 78 °C.

n-butyllithium (43 mL, 26.9 mmol) was added during 5 minutes. The solution was heated slowly to room temperature during 15 minutes and cooled again to –78 °C. $ZnCl_2$ in THF (120 mL, 120 mmol) was added and the solution was stirred at –78 °C for 30 minutes. Reaction with **1** (14.2 g, 30 mmol) was performed following method B. Flash chromatography (EtOAc/heptane/NEt_3 30/70/5 → 50/50/5) and recrystallisation from CH_2Cl_2 afforded 11.5 g (80%) of **3a**: Mp 166-168 °C (CH_2Cl_2); ^{1}H-NMR ($CDCL_3$): 1.49 (s, 9H), 1.72 (q, 2H), 2.07 (d, 2H), 2.93 (t, 2H), 3.05 (t, 1H), 3.90 (s, 3H), 4.26 (s, broad, 2H), 6.32 (s, 1H), 7.10 (s, 1H), 7.20-7.30 (m, 3H), 7.40-7.47 (m, 2H), 7.50 (d, 1H), 7.54 (s, 1H), 7.69 (s, 1H); Anal. ($C_{28}H_{31}FN_4O_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(1-methylimidazol-2-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (3b). 1-Methylimidazole (1.39 g, 16.9 mmol) in THF (195 mL) was cooled to –78 °C. *n*-Butyllithium (14.7 mL, 23.5 mmol) was added during 2 minutes. The solution was stirred for 5 minutes at –78 °C and $ZnCl_2$ in THF (60 mL, 60 mmol) was added. After stirring at –78 °C for 1 h reaction with **1** (8.30 g, 16.9 mmol) was performed following method B. Flash chromatography (EtOAc/heptane/NEt_3 30/70/4 → 70/30/4) afforded 6.77 g which was recrystallised from toluene/heptane 1:1 to give 4.73 g (59%): Mp 189-191 °C (toluene/heptane 1:1); ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 7.69 (q, 2H), 2.10 (d, 2H), 2.89 (t, 2H), 3.05 (t, 1H), 3.77 (s, 3H), 4.25 (s, broad, 2H), 6.99 (s, 1H), 7.09 (s, 1H), 7.15 (s, 1H), 7.15-7.25 (m, 2H), 7.4-7.55 (m, 4H), 7.97 (s, 1H); Anal. ($C_{28}H_{31}FN_4O_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(1-methyl-1,2,3-triazol-5-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (3c). 1-Methyl-1,2,3-triazole (1,71 g, 20,6 mmol) was dissolved in THF (200 mL) and cooled to –78 °C. *n*-Butyllithium (15.4 mL, 24.7 mmol) was added during 2 minutes and the solution was stirred for further 5 minutes before $ZnCl_2$ in THF (61.8 mL, 61.8 mmol) was added. After 30 minutes at –78 °C reaction with **1** (9.75 g, 20.6 mmol) was performed following method B. Purification by flash chromatography (EtOAc/heptane/EtOH 30/70/2) gave 6.8 g which was recrystallised from toluene/heptane 1:2 to yield 4.3 g (44%) of **3c**: Mp 137-141 °C (toluene/heptane 1:2); ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.70 (q, 2H), 22.08 (d, 2H), 2.93 (t, 2H), 3.05 (t, 1H), 4.09 (s, 3H), 4.30 (s, broad, 2H), 7.15 (s, 1H), 7.20-7.30 (m, 3H), 7.40-7.50 (m, 2H), 7.45 (d, 1H), 7.69 (s, 1H), 7.74 (s, 1H); Anal. ($C_{27}H_{30}FN_5O_2$): C, H, N.

4-(1-(4-Fluorophenyl)-5-(pyridin-3-yl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (3d). 3-Bromopyridine was lithiated as described by Furneaux et al. *Tetrahedron* **1997**, *53*, 2915. THF (200 mL) was cooled to –100 °C (Et_2O/liquid N_2) and *n*-butyllithium (19 mL, 30.4 mmol) was added. 3-Bromopyridine (4.00 g, 25.3 mmol) was added during 2 minutes. After 20 minutes at –100 °C $ZnCl_2$ in THF (60 mL, 60 mmol) was added. Hereby a white precipitate was

formed. The temperature was shortly raised to –30 °C to dissolve the precipitate and thereafter stirred at –78 °C for 30 minutes. Reaction with **1** (10 g, 21.1 mmol) was performed following method B. Flash chromatography (EtOAc/heptane/NEt_3 30/70/5) afforded 8.3 g which was recrystallised from EtOAc/heptane 1:1 to yield 6.0 g (60%) of **3d**: Mp 160-162 °C (EtOAc/heptane 1:1); MS m/z: 472 (MH+, 3%), 416 (100%), 372 (37 %); ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.74 (q, 2H), 2.14 (d, 2H), 2.93 (t, 2H), 3.10 (t, 1H), 4.29 (s, broad, 2H), 7.11 (s, 1H), 7.20-7.30 (m, 2H), 7.36 (dd, 1H), 7.40-7.50 (m, 3H), 7.55 (d, 1H), 7.85 (d, 1H), 7.95 (dt, 1H), 8.57 (dd, 1H), 8.91 (d, 1H); Anal. ($C_{29}H_{30}FN_3O_2$): C, H, N.

Preparation of Compounds of the Invention

Deprotection and alkylation of 5-heteroaryl substituted 4-(1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl esters (2a-h, 3a-d) Method C

The 5-heteroaryl substituted 4-(1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (**2a-h, 3a-d**) (6.3 mmol) was dissolved in THF (20 mL) and HCl/MeOH (30 mL) was added. The solution was stirred for 4 h, and the solvents were removed *in vacuo*. 4-Methyl-2-pentanone (30 mL) was added and the solvent was again removed *in vacuo*. K_2CO_3 (5 g, 36 mmol), KI (0.5 g, 3 mmol), 4-methyl-2-pentanone (100 mL) and an alkyl halide (9.5 mmol if nothing else stated) were added and the solution was stirred under reflux for 8 h. The amounts of reagents and solvents were scaled according to the actual amount of 5-heteroaryl substituted 4-(1-(4-fluorophenyl)-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester used.

Work-up procedure 1: H_2O (50 mL) was added to the warm mixture and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with H_2O and with saturated aqueous $CaCl_2$, dried ($MgSO_4$) and the solvents were removed in vacuo. The resulting compound was purified by flash chromatography.

Work-up procedure 2: H_2O (50 mL) was added to the warm mixture and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL). Kieselgel was added to the combined organic phases and the solvents were removed in vacuo. The resulting compound adsorbed to kieselgel was purified using Biotage flash 40 equipped with a FZIM-0035 solid injection module.

3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile·oxalate (4a). Reaction of **2c** (1.2 g, 2.5 mmol) with 3-bromo-propionitrile (1.1g, 8.2 mmol) was performed according to method C followed by work-up procedure 2. The crude product was purified by flash chromatography (EtOAc/heptane 50/50 → EtOAc/MeOH 90/10) and precipitated with oxalic acid from EtOH to give 0.45 g (34 %) of the oxalate of **4a**: Mp. 216-217 °C (EtOH); ^{1}H-NMR (DMSO-d_6) 1.95 (qd, 2H), 2.12 (d, 2H), 2.76 (t, 2H), 2.93 (t, 2H), 3.02-

3.15 (m, 3H), 3.32 (d, 2H), 3.93 (s, 3H), 7.40-7.47 (m, 2H), 7.48 (s, 1H), 7.54 (d, 1H), 7.60-7.68 (m, 2H), 7.89 (d, 1H), 8.32 (s, 1H), 8.48 (s, 1H); MS m/z: 429 (100%, MH^+), 388 (12%), 241 (3%); Anal. ($C_{25}H_{25}FN_6 \cdot C_2H_2O_4 \cdot 0.55\ \% H_2O$): C, H, N.

The following derivative was prepared accordingly from **2f**:

3-{4-[1-(4-Fluoro-phenyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (4b). The free base was recrystallised from EtOAc/CH_2Cl_2 90/10 to give 0.96 g (63%) of **4b**: Mp 182-183 °C (EtOAc/CH_2Cl_2); ^{1}H-NMR (DMSO-d_6) 1.81 (q, 2H), 2.03 (d, 2H), 2.25 (t, 2H), 2.60-2.70 (s, broad, 2H), 2.70-2.80 (m, 2H), 2.83-2.95 (m, 1H), 3.02 (d, 2H), 3.33 (s, 3H), 7.38 (t, 1H), 7.41-7.48 (m, 2H), 7.52 (s, 1H), 7.58 (d, 1H), 7.62-7.70 (m, 2H) 8.31 (d, 1H), 8.77 (s, 1H), 8.89 (d, 2H); MS m/z: 426 (100%, MH^+), 384 (95%), 373 (95%); Anal. ($C_{26}H_{24}FN_5$): C, H, N.

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxyphenyl)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (4c). Reaction of **2c** (1.0 g, 2.10 mmol) with 1-(2-chloroethyl)-4-methoxybenzene (0.75 g, 4.4 mmol) was performed according to method C followed by work-up procedure 2. Flash chromatography (EtOAc/heptane 70/30 → EtOAc/MeOH/NEt_3 90/10/2) gave an oil (0.20 g) which was crystallised from EtOAc to give 0.13 g (12%) of compound **4c**: Mp 152-153 °C (EtOAc); ^{1}H-NMR (DMSO-d_6) 1.80 (qd, 2H), 2.00 (d, 2H), 2.18 (t, 2H), 2.54 (t, 2H), 2.73 (t, 2H), 2.80-2.90 (m, 1H), 3.07 (d, 2H), 3.72 (s, 3H), 3.93 (s, 3H), 6.84 (d, 2H), 7.16 (d, 2H), 7.35-7.42 (m, 2H), 7.47 (s, 1H), 7.53 (d, 1H), 7.60-7.70 (m, 2H), 7.86 (d, 1H), 8.30 (s, 1H), 8.49 (s, 1H); MS m/z: 510 (100%, MH^+); Anal. ($C_{31}H_{32}FN_5O$): C, H, N.

1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-3-[1-(2-phenylethyl)-piperidin-4-yl]-1H-indole (4d). Reaction of **2c** (1.0 g, 2.10 mmol) with (2-bromo-ethyl)-benzene (0.81 g, 4.4 mmol) was performed according to method C followed by work-up procedure 2. flash chromatography (EtOAc/heptane 70/30 → EtOAc/MeOH/NEt_3 90/10/2) gave 0.80 g which was recrystallised from EtOAc/heptane 1/3 to give 0.30 g (30%) of **4d**: Mp 244-245 °C (EtOAc/heptane 1/3); ^{1}H-NMR (DMSO-d_6) 1.90 (s, broad, 4H), 2.10 (s, broad, 2H), 2.51 (t, 2H), 2.90 (s, broad, 4H), 3.05 (s, broad, 1H), 3.93 (s, 3H), 7.23 (t, 1H), 7.30 (t, 2H), 7.31 (d, 2H), 7.40-7.48 (m, 2H), 7.52 (s, broad, 1H), 7.54 (d, 1H), 7.62-6.68 (m, 2H), 7.90 (d, 1H), 8.35 (s, 1H), 8.50 (s, 1H); MS m/z: 480 (100%, MH^+); Anal. ($C_{30}H_{30}FN_5$): C, H, N.

3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propan-1-ol (4e). Reaction of **2c** (1.0 g, 2.10 mmol) with 3-bromo-1-propanol (0,34 g, 2.40 mmol) was performed according to method C followed by workup procedure 2. Flash chromatography EtOAc/MeOH/NEt3 (100/0/2 → 75/25/2) gave 500 mg of crude product which

was crystallised from EtOAc/heptane (70/30) to give 250 mg of the title compound. Mp. 138-139 °C (EtOAc/heptane); ^{1}H-NMR (DMSO-d_6) 1.65 (q, 2H), 1.80 (qd, 2H), 2.02 (d, 2H), 2.20 (t, 2H), 2.49 (d, 2H), 2.90 (t, 1H), 3.05 (d, 2H), 3.32 (s, broad, 1H), 3.49 (t, 2H), 3.92 (s, 3H), 7.39-7.43 (m, 2H), 7.45 (s, 1H), 7.52 (d, 1H), 7.49-7.55 (m, 2H), 7.88 (d, 1H), 8.30 (s, 1H), 8.50 (s, 1H).

Preparation of further Compounds of the Invention

Each of the intermediates **2a-h** and **3a-d** (1 mmol) were dissolved in THF (30 mL) and reacted overnight with a saturated solution of HCl in MeOH (15 mL) at room temperature. The solvents were removed *in vacuo*, H_2O was added and pH adjusted to 10 by addition of aqueous ammonium hydroxide (25%). The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent, stock solutions of the piperidinyl derivatives were prepared by dissolving to 0.2 M by addition of DMSO. Stock solutions of alkyl halides were prepared by dissolving the halides in as little DMF as possible. Solutions were subsequently diluted to 0.2 M by addition of CH_3CN. Blocks (Multisyntech Microchem Blocks (MultiSynTech GmbH. **2002)** containing 96 1.2 mL reactors fitted with frits were loaded with K_2CO_3 (40 mg, 0.3 mmol) and KI (10 mg, 0.06 mmol). From the stock solutions the piperidinyl derivatives (0.15 mL, 0.03 mmol), the alkyl halide (0.225 mL, 0.045 mmol) and CH_3CN (0.3 mL) were added and the reactors were closed and rotated in an oven at 70 °C for 14 h. After cooling to 50 °C isocyanate resin (30 mg, 1 mmol/g) was added and the reactors were again closed and rotated at 50 °C for 2 h. After cooling to room temperature, solids were filtered off and washed with CH_3CN (2 × 0.3 mL). The combined organic phases were purified using SCX ion exchange chromatography as follows: Columns (Varian Bond Elut-SCX 500 mg/3 mL) were conditioned with acetic acid in methanol (10%, 3 mL). The combined organic phases from the sample was added and washed with MeOH (3 mL) and CH_3CN (3 mL). Finally, the sample was eluted with ammonia in MeOH (3 mL, 4 M). Between each step a slight air pressure was applied. The solvents were evaporated *in vacuo* and the solutions diluted to 2 mM in DMSO. The identity and purity of the compounds was determined by HPLC/MS analysis with UV and ELSD detection. Compounds with a purity of 70% or above were submitted for biological evaluation. The remaining compounds were purified by preparative LC/MS (Zeng, et al., *Comb Chem High Throughput Screen JID – 9810948,* **1998,** *1,* 101).

The following alkylating agents were used for the preparation of the examples listed below: 3-bromo-propionitrile, 3-(2-chloroethyl)-oxazolidin-2-one, 3-(2-chloroethyl)-1H-quinazoline-2,4-dione, 3-(2-chloroethyl)-1-methylpyrolidin-2-one, 1-(2-Chloro-ethyl)-4-methoxy-benzene, 1-(2-Bromo-ethoxy)-2-methoxy-ethane, 3-Bromo-*N*-(2,5-dimethoxy-phenyl)-propionamide, 3-Bromo-*N*-(2,5-dimethoxy-phenyl)-propionamide, 5-(3-Bromo-propoxy)-2,3-dihydro-benzo[1,4]dioxine,

1-(2-Chloro-ethoxy)-propane, 2-(3-Bromo-propoxy)-benzonitrile, 1-(3-Bromo-propoxy)-4-fluoro-2-methoxy-benzene, 3-(2-Bromo-ethyl)-benzofuran, 3-(2-Bromo-ethyl)-*1H*-indole, 3-(3-Bromo-propyl)-*1H*-indole

The following examples were prepared according to the general procedure d):

3-{4-[1-(4-Fluoro-phenyl)-5-(2-methyl-2H-pyrazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (5aa): R_f = 2.02; Purity UV/ELSD: 97.2/99.8

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-pyrazol-3-yl)-1*H*-indole (5ab): R_f = 2.47; Purity UV/ELSD: 78.9/96.7

3-[1-(2-1*H*-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-pyrazol-3-yl)-1*H*-indole (5ac): R_f = 2.38; Purity UV/ELSD: 99.0/100.0

3-{4-[1-(4-Fluoro-phenyl)-5-pyridin-3-yl-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (5ad): R_f = 1.59; Purity UV/ELSD: 91.5/100.0

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-pyridin-3-yl-1*H*-indole (5ae): R_f = 1.92; Purity UV/ELSD: 94.7/100.0

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-pyridin-3-yl-1*H*-indole (5af): R_f = 2.04; Purity UV/ELSD: 95.0/99.1

3-[1-(2-1*H*-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-pyridin-3-yl-1*H*-indole (5ag): R_f = 1.95; Purity UV/ELSD: 90.1/99.0

3-{1-[3-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole (5ah): R_f = 2.37; Purity UV/ELSD: 90.0/99.0

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole (5ai): R_f = 2.40; Purity UV/ELSD: 70.0/95.8

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indole (5aj): R_f = 2.47; Purity UV/ELSD: 70.0/95.5

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-pyrimidin-2-yl-1*H*-indole (5ak): R_f = 2.55; Purity UV/ELSD: 70.0/91.3

3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-imidazol-2-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (5al): R_f = 1.46; Purity UV/ELSD: 90.0/100.0

3-{4-[1-(4-Fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (5am): R_f = 1.76; Purity UV/ELSD: 95.0/100.0

3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (5an): R_f = 1.85; Purity UV/ELSD: 90.0/100.0

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-imidazol-2-yl)-1*H*-indole (5ao): R_f = 1.78; Purity UV/ELSD: 79.2/97.2

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (5ap): R_f = 2.28; Purity UV/ELSD: 70.0/97.5

1-(4-Fluoro-phenyl)-3-{1-[2-(2-methoxy-ethoxy)-ethyl]-piperidin-4-yl}-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole (5aq): R_f = 1.83; Purity UV/ELSD: 78.0/99.2

1-(4-Fluoro-phenyl)-3-{1-[2-(2-methoxy-ethoxy)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (5ar): R_f = 1.96; Purity UV/ELSD: 90.0/98.3

3-{1-[2-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)-ethyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole (5as): R_f = 2.16; Purity UV/ELSD: 90.0/100.0

3-{1-[3-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole (5at): R_f = 2.18; Purity UV/ELSD: 80.0/98.3

2-(2-{4-[1-(4-Fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-ethoxy)-ethanol (5au): R_f = 1.73; Purity UV/ELSD: 84.8/99.9

2-(2-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-ethoxy)-ethanol (5av): R_f = 1.81; Purity UV/ELSD: 84.6/100.0

2-(3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propoxy)-benzonitrile (5aw): R_f = 2.42; Purity UV/ELSD: 90.0/99.9

3-{1-[3-(4-Fluoro-2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole (5ax): R_f = 2.30; Purity UV/ELSD: 71.0/98.7

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole (5ay): R_f = 2.33; Purity UV/ELSD: 72.9/98.2

3-{1-[3-(4-Fluoro-2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(3-methyl-3H-1,2,3-triazol-4-yl)-1*H*-indole (5az): R_f = 2.41; Purity UV/ELSD: 70.8/97.3

3-{4-[1-(4-Fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (5ba): R_f = 1.96; Purity UV/ELSD: 85.1/99.2

3-{4-[1-(4-Fluoro-phenyl)-5-pyrimidin-2-yl-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile (5bb): R_f = 2.10; Purity UV/ELSD: 85.8/99.4

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-pyrimidin-2-yl-1*H*-indole (5bc): R_f = 2.49; Purity UV/ELSD: 96.2/99.5

N-(2,5-Dimethoxy-phenyl)-3-{4-[1-(4-fluoro-phenyl)-5-(2-methyl-2H-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionamide (5bd): R_f = 2.12; Purity UV/ELSD: 93.3/99.6

3-{1-[3-(4-Fluoro-2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (5be): R_f = 2.42; Purity UV/ELSD: 90.0/99.4

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole (5bf): R_f = 2.29; Purity UV/ELSD: 92.9/99.5

3-[1-(2-1*H*-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole (5bg): R_f = 2.37; Purity UV/ELSD: 99.0/99.1

3-[1-(2-1*H*-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1H-indole (5bh): R_f = 2.20; Purity UV/ELSD: 80.3/98.3

3-[1-(3-1*H*-indol-3-yl-propyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole (5bi): R_f = 2.39; Purity UV/ELSD: 89.9/98.9

3-[1-(3-1*H*-indol-3-yl-propyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indole (5bj): R_f = 2.49; Purity UV/ELSD: 87.9/98.7

Pharmacological Testing

The compounds of the invention have been tested using well-recognised and reliable methods. The tests are as follows:

INHIBITION OF ^{3}H-PRAZOSIN BINDING TO α_1-ADRENOCEPTORS IN RAT BRAIN IN VITRO

By this method the inhibition by drugs of the binding of ^{3}H-prazosin (0.25 nM) to α_1-adrenoceptors in membranes from rat brain is determined *in vitro*. Method and results in Hyttel & Larsen, J. Neurochem. **1985**, *44*, 1615 - 1622: Skarsfeldt & Hyttel, Eur. J. Pharmacol. **1986**, 125, 323 - 340; Hyttel & Larsen, In: Research advances in New Psychopharmacological Treatments for Alcoholism (eds. Naranjo & Sellers). Elsevier **1985**, pp. 107 - 119.

The compounds of the invention showed high affinity for the α_1-adrenoceptor. Most of the compounds having an IC_{50} value below 30 nM in this test.

INHIBITION OF ^{3}H-PRAZOSIN BINDING TO CLONED α_{1a}, α_{1b}, and α_{1d}, -ADRENOCEPTORS

Cell lines: Cell lines expressing the bovine α_{1a}, rat α_{1d} receptors and the hamster α_{1b} receptor were used in the assays.

In vitro binding assays: Briefly, the cells were homogenised in ice-cold 50 mM Tris, pH 7.7, using an Ultra-Turrax and the homogenates either kept on ice or stored at -80 °C until used. The assay buffer subsequently used contained 50 mM Tris, pH 7.7. Non-specific displacer was WB-4101 (1 μM) for the α_{1a}, α_{1b}, and α_{1d} assays. All assays were incubated at 25 °C for 20 minutes.

All assays were terminated by vacuum filtration on GF/B filters and counted in a scintillation counter (Wallac Trilux). The radioligand used was [^{3}H]prazosin.

It was found that some of the compounds of the invention have stronger affinity to the α_{1a}-adrenoceptor than the α_{1b}-adrenoceptor and the α_{1d}-adrenoceptor.

Further, many of the compounds of the invention have much stronger affinity for the α_1-adrenoceptor compared to the D_2 and the 5-HT_2 receptor.

Pharmaceutical compositions

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 100 mg.

The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

Formulation Examples

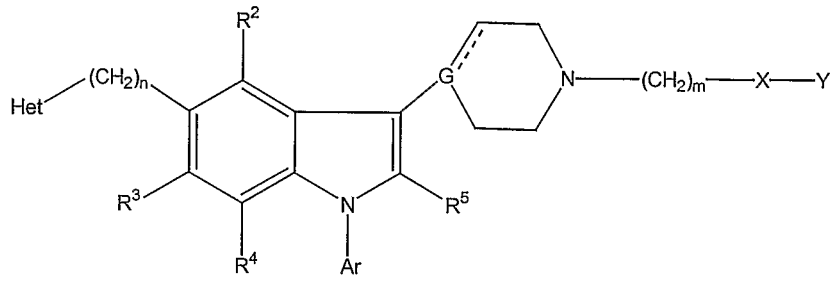
The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

Tablets may for example be prepared by mixing the active ingredient with ordinary adjuvants, carriers and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants, carriers or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilisation of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

CLAIMS

1. A compound having the general formula



I

wherein

Het is a five- or six-membered aromatic, heterocyclic ring containing at least one nitrogen atom as a ring member, and optionally substituted with C_{1-6}-alkyl;

n is 0 or 1;

G is N, C or CH; the dotted line meaning a bond when G is C, and the dotted line meaning no bond when G is CH or N;

Ar is phenyl optionally substituted with one or more substituents independently selected from halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl and cyano, or Ar is 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl or 4-pyridyl;

R^2, R^3, R^4 and R^5 are independently selected from hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, C_{1-6}-alkylamino and C_{1-6}-dialkylamino;

m is 1, 2 or 3;

X is a bond, $-CH_2-$, -O-, -S-, -NH-, -NHCO- or -CONH-; and

Y is cyano, C_{1-6}-alkyloxy, C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkoxy, or C_{1-6}-alkylcarbonyloxy or Y is phenyl which may optionally be substituted one or more times with substituents selected from halogen, C_{1-6}-alkyl, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyloxy, nitro, cyano, amino, C_{1-6}-alkylamino and C_{1-6}-dialkylamino, methylenedioxy and ethylenedioxy, or Y is an aromatic mono- or bicyclic heterocyclic ring containing only one

heteroatom which may optionally be substituted one or more times with substituents selected from halogen, C_{1-6}-alkyl, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyloxy, nitro, cyano, amino, C_{1-6}-alkylamino and C_{1-6}-dialkylamino; provided Y is not cyano when X is O, S, NH, NHCO or CONH; and Y is not C_{1-6}-alkoxy when X is O, S or NH;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, characterized in that Het is optionally substituted triazolyl, pyrazolyl, pyrimidyl, pyridinyl or imidazolyl.

3. A compound according to claim 2, characterized in that Het is 1-methyl-1*H*-1,2,4-triazol-3-yl, 2-methyl-2*H*-1,2,4-triazol-3-yl, 3-methyl-3*H*-1,2,3-triazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, 2-methyl-2*H*-pyrazol-3-yl, 1-methyl-1*H*-imidazol-2-yl, pyrimidin-2-yl or pyridin-3-yl.

4. A compound according to claims 1-3 wherein Y is C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkoxy or C_{1-6}-alkylcarbonyloxy, or Y is optionally substituted phenyl.

5. A compound according to claim 4 wherein X is a bond , $-CH_2-$, O or S.

6. A compound according to claim 5 wherein X is O or S.

7. A compound according to claims 1-3 wherein Y is an optionally substituted, aromatic bicyclic heterocyclic ring containing only one heteroatom.

8. A compound according to claim 7 wherein Y is indolyl, benzofuranyl or dihydro-1,4-benzodioxinyl.

9. A compound according to claims 7-8 wherein X is a bond , $-CH_2-$, O or S.

10. A compound according to claim 4 wherein X is -NHCO- or -CONH-.

11. A compound according to claim 10 wherein Y is optionally substituted phenyl.

12. A compound according to claims 1-3 wherein Y is cyano.

13. A compound according to claims 1 to 3, characterized in that it is selected from:

3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

3-{4-[1-(4-Fluoro-phenyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxyphenyl)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole;

1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-3-[1-(2-phenylethyl)-piperidin-4-yl]-1*H*-indole;

3-{4-[1-(4-Fluoro-phenyl)-5-(2-methyl-2*H*-pyrazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-pyrazol-3-yl)-1*H*-indole;

3-[1-(2-1H-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-pyrazol-3-yl)-1*H*-indole;

3-{4-[1-(4-Fluoro-phenyl)-5-pyridin-3-yl-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-pyridin-3-yl-1*H*-indole;

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-pyridin-3-yl-1*H*-indole;

3-[1-(2-1*H*-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-pyridin-3-yl-1*H*-indole;

3-{1-[3-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole;

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole;

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indole;

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-pyrimidin-2-yl-1*H*-indole;

3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-imidazol-2-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

3-{4-[1-(4-Fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-imidazol-2-yl)-1*H*-indole;

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole;

1-(4-Fluoro-phenyl)-3-{1-[2-(2-methoxy-ethoxy)-ethyl]-piperidin-4-yl}-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole;

1-(4-Fluoro-phenyl)-3-{1-[2-(2-methoxy-ethoxy)-ethyl]-piperidin-4-yl}-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole;

3-{1-[2-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)-ethyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole;

3-{1-[3-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole;

2-(2-{4-[1-(4-Fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-ethoxy)-ethanol;

2-(2-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-ethoxy)-ethanol;

2-(3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propoxy)-benzonitrile;

3-{1-[3-(4-Fluoro-2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(2-methyl-2H-1,2,4-triazol-3-yl)-1*H*-indole;

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole;

3-{1-[3-(4-Fluoro-2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(3-methyl-3H-1,2,3-triazol-4-yl)-1*H*-indole;

3-{4-[1-(4-Fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

3-{4-[1-(4-Fluoro-phenyl)-5-pyrimidin-2-yl-1*H*-indol-3-yl]-piperidin-1-yl}-propionitrile;

1-(4-Fluoro-phenyl)-3-{1-[2-(4-methoxy-phenyl)-ethyl]-piperidin-4-yl}-5-pyrimidin-2-yl-1*H*-indole;

N-(2,5-Dimethoxy-phenyl)-3-{4-[1-(4-fluoro-phenyl)-5-(2-methyl-2H-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propionamide;

3-{1-[3-(4-Fluoro-2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-1-(4-fluoro-phenyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole;

3-[1-(2-Benzofuran-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole;

3-[1-(2-1*H*-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1H-indole;

3-[1-(2-1*H*-indol-3-yl-ethyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(2-methyl-2*H*-1,2,4-triazol-3-yl)-1*H*-indole;

3-[1-(3-1*H*-indol-3-yl-propyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(3-methyl-3*H*-1,2,3-triazol-4-yl)-1*H*-indole and
3-[1-(3-1*H*-indol-3-yl-propyl)-piperidin-4-yl]-1-(4-fluoro-phenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indole,
3-{4-[1-(4-Fluoro-phenyl)-5-(1-methyl-1*H*-[1,2,4]triazol-3-yl)-1*H*-indol-3-yl]-piperidin-1-yl}-propan-1-ol, or a pharmaceutically acceptable acid addition salt thereof.

14. A compound according to claims 1 to 3 which is radio-labelled.

15. A compound according to claim 14 which is radiolabelled with [^{11}C]-methyl.

16. A compound according to claim 14 which is radiolabelled with ^{18}F, ^{123}I or ^{125}I.

17. A pharmaceutical composition comprising at least one compound according to claims 1 to 13 a pharmaceutically acceptable acid addition salt thereof and optionally a second pharmaceutically active ingredient in combination with one or more pharmaceutically acceptable carrier or diluents.

18. The use of a compound according to Claims 1 to 13 or an acid addition salt thereof and optionally a second pharmaceutically active ingredient for the preparation of a medicament for the treatment of a disorder or disease responsive to antagonism of α_1-adrenoceptors.

19. The use of a compound according to claims 1 to 13 or an acid addition salt thereof and optionally a second agent having antipsychotic activity for the preparation of a medicament for the treatment of psychosis.

20. A method for the treatment of a disorder or disease responsive to antagonism of α_1-adrenoceptors in a mammal comprising administering a compound according to claims 1 to 13 or an acid addition salt thereof and optionally a second pharmaceutically active ingredient to said mammal.

21. A method for the treatment of psychosis in a mammal comprising administering a compound according to claims 1 to 13 or an acid addition salt thereof and optionally a second agent having antipsychotic activity to said mammal.

22. The use of a compound according to Claims 1 to 13 or an acid addition salt thereof for the preparation of a radio-labelled compound of the Formula I.