of nicotinic transmission either because of a decrease in receptor number or increased desensitization.

Reductions in nicotinic receptors have also been hypothesized to mediate cognitive deficits seen in diseases such as Alzheimer's disease and schizophrenia.

The effects of nicotine from tobacco are also mediated by nicotinic receptors and since the effect of nicotine is to stabilize receptors in a desensitized state, an increased activity of nicotinic receptors may reduce the desire to smoke.

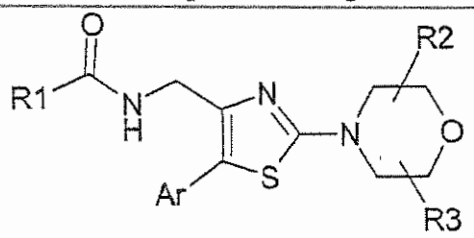
Compounds which bind nAChRs have been suggested for the treatment of a range of disorders involving reduced cholinergic function such as learning deficit, cognition deficit, attention deficit and memory loss. Modulation of alpha 7 nicotinic receptor activity is expected to be beneficial in a number of diseases including Alzheimer's disease, Lewy Body Dementia, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, mania, bipolar disorder, Parkinson's disease, Huntington's disease, Tourette's syndrome, brain trauma and other neurological, degenerative and psychiatric disorders in which there is loss of cholinergic synapses, including jetlag, nicotine addiction, and pain.

However, treatment with nicotinic receptor agonists which act at the same site as ACh is problematic because ACh not only activates, but also blocks receptor activity through processes which include desensitization and uncompetitive blockade. Furthermore, prolonged activation appears to induce a long-lasting inactivation. Therefore, agonists of ACh can be expected to lose effectiveness upon chronic administration.

At nicotinic receptors in general, and of particular note at the alpha 7 nicotinic receptor, desensitization limits the duration of action of an applied agonist.

**Summary**

In a first aspect, there is provided a compound having the formula (I)




(I)

or a stereochemical isomer thereof, wherein

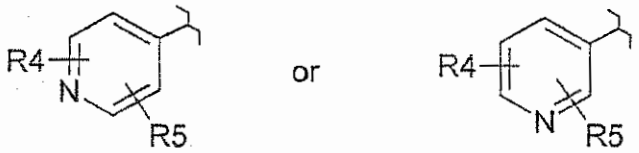
$R^1$ is $C_{1-6}$alkyl, $C_{1-6}$alkyl substituted with 1, 2 or 3 halogen substituents, $C_{1-6}$alkyl substituted with 1 cyano group, $C_{1-6}$alkyl substituted with 1 heteroaryl group, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl substituted with 1, 2, 3, or 4 methyl groups, $C_{3-6}$cycloalkyl substituted with 1 hydroxy group, ($C_{3-6}$cycloalkyl)$C_{1-6}$alkyl, ($C_{1-6}$alkyloxy)$C_{1-6}$alkyl, (halo$C_{1-4}$alkyloxy)$C_{1-6}$alkyl, tetrahydrofuryl, aryl, heteroaryl, pyrrolidinyl, pyrrolidinyl substituted with 1 $C_{1-4}$alkyl group, or tetrahydrofuryl substituted with 1, 2 or 3 substituents selected from methyl and oxo;

aryl is 2,2-difluoro-1,3-benzodioxolyl; phenyl; or phenyl substituted with 1, 2 or 3 substituents selected from halogen, trifluoromethyl, trifluoromethoxy, cyano, $C_{1-6}$alkyl, $C_{1-4}$alkyloxy, and aminosulfonyl;

heteroaryl is a mono- or bicyclic 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 $C_{1-4}$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;
or $R^2$ and $R^3$ are taken together to form 1,2-ethanediyl or 1,3-propanediyl;

Ar is




$R^4$ and $R^5$ are independently H, $C_{1-4}$alkyl, trifluoromethyl, $C_{3-6}$cycloalkyl or $C_{1-4}$alkyloxy;

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]-Anabaseine 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 pharmaceutical acceptable carrier with a therapeutically effective amount of a compound as defined above.

**Description of the invention**

We have found that certain novel morpholinothiazole derivatives can increase the efficacy of agonists at nicotinic acetylcholine receptors (nAChR). Compounds having this type of action (hereinafter referred to as "positive allosteric modulators") are likely to be useful for treatment of conditions associated with reductions in nicotinic transmission. In a therapeutic setting such compounds could restore normal interneuronal communication without affecting the temporal profile of activation. In addition, positive allosteric modulators are not expected to produce long-term