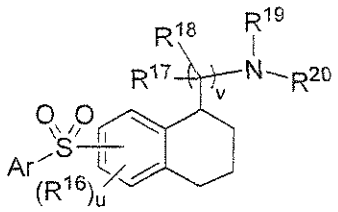
The present disclosure~~invention~~ therefore relates to the use of antagonists of the 5-HT2A and 5-HT6 receptors for the preparation of a medicament for treating a disease state associated with a cognitive disorder, and a pharmaceutical composition comprising an effective amount of a composition capable of selectively antagonizing the 5-HT6 receptor and the 5-HT2A receptor. Thus, ~~one aspect of~~ the present disclosure~~invention~~ is the use of a selective 5-HT6 receptor antagonist and a selective 5-HT2A receptor antagonist, or a combined selective 5-HT6/5-HT2A receptor antagonist for the preparation of a medicament for treating a disease state associated with a cognitive disorder.

In one aspect, there is provided the use of a combined selective 5-HT6/5-HT2A antagonist of formula V wherein said compound has an affinity for the 5-HT6 receptor with pKi value of greater than or equal to 8, an affinity for the 5-HT2A receptor with pKi value of greater than or equal to 8, and has a selectivity of at least 30 over the dopamine D2 receptor, the histamine H1 receptor, and the muscarinic M1 and M2 receptors for the manufacture of a medicament for treating a disease state associated with a cognitive disorder selected from the group consisting of degenerative disorders associated with learning, learning disabilities, mild cognitive impairment, age-related cognitive decline, cerebral senility, vascular dementia, AIDS-associated dementia, electric shock induced amnesia, memory impairment associated with anxiety, Down's syndrome, stroke and traumatic brain injury



Formula V;

wherein

u is from 0 to 3;

v is from 1 to 3;

Ar is optionally substituted aryl or optionally substituted heteroaryl;

each R^{16} is independently halo, alkyl, haloalkyl, cyano, $-SO_2R^f$, $-C(=O)-NR^gR^h$, $-SR^g$, $-C(=O)-R^g$, wherein each R^f, R^g and R^h and is independently hydrogen or alkyl;

R^{17} and R^{18} each independently is hydrogen or alkyl, or R^{17} and R^{18} together may form $=NR^i$ wherein R^i is hydrogen or alkyl;

R^{19} and R^{20} each independently is hydrogen or alkyl, or one of R^{19} and R^{20} is hydrogen and the other is an optionally substituted heteroaryl, or R^{19} and R^{20} together with the nitrogen to which they are attached may form an amidinyl group, a urea group, a guanidinyl group, or a five-or six-membered ring that optionally includes an additional heteroatom selected from O, N and S, or one of R^{19} and R^{20} and one of R^{17} and R^{18} together with the atoms to which they are attached may form a five- or six-membered ring that optionally includes an additional heteroatom selected from O, N and S;

and the pharmaceutically acceptable acid addition salts thereof.

In another embodiment the disclosure~~invention~~ provides a pharmaceutical composition for treating a disease state associated with a cognitive disorder comprising an effective amount of a composition comprising a selective 5-HT6 receptor antagonist and a selective 5-HT2A receptor antagonist, or a combined selective 5-HT6/5-HT2A receptor antagonist, and a pharmaceutically acceptable excipient.

FIG. 1 shows the effect of Compound 18 (A) or Compound 3 (B) on the discrimination performance in an object recognition task investigated in 5-month-old male rats whose performance in this task was disrupted by administration of scopolamine.

FIG. 2 shows the effect of coadministered selective 5-HT2A antagonist (MDL-100907) and selective 5-HT6 antagonist (Compound 32) on the discrimination performance in an object recognition task investigated in 5-month-old male rats whose performance in this task was disrupted by administration of scopolamine.

FIG. 3 shows the long term potentiation (LTP) of synaptic signaling in rat brain hippocampal slices (CA1 region). (A) Increase in long term potentiation by MDL100907, but not by Compound 32, shown as increase in slope of field excitatory post-synaptic potentials (fEPSP) relative to pre-tetanus baseline. (B) Mean increase in fEPSP over pre-tetanus baseline in hippocampal slices treated with MDL100907, SR46349, Olanzapine Compounds 3, 18 and 32.

The term "selective 5-HT6 receptor antagonist" refers to a compound which binds to and antagonizes the 5-HT6 receptor, acting as either a neutral antagonist or an inverse agonist, and which does not substantially bind to and antagonize other 5-HT receptor subtypes, and does not substantially bind to and antagonize any dopamine receptor