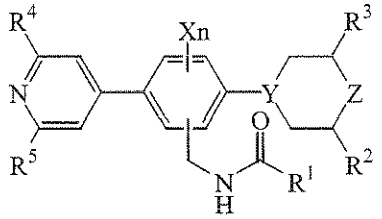
Positive nAChR modulators of the present ~~invention~~disclosure are useful for treatment and prophylaxis of psychotic disorders, intellectual impairment disorders and diseases, inflammatory diseases and conditions in which modulation of the alpha 7 nicotinic receptor is beneficial.

The present ~~invention~~disclosure concerns (pyridine-4-yl)benzylamides having positive allosteric modulator properties, in particular increasing the efficacy of agonists at the alpha 7 nicotinic receptor. The ~~invention~~disclosure further relates to methods for their preparation and pharmaceutical compositions comprising them. The ~~invention~~disclosure also relates to the use of these derivatives for the manufacture of a medicament for the treatment and prophylaxis of psychotic disorders, intellectual impairment disorders and diseases, inflammatory diseases and conditions in which modulation of the alpha 7 nicotinic receptor is beneficial. The ~~invention~~disclosure further relates to these derivatives for use in the treatment and prophylaxis of psychotic disorders, intellectual impairment disorders and diseases, inflammatory diseases and conditions in which modulation of the alpha 7 nicotinic receptor is beneficial.

In a first aspect, the present ~~invention~~disclosure relates to a compound having the formula (I)



(I)

or a stereoisomer thereof, wherein

n is 0, 1 or 2;

X is fluoro or chloro;

Y is N or CH;

Z is O or $CH_2$;

$R^1$ is $C_{1-8}$alkyl; $C_{1-8}$alkyl substituted with 1, 2 or 3 halogen substituents; $C_{3-6}$cycloalkyl; ($C_{3-6}$cycloalkyl)$C_{1-6}$alkyl; ($C_{1-6}$alkyloxy)$C_{1-6}$alkyl; (trihalo$C_{1-4}$alkyloxy)$C_{1-6}$alkyl; tetrahydrofuryl; tetrahydropyranyl; phenyl; phenyl substituted with 1, 2 or 3 substituents selected from halogen, trifluoromethyl, trifluoromethoxy, cyano, $C_{1-6}$alkyl, and $C_{1-4}$alkyloxy; or a monocyclic aromatic heterocyclic radical containing at least one heteroatom selected from N, O and S, optionally substituted with 1, 2 or where possible with 3 substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkyloxy, $C_{3-6}$cycloalkyl, and trifluoromethyl;

$R^2$ and $R^3$ are independently H, $C_{1-4}$alkyl or trifluoromethyl;

A particular compound is N-[[5-[(2R,6S)-2,6-dimethyl-4-morpholinyl]-2-(2,6-dimethyl-4-pyridinyl)phenyl]methyl]-2-methyl-propanamide.

All possible combinations of the above-indicated interesting embodiments are considered to be embraced within the scope of this ~~invention~~application.

In a second aspect, there is provided a pharmaceutical composition comprising as active ingredient a compound as defined above.

In a third aspect, there is provided a product comprising

(a) a compound of formula (I) as defined above, and

(b) a α7 nicotinic receptor agonist selected from

1,4-Diazabicyclo[3.2.2]nonane-4-carboxylic acid, 4-bromophenyl ester, monohydrochloride (SSR180711A);
(-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one;
(+)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzo[b]furan-2-carboxamide;
3-[(2,4-Dimethoxy)Benzylidene]-Anabascine Dihydrochloride (GTS-21);
[*N*-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide Hydrochloride] PNU-282987; nicotine; varenicline; A-582941; AR-R17779; TC-1698; PHA-709829; tropisetron; WAY-317538; MEM3454; EVP-6124; TC-5619; MEM-63908; and AZD-0328, as a combined preparation for simultaneous, separate or sequential use in preventing or treating of psychotic disorders, intellectual impairment disorders, or inflammatory diseases.

In a fourth aspect, there is provided a compound as defined above for use as a medicine.

In a fifth aspect, there is provided a compound as defined above for use in treating Alzheimer's disease, Lewy Body Dementia, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, mania, manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, brain trauma, jetlag, nicotine addiction, pain; endotoxaemia, endotoxic shock, sepsis, rheumatoid arthritis, asthma, multiple sclerosis, psoriasis, urticaria, inflammatory bowel disease, inflammatory bile disease, Crohn's disease, ulcerative colitis, post-operative ileus, pancreatitis, heart failure, acute lung injury or allograft rejection; cognition in schizophrenia, cognition in Alzheimer's disease, mild cognitive impairment, Parkinson's disease, attention deficit hyperactivity disorder, ulcerative colitis, pancreatitis, arthritis, sepsis, postoperative ileus or acute lung injury.

In a sixth aspect, there is provided a process of preparing a pharmaceutical composition as defined above comprising the step of intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound as defined above.

When describing the compounds of the ~~invention~~application, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, iodo unless otherwise is indicated or is clear from the context.

The term "$C_{1-8}$alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula $C_nH_{2n+1}$ wherein n is a number ranging from 1 to 8. $C_{1-8}$alkyl groups comprise from 1 to 8 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably from 1 to 4 carbon atoms, still more preferably 1 to 2 carbon atoms.
Alkyl groups may be linear or branched and may be substituted as indicated herein.
When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain.
Thus, for example, $C_{1-8}$alkyl includes all linear, or branched alkyl groups with between 1 and 8 carbon atoms, and thus includes such as for example methyl, ethyl, n-propyl, isopropyl, butyl and its isomers (e.g. n-butyl, isobutyl and tert-butyl), pentyl, hexyl, heptyl, octyl and their isomers.

The term "$C_{1-4}$alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula $C_nH_{2n+1}$ wherein n is a number ranging from 1 to 4. $C_{1-4}$alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. $C_{1-4}$alkyl includes all linear, or branched alkyl groups with between 1 and 4 carbon atoms, and thus includes such as for example methyl, ethyl, n-propyl, isopropyl, butyl and its isomers e.g. n-butyl, isobutyl, sec-butyl and tert-butyl.

The term "$C_{1-6}$alkyloxy" as a group or part of a group refers to a radical having the Formula $-OR^a$ wherein $R^a$ is $C_{1-6}$alkyl. Non-limiting examples of suitable alkyloxy include methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy, pentyloxy, and hexyloxy.

The term "$C_{1-4}$alkyloxy" as a group or part of a group refers to a radical having the Formula $-OR^b$ wherein $R^b$ is $C_{1-4}$alkyl. Non-limiting examples of suitable $C_{1-4}$alkyloxy include methyloxy (also methoxy), ethyloxy (also ethoxy), propyloxy, isopropyloxy, butyloxy, isobutyloxy, sec-butyloxy and tert-butyloxy.