COMPOUNDS FOR USE IN PREVENTION AND TREATMENT OF NEURODEGENERATIVE DISEASES AND PAIN

FIELD OF THE INVENTION

The present invention relates to compounds for use in preventing and/or treating neurodegenerative diseases or pain, or both.

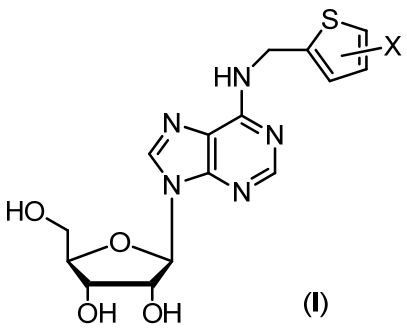
BACKGROUND OF THE INVENTION

United States patent publication No. US20120295863 discloses dual-action compounds targeting adenosine A2A receptor and adenosine transporter for prevention and treatment of neurodegenerative diseases. A selective A_{2A} adenosine receptor ($A_{2A}R$) agonist named CGS21680 (in short, CGS) has been shown to be able to attenuate Huntington's disease (HD) symptoms in a transgenic mouse model, and rescue the urea cycle deficiency of HD disease by enhancing the activity of the ubiquitin-proteasome system (Chiang et al., 2009 *Hum Mol Genet*. 18:2929-2942; Chou et al., 2005 *J Neurochem*. 93:310-320). However, CGS is known to exert strong immunosuppressive effect and other side effects, and is therefore not suitable for clinical use.

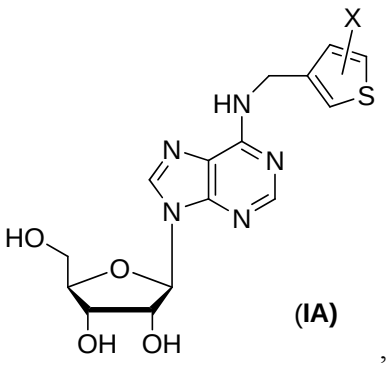
N^6-(4-hydroxybenzyl)adenosine, designated as T1-11 in US20120295863 and also an $A_{2A}R$ agonist, has been suggested to have a therapeutic potential in treating neural degenerative diseases. However, it is still difficult to develop T1-11 as an orally available drug due to its poor bioavailability ($F < 5\%$). Oral bioavailability is an important property in drug development because it represents the percentage of a substance that reaches systemic circulation after absorption and metabolism.

SUMMARY

In one aspect, the present disclosure relates to a compound of formula (I) or (IA):



(I) ;



(IA) ,

or a pharmaceutically acceptable salt thereof, wherein X is halogen.

The halogen (F, Cl, Br or I) may be located at 3-, 4- or 5-position in formula (**I**), or at 2-, 4- or 5-position in formula (IA).

In one embodiment of the present disclosure, the compound is selected from the group consisting of N^6-[(3-halothien-2-yl)methyl]adenosine, N^6-[(4-halothien-2-yl)methyl]adenosine, and N^6-[(5-halothien-2-yl)methyl]adenosine.

In another embodiment of the present disclosure, the compound is selected from the group consisting of N^6-[(2-halothien-3-yl)methyl]adenosine, N^6-[(4-halothien-3-yl)methyl]adenosine, and N^6-[(5-halothien-3-yl)methyl]adenosine.

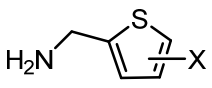
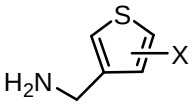
Further in another embodiment of the present disclosure, the compound is selected from the group consisting of N^6-[(5-bromothien-2-yl)methyl]adenosine, N^6-[(4-bromothien-2-yl)methyl]adenosine, N^6-[(3-bromothien-2-yl)methyl]adenosine, N^6-[(5-chlorothien-2-yl)methyl]adenosine, N^6-[(4-chlorothien-2-yl)methyl]adenosine, and N^6-[(3-chlorothien-2-yl)methyl]adenosine.

In another embodiment of the present disclosure, the compound is selected from the group consisting of N^6-[(2-bromothien-3-yl)methyl]adenosine, N^6-[(4-bromothien-3-yl)methyl]adenosine, N^6-[(5-bromothien-3-yl)methyl]adenosine N^6-[(2-chlorothien-3-yl)methyl]adenosine, N^6-[(4-chlorothien-3-yl)methyl]adenosine, and N^6-[(5-chlorothien-3-yl)methyl]adenosine.

In another aspect, the present disclosure relates to a method for preparing the compound of formula (I) or formula (IA) as aforementioned, comprising the step of (I) or (II):

(I):

(a) reacting 6-chloropurine ribofuranoside in the presence of a base with (thienyl)methanamine that is substituted with fluorine, chlorine, bromine or iodine and has formula 3 or 3A:


(**3**);

(**3A**),

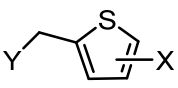
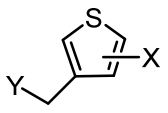
to afford the compound of formula (I) or (IA); or

(II):

(a1) reacting (2',3'-*O*-isopropylidene)adenine in the presence of a base with a hydroxyl group-protecting agent to afford a derivative of (2',3'-*O*-isopropylidene)adenine having a hydroxyl protecting group;

(b) reacting the derivative of (2',3'-*O*-isopropylidene)adenine having the hydroxyl protecting group with an amine group-protecting agent to afford a derivative of (2',3'-*O*-isopropylidene)adenine having the hydroxyl protecting group and an amine protecting group;

(c) performing a coupling reaction by reacting the derivative of (2',3'-*O*-isopropylidene)adenine having the hydroxyl and amine protecting groups with a substituted (thienyl)methyl group-containing compound of formula 7 or 7A:


(**7**);

(**7A**),

wherein X is F, Cl, Br, or I, and Y is X, OH, methanesulfonate (OSO_2CH_3, OMs), *p*-toluenesulfonate ($OSO_2C_6H_4$-*p*-CH_3, OTs), or trifluoromethanesulfonate (OSO_2CF_3, OTf), to afford a product containing the protecting groups and the substituted (thienyl)methyl group and; and

(d) removing the protecting groups from the product of step (c) in an acidic condition to afford the compound of formula (I) or (IA).

In one embodiment of the present disclosure, the base in step (a) may be diisopropylethylamine. The hydroxyl group-protecting agent may be *tert*-butyldimethylsilyl chloride. The amine group-protecting agent may be Di-*tert*-butyl dicarbonate. The base in step (a1) may be imidazole.

In another embodiment of the present disclosure, in step (I)(a), the base is diisopropylethylamine and the substituted (thienyl)methanamine is: (i) (5-bromothien-2-yl)methanamine to afford N^6-[(5-bromothien-2-yl)methyl]adenosine; or (ii) (5-chlorothien-2-yl)methanamine to afford N^6-[(5-chlorothien-2-yl)methyl]adenosine.

Further in another embodiment of the present disclosure, the coupling reaction is preformed in the presence of triphenylphosphine and diisopropyl azodicarboxylate. The substituted (thienyl)methyl group-containing compound may be (5-bromothien-2-yl)methanol.

Further in another aspect, the present disclosurerelates to a composition comprising:

(a) a therapeutically effective amount of the compound as aforementioned or a pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier, excipient or vehicle.

Yet in another aspect, the present disclosurerelates to use of the compound as aforementioned in the manufacture of a medicament for treating a neurodegenerative disease and/or pain in a subject in need thereof. Alternatively, the present disclosurerelates to the compound as aforementioned for use in treating a neurodegenerative disease and/or pain in a subject in need thereof. The neurodegenerative disease may be a protein-misfolding disease.

In one embodiment of the present disclosure, the neurodegenerative disease is selected from the group consisting of Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, Prion disease, Huntington's disease, and spinal cerebellar ataxias. The spinal cerebellar ataxias may be selected from the group consisting of spinal cerebellar ataxias 2, spinal cerebellar ataxias 3, and spinal cerebellar ataxias 7. The pain may be acid-induced pain. The acid-induced pain may be acid-induced muscle pain. The acid-induced muscle pain may be acid-induced chronic muscle pain.

In one embodiment of the present disclosure, the pain is selected from the group consisting of inflammatory pain, cancer pain, chest pain, back pain, neck pain, shoulder pain, migraine, headache,

myofascial pain, join pain, muscular pain syndromes, neuropathic pain, peripheral pain, sympathetic pain, postoperative pain, post-traumatic pain, and multiple sclerosis pain.

In another embodiment of the present disclosure, the pain may be a dysfunctional pain. The dysfunctional pain may be selected from the group consisting of fibromyalgia, myofascial pain, bladder pain syndrome, and a pain caused by irritable bowel syndrome.

These and other aspects will become apparent from the following description of the preferred embodiment taken in conjunction with the following drawings, although variations and modifications therein may be affected without departing from the spirit and scope of the novel concepts of the disclosure.

The accompanying drawings illustrate one or more embodiments of the present disclosureand, together with the written description, serve to explain the principles of the present disclosure. Wherever possible, the same reference numbers are used throughout the drawings to refer to the same or like elements of an embodiment.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the blood concentrations of T1-11 (A) and JMF3464 (B) in ICR mice receiving intravenous (1 mg/kg) or oral (10 mg/kg) of T1-11 or JMF3464. The oral bioavailability of T1-11 and JMF3464 were estimated to be 2.8% and 17.4%, respectively.

FIG. 2 shows the effects of $A_{2A}R$ agonists (CGS21680, T1-11, JMF3464, and JMF3818) on serum deprivation-induced cell death. Serum-deprived PC12 cells were treated with or without the indicated reagent(s) for 24 h. Cell viability was expressed as a percentage of the results from MTT assays compared to the mean of a serum-containing control group. Data points represent the mean ± SEM (n=3~6).

FIGs. 3A-B show the effect of JMF3464 on motor deficits and lifespan. JMF3464 (0.11 μg/mouse/day), JMF1907 (0.11 μg/mouse/day) or vehicle (CON) was administrated subcutaneously to the indicated mice of 7 weeks old using ALZET osmotic minipumps for 6 weeks. Rotarod performance (A) and lifespan (B) of these mice were assessed. * $p < 0.05$. *** $p < 0.005$.

FIGs. 4A-B show the effects of T1-11 in preventing mutant SCA2 gene overexpression-induced protein aggregations and behavioral performance in SCA2 transgenic mice. (A) pSCA2-22Q-EGFP or pSCA2-104Q-EGFP-transfected cells were treated with 10 μM T1-11 or 10 μM JMF1907 (a T1-11-derived A_{2A}-R agonist) for 24 h. Cells were harvested and subjected to a filter retardation assay or image acquisition. (B) Wild type (WT) or transgenic mice (SCA2) drank water with or without T1-11. Rotarod performance was used to measure the behavioral function of mice.

FIGs. 5A-C show that T1-11ameliorates the motor dysfunction and pontine neuronal death of SCA3 transgenic mice. (A) SCA3 transgenic mice were given drinking water containing vehicle (0.2% DMSO)