

INHIBITORS OF TREK (TWIK RELATED K⁺ CHANNELS) CHANNEL FUNCTION

[Technical Field]

[0001]

The present disclosure relates to compounds, compositions, and methods for preventing and/or treating disorders associated with K2P K⁺ channels, specifically TREK (TWIK Related K⁺ Channel) dysfunction for which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would provide therapeutic benefit.

[Background Art]

[0002]

Potassium (K⁺) channels are membrane proteins that are expressed in virtually every cell of the organism. K⁺ channel subunits (~80 genes) can be divided into three main structural classes comprising shaker type voltage-gated (Kv), inward rectifier (Kir) and K⁺ channels with two-pore domains (K2P) (Kubo et al., Pharmacol Rev. 2005, 57, 509, Gutman, et al. Pharmacol Rev. 2005, 57, 473, Goldstein et al. Pharmacol Rev. 2005, 57, 527). The third family of K⁺ channels was discovered 20 years ago (Leasge et al. EMBO J. 1996, 15, 1004). The 15 human K2P K⁺ channels have been identified so far and classified into 6 structural subgroups: TWIK, TREK (TWIK Related K⁺ channels), TASK (TWIK related Acid-Sensitive K⁺ channels), TALK (TWIK related ALkaline pH-activated K⁺ channels), THIK (Tandem pore domain Halothane Inhibited K⁺ channels) and TRESK (TWIK Related Spinal cord K⁺ channel) (Enyedi et al. Physiol. Rev. 2010, 90, 559). K2P K⁺ channels are responsible for background or 'leak' K⁺ currents. These channels are regulated by various physical and chemical stimuli, including membrane stretch, temperature, acidosis, lipids and inhalational anaesthetics. Furthermore, channel activity is tightly controlled by membrane receptor stimulation and second messenger phosphorylation pathways. Several members of this novel family of K⁺ channels are highly expressed in the central and peripheral nervous systems in which they are proposed to play an important physiological role (TRENDS in Neurosci. 2001).

[0003]

TREK-1, TREK-2, which belong to TREK subgroup, are thermo- and mechano-gated K⁺ channel that is activated by lysophospholipids and PUFAs including arachidonic acid. They are regulated by G-protein-coupled receptors through PKA and PKC phosphorylation (Channels (Austin). 2011 Sep-Oct;5(5):402-9). TREK-1 gene is widely expressed in the Central Nervous System (CNS) with limited distribution in the periphery. In the CNS, TREK-1 expression is highest in the striatal tissues, the caudate and the putamen, as well as in spinal cord, foetal brain, amygdala and thalamus. In the periphery, TREK-1 expression is observed in heart, stomach and

small intestine. TREK-2 gene has quite a similar expression profile compared to TREK-1 with high expression in particularly caudate, putamen and foetal brain. However, in contrast to TREK-1, TREK-2 is also highly expressed in cerebellum and corpus callosum as well as in several peripheral tissues, particularly kidney (Mol. Brain Res. 2001, 86, 101).

[0004]

TREK-1 deficient mice display an increased efficacy of serotonin (5-HT) neurotransmission, and a depression-resistant phenotype (Nature Neurosci. 2006, 9, 1134). Spadin, a naturally occurring peptide, blocks TREK-1 and results in a rapid onset of antidepressant efficacy (Br. J. Pharmacol. 2014, 172, 771). Moreover, antidepressants such as fluoxetine and paroxetine directly inhibit TREK channels (Nat. Neurosci. 2006, 9, 1134; Br. J. Pharmacol. 2005, 144, 821). Thus, inhibition of TREK-1 with a small molecule holds promise for the treatment of depression, as well as other mood disorders (Front. Pharmacol. 2018, 9, 863).

[0005]

Inhibition of TREK-1 protects mice from cognitive impairment induced by anesthesia and, coupled with a high density in the hippocampus, TREK-1 is a potential therapeutic target against memory impairment induced by volatile anesthetics and in other CNS disorders with cognitive deficits (Neurobiology of Learning and Memory, 2017, 145, 199). TREK-1 gene expression is increased in hippocampus of patients with schizophrenia compared to healthy control (Neuropsychopharmacology 2010, 35, 239-57.). Intrathecal injection of microRNA targeting to TREK-1 ameliorates neuropathic pain induced by chronic constriction sciatic nerve injury (Neurochem Res. 2018, 43, 1143), suggesting that inhibition of TREK-1 may be efficacious in cognitive disorders and neuropathic pain. Knockdown of TREK-1 significantly inhibits prostatic cancer cell proliferation in vitro and in vivo, and induces a G1/S cell cycle arrest (Cancer Res. 2008, 68, 1197-203., Oncotarget. 2015, 6, 18460-8.). TREK-1 is also overexpressed in human ovarian cancer tissues, and the treatment of TREK-1 inhibitors (curcumin and L-methionine) suppress ovarian cancer cell proliferation and increase late apoptosis (Clin. Transl. Oncol. 2013, 15, 910-8.). Thus, TREK-1 inhibitors can be useful for the treatment of prostatic and ovarian cancer. TREK-1 gene is also expressed in lung and TREK-1 knockdown leads to amelioration of bleomycin-induced lung fibrosis (Biomedicines. 2023, 11(5), 1279.), indicating that TREK-1 inhibitors can be useful for the treatment of lung fibrosis.

[0006]

Neurotensin (NT) suppresses TREK-2 current through NT receptor 1-mediated activation of PLC/PKC pathway in entorhinal cortex layer II stellate neurons, leading to depolarization of membrane potential and enhancement of neuronal excitability. Furthermore, NT-induced enhancement of spatial learning is diminished in TREK-2 KO mice, suggesting that TREK-2

inhibitors may be useful for the treatment of cognitive impairment, such as Alzheimer's disease (J. Neurosci. 2014, 34, 7027-42.). TREK-2 is expressed in human bladder carcinoma cell in which TREK-2 contributes to the regulation of resting membrane potential. TREK-2 KD decreases the cell proliferation (Korean J. Physiol. Pharmacol. 2013, 17, 511-6.). Thus, TREK-2 inhibitors also may be efficacious in the treatment of bladder carcinoma.

[0007]

Selective inhibition of TREK-1, by a small inhibitor, has potential therapeutic benefit for: depression, schizophrenia, cognitive disorders including dementia, neuropathic pain, stroke, prostatic, ovarian cancer and lung fibrosis (Nat. Neurosci. 2006, 9, 1134, Neuropsychopharmacology 2010, 35, 239, Neurobiol. Learn Mem. 2017, 145, 199, Neurochem Res. 2018, 43, 1143, Neurosci Lett. 2018, 671, 93, Cancer Res. 2008, 68, 1197, Clin. Transl. Oncol. 2013, 15, 910, Biomedicines. 2023, 11(5), 1279.).

[0008]

Selective inhibition of TREK-2, by a small molecule inhibitor, has potential therapeutic benefit for: cognitive disorders including dementia, stroke and bladder carcinoma (J. Neurosci. 2014, 34, 7027, Biochem. Biophys. Res. Commun. 2005, 327, 1163, Korean J. Physiol. Pharmacol. 2013, 17, 511). The expression level of TREK-2 is increased in cortex and hippocampus of acute rat cerebral ischemia model (Biochem. Biophys. Res. Commun. 2005, 327, 1163-9.) Thus, TREK-2 inhibitors may be useful for the treatment of stroke.

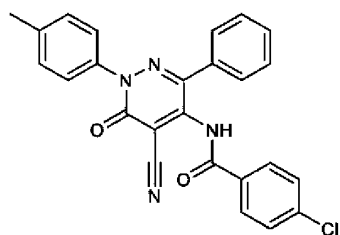
[0009]

All of the above mentioned disorders may also be effectively treated by a both TREK-1 and TREK-2 inhibitor with varying degrees of TREK-1 and TREK-2 preference.

[0010]

The following compound is known to have a structure similar to the compounds in this disclosure.

[Chem. 1]



(CAS No.:385798-10-7)

[0011]

However, there is no statement or suggestion that the compounds in this disclosure have a prominent TREK-1, TREK-2 or both TREK-1 and TREK-2 inhibitory activity.

[Summary of Invention]

[Technical Problem]

[0012]

Despite advances in K2P channel research and TREK-1/TREK-2 pharmacology channel research, there is still a scarcity of compounds that are potent, efficacious, and selective inhibitors of the either TREK-1, TREK-2 or both TREK-1 and TREK-2, and also effective in the treatment of neurological, psychiatric, inflammatory, respiratory, renal and cardiovascular disorders, cancer or lung fibrosis associated with K2P K^+ channels, specifically TREK (TWIK Related K^+ channels) dysfunction for which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit.

[Solution to Problem]

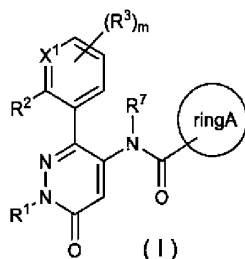
[0013]

In order to achieve the foregoing objects, the present inventors conducted intensive studies to find compounds having a TREK-1, TREK-2 or both TREK-1 and TREK-2 inhibitory effect, and found that compounds of formula (I) have prominent TREK-1, TREK-2 or both TREK-1 and TREK-2 inhibitory activity.

[0014]

In one aspect, disclosed are compounds of formula (I),

[Chem. 2]



or a pharmaceutically acceptable salt thereof;

wherein: all symbols are defined as below.

[0015]

Also disclosed are pharmaceutical compositions comprising the compounds, methods of making the compounds, kits comprising the compounds, and methods of using the compounds, compositions and kits for prevention and/or treatment of disorders, such as neurological and/or psychiatric disorders, associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction for which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal.

[Brief Description of Drawings]

[0016]

[Fig. 1]

Fig. 1; Shows that the effect of Compound 6, 14, 35, 59 and 73 in the mouse forced swim test. The vertical axis shows the immobility time, and the horizontal axis shows the group to which vehicle, the test compound or imipramine was administered. * $p < 0.05$ compared to vehicle-treated group (Dunnett's test), # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ compared to vehicle-treated group (Student t-test).

[Fig. 2]

Fig. 2; Shows that the effect of Compound 59 in the mouse MK-801-induced novel object recognition test. The vertical axis shows the discrimination index, and the horizontal axis shows the group to which vehicle, Compound 59 or clozapine followed by MK-801 induction, was administered. Mice treated with vehicle without MK-801 induction were tested as a control group. * $p < 0.05$ compared to vehicle-treated group (Dunnett's test), ## $p < 0.01$ compared to vehicle-treated group (Student t-test), \$ $p < 0.05$ compared to control group (Student t-test).

[Description of Embodiments]

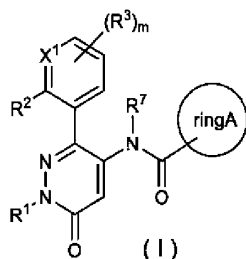
[0017]

Disclosed herein are inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2.

That is, the disclosure relates to;

[1] A compound of formula (I):

[Chem. 3]

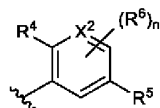


or a pharmaceutically acceptable salt thereof;

wherein

ring A is

[Chem. 4]



or 8 to 10-membered bicyclic which may be substituted by 1 to 6 halogen atoms;

R^1 is selected from the group consisting of (1) a hydrogen atom, (2) C1-8 alkyl, (3) C1-8 haloalkyl, (4) C2-8 alkenyl, (5) C2-8 haloalkenyl, (6) C2-8 alkynyl, (7) C2-8 haloalkynyl and (8) 4 to 6-membered saturated monocyclic heterocycle, wherein 1 or 2 carbon atoms in each of the

groups (2) to (7) may be independently replaced by (1) NR^8 , (2) an oxygen atom or (3) a sulfur atom which may be oxidized;

and each of the groups (2) to (8) in R^1 may be substituted by 1 to 6 R^{1-1} s;

R^{1-1} is selected from the group consisting of (1) a deuterium atom, (2) a halogen atom, (3) a hydroxy group, (4) C1-4 alkyl, (5) C1-4 haloalkyl, (6) C1-4 alkoxy, (7) C1-4 haloalkoxy, (8) - $\text{CO-NR}^{1-2}\text{R}^{1-3}$, (9) - O-CO-R^{1-4} , (10) - $\text{SO}_2\text{-R}^{1-5}$, (11) - $\text{S(=O)(=NR}^{1-6})\text{-R}^{1-7}$, (12) - $\text{NR}^{1-8}\text{R}^{1-9}$, (13) cyano and (14) 3 to 6-membered heterocycle;

when there are 2 to 6 R^{1-1} s, a plurality of R^{1-1} s may be the same as or different from each other; R^{1-2} , R^{1-3} , R^{1-4} , R^{1-5} , R^{1-6} , R^{1-7} , R^{1-8} and R^{1-9} is each independently selected from the group consisting of (1) a hydrogen atom, (2) C1-4 alkyl and (3) C1-4 haloalkyl;

R^2 is (1) C1-4 alkyl or (2) C1-4 haloalkyl;

R^3 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl and (4) C1-4 haloalkyl;

when there are 2 or 3 R^3 s, a plurality of R^3 s may be the same as or different from each other;

R^4 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkoxy and (3) C1-4 haloalkoxy;

R^5 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy and (6) C1-4 haloalkoxy;

R^6 is (1) a hydrogen atom or (2) a halogen atom;

when there are 2 R^6 s, a plurality of R^6 s may be the same as or different from each other;

R^7 is (1) a hydrogen atom or (2) C1-4 alkyl;

R^8 is (1) a hydrogen atom or (2) C1-4 alkyl;

R^9 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl and (4) C1-4 haloalkyl;

R^{10} is (1) a hydrogen atom or (2) a halogen atom;

X^1 is (1) CR^9 or (2) N;

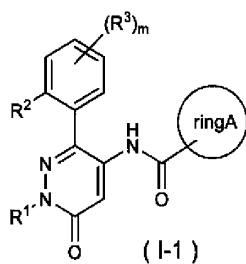
X^2 is (1) CR^{10} or (2) N;

m is an integer of 1 to 3;

n is an integer of 1 or 2.

[2] The compound according to [1], which is a compound of formula (I-1):

[Chem. 5]

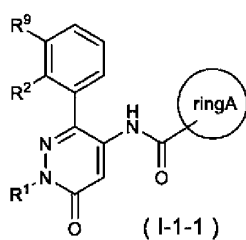


wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[2-1] The compound according to [1], which is a compound of formula (I-1-1):

[Chem. 6]

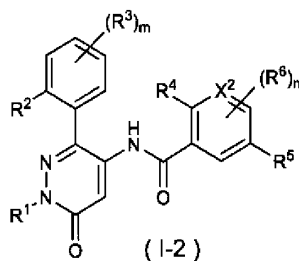


wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[3] The compound according to [1], which is a compound of formula (I-2):

[Chem. 7]

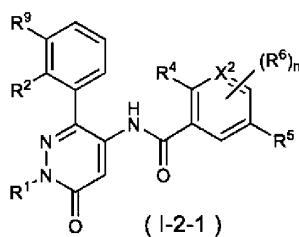


wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[3-1] The compound according to [1], which is a compound of formula (I-2-1):

[Chem. 8]

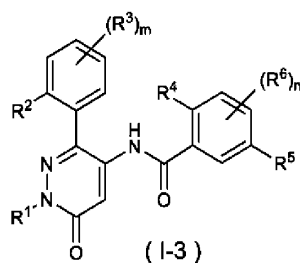


wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[4] The compound according to [1], which is a compound of formula (I-3):

[Chem. 9]

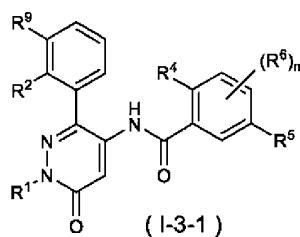


wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[4-1] The compound according to [1], which is a compound of formula (I-3-1):

[Chem. 10]

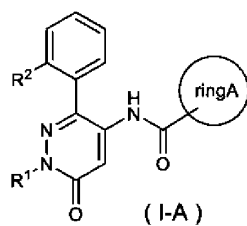


wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[5] The compound according to [1], which is a compound of formula (I-A):

[Chem. 11]

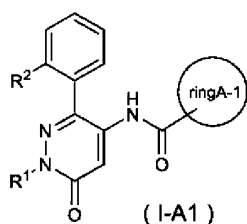


wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[6] The compound according to [1], which is a compound of formula (I-A1):

[Chem. 12]



wherein ring A-1 is 8 to 10-membered bicycle which may be substituted by 1 to 6 halogen atoms,

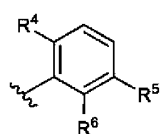
and the other symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[7] The compound according to any one of [1], [2] and [5],

wherein ring A is

[Chem. 13]



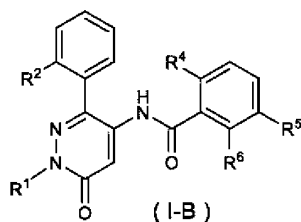
;

and the other symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[8] The compound according to any one of [1] to [5] and [7], which is a compound of formula (I-B):

[Chem. 14]



wherein all symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[9] The compound according to any one of [1] to [8],

wherein R^1 is C1-4 alkyl which may be substituted by 1 to 6 R^{1-1A} s;

R^{1-1A} is selected from the group consisting of (1) a deuterium atom, (2) a hydroxy group, (3) methyl, (4) methoxy, (5) cyano and (6) oxetane;

when there are 2 to 6 R^{1-1A} s, a plurality of R^{1-1A} s may be the same as or different from each other;

and the other symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[10] The compound according to any one of [1] to [9],

wherein R^1 is C1-4 alkyl which may be substituted by 1 to 6 R^{1-1B} ;

R^{1-1B} is (1) a deuterium atom or (2) a hydroxy group;

when there are 2 to 6 R^{1-1B} s, a plurality of R^{1-1B} s may be the same as or different from each other;

and the other symbols are as defined in [1];

or a pharmaceutically acceptable salt thereof.

[11] The compound according to [1], wherein the compound is

(1) 5-chloro-2-methoxy-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide;

(2) 5-chloro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide;

(3) 5-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide;

(4) 5-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide;

(5) 2-fluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;

(6) 2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;

(7) 2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;

(8) 5-chloro-2-methoxy-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide;

(9) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;

(10) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;

(11) N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide;

(12) 5-(difluoromethyl)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;

(13) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide;

(14) 5-(difluoromethoxy)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;

- (15) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide;
- (16) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide;
- (17) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide;
- (18) N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide;
- (19) 5-(difluoromethoxy)-2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;
- (20) N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide;
- (21) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide;
- (22) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide;
- (23) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;
- (24) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (25) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;
- (26) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (27) 2-fluoro-N-(1-(2-hydroxyethyl-2,2-*d*₂)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide;
- (28) 2-fluoro-N-(1-(2-hydroxyethyl-2,2-*d*₂)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethoxy)benzamide;
- (29) 2-fluoro-N-(1-(2-hydroxyethyl-2-*d*)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide or
- (30) 2-fluoro-N-(1-(2-hydroxyethyl-1,1,2,2-*d*₄)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide;
- or a pharmaceutically acceptable salt thereof.

[12] A pharmaceutical composition comprising a compound according to any one of [1] to [11], or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[13] The pharmaceutical composition according to [12], which is a TREK-1, TREK-2 or both

TREK-1 and TREK-2 inhibitor.

[14] The pharmaceutical composition according to [12], which is a preventive and/or therapeutic agent for a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction.

[15] The pharmaceutical composition according to [14], wherein the disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction is a neurological and/or psychiatric disorder.

[15-1] The pharmaceutical composition according to [14], wherein the disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction is a neurological and/or psychiatric disorder, cognitive disorder, pain, cancer or lung fibrosis.

[16] The pharmaceutical composition according to [15] or [15-1], wherein the neurological and/or psychiatric disorder is selected from the group consisting of depression, schizophrenia, anxiety disorders, bipolar disorder, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, 22q11.2 deletion syndrome, neuropathic pain and cerebral infarction.

[16-1] The pharmaceutical composition according to [16], wherein schizophrenia is cognitive impairment associated with schizophrenia.

[16-2] The pharmaceutical composition according to [16], wherein the neurological and/or psychiatric disorder is depression or cognitive impairment associated with schizophrenia.

[17] A method for preventing and/or treating a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction, comprising administering an effective amount of the compound according to any one of [1] to [11], or a pharmaceutically acceptable salt thereof to a mammal.

[18] A compound according to any one of [1] to [11], or a pharmaceutically acceptable salt thereof for use in prevention and/or treatment of a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction.

[19] Use of a compound according to any one of [1] to [11], or a pharmaceutically acceptable salt thereof for manufacturing of a preventive and/or therapeutic agent for a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction.

[20] A kit comprising a compound according to any one of [1] to [11], or a pharmaceutically acceptable salt thereof, and one or more of:

- (a) at least one agent known to decrease TREK-1 channel activity;
- (b) at least one agent known to decrease TREK-2 channel activity;
- (c) at least one agent known to prevent and/or treat a disorder associated with TREK channel dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal;

(d) instructions for preventing and/or treating a disorder associated with TREK channel dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal; and

(e) instructions for administering the compound in connection with cognitive behavioral therapy.

[0018]

Disclosed herein are inhibitors of the TREK (TWIK Related K⁺ channels) - subtypes 1 and 2 (TREK-1 and TREK-2), methods of making same, pharmaceutical compositions comprising same, and methods of preventing and/or treating neurological, psychiatric, inflammatory, respiratory, renal and cardiovascular disorders associated with TREK channel dysfunction using same.

[0019]

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present disclosure. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0020]

The terms “comprise(s),” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments “comprising,” “consisting of” and “consisting essentially of,” the embodiments or elements presented herein, whether explicitly set forth or not.

[0021]

The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier “about” should also be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression “from about 2 to about 4” also discloses the range “from 2 to 4.” The term “about” may refer to plus or minus 10% of the indicated number. For example, “about 10%” may indicate a range of 9% to 11%, and “about 1” may mean from 0.9-1.1. Other

meanings of “about” may be apparent from the context, such as rounding off, so, for example “about 1” may also mean from 0.5 to 1.4.

[0022]

Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein.

Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Organic Chemistry, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

[0023]

Examples of the “halogen” as used herein include fluorine, chlorine, bromine and iodine atoms.

[0024]

Examples of the “C1-8 alkyl” as used herein includes methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, isobutyl, pentyl, 1,2-dimethylpropyl, 1-ethylpropyl, methylbutyl, hexyl, 1,3-dimethylbutyl, heptyl and octyl groups.

Examples of the “C1-2 alkyl” as used herein include methyl and ethyl.

Examples of the “C1-3 alkyl” as used herein include methyl, ethyl, propyl and isopropyl.

Examples of the “C1-4 alkyl” as used herein include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and isobutyl.

[0025]

Examples of the “C1-4 alkoxy” as used herein include methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy and isobutoxy groups.

Examples of the “C1 haloalkyl” as used herein includes fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl and the like,

Examples of the “C1-8 haloalkyl” as used herein includes fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, perfluoropropyl, perfluoro(isopropyl), perfluorobutyl, perfluoro(sec-butyl), perfluoro(tert-butyl), perfluoro(isobutyl), perfluoropentyl, perfluorohexyl, perfluoroheptyl and perfluorooctyl groups and the like.

Examples of the “C1-4 haloalkyl” include fluoromethyl, chloromethyl, bromomethyl,

iodomethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2-chloroethyl, pentafluoroethyl, 1-fluoropropyl, 2-chloropropyl, 3-fluoropropyl, 3-chloropropyl, 4,4,4-trifluorobutyl, 1,1-difluoroethyl, 2-fluoro-2-propanyl and 4-bromobutyl and the like.

Examples of the “C1-4 haloalkoxy” include trifluoromethoxy, trichloromethoxy, chloromethoxy, bromomethoxy, fluoromethoxy, iodomethoxy, difluoromethoxy, dibromomethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy, 3-bromopropoxy, 3-chloropropoxy, 2,3-dichloropropoxy and the like.

[0026]

Examples of the “C2–8 alkenyl” include vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, and octenyl, and isomers thereof, and the like.

Examples of the “C2–8 haloalkenyl” include fluorovinyl, difluorovinyl, chlorovinyl, dichlorovinyl, perfluorovinyl, perchlorovinyl, 3,3,3-trifluoropropenyl, perfluoropropenyl, perfluorobutenyl, perfluoropentenyl, perfluorohexenyl, perfluoroheptenyl, and perfluorooctenyl, and isomers thereof, and the like.

[0027]

Examples of the “C2–8 alkynyl” include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, and isomers thereof, and the like.

Examples of the “C2–8 haloalkynyl” include fluoroethynyl, chloroethynyl, 3,3,3-trifluoropropynyl, perfluoroethynyl, perfluoropropynyl, perfluorobutynyl, perfluoropentynyl, perfluorohexynyl, perfluoroheptynyl, perfluorooctynyl, and isomers thereof, and the like.

[0028]

Examples of the “4 to 6-membered saturated monocyclic heterocycle” include oxetane, thietane, azetidine, diazetidine, pyrrolidine, pyrazolidine, imidazolidine, triazolidine, tetrazolidine, tetrahydrofuran, dioxolane, tetrahydrothiophene, oxathiolane, piperidine, piperazine, tetrahydropyran, dioxane, dithiane, and the like.

[0029]

Examples of the “8 to 10-membered bicycle” include pentalene, perhydropentalene, indene, perhydroindene, indane, azulene, perhydroazulene, naphthalene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, thienopyrazole, thienoimidazole, pyrazolothiazole, indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, purine, benzoxazole, benzothiazole, benzimidazole, imidazopyridine, benzofurazan, benzothiadiazaole, benzotriazole, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzoimidazole,

dioxaindane, benzodithiolane, dithianaphthalene, quinoline, isoquinoline, quinolidine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, chromene, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzooxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorpholine, benzodioxane, chroman, benzodithiane and the like.

[0030]

Examples of the 3 to 6-membered heterocycle is aziridine, azetidine, oxirane, oxetane, thiirane, thietane, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, pyran, thiophene, thiopyran, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, thiadiazole, thiazine, thiadiazine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrooxazole, tetrahydrooxazole(oxazolidine), dihydroisoxazole, tetrahydroisoxazole(isoxazolidine), dihydrothiazole, tetrahydrothiazole(thiazolidine), dihydroisothiazole, tetrahydroisothiazole(isothiazolidine), dihydrofurazan, tetrahydrofurazan ring, dihydrooxadiazole, tetrahydrooxadiazole(oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrothiadiazole, tetrahydrothiadiazole(thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, morpholine ring, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane and the like.

[0031]

For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, and the like.

[0032]

The term “inhibitor” as used herein refers to a molecular entity (e.g., but not limited to, a disclosed compound) that decreases or disappears the activity of the target receptor protein.

The term “thallium flux assay” herein refers to a fluorescence-based assay used to

monitor the activity of TREK channels. Thallium is a congener of potassium that readily fluxes through the pore of TREK channels. Thallium flux is measured using a commercially available, thallium-sensitive fluorescent dye called Thallos. The detail method is described below.

The term “patch clamp technique” herein refers to the “gold standard” technique for evaluating TREK channel pharmacology. The detail method is described below.

The term “MK-801-induced novel object recognition test” herein refers to the experiment to evaluate in vivo efficacy in the schizophrenic cognitive impairment animal model. The detail method is described below. MK-801 is also known as dizocilpine.

The term “dysfunction” as used herein refers to any abnormal functions that induce activation or inhibition of the channel in an animal, in particular a mammal, for example a human.

[0033]

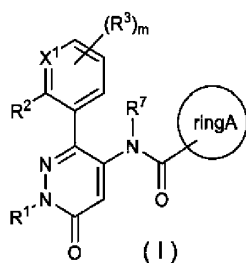
For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

[0034]

Compounds

In one aspect, disclosed is a compound of formula (I):

[Chem. 15]

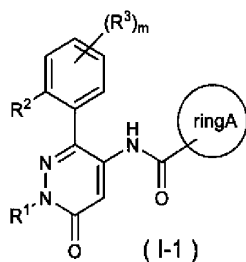


or a pharmaceutically acceptable salt thereof, wherein: all symbols are defined as above.

[0035]

In some embodiments, the formula (I) is preferably the formula (I-1):

[Chem. 16]

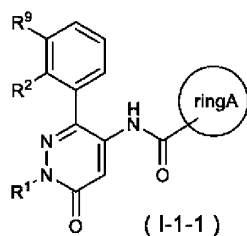


(wherein all symbols are as defined as above).

[0036]

In some embodiments, the formula (I) is preferably the formula (I-1-1):

[Chem. 17]

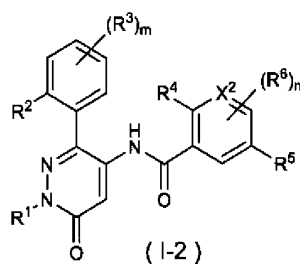


(wherein all symbols are as defined as above).

[0037]

In some embodiments, the formula (I) is preferably the formula (I-2):

[Chem. 18]

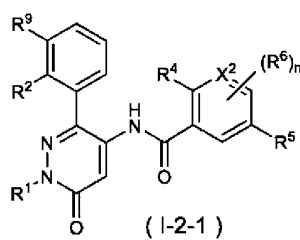


(wherein all symbols are as defined as above).

[0038]

In some embodiments, the formula (I) is preferably the formula (I-2-1):

[Chem. 19]

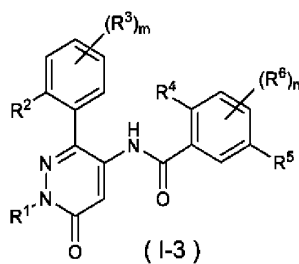


(wherein all symbols are as defined as above).

[0039]

In some embodiments, the formula (I) is preferably the formula (I-3):

[Chem. 20]

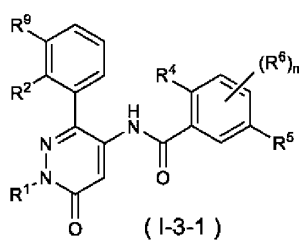


(wherein all symbols are as defined as above).

[0040]

In some embodiments, the formula (I) is preferably the formula (I-3-1):

[Chem. 21]

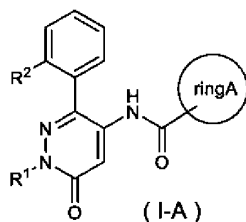


(wherein all symbols are as defined as above).

[0041]

In some embodiments, the formula (I) is preferably the formula (I-A):

[Chem. 22]

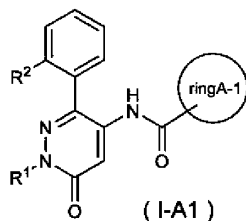


(wherein all symbols are as defined as above).

[0042]

In some embodiments, the formula (I) is preferably the formula (I-A1):

[Chem. 23]



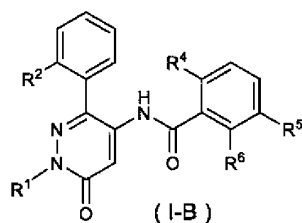
(wherein ring A-1 is 8 to 10-membered bicycle which may be substituted by 1 to 6 halogen atoms;

and the other symbols are as defined as above).

[0043]

In some embodiments, the formula (I) is preferably the formula (I-B):

[Chem. 24]



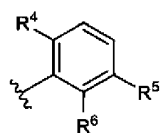
(wherein all symbols are as defined as above).

[0044]

Ring A is preferably

(1)

[Chem. 25]



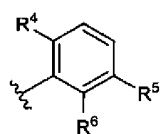
or (2) 8 to 10-membered bicycle which may be substituted by 1 to 3 halogen atoms;
and the other symbols are as defined as above.

[0045]

More preferable ring A is

(1)

[Chem. 26]



, (2) dihydrobenzofuran, (3) imidazopyridine or (4) quinoline;

wherein each of the groups (2) to (4) may be substituted by a halogen atom;

and the other symbols are as defined as above.

[0046]

Most preferable ring A is

[Chem. 27]



;

and the other symbols are as defined as above.

[0047]

ring A-1 is preferably 8 to 10-membered bicycle which may be substituted by 1 to 3 halogen atoms. More preferable ring A-1 is preferably 8 to 10-membered bicycle which may be substituted by 1 halogen atoms.

8 to 10-membered bicycle among ring A or ring A-1 is preferably (1) dihydrobenzofuran, (2) imidazopyridine or (3) quinoline.

4 to 6-membered saturated monocyclic heterocycle is preferably pyrrolidine.

3 to 6-membered heterocycle is preferably (1) oxetane, (2) thiazol or (3) pyrrolidine.

R^1 is preferably (1) a hydrogen atom, (2) C1-8 alkyl, (3) C1-8 haloalkyl or (8) 4 to 6-membered saturated monocyclic heterocycle. More preferable R^1 is C1-4 alkyl. Furthermore preferable R^1 is ethyl.

R^1 is preferably substituted with 1 to 4 R^{1-1} s. More preferable R^1 is substituted with 1 to 3 R^{1-1} s. Furthermore preferable R^1 is substituted with 1 or 2 R^{1-1} s.

R^{1-1} is preferably (1) a deuterium atom, (3) a hydroxy group, (4) C1-4 alkyl, (6) C1-4 alkoxy, (13) cyano or (14) 3-6 membered heterocycle. More preferable R^{1-1} is a deuterium atom, a hydroxy group, methyl, methoxy, cyano or oxetane. Furthermore preferable R^{1-1} is deuterium atom, a hydroxy group or methoxy. Most preferable R^{1-1} is a hydroxy group.

The number of R^{1-1} is preferably 1 to 5. More preferable the number of R^{1-1} is preferably 1 or 2. Most preferable the number of R^{1-1} is 1.

R^{1-1A} is preferably (1) a deuterium atom or (2) a hydroxy group. More preferable R^{1-1A} is (2) a hydroxy group.

The number of R^{1-1A} is preferably 1 to 5. More preferable the number of R^{1-1A} is preferably 1 or 2. Most preferable the number of R^{1-1A} is 1.

R^{1-1B} is preferably (2) a hydroxy group.

The number of R^{1-1B} is preferably 1 to 5. More preferable the number of R^{1-1B} is preferably 1 or 2. Most preferable the number of R^{1-1B} is 1.

R^{1-2} is preferably (1) a hydrogen atom or (2) C1-4 alkyl.

R^{1-3} is preferably (1) a hydrogen atom or (2) C1-4 alkyl.

R^{1-4} is preferably C1-4 alkyl.

R^{1-5} is preferably C1-4 alkyl.

R^{1-6} is preferably a hydrogen atom.

R^{1-7} is preferably C1-4 alkyl.

R^{1-8} is preferably a hydrogen atom.

R^{1-9} is preferably a hydrogen atom.

R^2 is preferably (1) isopropyl, (2) tert-butyl or (3) trifluoromethyl. More preferable R^2 is

(1) isopropyl or (2) trifluoromethyl. Most preferable R^2 is trifluoromethyl.

R^3 is preferably (1) a hydrogen atom or (2) methyl. More preferable R^3 is a hydrogen atom.

R^4 is preferably (1) a fluorine atom, (2) a chlorine atom, (3) methoxy or (4) trifluoromethoxy. More preferable R^4 is (1) a fluorine atom or (2) methoxy. Most preferable R^4 is a fluorine atom.

R^5 is preferably (1) a hydrogen atom, (2) a fluorine atom, (3) a chlorine atom, (4) methyl, (5) tert-butyl, (6) difluoromethyl, (7) trifluoromethyl, (8) difluoromethoxy or (9) trifluoromethoxy. More preferable R^5 is (1) a chlorine atom, (2) difluoromethyl, (3) trifluoromethyl, (4) difluoromethoxy or (5) trifluoromethoxy. Most preferable R^5 is trifluoromethyl.

R^6 is preferably (1) a hydrogen atom, (2) a fluorine atom. More preferable R^6 is a hydrogen atom

R^7 is preferably a hydrogen atom.

R^8 is preferably C1-4 alkyl.

R^9 is preferably (1) a hydrogen atom or (2) methyl. More preferable R^9 is a hydrogen atom.

R^{10} is preferably (1) a hydrogen atom, (2) a fluorine atom. More preferable R^{10} is a hydrogen atom

X^1 is preferably CH.

X^2 is preferably CH.

m is preferably an integer of 1 or 2. More preferable m is an integer of 1.

n is preferably an integer of 1 or 2. More preferable n is an integer of 1.

[0048]

In some embodiments, the compound is preferably, but is not limited to:

- (1) 5-chloro-2-methoxy-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide;
- (2) 5-chloro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide;
- (3) 5-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide;
- (4) 5-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide;
- (5) 2-fluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (6) 2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-

- pyridazinyl}-5-(trifluoromethyl)benzamide;
- (7) 2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;
- (8) 5-chloro-2-methoxy-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide;
- (9) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (10) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (11) N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide;
- (12) 5-(difluoromethyl)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;
- (13) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide;
- (14) 5-(difluoromethoxy)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;
- (15) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide;
- (16) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide;
- (17) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide;
- (18) N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide;
- (19) 5-(difluoromethoxy)-2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;
- (20) N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide;
- (21) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide;
- (22) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide;
- (23) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;
- (24) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-

pyridazinyl}-5-(trifluoromethyl)benzamide;

(25) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;

(26) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;

(27) 2-fluoro-N-(1-(2-hydroxyethyl-2,2-*d*₂)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide;

(28) 2-fluoro-N-(1-(2-hydroxyethyl-2,2-*d*₂)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethoxy)benzamide;

(29) 2-fluoro-N-(1-(2-hydroxyethyl-2-*d*)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide or

(30) 2-fluoro-N-(1-(2-hydroxyethyl-1,1,2,2-*d*₄)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide;

or a pharmaceutically acceptable salt thereof.

[0049]

The compound of the formula (I) is preferably such a compound that some or all the above-mentioned preferred examples for ring A, R¹, R², R³, R⁷, X¹ and m are combined.

The compound of the formula (I-1) is preferably such a compound that some or all the above-mentioned preferred examples for ring A, R¹, R², R³ and m are combined.

The compound of the formula (I-2) is preferably such a compound that some or all the above-mentioned preferred examples for R¹, R², R³, R⁴, R⁵, R⁶, X², m and n are combined.

The compound of the formula (I-3) is preferably such a compound that some or all the above-mentioned preferred examples for R¹, R², R³, R⁴, R⁵, R⁶, m and n are combined.

The compound of the formula (I-A) is preferably such a compound that some or all the above-mentioned preferred examples for ring A, R¹ and R² are combined.

The compound of the formula (I-A1) is preferably such a compound that some or all the above-mentioned preferred examples for ring A-1, R¹ and R² are combined.

The compound of the formula (I-B) is preferably such a compound that some or all the above-mentioned preferred examples for R¹, R², R⁴, R⁵ and R⁶ are combined.

[0050]

In some embodiments, a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction is preferably neurological and/or psychiatric disorder, cancer and/or lung fibrosis.

[0051]

More preferable disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction is depression, schizophrenia, anxiety disorders, bipolar disorder, Alzheimer's

disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, 22q11.2 deletion syndrome, neuropathic pain and/or cerebral infarction.

[0052]

Furthermore preferable disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction is depression, schizophrenia, anxiety disorders, and/or bipolar disorder.

[0053]

Most preferable disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction is depression and/or schizophrenia.

[0054]

In some embodiments, schizophrenia is preferably cognitive impairment associated with schizophrenia (CIAS).

[0055]

In some embodiments, the compounds have prominent TREK-1, TREK-2 or both TREK-1 and TREK-2 inhibitory activity.

[0056]

In some embodiments, the compounds may inhibit TREK-1 selectively. In some embodiments, the compounds may inhibit TREK-2 selectively. In some embodiments, the compounds may inhibit both TREK-1 and TREK-2 to varying degrees. The disclosed compounds may inhibit TREK-1 and/or TREK-2 via a competitive antagonist mechanism or through an allosteric, non-competitive mechanism.

[0057]

The disclosed compounds may inhibit TREK-1 and/or TREK-2 response in TREK-1 or TREK-2-transfected CHO-K1 cells with an IC₅₀ less than, or equivalent to the IC₅₀ for TREK-1 or TREK-2. That is, a disclosed compound can have selectivity for the TREK-1 vis-a-vis TREK-2, a disclosed compound can have selectivity for the TREK-2 vis-a-vis TREK-1, or no selectivity. For example, in some embodiments, a disclosed compound can inhibit TREK-1 response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for TREK-2. In some embodiments, a disclosed compound can inhibit TREK-2 response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for TREK-1. In some embodiments, a disclosed compound can inhibit TREK-1 and TREK-2 responses with comparable IC₅₀ values.

[0058]

In the present disclosure, the isomer includes all of these isomers, unless otherwise

specified. For example, each of an alkyl, a haloalkyl, an alkenyl, a haloalkenyl, an alkynyl, a haloalkynyl, an alkoxy and a haloalkoxy includes both of a linear form and a branched form thereof. In addition, an isomer in a double bond, a ring or a condensed ring (an E-, Z-, cis- or trans-form), an isomer due to the presence of an asymmetric carbon or the like (an R- or S-form, an α - or β -configuration, an enantiomer, a diastereomer), an optical isomer having an optical rotation (a D-, L-, d- or l-form), a polar body obtained by chromatographic separation (a highly polar body, a poorly polar body), an equilibrium compound and a rotational isomer, and a mixture and a racemic mixture thereof at an arbitrary mixing ratio are also included within the scope of the present disclosure. In the present disclosure, the isomer includes all of tautomeric isomers.

[0059]

In the present disclosure, unless otherwise specified,
the symbol:

[Chem. 28]



represents that a substituent binds to the back side on the paper surface (in other words, α -configuration),

the symbol:

[Chem. 29]



represents that a substituent binds to the front side on the paper surface (in other words, β -configuration),

the symbol:

[Chem. 30]



represents α -configuration or β -configuration,

the symbol:

[Chem. 31]



represents a mixture of α -configuration and β -configuration as long as the symbol is substituted at an asymmetric carbon atom.

[0060]

The compound may exist as a stereoisomer wherein asymmetric or chiral centers are present. The stereoisomer is “*R*” or “*S*” depending on the configuration of substituents around the chiral carbon atom. The terms “*R*” and “*S*” used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, in Pure Appl. Chem., 1976, 45: 13-30. The disclosure contemplates various stereoisomers and mixtures thereof and these are specifically included within the scope of this disclosure. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of the compounds may be prepared synthetically from commercially available starting materials, which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by methods of resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, “Vogel's Textbook of Practical Organic Chemistry,” 5th edition (1989), Longman Scientific & Technical, Essex CM20 2JE, England, or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns, or (3) fractional recrystallization methods.

[0061]

It should be understood that the compound may possess tautomeric forms, as well as geometric isomers, and that these also constitute embodiments of the disclosure.

[0062]

The present disclosure also includes an isotopically-labeled compound, which is identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the disclosure are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Substitution with heavier isotopes can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. The compound may incorporate positron-emitting isotopes for medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) are ^{11}C , ^{13}N , ^{15}O , and ^{18}F . Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using appropriate isotopically-labeled reagent in place of non-isotopically-labeled

reagent.

[0063]

Pharmaceutically Acceptable Salts

The disclosed compounds may exist as pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to salts or zwitterions of the compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit/risk ratio and effective for their intended use. The salts may be prepared during the final isolation and purification of the compounds or separately by reacting an amino group of the compounds with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as but not limited to methanol and water and treated with at least one equivalent of an acid, like hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide a salt. Representative salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate, para-toluenesulfonate, undecanoate, hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The amino groups of the compounds may also be quaternized with alkyl chlorides, bromides and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl and the like.

[0064]

Basic addition salts may be prepared during the final isolation and purification of the disclosed compounds by reaction of a carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation such as lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts can be prepared, such as those derived from methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-phenamine and *N,N'*-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

[0065]

In the present disclosure, all the mentions of the compound of the present disclosure include a compound represented by formula (I), or a salt, a solvate, or a cocrystal thereof.

The compound represented by formula (I) and a salt thereof may be present in a not-

solvation form, or in a solvation form with pharmaceutically acceptable solvent such as water or ethanol. Preferable solvates include hydrate. The compound represented by formula (I) and a salt thereof can be converted into a solvate by a well-known method.

[0066]

The compound represented by formula (I) can form a cocrystal with an appropriate cocrystal former. As the cocrystal, pharmaceutically acceptable cocrystal that is formed with a pharmaceutically acceptable cocrystal former is preferable. The cocrystal is typically defined as a crystal that is formed of two or more different molecules by intermolecular interaction that is different from ionic bond. Furthermore, the cocrystal may be a composite of a neutral molecule and a salt. The cocrystal can be prepared by recrystallization from a solvent by a well-known method, for example, melting crystallization, or physically pulverizing the components together. Appropriate cocrystal formers include ones described in WO2006/007448.

[0067]

The compound represented by the formula (I) can be administered as a prodrug. The prodrug of the compound represented by the formula (I) refers to a compound which is converted in vivo to the compound represented by the formula (I) by the reaction with enzymes, gastric acid and the like. Examples of the prodrug of the compound represented by the formula (I) include, when the compound represented by the formula (I) has an amino group, compounds in which the amino group is acylated, alkylated or phosphorylated (e.g. compounds represented by the formula (I) in which the amino group thereof is converted to eicosanoyl, aranyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, acetoxymethyl, tert-butyl or the like); when the compound represented by the formula (I) has a hydroxy group, compounds in which the hydroxy group is acylated, alkylated, phosphorylated or converted to borate (e.g. compounds represented by the formula (I) in which the hydroxy group thereof is converted to acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl or the like); when the compound represented by the formula (I) has a carboxy group, compounds in which the carboxy group is esterified or amidated (e.g. compounds represented by the formula (I) in which the carboxy group thereof is converted to methyl ester, ethyl ester, isopropyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, phthalidyl ester, 1-{{(ethoxycarbonyl)oxy}ethyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, 1-{{[(cyclohexyloxy)carbonyl]oxy}ethyl ester, methylamide or the like) and the like. The prodrug of the compound represented by the formula (I) may be the one which is converted to the compound represented by the formula (I) under the physiological condition such as those disclosed in "Iyakuhin no Kaihatsu", vol. 7 "Bunshi Sekkei", p. 163-198, 1990, Hirokawa Shoten Co.

[0068]

General Synthesis

Compounds of formula (I) may be prepared by synthetic processes or by metabolic processes. Preparation of the compounds by metabolic processes includes those occurring in the human or animal body (in vivo) or processes occurring in vitro.

[0069]

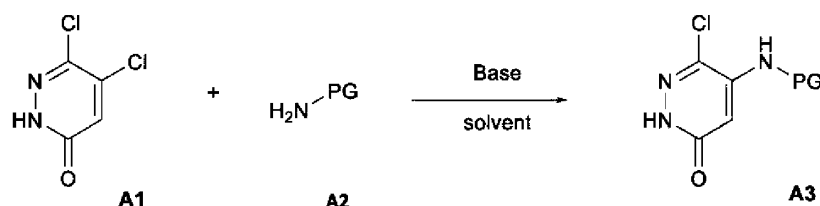
Abbreviations which have been used in the descriptions of the Schemes that follow are: DCM is dichloromethane; DIAD is diisopropyl azodicarboxylate; DIEA or DIPEA is N,N-diisopropylethylamine; EtOAc is ethyl acetate; LiAlH₄ is lithium aluminum hydride; LiAlD₄ is lithium aluminum deuteride; m-CPBA is m-chloro peroxybenzoic acid; MeCN is acetonitrile; NaBH₄ is sodium borohydride; NaBD₄ is sodium borodeuteride; NMI is N-methyl imidazole; NMM is N-methylmorpholine; Pd/C is Palladium-Activated Carbon; PPh₃ is triphenylphosphine; TCFH is chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate; TFA is trifluoroacetic acid; THF is tetrahydrofuran.

[0070]

Compounds of formula (I) can be synthesized as shown in Scheme I to XII.

Scheme I

[Chem. 32]

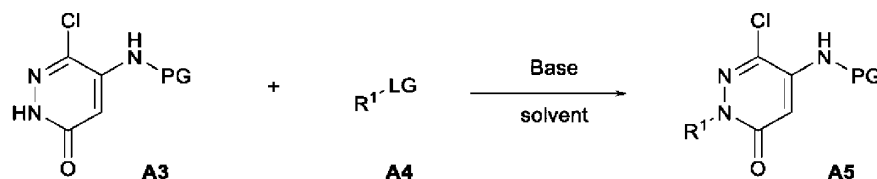


wherein PG is selected from the group consisting of (1) benzyl, (2) 4-methoxy-benzyl, and (3) 2,4-di-methoxy-benzyl. As shown in Scheme I, compounds A1 may be reacted with a variety of base, generally known in the art, to provide intermediates A3. For example, the reaction may be conducted in the presence of a base (e.g, DIEA) in a solvent such as N-methyl-pyrrolidone with heating up to around 150°C.

[0071]

Scheme II

[Chem. 33]



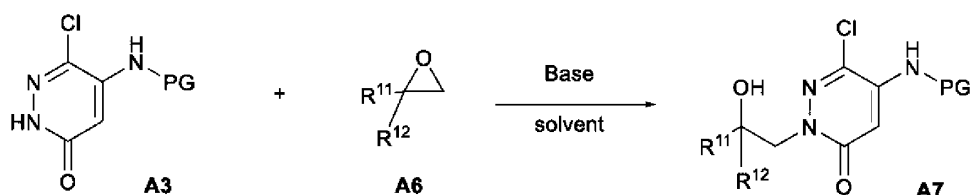
wherein LG is selected from the group consisting of (1) halogen, (2) tosylate, (3)

mesylate and (4) triflate and the other symbols are defined as above. As shown in Scheme II, compounds A3 may be reacted with intermediates A4 in the presence of base, generally known in the art, to provide intermediates A5. For example, the reaction may be conducted in the presence of a base (e.g, K_2CO_3) in a solvent such as N-methyl-pyrrolidone with heating up to around 60°C.

[0072]

Scheme III

[Chem. 34]

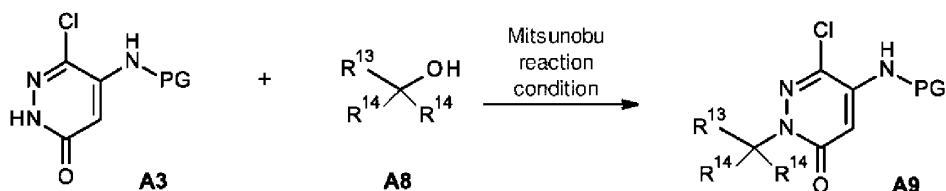


wherein R¹¹ and R¹² are selected from the group consisting of (1) a hydrogen atom, (2) a C1-2 alkyl group, and (3) a C1 haloalkyl group and the other symbols are defined as above. As shown in Scheme III, compounds A3 may be reacted with a variety of epoxide A6 in the presence of base, generally known in the art, to provide intermediates A7. For example, the reaction may be conducted in the presence of a base (e.g, K_2CO_3) in a solvent such as N-methyl-pyrrolidone with heating up to around 60°C.

[0073]

Scheme IV

[Chem. 35]

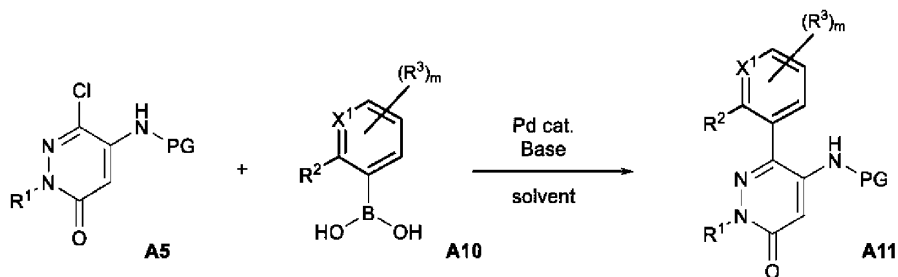


wherein R¹³ is selected from the group consisting of (1) a hydrogen atom and (2) a C1-3 alkyl group which may be substituted by 1 to 6 R^{1-1A}, wherein each R¹⁴ is (1) a hydrogen atom or (2) a deuterium atom, two R¹⁴s may be the same as or different from each other and the other symbols are defined as above. As shown in Scheme IV, intermediate A3 may be reacted with an alcohol A8 under standard conditions of Mitsunobu reaction (e.g. PPh₃ and DIAD) in solvent (e.g. THF) to provide intermediates A9.

[0074]

Scheme V

[Chem. 36]



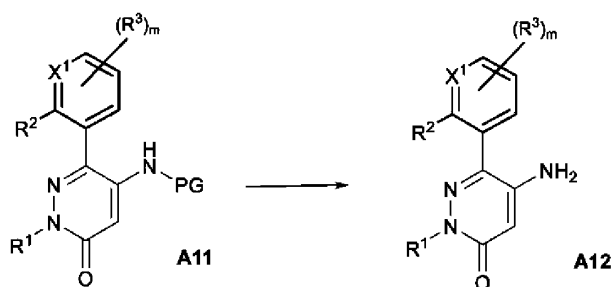
wherein all symbols are defined as above.

[0075]

Scheme V illustrates a general route to the intermediates A11. Intermediate A5 may be coupled with a boronic acid A10 under standard conditions of Suzuki-Miyaura coupling reaction (e.g. Pd(PPh₃)₄ and K₃PO₄) in solvent (e.g. 1,4-dioxane/H₂O) to provide intermediates A11.

Scheme VI

[Chem. 37]



wherein all symbols are defined as above.

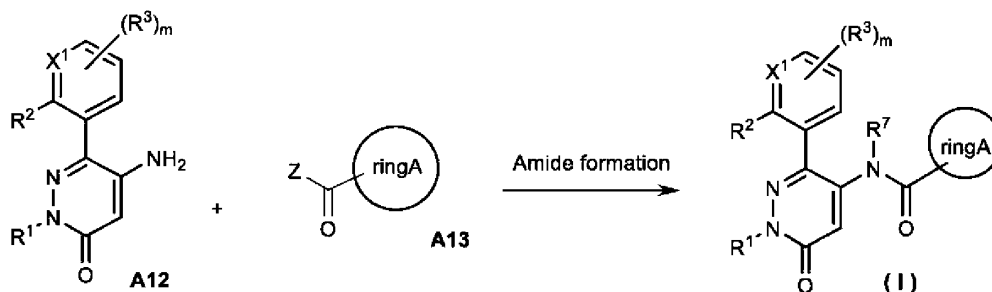
[0076]

Scheme VI illustrates a general route to the intermediates A12. Intermediate A11 may be deprotected with a standard hydrogenation conditions (e.g. Pd/C, H₂, EtOAc/MeOH) or acidic condition (TFA) to provide intermediates A12.

[0077]

Scheme VII

[Chem. 38]



wherein Z is (1) a halogen atom, or (2) hydroxyl group and the other symbols are

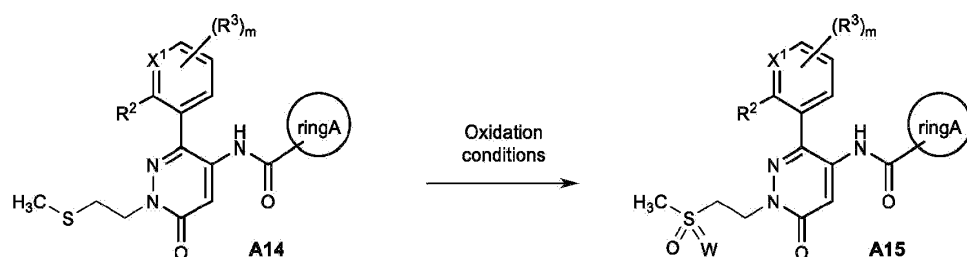
defined as above.

Scheme VII illustrates a general route to compounds of formula (I). Intermediates A12 may be reacted with compounds A13 by standard amide coupling conditions (e.g. TCFH, NMI or NMM, MeCN) heating to around 30°C or by standard acylation conditions (e.g. DIPEA, DCM) under 0°C to afford formula (I) with a hydrogen atom as R⁷. R⁷ may subsequently be replaced with a C1-4 alkyl substituent by standard alkylation conditions, generally known in the art.

[0078]

Scheme VIII

[Chem. 39]



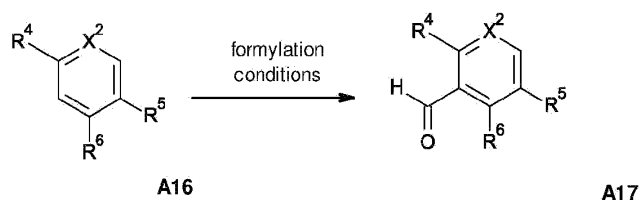
wherein W is (1) an oxygen atom, or (2) a nitrogen atom and the other symbols are defined as above.

Scheme VIII illustrates a general route to compounds A15. Compounds A14 of formula (I), where R¹ is ethylmethylsulfide, may be reacted by standard oxidation conditions (e.g. m-CPBA) in solvent such as DCM to afford compounds A15 (wherein W is an oxygen atom). Additionally, compound A15 (wherein W is a nitrogen atom) may be prepared under standard sulfoximine formation conditions, generally known in the art. Compounds A14 of formula (I) may be subjected to an oxidation reagent (e.g., *p*-iodobenzene diacetate) and ammonium carbonate and solvent (e.g., methanol) to provide compounds A15 (wherein W is a nitrogen atom).

[0079]

Scheme IX

[Chem. 40]



wherein all symbols are defined as above.

[0080]

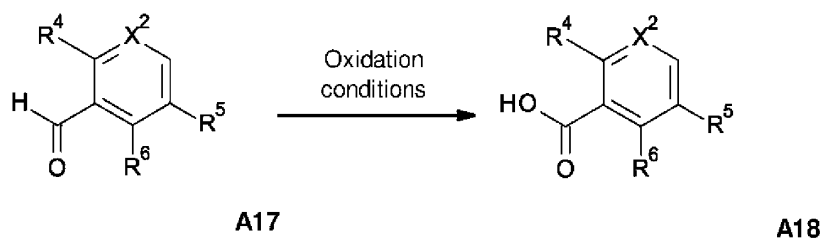
Scheme IX illustrates a general route to the intermediates A17. Intermediate A16 may be reacted with a standard formylation conditions (e.g. *n*-BuLi/DMF, POCl₃/DMF, hexamethylene

tetramine/AcOH) to provide intermediates A17 when at least one of R⁴ and R⁶ is a direct metalation group or electron donating group.

[0081]

Scheme X

[Chem. 41]



wherein all symbols are defined as above.

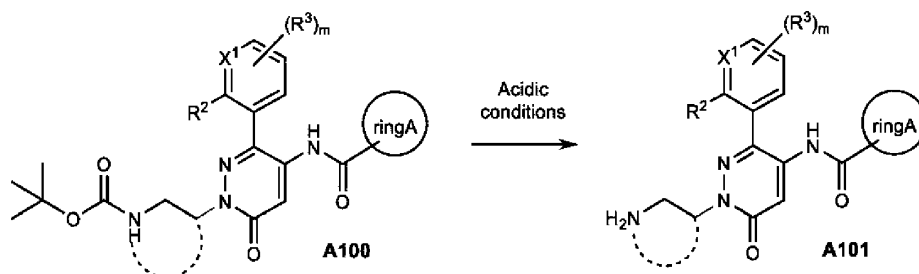
[0082]

Scheme X illustrates a general route to the intermediates A18. Intermediate A17 may be reacted with a standard oxidation conditions (e.g. NaClO₂/NaH₂PO₄, H₂CrO₄, KMnO₄, RuO₄) to provide intermediates A18.

[0083]

Scheme XI

[Chem. 42]



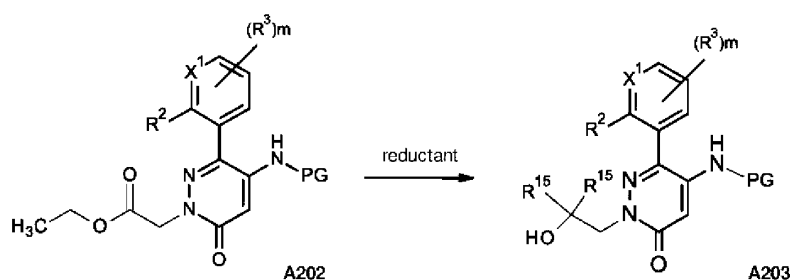
[0084]

Scheme XI illustrates a general route to compounds A101. Compounds A100 of formula (I), where R¹ is tert-butyl ethylcarbamate, wherein the nitrogen of the tert-butyl ethylcarbamate and the methylene carbon adjacent to the nitrogen on the pyridazinone ring may be connected by a carbon chain, may be reacted by standard acidic conditions (e.g. HCl) in solvent such as EtOAc to afford compounds A101.

[0085]

Scheme XII

[Chem. 43]



[0086]

Scheme XII illustrates a general route to intermediates A203. Intermediate A202 (intermediate A11 in which R^1 is ethoxycarbonylmethyl) may be reacted with a standard reduction conditions (e.g. NaBH_4 , NaBD_4 , LiAlH_4 , LiAlD_4) to provide intermediates A203, wherein each R^{15} is (1) a hydrogen atom or (2) a deuterium atom, and two R^{15} s may be the same as or different from each other.

[0087]

The compounds used as the starting material in each of the reactions such as 3,4-dichloro-1H-pyridazin-6-one (**A1**) (CAS No.:17285-36-8) is known or can be easily prepared by known method.

[0088]

The compounds and intermediates may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry", 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

[0089]

A disclosed compound may have at least one basic nitrogen whereby the compound can be treated with an acid to form a desired salt. For example, a compound may be reacted with an acid at or above room temperature to provide the desired salt, which is deposited, and collected by filtration after cooling. Examples of acids suitable for the reaction include, but are not limited to tartaric acid, lactic acid, succinic acid, as well as mandelic, atrolactic, methanesulfonic, ethanesulfonic, toluenesulfonic, naphthalenesulfonic, benzenesulfonic, carbonic, fumaric, maleic, gluconic, acetic, propionic, salicylic, hydrochloric, hydrobromic, phosphoric, sulfuric, citric, hydroxybutyric, camphorsulfonic, malic, phenylacetic, aspartic, or glutamic acid, and the

like.

[0090]

Reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Specific procedures are provided in the Examples section. Reactions can be worked up in the conventional manner, e.g. by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature. Starting materials, if not commercially available, can be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

[0091]

Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the disclosure. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book titled Protective Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the disclosure can be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

[0092]

When an optically active form of a disclosed compound is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

[0093]

Similarly, when a pure geometric isomer of a compound is required, it can be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

[0094]

It can be appreciated that the synthetic schemes and specific examples as described are illustrative and are not to be read as limiting the scope of the disclosure as it is defined in the appended claims. All alternatives, modifications, and equivalents of the synthetic methods and specific examples are included within the scope of the claims.

[0095]

Pharmaceutical Compositions and Formulations

The disclosed compounds may be incorporated into pharmaceutical compositions suitable for administration to a subject (such as a patient, which may be a human or non-human). The disclosed compounds may also be provided as formulations, such as spray-dried dispersion formulations.

[0096]

The pharmaceutical compositions and formulations may include a “therapeutically effective amount” or a “prophylactically effective amount” of the agent. A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the composition may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of a compound of the disclosure (e.g., a compound of formula (I)) are outweighed by the therapeutically beneficial effects. A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0097]

For example, a therapeutically effective amount of a compound of formula (I), may be about 0.01 mg to about 1000 mg at a time by oral administration to a patient for once to several times per day, or about 0.01 mg to about 1000 mg at a time by parenteral administration to a patient, or continuous administration to a patient for 30 minutes to 24 hours per day intravenously. It may be administrated to patients once to several times per day.

[0098]

Needless to say, as mentioned above, the effective amount to be used vary dependent upon various conditions. Therefore, effective amount lower than the ranges specified above may be sufficient in some cases, and effective amount higher than the ranges specified above are needed in some cases.

[0099]

The pharmaceutical compositions and formulations may include pharmaceutically acceptable carriers. The term “pharmaceutically acceptable carrier,” as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0100]

Thus, the compounds and their physiologically acceptable salts may be formulated for administration by, for example, solid dosing, eye drop, in a topical oil-based formulation, injection, inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral, or rectal administration. Techniques and formulations may generally be found in “Remington's Pharmaceutical Sciences,” (Meade Publishing Co., Easton, Pa.). Therapeutic compositions must typically be sterile and stable under the conditions of manufacture and storage.

[0101]

The route by which the disclosed compounds are administered and the form of the composition will dictate the type of carrier to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, implants, or parenteral) or topical administration (e.g., dermal, pulmonary, nasal, aural, ocular, liposome delivery systems, or iontophoresis).

[0102]

Carriers for systemic administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives, glidants, solvents, suspending agents, wetting agents, surfactants, combinations thereof, and others. All carriers are optional in the compositions.

[0103]

Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical composition is typically about 50 to about 90%.

[0104]

Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about 5 to about 10%.

[0105]

Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of binder(s) in a systemic composition is typically about 5 to about 50%.

[0106]

Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1 to about 10%.

[0107]

Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005 to about 0.1%.

Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1 to about 1.0%.

Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s) in a systemic or topical composition is typically about 0.001 to about 1%.

Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1 to about 5%.

Suitable preservatives include benzalkonium chloride, methyl paraben and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically about 0.01 to about 5%.

Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1 to about 5%.

Suitable solvents include water, isotonic saline, ethyl oleate, glycerine, hydroxylated castor oils, alcohols such as ethanol, and phosphate buffer solutions. The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100%.

Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of suspending agent(s) in a systemic or topical composition is typically about 1 to about 8%.

Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5%.

[0108]

Although the amounts of components in the systemic compositions may vary depending on the type of systemic composition prepared, in general, systemic compositions include 0.01% to 50% of an active compound (e.g., a compound of formula (I)) and 50% to 99.99% of one or more carriers. Compositions for parenteral administration typically include 0.1% to 10% of actives and 90% to 99.9% of a carrier including a diluent and a solvent.

[0109]

Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms include a safe and effective amount, usually at least about 5%, and more particularly from about 25% to about 50% of actives. The oral dosage compositions include about 50% to about 95% of carriers, and more particularly, from about 50% to about 75%.

[0110]

Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically include an active component, and a carrier comprising ingredients selected from diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmellose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain sweeteners such as aspartame and saccharin, or flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

[0111]

Capsules (including implants, time release and sustained release formulations) typically

include an active compound (e.g., a compound of formula (I)), and a carrier including one or more diluents disclosed above in a capsule comprising gelatin. Granules typically comprise a disclosed compound, and preferably glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type.

[0112]

The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this disclosure.

[0113]

Solid compositions may be coated by conventional methods, typically with pH or time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT (Registered Trademark) coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

[0114]

Compositions for oral administration can have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically include a disclosed compound and a carrier, namely, a carrier selected from diluents, colorants, flavors, sweeteners, preservatives, solvents, suspending agents, and surfactants. Peroral liquid compositions preferably include one or more ingredients selected from colorants, flavors, and sweeteners.

[0115]

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically include one or more of soluble filler substances such as diluents including sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further include lubricants, colorants, flavors, sweeteners, antioxidants, and glidants.

[0116]

The disclosed compounds can be topically administered. Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers,

moisturizers, sprays, skin patches, and the like. Topical compositions include: a disclosed compound (e.g., a compound of formula (I)), and a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the skin. The carrier may further include one or more optional components.

[0117]

The amount of the carrier employed in conjunction with a disclosed compound is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this disclosure are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

[0118]

A carrier may include a single ingredient or a combination of two or more ingredients. In the topical compositions, the carrier includes a topical carrier. Suitable topical carriers include one or more ingredients selected from phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, and symmetrical alcohols.

[0119]

The carrier of a topical composition may further include one or more ingredients selected from emollients, propellants, solvents, humectants, thickeners, powders, fragrances, pigments, and preservatives, all of which are optional.

[0120]

Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane. The amount of emollient(s) in a skin-based topical composition is typically about 5% to about 95%.

[0121]

Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof. The amount of propellant(s) in a topical composition is typically about 0% to about 95%.

[0122]

Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Specific solvents include ethyl alcohol and homotopic alcohols. The amount of solvent(s) in a topical composition is typically about 0% to about 95%.

[0123]

Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin. The amount of humectant(s) in a topical composition is typically 0% to 95%.

[0124]

The amount of thickener(s) in a topical composition is typically about 0% to about 95%.

[0125]

Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. The amount of powder(s) in a topical composition is typically 0% to 95%.

[0126]

The amount of fragrance in a topical composition is typically about 0% to about 0.5%, particularly, about 0.001% to about 0.1%.

[0127]

Suitable pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of a topical pharmaceutical composition.

[0128]

In some embodiments, the following components are mixed with each other in a usual method and punched out to obtain 10,000 tablets each containing 5 mg of the active ingredient.

5-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide (50 g);

carboxymethylcellulose calcium (disintegrating agent) (20 g);

magnesium stearate (lubricant) (10 g);

microcrystalline cellulose (920 g).

[0129]

Spray-Dried Dispersion Formulations

The disclosed compounds may be formulated as a spray-dried dispersion (SDD). A SDD is a single-phase, amorphous molecular dispersion of a drug in a polymer matrix. It is a solid solution with the compound molecularly “dissolved” in a solid matrix. SDDs are obtained by dissolving drug and a polymer in an organic solvent and then spray-drying the solution. The use of spray drying for pharmaceutical applications can result in amorphous dispersions with increased solubility of Biopharmaceutics Classification System (BCS) class II (high permeability, low solubility) and class IV (low permeability, low solubility) drugs. Formulation and process conditions are selected so that the solvent quickly evaporates from the droplets, thus allowing insufficient time for phase separation or crystallization. SDDs have demonstrated long-term stability and manufacturability. For example, shelf lives of more than 2 years have been demonstrated with SDDs. Advantages of SDDs include, but are not limited to, enhanced oral bioavailability of poorly water-soluble compounds, delivery using traditional solid dosage forms (e.g., tablets and capsules), a reproducible, controllable and scalable manufacturing process and broad applicability to structurally diverse insoluble compounds with a wide range of physical properties.

[0130]

This in one embodiment, the disclosure may provide a spray-dried dispersion formulation comprising a compound of formula (I).

[0131]

Methods of Use

The disclosed compounds, pharmaceutical compositions and formulations may be used in methods for treatment of disorders, such as neurological, psychiatric, inflammatory, respiratory, renal and cardiovascular disorders, cancer or lung fibrosis associated with K2P K⁺ channels, specifically TREK (TWIK Related K⁺ channels) dysfunction for which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit.

[0132]

Treating disorders

The disclosed compounds, pharmaceutical compositions and formulations may be used in methods for prevention and/or treatment of disorders, such as neurological and/or psychiatric disorders, associated with TREK channel dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit. The methods of prevention and/or treatment may comprise administering to a subject in need of such prevention and/or treatment a

therapeutically effective amount of the compound of formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I).

[0133]

In some embodiments, the disclosure provides to a method for enhancing cognition and/or treating, preventing, ameliorating, controlling or reducing the risk of psychiatric symptoms such as schizophrenia and depression in a mammal comprising the step of administering to the mammal a therapeutically effective amount of the compound of formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I).

[0134]

The compounds and compositions disclosed herein may be useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of disorders associated with selective TREK channel inhibition. Thus, provided is a method of treating or preventing a disorder in a subject comprising the step of administering to the subject at least one disclosed compound or at least one disclosed pharmaceutical composition, in an amount effective to treat the disorder in the subject.

[0135]

Also provided is a method for the prevention and/or treatment of one or more disorders associated with TREK channel activity in a subject comprising the step of administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I).

[0136]

In some embodiments, the disclosure provides a method for the prevention and/or treatment of a disorder associated with TREK channel dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal, comprising the step of administering to the mammal an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising at least one disclosed compound or pharmaceutically acceptable salt thereof.

[0137]

In some embodiments, the disclosed compounds and compositions have utility in preventing and/or treating a variety of neurological, psychiatric and cognitive disorders, cancer or lung fibrosis associated with the TREK-1 and/or 2 inhibition in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit, including one or more of the following conditions or diseases: depression, schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic

depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, substance-induced psychotic disorder, neuropathic pain, prostatic, ovarian cancer and lung fibrosis.

[0138]

In some embodiments, the psychotic disorder or psychiatric disorder is a psychosis associated with an illness selected from depression, major depressive disorder, postpartum depression, treatment-resistant depression, affective disorder, bipolar disorder, electrolyte disorder, Alzheimer's disease, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder, anxiety disorder and 22q11.2 deletion disorder.

[0139]

In some embodiments, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, cerebrovascular dementia, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis (ALS) and anti-NMDA receptor encephalitis.

[0140]

In some embodiments, the psychotic or psychiatric disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In some embodiments, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In some embodiments, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder. In some embodiments, the psychotic disorder is due to a general medical condition and is substance-induced or drug-induced (phencyclidine, ketamine and other dissociative anesthetics, amphetamine and other psychostimulants, and cocaine).

[0141]

In some embodiments, schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder are preferred for the neurological disorder.

[0142]

The term "schizophrenia" used herein includes negative symptoms of schizophrenia and cognitive impairment associated with schizophrenia (CIAS).

[0143]

In some embodiments, the present disclosure provides a method for preventing and/or treating a cognitive disorder, comprising administering to a patient in need thereof an effective

amount of a compound or a composition of the present disclosure. In some embodiments, cognitive disorders include dementia (associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse), delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[0144]

The text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes cognitive disorders including dementia, delirium, amnestic disorders and age-related cognitive decline. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (2013, American Psychiatric Association, Washington DC) provides a diagnostic tool for neurocognitive disorders (NCDs) that include delirium, followed by the syndromes of major NCD, mild NCD, and their etiological subtypes. The major or mild NCD subtypes include NCD due to Alzheimer's disease, vascular NCD, NCD with Lewy bodies, NCD due to Parkinson's disease, frontotemporal NCD, NCD due to traumatic brain injury, NCD due to HIV infection, substance/medication-induced NCD, NCD due to Huntington's disease, NCD due to prion disease, NCD due to another medical condition, NCD due to multiple etiologies, and unspecified NCD. The NCD category in DSM-5 encompasses the group of disorders in which the primary clinical deficit is in cognitive function, and that are acquired rather than developmental. As used herein, the term "cognitive disorders" includes prevention and/or treatment of those cognitive disorders and neurocognitive disorders as described in DSM-IV-TR or DSM-5. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term "cognitive disorders" is intended to include like disorders that are described in other diagnostic sources.

[0145]

In some embodiments, the present disclosure provides a method for preventing and/or treating schizophrenia or psychosis, comprising administering to a patient in need thereof an effective amount of a compound or composition of the present disclosure. Particular schizophrenia or psychosis pathologies are paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder. DSM-IV-TR provides a diagnostic tool that includes paranoid, disorganized, catatonic, undifferentiated or residual schizophrenia, and substance-induced psychotic disorder. DSM-5 eliminated the subtypes of schizophrenia, and

instead includes a dimensional approach to rating severity for the core symptoms of schizophrenia, to capture the heterogeneity in symptom type and severity expressed across individuals with psychotic disorders. As used herein, the term “schizophrenia or psychosis” includes prevention and/or treatment of those mental disorders as described in DSM-IV-TR or DSM-5. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term “schizophrenia or psychosis” is intended to include like disorders that are described in other diagnostic sources.

[0146]

In some embodiments, the present disclosure provides a method for preventing and/or treating pain, comprising administering to a patient in need thereof an effective amount of a compound or composition of the present disclosure. Partikidneycular pain embodiments are bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain and neuropathic pain.

[0147]

In some embodiments, the present disclosure provides a method for preventing and/or treating inflammatory disorder, comprising administering to a patient in need thereof an effective amount of a compound or a composition of the present disclosure. In some embodiments, inflammatory disorders include intestinal allergies, inflammatory bowel disease, allergic asthma, allergic dermatitis and allergic rhinitis.

[0148]

In some embodiments, the present disclosure provides a method for preventing and/or treating respiratory disorder, comprising administering to a patient in need thereof an effective amount of a compound or a composition of the present disclosure. In some embodiments, respiratory disorders include asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, pneumonia, and lung cancer.

[0149]

In some embodiments, the present disclosure provides a method for preventing and/or treating renal disorder, comprising administering to a patient in need thereof an effective amount of a compound or a composition of the present disclosure. In some embodiments, renal disorders include nephritic syndrome and kidney failure.

[0150]

In some embodiments, the present disclosure provides a method for preventing and/or treating cardiovascular disorder, comprising administering to a patient in need thereof an effective amount of a compound or a composition of the present disclosure. In some

embodiments, cardiovascular disorders include coronary artery diseases, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis.

[0151]

In some embodiments, the present disclosure provides a method for preventing and/or treating cancer, comprising administering to a patient in need thereof an effective amount of a compound or a composition of the present disclosure. In some embodiments, cancers include cancer associated with cerebral nerve (for example, pediatric brain tumors (for example, neuroblastoma, medulloblastoma, astrocytoma (for example, juvenile pilocytic astrocytoma), ependymoma, craniopharyngioma, germ cell tumors, optic nerve glioma, choroid plexus papilloma and pontine glioma), adult brain tumors (for example, adult astrocytoma, adult malignant astrocytoma, adult glioblastoma, adult ependymoma, adult malignant ependymoma, adult malignant oligodendroglioma, adult medulloblastoma, adult meningioma and adult malignant meningioma), glioma (for example, astrocytoma, oligodendroglioma, ependymoma and brain stem glioma), pituitary adenoma, acoustic schwannoma, retinoblastoma and uveal malignant melanoma), respiratory tract cancer (for example, pharyngeal cancer (for example, nasopharyngeal cancer, oropharyngeal cancer and hypopharyngeal cancer), laryngeal cancer, nasal sinus cancer, lung cancer (for example, small cell cancer and non-small-cell cancer), thymoma and mesothelioma), gastrointestinal cancer (for example, esophageal cancer, gastric cancer, duodenal cancer and large bowel cancer (for example, colon cancer, rectal cancer and anal cancer)), oral cancer (for example, gingival cancer, tongue cancer and salivary gland cancer), urinary system cancer (for example, penile cancer, renal pelvis · ureter cancer, renal cell cancer, testicular tumor, prostate cancer, prostatic cancer and bladder cancer), cancers that affect women (for example, vulvar cancer, uterine cancer (for example, cervical cancer and endometrial cancer), uterine sarcoma, trophoblastic disease (for example, hydatidiform mole, choriocarcinoma, placental-site trophoblastic tumor and persistent trophoblastic disease), vaginal cancer, breast cancer, breast sarcoma, ovarian cancer and ovarian germ cell tumor), skin cancer (for example, melanoma (also known as malignant melanoma) (for example, malignant lentiginous melanoma, superficial spreading melanoma, nodular melanoma, acral lentiginous melanoma and erosive melanoma), mycosis fungoides, squamous cell carcinoma, basal cell carcinoma, premonitory signs of skin cancer · intraepidermal carcinoma (for example, actinic keratosis, Bowen's disease and Paget's disease), lymphomatoid papulosis, cutaneous CD30 positive anaplastic large cell lymphoma, Sezary syndrome and cutaneous B-cell lymphoma), bone and muscle cancer (for example, osteosarcoma, soft tissue sarcoma, rhabdomyosarcoma, synovial sarcoma and liposarcoma), thyroid cancer, carcinoid, liver cancer (also known as

hepatoma), hepatoblastoma, bile duct cancer, gallbladder cancer, pancreatic cancer, pancreatic endocrine tumors (for example, insulinoma, gastrinoma and VIPoma), carcinoma of unknown primary, hereditary tumors · familial tumors (for example, hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, hereditary breast and ovarian cancer syndrome, Li-Fraumeni syndrome, hereditary melanoma, Wilms' tumor, hereditary papillary renal cell carcinoma, von Hippel-Lindau syndrome and multiple endocrine neoplasia), leukemia (for example, acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, chronic myeloid leukemia, chronic myeloproliferative disorder, adult T-cell leukemia-lymphoma, chronic lymphocytic leukemia and small lymphocytic lymphoma), multiple myeloma, primary macroglobulinemia, malignant lymphoma (for example, Hodgkin's lymphoma, non-Hodgkin's lymphoma (intermediate- and high-grade lymphomas, Burkitt's lymphoma, lymphoblastic lymphoma, follicular lymphoma, mantle-cell lymphoma, MALT (Mucosa-Associated Lymphoid Tissue) lymphoma and NK (natural killer) cell lymphoma)). In some embodiments, cancer is preferably lung, prostatic and ovarian cancer.

[0152]

The compounds and compositions may be further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The compounds and compositions may be further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions, in combination with other agents.

[0153]

In the prevention and/or treatment of conditions which require inhibition of a TREK channel (TREK-1, TREK-2 or both TREK-1 and TREK-2), an appropriate dosage level may be about 0.01 to 1000 mg per day, which can be administered to a patient in single or multiple doses. For oral administration, the compositions may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day. This dosage regimen can be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0154]

In some embodiments, the disorder in which inhibitors of TREK-1, TREK-2 or both

TREK-1 and TREK-2 would offer therapeutic benefit can be selected from psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, autistic disorder, movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

[0155]

In some embodiments, the disorder in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit is Alzheimer's disease.

[0156]

Co-therapeutic methods

The present disclosure is further directed to administration of a selective TREK channel inhibitor for improving treatment outcomes in the context of cognitive or behavioral therapy. That is, in some embodiments, the disclosure relates to a co-therapeutic method comprising a step of administering to a mammal an effective amount and dosage of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0157]

In some embodiments, administration improves treatment outcomes in the context of cognitive or behavioral therapy. Administration in connection with cognitive or behavioral therapy can be continuous or intermittent. Administration need not be simultaneous with therapy and can be before, during, and/or after therapy.

[0158]

It is understood that the disclosed cotherapeutic methods can be used in connection with the disclosed compounds, compositions, kits, and uses.

[0159]

Combination Therapies

In the methods of use described herein, additional therapeutic agent(s) may be administered simultaneously or sequentially with the disclosed compounds and compositions. Sequential administration includes administration before or after the disclosed compounds and compositions. In some embodiments, the additional therapeutic agent or agents may be administered in the same composition as the disclosed compounds. In other embodiments, there may be an interval of time between administration of the additional therapeutic agent and the disclosed compounds. In some embodiments, administration of an additional therapeutic agent

with a disclosed compound may allow lower doses of the other therapeutic agents and/or administration at less frequent intervals. When used in combination with one or more other active ingredients, the compounds of the present disclosure and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present disclosure include those that contain one or more other active ingredients, in addition to a compound of Formula (I). The above combinations include combinations of a compound of the present disclosure not only with one other active compound, but also with two or more other active compounds.

[0160]

The disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which the compound or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefor, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound may be used. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound can be more efficacious than either as a single agent. Thus, when used in combination with one or more other active ingredients, the disclosed compounds and the other active ingredients can be used in lower doses than when each is used singly.

[0161]

The pharmaceutical compositions and methods of the present disclosure can further comprise other therapeutically active compounds as noted herein which are usually applied in the prevention and/or treatment of the above mentioned pathological conditions.

[0162]

The above combinations include combinations of a disclosed compound not only with one other active compound, but also with two or more other active compounds. Likewise, disclosed compounds can be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which disclosed compounds are useful. Such other drugs can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present disclosure. When a compound of the present disclosure is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to a disclosed compound is preferred. Accordingly, the pharmaceutical compositions include

those that also contain one or more other active ingredients, in addition to a compound of the present disclosure.

[0163]

The weight ratio of a disclosed compound to the second active ingredient can be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present disclosure is combined with another agent, the weight ratio of a disclosed compound to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present disclosure and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0164]

In such combinations a disclosed compound and other active agents can be administered separately or in conjunction. In addition, the administration of one element can be prior to, concurrent to, or subsequent to the administration of other agent(s).

[0165]

Accordingly, the disclosed compounds can be used alone or in combination with other agents which are known to be beneficial in the subject indications or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the disclosed compounds. The subject compound and the other agent can be coadministered, either in concomitant therapy or in a fixed combination.

[0166]

In some embodiments, the compound can be employed in combination with anti-Alzheimer's agents, beta-secretase inhibitors, cholinergic agents, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, M₁ allosteric agonists, M₁ positive allosteric modulators, NSAIDs including ibuprofen, vitamin E, and anti-amyloid antibodies. In another embodiment, the subject compound can be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics (typical and atypical), antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flupentixol, fluphenazine,

flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quetiapine, reclazepam, risperidone, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, thiothixene, tracazolate, tranlycypromaine, trazodone, triazolam, trepipedam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound can be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

[0167]

In some embodiments, the compound can be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alantemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist can be in the form of a pharmaceutically acceptable salt, for example, alantemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexol are commonly used in a non-salt form.

[0168]

In some embodiments, the compound can be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination with the subject compound can be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine

decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form. Thus, the subject compound can be employed in combination with acetophenazine, alantemol, aripiprazole, amisulpride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

[0169]

In some embodiments, the compound can be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranlycypromine and selegiline; moclobemide; venlafaxine; duloxetine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

[0170]

In some embodiments, the compounds can be coadministered with orthosteric muscarinic agonists, muscarinic potentiators, or cholinesterase inhibitors. In some embodiments, the compounds can be coadministered with GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbital, and salts thereof and combinations thereof.

[0171]

In some embodiments, the other drugs for the prevention and/or treatment of schizophrenia is at least one drug selected from typical antipsychotics, atypical antipsychotics, and the like.

[0172]

The typical antipsychotics may include, for example, chlorpromazine, fluphenazine, haloperidol, sulpiride and the like.

The atypical antipsychotics may include, for example, serotonin-dopamine antagonist, multi-acting receptor targeted antipsychotics, dopamine partial agonist and the like.

The serotonin-dopamine antagonist may include, for example, risperidone, perospirone, ziprasidone, blonanserin and the like.

The multi-acting receptor targeted antipsychotics may include, for example, olanzapine, quetiapine, clozapine, lurasidone and the like.

The dopamine partial agonist may include, for example, aripiprazole, cariprazine and the like.

[0173]

In some embodiments, the other drugs for the prevention and/or treatment of depression is at least one drug selected from benzodiazepine antianxiety drug, thienodiazepine antianxiety drug, non-benzodiazepine antianxiety drug, neurokinin-1 (NK1) antagonist, tricyclic antidepressant, tetracyclic antidepressant, monoamine oxidase (MAO) inhibitor, triazolopyridine antidepressant, serotonin and noradrenaline reuptake inhibitor (SNRI), selective serotonin reuptake inhibitor (SSRI), serotonin reuptake inhibitor, noradrenergic and specific serotonergic antidepressant (NaSSA), noradrenaline and dopamine disinhibition drug (NDDI), selective serotonin reuptake enhancer (SSRE), and the like.

[0174]

The benzodiazepine antianxiety drug may include, for example, alprazolam, oxazepam, oxazolam, clonazepam, lorazepam, diazepam, clordiazepoxide, diazepam, tofisopam, triazolam, prazepam, fludiazepam, flutazolam, flutoprazepam, bromazepam, mexazolam, medazepam, ethyl loflazepam, lorazepam and the like.

The thienodiazepine antianxiety drug may include, for example, etizolam, clonazepam and the like.

The non-benzodiazepine antianxiety drug may include, for example, citric acid tandospirone, hydroxyzine hydrochloride and the like.

[0175]

The neurokinin-1 (NK1) antagonist may include, for example, aprepitant, fosaprepitant meglumine and the like.

The tricyclic antidepressant may include, for example, amitriptyline hydrochloride, imipramine hydrochloride, clomipramine hydrochloride, dosulepin hydrochloride, nortriptyline hydrochloride, lofepramine hydrochloride, trimipramine maleate, amoxapine and the like.

The tetracyclic antidepressant may include, for example, maprotiline hydrochloride, mianserin hydrochloride, setipiline maleate and the like.

The monoamine oxidase (MAO) inhibitor may include, for example, safrazine hydrochloride and the like.

The triazolopyridine antidepressant may include, for example, Trazodone Hydrochloride and the like.

The serotonin and noradrenaline reuptake inhibitor (SNRI) may include, for example, milnacipran hydrochloride, venlafaxine hydrochloride, duloxetine hydrochloride and the like.

The selective serotonin reuptake inhibitor (SSRI) may include, for example, fluvoxamine maleate, paroxetine hydrochloride, fluoxetine hydrochloride, citalopram hydrochloride, sertraline hydrochloride, escitalopram oxalate and the like.

The serotonin reuptake inhibitor may include, for example, trazodone hydrochloride and the like.

The noradrenergic and specific serotonergic antidepressant (NaSSA) may include, for example, mirtazapine and the like.

The noradrenaline and dopamine disinhibition drug (NDDI) may include, for example, agomelatine and the like.

The selective serotonin reuptake enhancer (SSRE) may include, for example, tianeptine and the like.

[0176]

In some embodiments, the other drugs for the prevention and/or treatment of pain is at least one drug selected from acetaminophen, a nonsteroid anti-inflammatory drug, an opioid, an antidepressant, an antiepileptic agent, an *N*-methyl-D-aspartate antagonist, a muscle relaxant, an antiarrhythmic agent, a steroid, a bisphosphonate and the like.

The antiarrhythmic agent may include, for example, lidocaine, mexiletine and the like.

[0177]

The nonsteroid anti-inflammatory drug may include, for example, sasapyrine, sodium salicylate, aspirin, aspirin formulations such as those containing aspirin-dialuminate, diflunisal, indomethacin, suprofen, ufenamate, dimethylisopropylazulene, bufexamac, felbinac, diclofenac, tolmetin sodium, Clinoril, fenbufen, nabumetone, proglumetacin, indomethacin farnesil, acetmetacin, proglumetacin maleate, amfenac sodium, mofezolac, etodolac, ibuprofen, ibuprofen piconol, naproxen, flurbiprofen, flurbiprofen axetil, ketoprofen, fenoprofen calcium, tiaprofen, oxaprozin, pranoprofen, loxoprofen sodium, alminoprofen, zaltoprofen, mefenamic acid, aluminium mefenamate, tolfenamic acid, floctafenine, ketophenylbutazone, oxyphenbutazone, piroxicam, tenoxicam, ampiroxicam, Napageln ointment, epirizole, tiaramide hydrochloride, tinoridine hydrochloride, emorfazone, sulpyrine, Migrenin, Saridon, Sedes G, Amipylo-N, Sorbon, pilin cold remedies, acetaminophen, phenacetin, dimetotiazine mesilate, meloxicam, celecoxib, rofecoxib, valdecoxib, simetride-containing formulations and non-pilin cold remedies

and the like.

[0178]

The opioid may include, for example, codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene and the like.

[0179]

The antidepressant may include, for example, tricyclic antidepressants (e.g., imipramine hydrochloride, clomipramine hydrochloride, dosulepin hydrochloride, nortriptyline hydrochloride, lofepramine hydrochloride, trimipramine maleate, amoxapine), tetracyclic antidepressants (e.g., maprotiline hydrochloride, mianserin hydrochloride, setiptiline maleate), monoamine oxidase (MAO) inhibitors (safrazine hydrochloride), serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g., milnacipran hydrochloride, venlafaxine hydrochloride), selective serotonin reuptake inhibitors (SSRIs) (e.g., fluvoxamine maleate, paroxetine hydrochloride,), serotonin reuptake inhibitors (e.g., trazodone hydrochloride) and the like.

[0180]

The antiepileptic agent may include, for example, phenobarbital, Puridomin, phenytoin, ethosuximide, zonisamide, nitrazepam, clonazepam, carbamazepine, sodium valproate, acetazolamide, sulthiame, gabapentin, pregabalin and the like.

The *N*-methyl-D-aspartate antagonist may include, for example, ketamine hydrochloride, amantadine hydrochloride, memantine hydrochloride, dextromethorphan, methadone and the like.

The muscle relaxant may include, for example, succinylcholine, suxamethonium, vecuronium bromide, pancronium bromide, dantrolene sodium and the like.

[0181]

The steroid may include, for example, as topical agents, clobetasol propionate, diflorasone diacetate, fluocinonide, mometasone furoate, betamethasone dipropionate, betamethasone butyrate propionate, betamethasone valerate, difluprednate, budesonide, diflucortolone valerate, amcinonide, halcinonide, dexamethasone, dexamethasone propionate, dexamethasone valerate, dexamethasone acetate, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone butyrate propionate, deprodone propionate, prednisolone valerate acetate, fluocinolone acetonide, beclometasone propionate, triamcinolone acetonide, flumetasone pivalate, alclometasone dipropionate, clobetasone butyrate, prednisolone, beclometasone propionate, fludroxycortide and the like.

[0182]

The bisphosphonate may include, for example, etidronate, pamidronate, alendronate, risedronate, zoledronate, minodronate and the like.

[0183]

Modes of Administration

Methods of prevention and/or treatment may include any number of modes of administering a disclosed composition. Modes of administration may include tablets, pills, sugar-coated tablet, hard and soft gel capsules, granules, pellets, aqueous, lipid, oily or other solutions, emulsions such as oil-in-water emulsions, liposomes, aqueous or oily suspensions, syrups, elixirs, solid emulsions, solid dispersions or dispersible powders. For the preparation of pharmaceutical compositions for oral administration, the agent may be admixed with commonly known and used adjuvants and excipients such as for example, gum arabic, talcum, starch, sugars (such as, e.g., mannitolose, methyl cellulose, lactose), gelatin, surface-active agents, magnesium stearate, aqueous or non-aqueous solvents, paraffin derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents, flavoring agents (e.g., ethereal oils), solubility enhancers (e.g., benzyl benzoate or benzyl alcohol) or bioavailability enhancers (e.g. Gelucire.TM.). In the pharmaceutical composition, the agent may also be dispersed in a microparticle, e.g. a nanoparticulate composition.

[0184]

For parenteral administration, the agent can be dissolved or suspended in a physiologically acceptable diluent, such as, e.g., water, buffer, oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed oil, soybean oil, castor oil and sesame oil may be used. More generally spoken, for parenteral administration, the agent can be in the form of an aqueous, lipid, oily or other kind of solution or suspension or even administered in the form of liposomes or nano-suspensions.

[0185]

The term “parenteral administration” as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The present compound has low toxicity and thus can be safely used as a medicament.

[0186]

Kits

In one aspect, the disclosure provides kits comprising at least one disclosed compound or a pharmaceutically acceptable salt thereof, and one or more of:

- (a) at least one agent known to decrease TREK-1 activity;
- (b) at least one agent known to decrease TREK-2 activity;
- (c) at least one agent known to prevent and/or treat a disorder associated with TREK dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal;

(d) instructions for preventing and/or treating a disorder associated with TREK dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal; or

(e) instructions for administering the compound in connection with cognitive or behavioral therapy.

[0187]

In some embodiments, the at least one disclosed compound and the at least one agent are co-formulated. In some embodiments, the at least one disclosed compound and the at least one agent are co-packaged. The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

That the disclosed kits can be employed in connection with disclosed methods of use.

[0188]

The kits may include information, instructions, or both that use of the kit will provide prevention and/or treatment for medical conditions in mammals (particularly humans). The information and instructions may be in the form of words, pictures, or both, and the like. In addition or in the alternative, the kit may include the compound, a composition, or both; and information, instructions, or both, regarding methods of application of compound, or of composition, preferably with the benefit of preventing and/or treating medical conditions in mammals (e.g., humans).

[0189]

The compounds and processes of the disclosure will be better understood by reference to the following examples, which are intended as an illustration of and not a limitation upon the scope of the disclosure.

[Examples]

[0190]

The present disclosure is hereinafter specifically described by way of Examples and Biological Examples which do not limit the present disclosure. The present compounds and compounds described in Examples are denominated according to the IUPAC nomenclature. Naming according to the IUPAC nomenclature can be done using, for example, ACD/Name (Registered Trademark, version 2019.2.0, available from Advanced Chemistry Development Inc.), ACD/Name Batch (Registered Trademark, version 12.02.45356, available from Advanced Chemistry Development Inc.) or ChemDraw Professional (Registered Trademark, version 17.1.0.105 or 18.0.0.231, available from PerkinElmer Inc.). In each of the following Examples, the name of the objective compound of the Example is described subsequently to the number of

the Example, and the compound is sometimes referred to as the “title compound”.

[0191]

All NMR spectra were recorded on a 400 MHz AMX Bruker NMR spectrometer or a Bruker AVANCE III 400MHz NMR or 600MHz spectrometer. ¹H chemical shifts are reported in δ values in ppm downfield with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, ABq = AB quartet), coupling constant, integration.

LCMS analysis conditions are as below. The MS data in Examples were measured by Reversed-phase LCMS method (1) unless otherwise specified.

[0192]

Reversed-phase LCMS (1):

Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2010 with ESI source. MS parameters were as follows: Mobile Phase: 1.5 mL/4 L TFA in water (solvent A) and 0.75 mL/4 L TFA in acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over 0.7 minutes, then holding at 95% for 0.4 minutes, at 5% for 0.4 min, at a flow rate of 1.5 ml/min; Column: Agilent Pursuit 5 C18 20*2.0 mm; Wavelength: UV 220nm, 254nm, 215nm; Column temperature: 50 °C; MS ionization: ESI.

[0193]

Reversed-phase LCMS (2):

Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2020 with ESI source. MS parameters were as follows: Mobile Phase: 0.8 mL/4 L NH₃H₂O in water (solvent A) and acetonitrile (solvent B), using the elution gradient 10%-80% (solvent B) over 6.5 minutes and holding at 95% for 0.5 minutes at a flow rate of 0.8 ml/min; Column: Xbridge Shield RP-18, 5 μm, 2.1*50 mm; Wavelength: UV 220nm, 254nm, 215nm; Column temperature: 50°C; MS ionization: ESI.

[0194]

Reversed-phase LCMS (3):

Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2020 with ESI source. MS parameters were as follows: Mobile Phase: 0.8 mL/4 L NH₃H₂O in water (solvent A) and acetonitrile (solvent B), using the elution gradient 50%-100% (solvent B) over 2.5 minutes then holding at 95% for 0.5 minutes, at 50% for 0.5 min, at a flow rate of 0.8 ml/min; Column: Xbridge Shield RP-18, 5 μm, 2.1*50 mm; Wavelength: UV 220nm, 254nm, 215nm; Column temperature: 50°C; MS ionization: ESI.

[0195]

Reversed-phase LCMS (4):

Reversed-phase LCMS analysis was performed using an Agilent 1200 system comprised of a binary pump with degasser, high-performance autosampler, thermostatted column compartment, C18 column, diode-array detector (DAD) and an Agilent 6150 MSD with the following parameters. The gradient conditions were 5% to 95% acetonitrile with the aqueous phase 0.1% TFA in water over 1.4 minutes. Samples were separated on a Waters Acquity UPLC BEH C18 column (1.7 μm , 1.0 x 50 mm) at 0.5 mL/min, with column and solvent temperatures maintained at 55 °C. The DAD was set to scan from 190 to 300 nm, and the signals used were 220 nm and 254 nm (both with a band width of 4nm). The MS detector was configured with an electrospray ionization source, and the low-resolution mass spectra were acquired by scanning from 140 to 700 AMU with a step size of 0.2 AMU at 0.13 cycles/second, and peak width of 0.008 minutes. The drying gas flow was set to 13 liters per minute at 300 °C and the nebulizer pressure was set to 30 psi. The capillary needle voltage was set at 3000 V, and the fragmentor voltage was set at 100V. Data acquisition was performed with Agilent Chemstation and Analytical Studio Reviewer software.

[0196]

Reversed-phase LCMS (5):

Reversed-phase LCMS analysis was obtained on a SHIMADZU LCMS-2020 with ESI source. MS parameters were as follows: Mobile Phase: 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B), using the elution holding at 5% (solvent B) for 0.1 minutes, gradient 5%-95% (solvent B) over 1.1 minutes and holding at 95% for 0.4 minutes at a flow rate of 1.0 ml/min; Column: YMC Triart C18 Φ 2.0 mm* L30mm; Wavelength: UV 220nm, 254nm; Column temperature: 30°C; detector MS, ELSD; MS ionization: ESI.

[0197]

Prep-HPLC (FA):

An example: Mobile Phase: 0.225% FA in water (solvent A) and acetonitrile (solvent B), using the elution gradient 55%-85% (solvent B) over 7.8 minutes then holding at 100% for 2 minutes, at a flow rate of 25 ml/min; Column: Welch Xtimate C18 150*25mm*5 μm

[0198]

Prep-HPLC (TFA):

An example: Mobile Phase: 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B), using an appropriate elution gradient according to a compound, at a flow rate of 40 ml/min; Column: YMC TriartC18 75*30mm*5 μm

[0199]

Prep-HPLC (NH₃H₂O):

An example: Mobile Phase: 0.05% NH₃H₂O and 10 mM NH₄HCO₃ in water (solvent A) and acetonitrile (solvent B), using the elution gradient 37%-67% (solvent B) over 9.5 minutes

then holding at 100% for 2 minutes, at a flow rate of 25 ml/min; Column: Phenomenex Gemini 150*25mm*10 μ m.

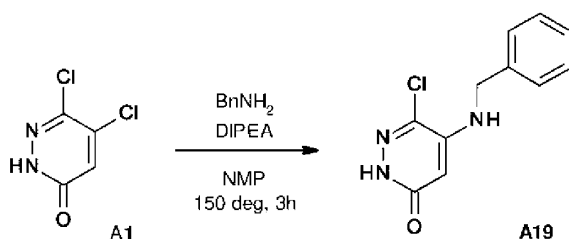
[0200]

Abbreviations which have been used in the descriptions of following examples are: AcCl is acetyl chloride; AcOH is acetic acid; Ac₂O is acetic anhydride; AlMe₃ is trimethylaluminium; BnNH₂ is benzylamine; CMBP is cyanomethylenetriethylphosphorane; DCM is dichloromethane; DIAD is diisopropyl diazene-1,2-dicarboxylate; DIEA or DIPEA is *N,N*-diisopropylethylamine; DMF is *N,N*-dimethylformamide; DMSO is dimethyl sulfoxide; EtOAc or EA is ethyl acetate; FA is formic acid; Hex is Hexane; *m*-CPBA is *m*-chloroperoxybenzoic acid; MeCN is acetonitrile; MTBE is methyl *tert*-butyl ether or *tert*-butyl methyl ether; NaBH₄ is sodium borohydride; NaBD₄ is sodium borodeuteride; NMI is *N*-methylimidazole; NMM is *N*-methylmorpholine; NMP is *N*-methylpyrrolidone; Pd A-taPhos is bis[di-*tert*-butyl(4-dimethylaminophenyl)phosphine]palladium(0); PE is petroleum ether; PhMe is toluene; Py is pyridine; TCFH is chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate; TEA is triethylamine; TFA is trifluoroacetic acid.

[0201]

Scheme 1

[Chem. 44]

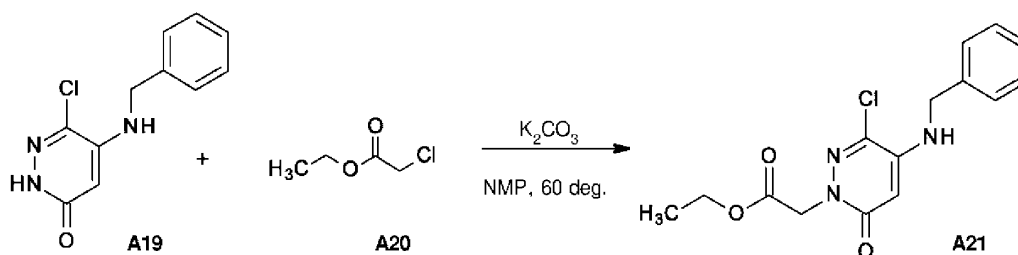


4-(benzylamino)-3-chloro-1H-pyridazin-6-one (A19): To a solution of compound 3,4-dichloro-1H-pyridazin-6-one (**A1**) (CAS No.:17285-36-8, 25.0 g, 152 mmol, 1.00 eq) in NMP (150 mL) was added BnNH₂ (17.9 g, 167 mmol, 18.1 mL, 1.10 eq) and DIPEA (29.4 g, 227 mmol, 39.3 mL, 1.50 eq). The mixture was stirred at 150°C for 3 hrs. LCMS showed the compound **A1** was consumed completely. The reaction mixture was poured into 1M HCl (1.00 L). The resulting mixture was stirred at room temperature for 30 min. The resulting precipitate was filtered and washed with H₂O to afford a crude product. The crude product was triturated with EtOAc/Hex (2/1, 400 mL) to afford Compound **A19** (30.6 g, 130 mmol, crude yield: 85.7%). MS (ESI) *m/z* = 236.0 [M+H]⁺. ¹H NMR: (400 MHz, DMSO-d₆) δ = 12.23 (s, 1H), 7.50 - 7.09 (m, 6H), 5.40 (s, 1H), 4.37 (d, *J* = 6.0 Hz, 2H).

[0202]

Scheme 2

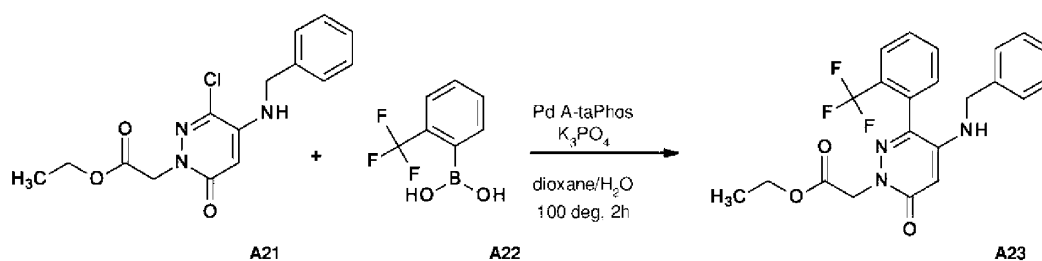
[Chem. 45]



ethyl 2-[4-(benzylamino)-3-chloro-6-oxo-pyridazin-1-yl] acetate (A21): To a solution of compound **A19** (1.35 g, 5.73 mmol, 1.00 eq) and K_2CO_3 (1.58 g, 11.5 mmol, 2.00 eq) in NMP (10 mL) was added ethyl chloroacetate (**A20**) (CAS No.:105-39-5, 1.05 g, 8.59 mmol, 0.92 mL, 1.50 eq). The mixture was stirred at 60°C for 4 hrs. LCMS showed the compound **A19** was consumed completely. The reaction mixture was filtered through Celite (Registered Trademark), and then washed with EtOAc (100 mL). To the filtrate was added H_2O (100 mL), and the mixture was extracted with EtOAc (50 mL x 3). The organic phase was washed with brine and dried over Na_2SO_4 . The filtrate was evaporated under reduced pressure. The resulting residue was triturated with Hex/EtOAc (4/1, 30 mL), filtered and dried. Compound **A21** (1.39 g, 4.32 mmol, 75.4% yield in 2 steps) was obtained. MS (ESI) $m/z = 322.1 [M+H]^+$. 1H NMR:(400 MHz, DMSO- d_6) $\delta = 7.57$ (br t, $J = 6.0$ Hz, 1H), 7.39 - 7.30 (m, 4H), 7.31 - 7.22 (m, 1H), 5.54 (s, 1H), 4.65 (s, 2H), 4.40 (d, $J = 6.0$ Hz, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H). [0203]

Scheme 3

[Chem. 46]



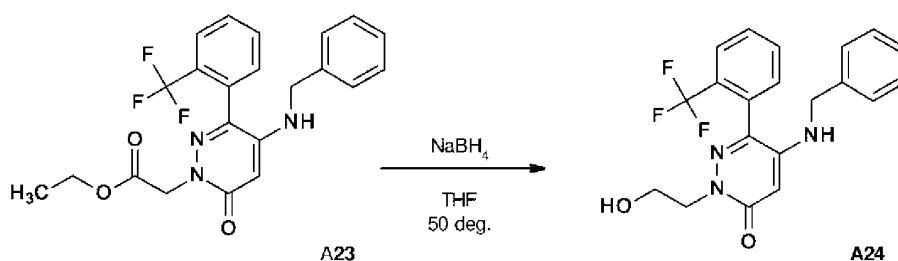
2-[4-(benzylamino)-6-oxo-3-[2-(trifluoromethyl) phenyl] pyridazin-1-yl] ethyl acetate (A23): To a degassed suspension of compound **A21** (11.1 g, 34.5 mmol, 1.00 eq), 2-trifluoromethylphenylboronic acid (**A22**) (CAS No.:1423-27-4, 9.83 g, 51.7 mmol, 1.50 eq) and K_3PO_4 (11.0 g, 51.7 mmol, 1.50 eq) in 1,4-dioxane (180 mL) and H_2O (20 mL) was added Pd A-taPhos (1.22 g, 1.72 mmol, 0.05 eq). The reaction mixture was stirred at 100°C for 2 hrs. To the reaction mixture was added saturated NH_4Cl -aq (300 mL). The mixture was extracted with EtOAc (200 mL x 2). The combined organic phase was washed with brine and dried over Na_2SO_4 . The filtrate was evaporated under reduced pressure and purified by silica gel column

chromatography. The crude product was triturated with EtOAc/Hex (2/1, 200 mL) to afford Compound **A23** (10.8 g, 25.0 mmol, 72.4% yield). MS (ESI) $m/z = 432.1$ $[M+H]^+$. $^1\text{H NMR}$: (400 MHz, CDCl_3) δ 7.84 (d, $J = 7.6$ Hz, 1H), 7.73 - 7.60 (m, 2H), 7.50 (d, $J = 7.6$ Hz, 1H), 7.37 - 7.27 (m, 3H), 7.19 (d, $J = 6.8$ Hz, 2H), 5.86 (s, 1H), 4.94 - 4.69 (m, 2H), 4.34 - 4.16 (m, 4H), 4.15 - 4.00 (m, 1H), 1.27 (t, $J = 7.2$ Hz, 3H).

[0204]

Scheme 4

[Chem. 47]



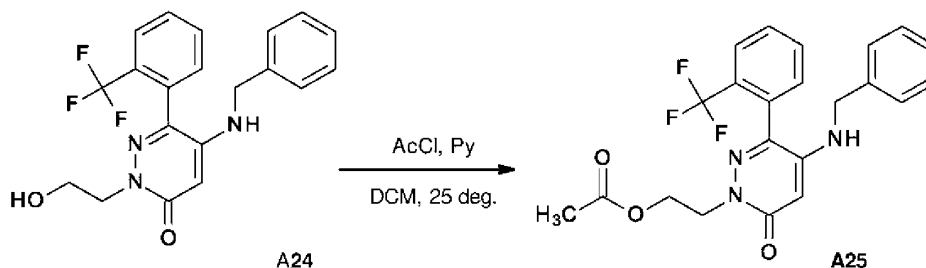
5-(benzylamino)-2-(2-hydroxyethyl)-6-[2-(trifluoromethyl)phenyl]pyridazin-3-one (A24):

To a solution of compound **A23** (60 g, 139 mmol, 1.00 eq) in THF (700 mL) was added NaBH_4 (30.46 g, 805.1 mmol, 5.79 eq) at 0°C . The reaction mixture was stirred at 50°C for 12 hrs. LCMS showed the starting material was consumed completely. The reaction mixture was quenched with 0.5 mol/L HCl -aq (500 mL). The resulting mixture was extracted with EtOAc (500 mL x 3). The combined organic phase was washed with brine and dried over Na_2SO_4 . The filtrate was evaporated under reduced pressure to give Compound **A24** (63.1 g, crude). MS (ESI) $m/z = 390.1$ $[M+H]^+$. $^1\text{H NMR}$: (400 MHz, CDCl_3) δ = 7.92 - 7.81 (m, 1H), 7.76 - 7.60 (m, 2H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.37 - 7.28 (m, 3H), 7.19 (d, $J = 7.2$ Hz, 2H), 5.91 (s, 1H), 4.41 - 4.25 (m, 4H), 3.96 (t, $J = 4.8$ Hz, 2H).

[0205]

Scheme 5

[Chem. 48]



2-(4-(benzylamino)-6-oxo-3-(2-(trifluoromethyl)phenyl)pyridazin-1(6H)-yl)ethyl acetate

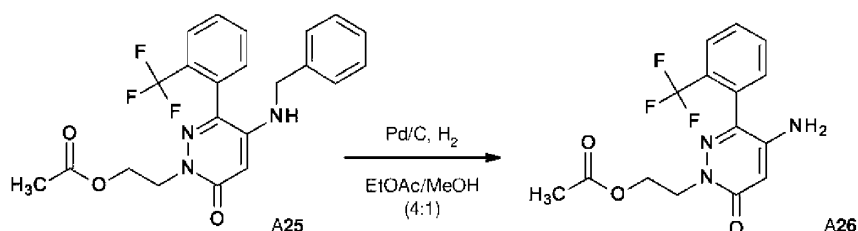
(A25): To a solution of compound **A24** (63 g, 162 mmol, 1.00 eq) in DCM (600 mL) was added acetyl chloride (19.1 g, 243 mmol, 17.3 mL, 1.50 eq) and pyridine (25.6 g, 323 mmol, 26.1 mL,

2.00 eq) at 25°C. The reaction mixture was stirred at 25°C for 16 hrs. LCMS showed the starting material was consumed completely. The reaction mixture was quenched with saturated NaHCO₃-aq (2.00 L). The mixture was extracted with EtOAc (1.00 L x 3). The combined organic phase was washed with 0.5 mol/L HCl-aq (2.00 L) and dried over Na₂SO₄. The filtrate was evaporated under reduced pressure and triturated with EtOAc/MTBE (1/10, 500 mL) to give Compound **A25** (41.4 g, 96.0 mmol, 69% yield in 2 steps). $m/z = 432.2$ [M+H]⁺. ¹H NMR: (400 MHz, CDCl₃) δ = 7.85 (d, J = 7.6 Hz, 1H), 7.74 - 7.59 (m, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.38 - 7.27 (m, 3H), 7.19 (br d, J = 7.2 Hz, 2H), 5.86 (s, 1H), 4.50 - 4.28 (m, 4H), 4.26 (m, 2H), 2.00 (s, 3H).

[0206]

Scheme 6

[Chem. 49]

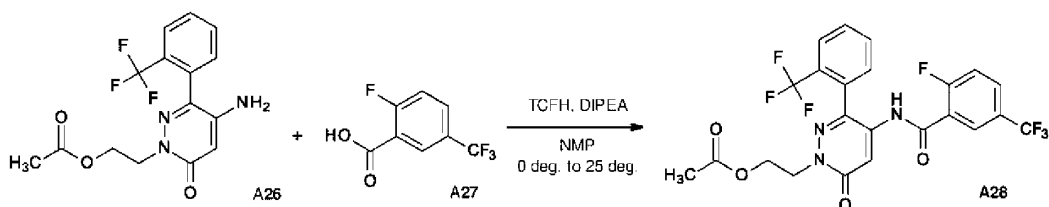


2-[4-amino-6-oxo-3-[2-(trifluoromethyl)phenyl]pyridazin-1-yl]ethyl acetate (A26): To a solution of compound **A25** (10 g, 23.2 mmol, 1.00 eq, 4 batches) in EtOAc (80 mL) and MeOH (20 mL) was added Pd/C (20.0 g, 10% purity, 1.00 eq). The mixture was stirred at 60°C for 16 hrs under H₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was filtered through Celite (Registered Trademark), then washed with EtOAc (200 mL x 2). The filtrate was evaporated under reduced pressure to afford Compound **A26** (26.9 g, 78.8 mmol, 85% yield). MS (ESI) $m/z = 342.1$ [M+H]⁺. ¹H NMR: (400 MHz, CDCl₃) δ = 7.85 (d, J = 7.6 Hz, 1H), 7.76 - 7.60 (m, 2H), 7.45 (d, J = 7.2 Hz, 1H), 6.04 (s, 1H), 4.51 - 4.22 (m, 4H), 4.06 (br s, 2H), 2.01 (s, 3H).

[0207]

Scheme 7

[Chem. 50]



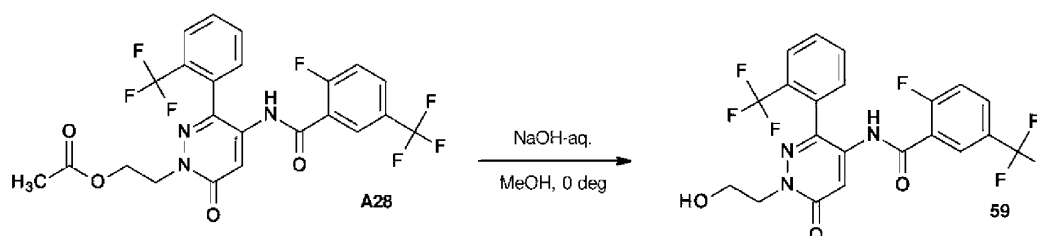
2-[4-[[2-fluoro-5-(trifluoromethyl)benzoyl]amino]-6-oxo-3-[2-

(trifluoromethyl)phenyl]pyridazin-1-yl]ethyl acetate (A28): To a solution of compound **A26** (20 g, 58.60 mmol, 1.00 eq), 2-fluoro-5-(trifluoromethyl)benzoic acid (**A27**) (CAS No.:115029-23-7, 30.5 g, 147 mmol, 2.50 eq) and DIPEA (26.5 g, 205 mmol, 35.7 mL, 3.50 eq) in NMP (220 mL) was added TCFH (41.1 g, 147 mmol, 2.50 eq) at 0°C. The reaction mixture was stirred at 25°C for 12 hrs. LCMS showed the starting material was consumed completely. To the reaction mixture was quenched with saturated NH₄Cl-aq (2.00 L) and the mixture was extracted with EtOAc (500 mL x 3). The combined organic phase was washed with brine and dried over Na₂SO₄. The filtrate was evaporated under reduced pressure to afford Compound **A28** (34.25 g, crude). MS (ESI) $m/z = 532.3$ [M+H]⁺.

[0208]

Scheme 8

[Chem. 51]

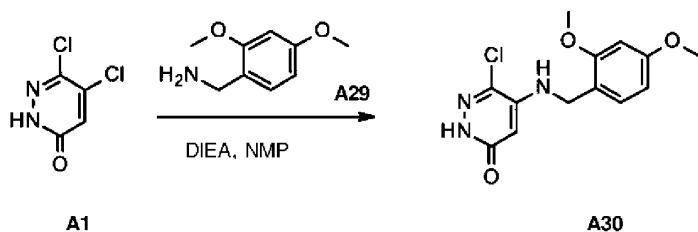


2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide (Compound (Cpd) 59): To a solution of compound **A28** (34.2 g, crude) in MeOH (400 mL) was added NaOH-aq (5 M, 15.5 mL, 77.5 mmol, 1.20 eq) into the mixture at 0°C. The mixture was stirred at 0°C for 20 min. LCMS showed the starting material was consumed completely. H₂O (2.00 L) was added to the reaction mixture (pH ~ 9.0). The mixture was extracted with EtOAc (500 mL x 4). The combined organic phase was washed with brine and dried over Na₂SO₄. The filtrate was evaporated under reduced pressure to afford a crude product. The crude residue was recrystallized from EtOH (300 mL) / H₂O (300 mL) to afford Compound **59** (18.8 g, 38.4 mmol, 65.5% yield in 2 steps) as a light yellow solid.

[0209]

Scheme 9

[Chem. 52]

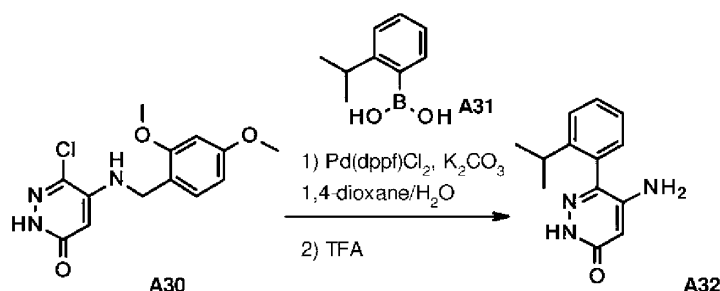


6-chloro-5-((2,4-dimethoxybenzyl)amino)pyridazin-3(2H)-one (A30): To a solution of **A1** (1.0 g, 6.1 mmol) in NMP (20 mL) was added DIEA (1.6 mL, 9.1 mmol) and 2,4-dimethoxybenzylamine (**A29**) (1.0 mL, 6.7 mmol). The reaction was heated to 130° C. After 1h, the reaction was cooled to rt and extracted with DCM/water (2x). The combined organic layers were then washed with water (3x). The organic layer was dried (Na₂SO₄), filtered and concentrated. The residue was purified by normal phase column chromatography (gradient: 0-100% EtOAc/Hexanes) to yield the desired compound **A30** (1.56 g, 87% yield). ES-MS [M+H]⁺: 296.0.

[0210]

Scheme 10

[Chem. 53]

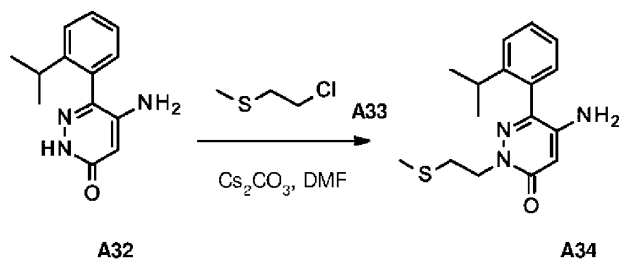


5-amino-6-(2-isopropylphenyl)pyridazin-3(2H)-one (A32): To a solution of compound **A30** (600 mg, 2.03 mmol) in 1,4-dioxane and water (15 mL; 2:1) was added 2-isopropylphenyl boronic acid (**A31**) (366 mg, 2.23 mmol), [1,1'-Bis(diphenylphosphino)ferrocene](dppf) dichloropalladium (II) (149 mg, 0.20 mmol), and potassium carbonate (711 mg, 5.1 mmol). The sealed vial was evacuated and purged with nitrogen (3x) and the reaction was heated to 130° C. After 16 h, the heating source was removed and to the reaction mixture was added DCM (10 mL). The mixture was filtered through a hydrophobic frit and the organic layer was concentrated under reduced pressure. To the residue was added TFA. After 15 min at rt, the reaction was neutralized with the slow addition of saturated solution of sodium bicarbonate. The mixture was extracted with DCM (3 x 50 mL) and the organic layers were combined and concentrated. The residue was purified by normal phase column chromatography (gradient: 0-7% DCM/MeOH) to afford the desired compound **A32** (183 mg, 39% yield). ES-MS [M+H]⁺: 230.2.

[0211]

Scheme 11

[Chem. 54]

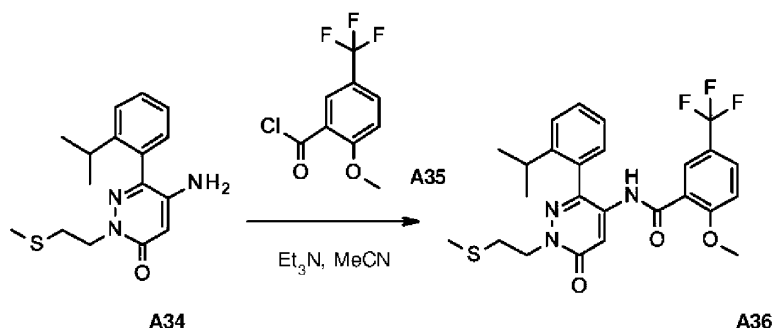


5-amino-6-(2-isopropylphenyl)-2-(2-(methylthio)ethyl)pyridazin-3(2H)-one (A34): To a solution of compound **A32** (110 mg, 0.48 mmol) in DMF (4 mL) was added 2-chloroethyl methyl sulfide (**A33**) (0.09 mL, 0.86 mmol), cesium carbonate (236 mg, 0.72 mmol). The mixture was heated to 80° C. After 3h, the solvent was removed. The residue was dissolved in DMSO and purified by reverse phase chromatography (gradient: 17-80% MeCN in H₂O with 0.05% NH₄OH) to provide the desired compound **A34** (84 mg, 58% yield). ES-MS [M+H]⁺: 304.1.

[0212]

Scheme 12

[Chem. 55]

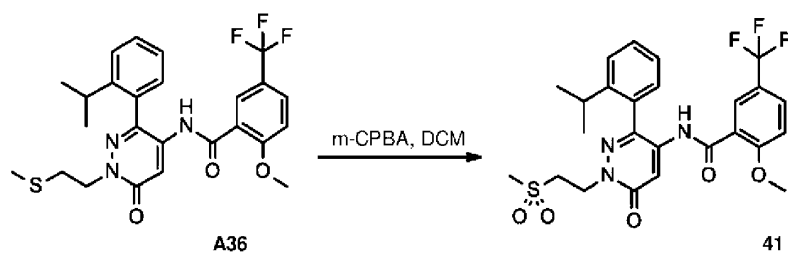


N-(3-(2-isopropylphenyl)-1-(2-(methylthio)ethyl)-6-oxo-1,6-dihydropyridazin-4-yl)-2-methoxy-5-(trifluoromethyl)benzamide (A36): To a solution of compound **A34** (28 mg, 0.09 mmol) in MeCN (1 mL) was added 2-methoxy-5-(trifluoromethyl)benzoyl chloride (**A35**) (31 mg, 0.13 mmol) and triethylamine (0.06 mL, 0.46 mmol). After 1h at room temperature, the solvent was concentrated, and the residue was dissolved in DMSO (1 mL). The mixture was purified by reverse phase chromatography (gradient: 50-88% MeCN in H₂O with 0.1% TFA) to yield the desired compound **A36** (46 mg, 99% yield). ES-MS [M+H]⁺: 506.0.

[0213]

Scheme 13

[Chem. 56]

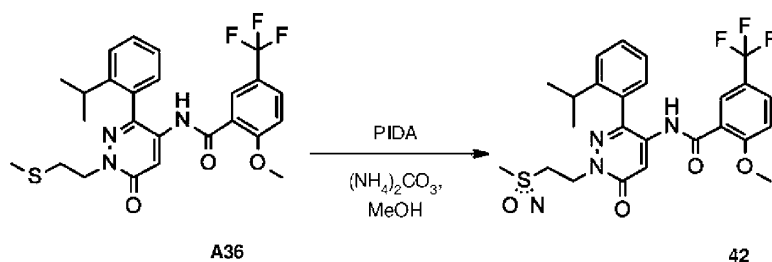


N-{3-(2-isopropylphenyl)-1-[2-(methylsulfonyl)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide (Compound 41): To a solution of compound A36 (24 mg, 0.05 mmol) in DCM (0.5 mL) was added m-CPBA (16 mg, 0.09 mmol). After 1 h at room temperature, the solvent was evaporated and the resulting residue was purified by reverse phase chromatography (gradient: 35-65% MeCN in H₂O with 0.05% NH₄OH) to afford Compound 41 (9 mg, 37% yield).

[0214]

Scheme 14

[Chem. 57]

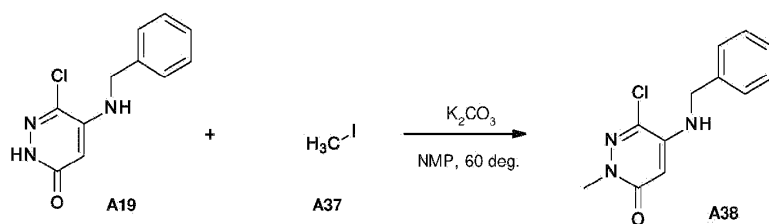


N-{3-(2-isopropylphenyl)-1-[2-(S-methylsulfonimidoyl)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide (Compound 42): To solution of compound A36 (24 mg, 0.05 mmol) in MeOH (0.5 mL) was added *p*-iodobenzene diacetate (PIDA) (31 mg, 0.10 mmol), ammonium carbonate (7 mg, 0.07 mmol). After 1 h at rt, the solvent was removed and the reaction was purified by reverse phase chromatography (gradient: 30-75% MeCN in H₂O with 0.05% NH₄OH) to provide Compound 42 (1.5 mg).

[0215]

Scheme 15

[Chem. 58]

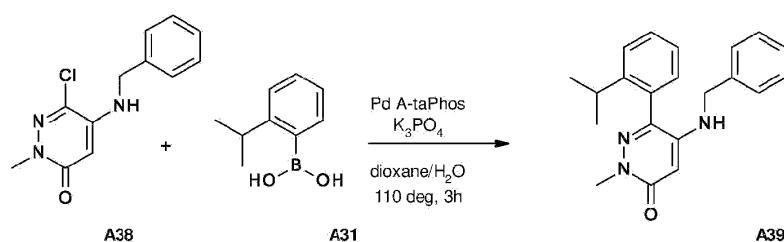


5-(benzylamino)-6-chloro-2-methyl-pyridazin-3-one (A38): To a solution of compound **A19**

(1.36 g, 5.77 mmol, 1.00 eq) and K_2CO_3 (1.04g, 7.50 mmol, 1.30 eq) in NMP (10 mL) was added iodomethane (**A37**) (CAS No.:74-88-4, 1.23 g, 8.66 mmol, 0.54 mL, 1.50 eq). The mixture was stirred at 60°C for 4 hrs. LCMS showed the compound **A19** was consumed completely. The reaction mixture was quenched with 0.1 mol/L HCl-aq (150 mL). The resulting mixture was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine and dried over Na_2SO_4 . The filtrate was evaporated under reduced pressure. The resulting residue was triturated with Hex/EtOAc (1/1, 50 mL), filtered and dried. Compound **A38** (605 mg, 4.32 mmol, the two steps yield is 42%) was obtained. MS (ESI) $m/z = 249.9 [\text{M}]^+$ [0216]

Scheme 16

[Chem. 59]

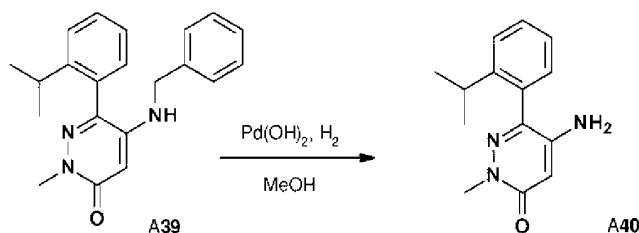


5-(benzylamino)-6-(2-isopropylphenyl)-2-methyl-pyridazin-3-one (A39): To a degassed suspension of compound **A38** (430 mg, 1.72 mmol, 1.00 eq), compound **A31** (CAS No.:89787-12-2, 527 mg, 3.21 mmol, 1.87 eq) and K_3PO_4 (731 mg, 3.44 mmol, 2.00 eq) in 1,4-dioxane (10 mL) and H_2O (1 mL) was added Pd A-taPhos (152 mg, 0.21 mmol, 0.12 eq). The reaction mixture was stirred at 110°C for 3hrs. LCMS showed the starting material was consumed completely. To the reaction mixture was added saturated NH_4Cl -aq (100 mL). The mixture was extracted with EtOAc (60 mL x 3). The combined organic phase was washed with brine and dried over Na_2SO_4 . The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography to afford Compound **A39** (499 mg, 1.50 mmol, 86.9% yield). MS (ESI) $m/z = 334.0 [\text{M}+\text{H}]^+$.

[0217]

Scheme 17

[Chem. 60]

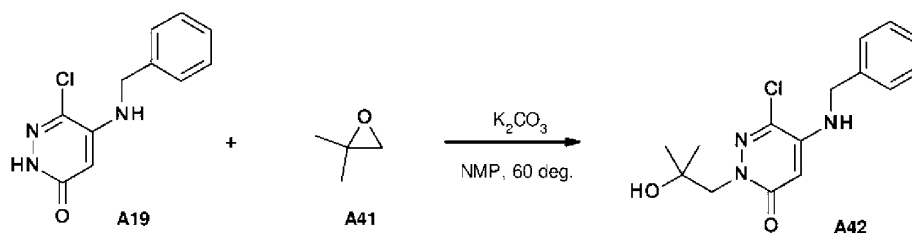


5-amino-6-(2-isopropylphenyl)-2-methylpyridazin-3-one (A40): To a solution of compound **A39** (490 mg, 1.47 mmol, 1.00 eq) in MeOH (14 mL) was added Pd (OH)₂ (420 mg, 20% purity, 0.40 eq). The mixture was stirred at 50 °C for 16 hrs under H₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was filtered through Celite (Registered Trademark), then washed with EtOAc (100 mL x 2). The filtrate was evaporated under reduced pressure to afford Compound **A40** (3.72g, 1.53 mmol, quant.). MS (ESI) m/z = 244.0 [M+H]⁺.

[0218]

Scheme 18

[Chem. 61]



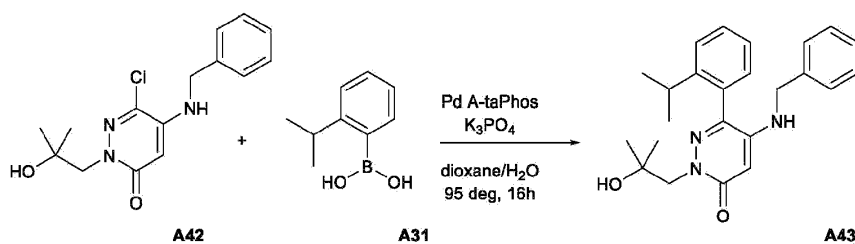
5-(benzylamino)-6-chloro-2-(2-hydroxy-2-methylpropyl)pyridazin-3-one (A42): To a solution of compound **A19** (2.6 g, 9.9 mmol, 1.00 eq) and K₂CO₃ (3.4 g, 25 mmol, 2.50 eq) in NMP (20 mL) was added isobutylene oxide (**A41**) (CAS No.: 558-30-5, 1.4 g, 20 mmol, 2.00 eq). The mixture was stirred at 60°C for 4 hrs. LCMS showed the compound **A19** was consumed completely. The reaction mixture was quenched with sat. NH₄Cl-aq (150 mL). The resulting mixture was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine and dried over Na₂SO₄. The filtrate was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford Compound **A42** (3.16 mg, 10.3 mmol, 100% yield).

MS (ESI) m/z = 308.7 [M+H]⁺

[0219]

Scheme 19

[Chem. 62]



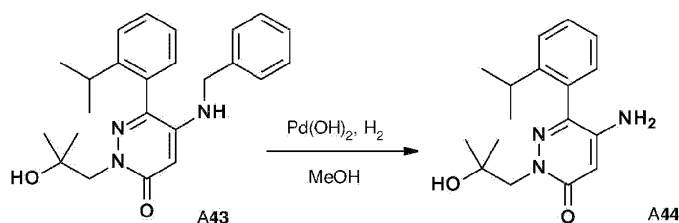
5-(benzylamino)-2-(2-hydroxy-2-methyl-propyl)-6-(2-isopropylphenyl)pyridazin-3-one

(**A43**): To a degassed suspension of compound **A42** (1.26 g, 4.09 mmol, 1.00 eq), compound **A31** (CAS No.:89787-12-2, 2.02 g, 12.3 mmol, 3.00 eq) and K₃PO₄ (2.61 g, 12.3 mmol, 3.00 eq) in 1,4-dioxane (15 mL) and H₂O (2 mL) was added Pd A-taPhos (580 mg, 0.82 mmol, 0.20 eq). The reaction mixture was stirred at 95°C for 16 hrs. LCMS showed the starting material was consumed completely. To the reaction mixture was added NH₄Cl-aq (100 mL). The mixture was extracted with EtOAc (60 mL x 3). The combined organic phase was washed with brine and dried over Na₂SO₄. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography to afford Compound **A43** (1.44 g, 3.68 mmol, 89.9% yield). MS (ESI) $m/z = 392.2$ [M+H]⁺.

[0220]

Scheme 20

[Chem. 63]

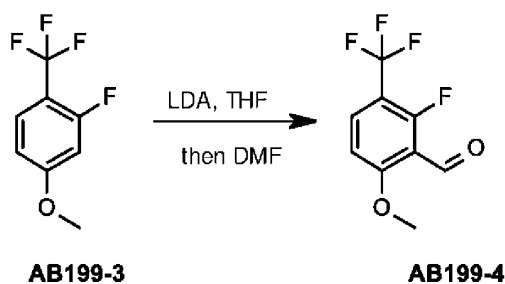


5-amino-2-(2-hydroxy-2-methyl-propyl)-6-(2-isopropylphenyl)pyridazin-3-one (A44): To a solution of compound **A43** (1.44 g, 3.68 mmol, 1.00 eq) in MeOH (20 mL) was added Pd (OH)₂ (3.0 g, 20% purity, 1.16 eq). The mixture was stirred at room temperature for 4 hrs under H₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was filtered through Celite (Registered Trademark), then washed with EtOAc (100 mL x 2). The filtrate was evaporated under reduced pressure to afford Compound **A44** (1.03 g, 3.42 mmol, 92.9% yield). MS (ESI) $m/z = 302.1$ [M+H]⁺.

[0221]

Scheme 21

[Chem. 64]

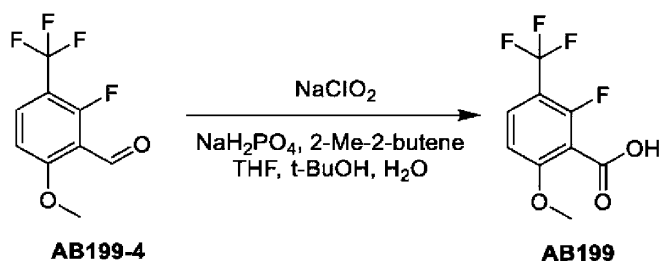


2-fluoro-6-methoxy-3-(trifluoromethyl)benzaldehyde (AB199-4) : To a solution of 2-fluoro-4-methoxy-1-(trifluoromethyl)benzene (**AB199-3**) (CAS No.: 1214344-33-8, 1.5 g, 7.73 mmol) in THF (15 mL) was added lithium diisopropylamine (LDA) (4.64 mL, 9.27 mmol) at -70°C under nitrogen. After the reaction mixture was stirred at -70°C for 1h, DMF (1.4 mL, 18.2 mmol) was added to the reaction mixture. After the addition, the reaction mixture was stirred at -70°C for 1h. TLC (PE/EtOAc=3/1) showed a new spot ($R_f = 0.3$) was observed. The reaction mixture was poured into sat. NH_4Cl -aq. (10 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give compound **AB199-4** (1.78 g, 8.01 mmol, quantitative yield).

[0222]

Scheme 22

[Chem. 65]



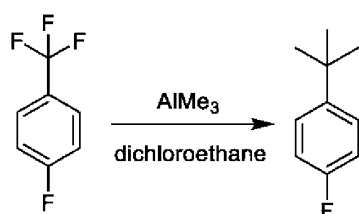
2-fluoro-6-methoxy-3-(trifluoromethyl)benzoic acid (AB199): To a solution of compound **AB199-4** (2.86 g, 12.9 mmol) in tert-Butanol (15 mL) and THF (15 mL) was added 2-Me-2-butene (27.3 mL, 258 mmol). Then a solution of NaClO_2 (11.64 g, 128.8 mmol) and NaH_2PO_4 (12.97 g, 93.99 mmol) in water (30 mL) was added at 0°C . The mixture was stirred at 20°C for 3h. TLC (PE/EtOAc=3/1) showed a new spot ($R_f = 0$) was observed. The reaction mixture was concentrated, then poured into water (20 mL), acidified with 6N HCl aq. to $\text{pH} = 1$, extracted with EtOAc (40 mL x 4). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford a yellow oil. The residue was purified by normal phase column chromatography (gradient: 0-50% PE/EtOAc) to give compound **AB199** (1.94 g, 8.15 mmol, 63% yield).

¹H NMR (400MHz, CHLOROFORM-d) δ = 7.66 (t, 1H), 6.84 (d, 1H), 3.70 (s, 3H).

[0223]

Scheme 22-1

[Chem. 66]



AB184-1

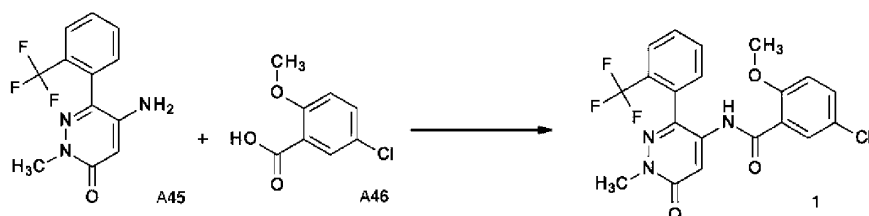
AB184-2

1-(tert-butyl)-4-fluorobenzene (AB184-2): To a solution of 1-fluoro-4-(trifluoromethyl)benzene (**AB184-1**) (CAS No.: 402-44-8, 0.080 mL, 0.61 mmol) in dichloroethane (3 mL) was added AlMe_3 (1.52 mL, 3.05 mmol) at 25°C. The mixture was stirred at 50°C for 16hrs. The reaction mixture was poured into 1N HCl (4 mL) and extracted with DCM (10 mL x 4). The combined organic layers were washed with saturated NaCl-aq. (10 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE) to give **AB184-2** (30 mg, 0.20mmol, 32% yield) as a white oil.

[0224]

Scheme 23

[Chem. 67]

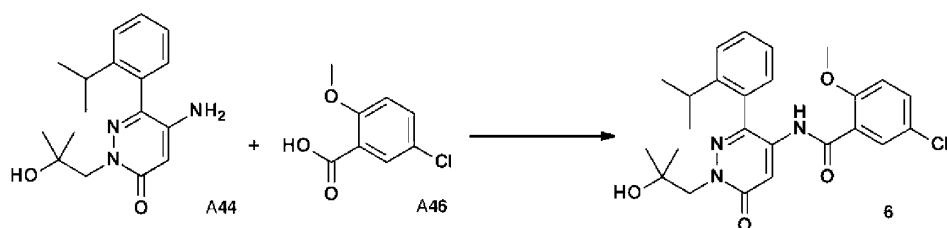


5-chloro-2-methoxy-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide (Compound 1): The compound **1** was prepared in an analogous manner to Scheme 7, where the reaction was carried out using 5-amino-2-methyl-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (**A45**) and 5-chloro-2-methoxybenzoic acid (**A46**) (CAS No.: 3438-16-2). Wherein, compound **A45** was prepared in an analogous manner to Scheme 16 $\rightarrow$ Scheme 17, where the reactions were carried out using a corresponding boronic acid compound in place of compound **A31**.

[0225]

Scheme 24

[Chem. 68]

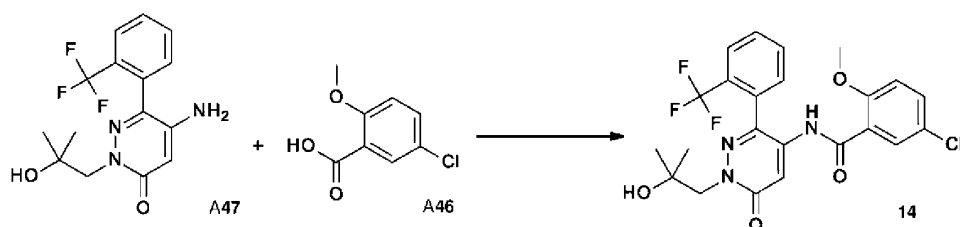


5-chloro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide (Compound 6): The compound 6 was prepared in an analogous manner to Scheme 7.

[0226]

Scheme 25

[Chem. 69]

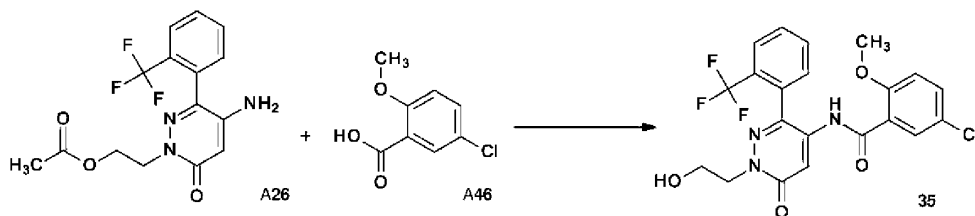


5-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide (Compound 14): The compound 14 was prepared in an analogous manner to Scheme 7. Wherein, 5-amino-2-(2-hydroxy-2-methylpropyl)-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (A47) was prepared in an analogous manner to Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding boronic acid compound in place of compound A31.

[0227]

Scheme 26

[Chem. 70]

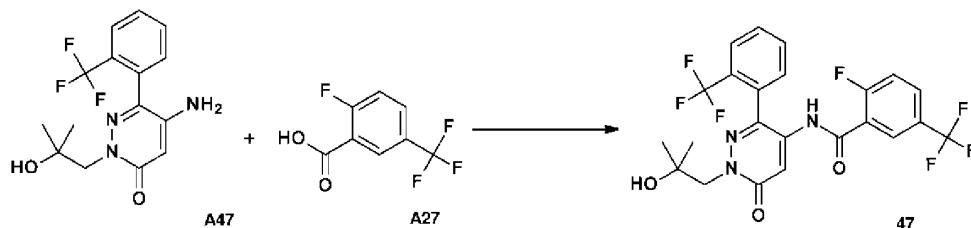


5-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide (Compound 35): The compound 35 was prepared in an analogous manner to Scheme 7 → Scheme 8.

[0228]

Scheme 27

[Chem. 71]

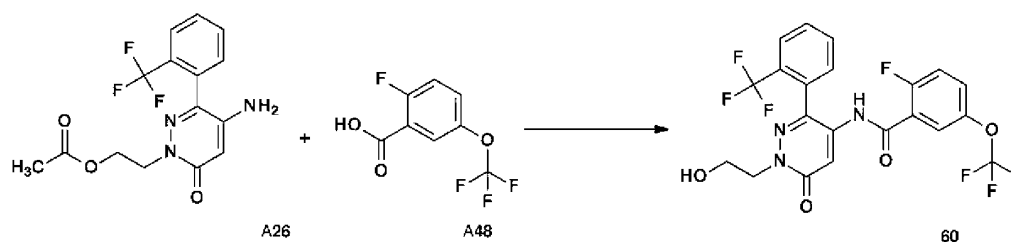


2-fluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide (Compound 47): The compound 47 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A47 and compound A27 (CAS No.: 115029-23-7).

[0229]

Scheme 28

[Chem. 72]

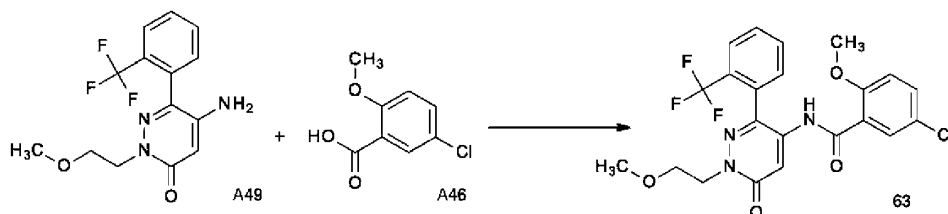


2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide (Compound 60): The compound 60 was prepared in an analogous manner to Scheme 7 → Scheme 8, where the reaction was carried out using compound A26 and 2-fluoro-5-(trifluoromethoxy)benzoic acid (A48) (CAS No.: 115029-23-7).

[0230]

Scheme 29

[Chem. 73]



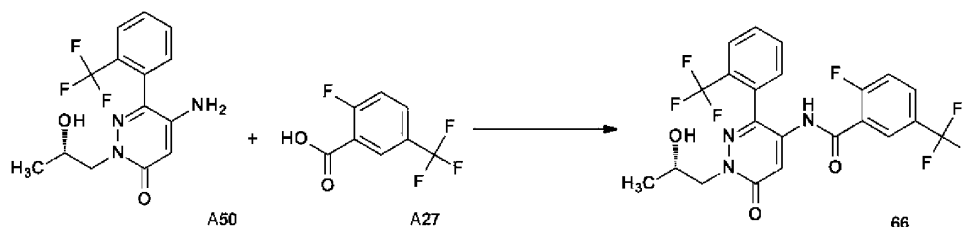
5-chloro-2-methoxy-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide (Compound 63): The compound 63 was prepared in an analogous manner to Scheme 7. Wherein, 5-amino-2-(2-methoxyethyl)-6-(2-

(trifluoromethyl)phenyl)pyridazin-3(2H)-one (**A49**) was prepared in an analogous manner to Scheme 2 → Scheme 3 → Scheme 6, where the reactions were carried out using a corresponding alkylating reagent in place of compound **A20**.

[0231]

Scheme 30

[Chem. 74]

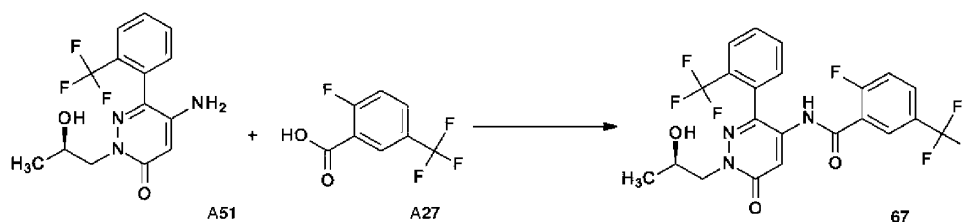


2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide (Compound 66): The compound **66** was prepared in an analogous manner to Scheme 7. Wherein, (*S*)-5-amino-2-(2-hydroxypropyl)-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (**A50**) was prepared in an analogous manner to Scheme 2 → Scheme 3 → Scheme 6, where the reactions were carried out using a corresponding alkylating reagent in place of compound **A20**.

[0232]

Scheme 31

[Chem. 75]

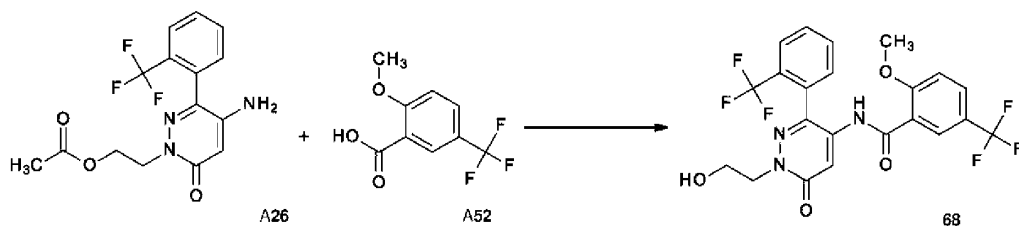


2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide (Compound 67): The compound **67** was prepared in an analogous manner to Scheme 7. Wherein, (*R*)-5-amino-2-(2-hydroxypropyl)-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (**A51**) was prepared in an analogous manner to Scheme 2 → Scheme 3 → Scheme 6, where the reactions were carried out using a corresponding alkylating reagent in place of compound **A20**.

[0233]

Scheme 32

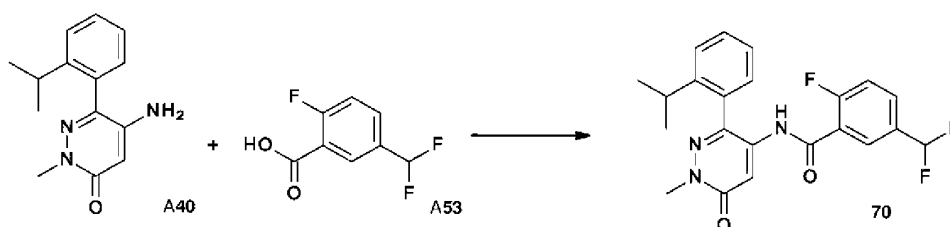
[Chem. 76]



N-{1-(2-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl)-2-methoxy-5-(trifluoromethyl)benzamido} (Compound 68): The compound **68** was prepared in an analogous manner to Scheme 7 → Scheme 8, where the reaction was carried out using compound **A26** and 2-methoxy-5-(trifluoromethyl)benzoic acid (**A52**) (CAS No.: 4864-01-1). [0234]

Scheme 33

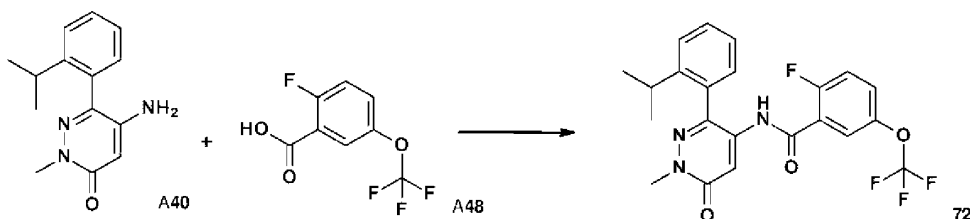
[Chem. 77]



5-(difluoromethyl)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide (Compound 70): The compound **70** was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound **A40** and 5-(difluoromethyl)-2-fluorobenzoic acid (**A53**) (CAS No.: 1429421-95-3). [0235]

Scheme 34

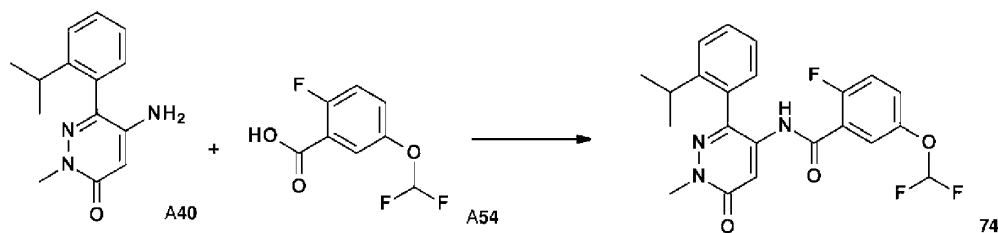
[Chem. 78]



2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide (Compound 72): The compound **72** was prepared in an analogous manner to Scheme 7, where the reaction was carried out using **A40** and compound **A48** (CAS No.: 115029-23-7). [0236]

Scheme 35

[Chem. 79]

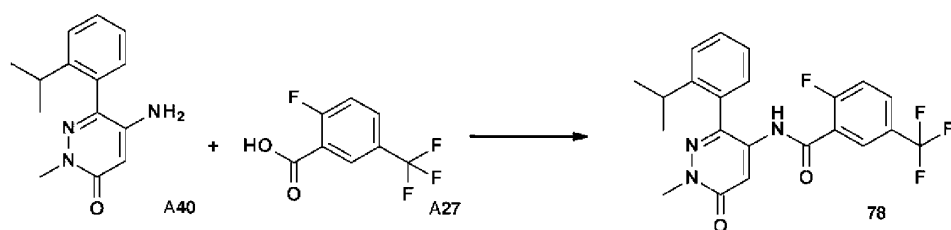


5-(difluoromethoxy)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide (Compound 74): The compound **74** was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound **A40** and 5-(difluoromethoxy)-2-fluorobenzoic acid (**A54**) (CAS No.: 1214383-11-5).

[0237]

Scheme 36

[Chem. 80]

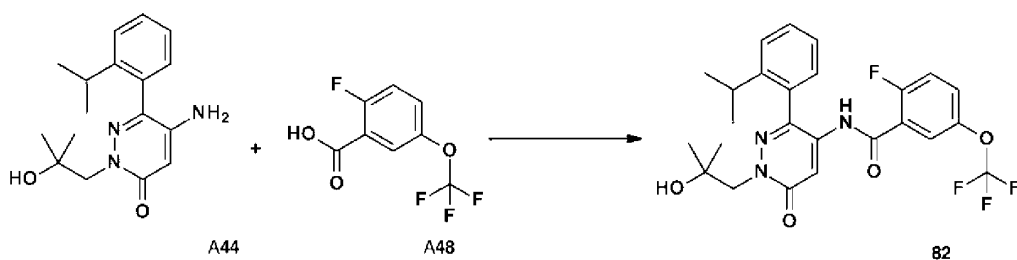


2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide (Compound 78): The compound **78** was prepared in an analogous manner to Scheme 7.

[0238]

Scheme 37

[Chem. 81]

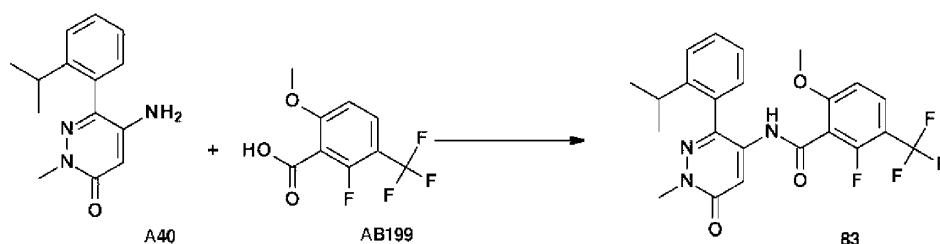


2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide (Compound 82): The compound **82** was prepared in an analogous manner to Scheme 7.

[0239]

Scheme 38

[Chem. 82]

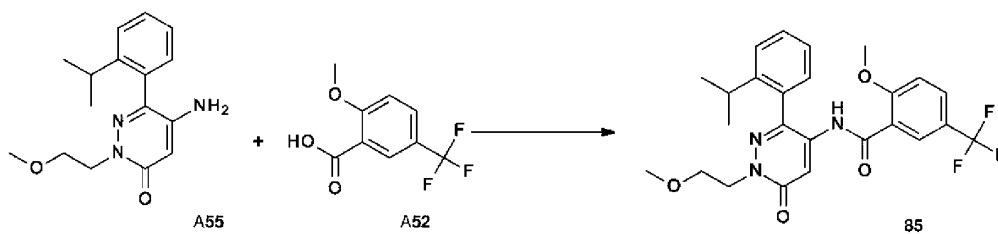


2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide (Compound 83): The compound **83** was prepared in an analogous manner to Scheme 7.

[0240]

Scheme 39

[Chem. 83]

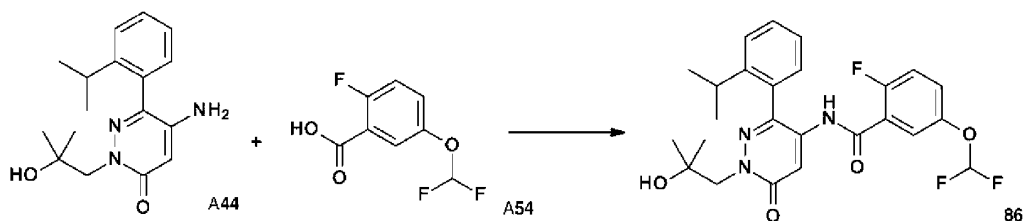


N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide (Compound 85): The compound **85** was prepared in an analogous manner to Scheme 7. Wherein, 5-amino-6-(2-isopropylphenyl)-2-(2-methoxyethyl)pyridazin-3(2H)-one (**A55**) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, which the reactions were carried out using a corresponding alkylating reagent in place of compound **A41**.

[0241]

Scheme 40

[Chem. 84]

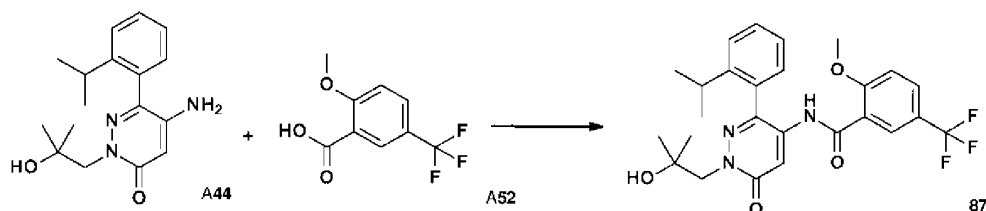


5-(difluoromethoxy)-2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide (Compound 86): The compound **86** was prepared in an analogous manner to Scheme 7.

[0242]

Scheme 41

[Chem. 85]

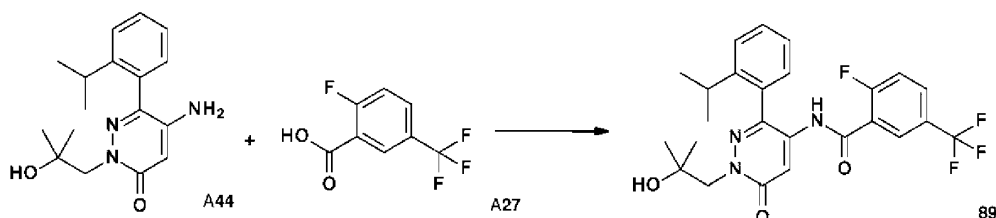


N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide (Compound 87): The compound 87 was prepared in an analogous manner to Scheme 7.

[0243]

Scheme 42

[Chem. 86]

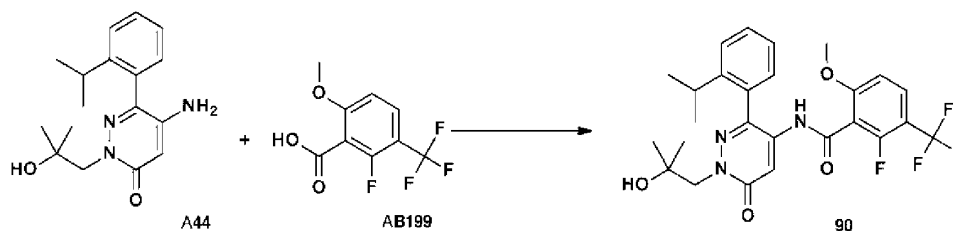


2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide (Compound 89): The compound 89 was prepared in an analogous manner to Scheme 7.

[0244]

Scheme 43

[Chem. 87]

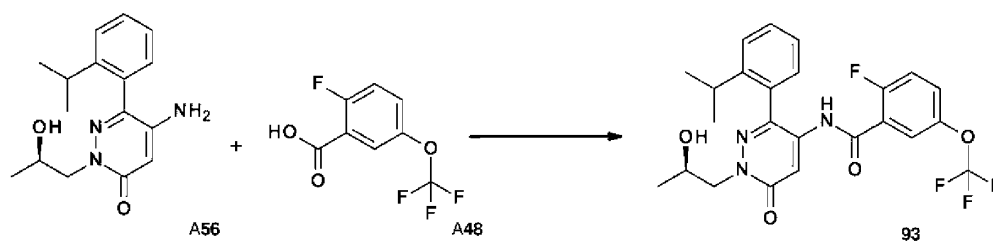


2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide (Compound 90): The compound 90 was prepared in an analogous manner to Scheme 7.

[0245]

Scheme 44

[Chem. 88]

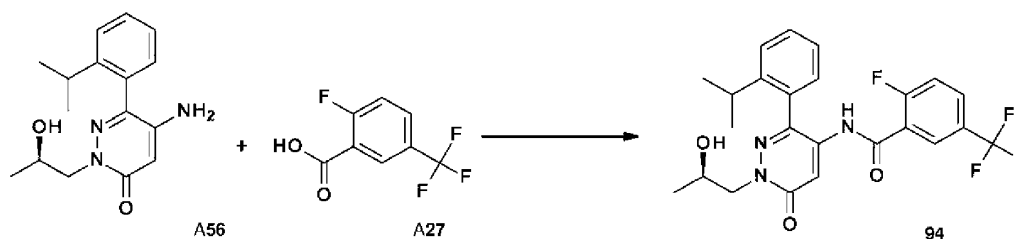


2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide (Compound 93): The compound **93** was prepared in an analogous manner to Scheme 7. Wherein, (*R*)-5-amino-2-(2-hydroxypropyl)-6-(2-isopropylphenyl)pyridazin-3(2H)-one (**A56**) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, which the reactions were carried out using a corresponding alkylating reagent in place of compound **A41**.

[0246]

Scheme 45

[Chem. 89]

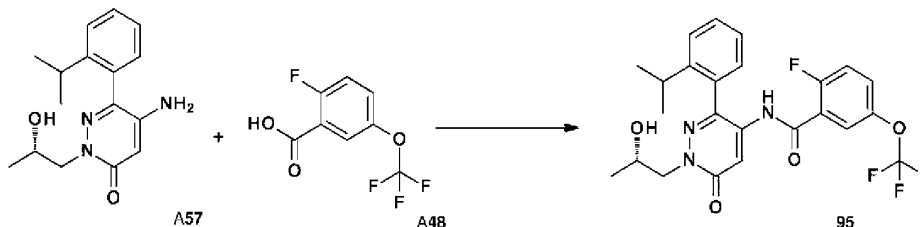


2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide (Compound 94): The compound **94** was prepared in an analogous manner to Scheme 7.

[0247]

Scheme 46

[Chem. 90]



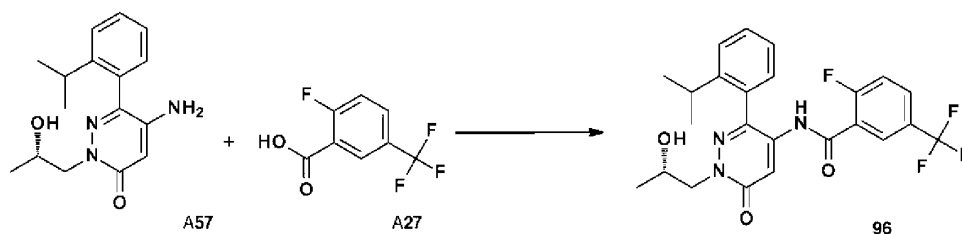
2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide (Compound 95): The compound **95** was prepared in an analogous manner to Scheme 7. Wherein, (*S*)-5-amino-2-(2-hydroxypropyl)-6-(2-isopropylphenyl)pyridazin-3(2H)-one (**A57**) was prepared in an analogous manner to Scheme 18

→ Scheme 19 → Scheme 20, which the reactions were carried out using a corresponding alkylating reagent in place of compound **A41**.

[0248]

Scheme 47

[Chem. 91]

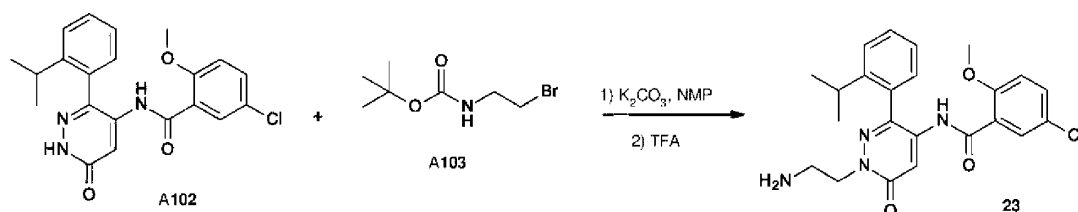


2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide (Compound 96): The compound **96** was prepared in an analogous manner to Scheme 7.

[0249]

Scheme 48

[Chem. 92]

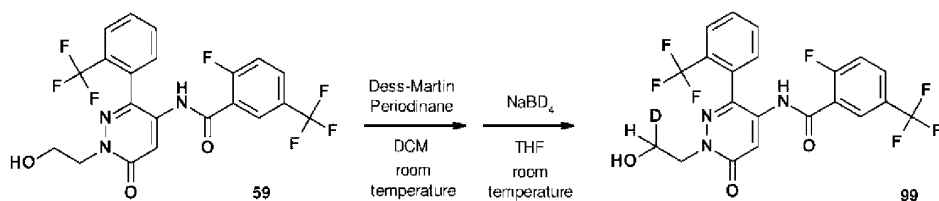


N-[1-(2-aminoethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-chloro-2-methoxybenzamide (Compound 23): **A102** was synthesized by amide formation using compound **A32** and compound **A46** in an analogous manner to Scheme 7. To a solution of compound **A102** (28 mg, 0.070 mmol, 1.00 eq) and K_2CO_3 (29.1 mg, 0.211 mmol, 3.00 eq) in NMP (2 mL) was added *tert*-butyl N-(2-bromoethyl)carbamate (**A103**) (CAS No.: 39684-80-5, 31.5 mg, 0.140 mmol, 2.00 eq). The mixture was stirred at 60°C for 1 hr. LCMS showed the compound **A102** was consumed completely. To the reaction mixture was added H_2O (10 mL), and the mixture was extracted with EtOAc (20 mL x 2). The organic phase was washed with brine and dried over Na_2SO_4 . The filtrate was evaporated under reduced pressure. To a solution of the resulting residue in EtOAc (2 mL) was added 4M HCl in EtOAc (2 mL). The mixture was stirred at room temperature for 1h, then evaporated under reduced pressure. The residue was purified by reverse phase column chromatography (gradient: 50-88% MeCN in H_2O with 0.225% FA) to afford the desired compound **23** (19.6 mg, 63% yield).

[0250]

Scheme 49

[Chem. 93]

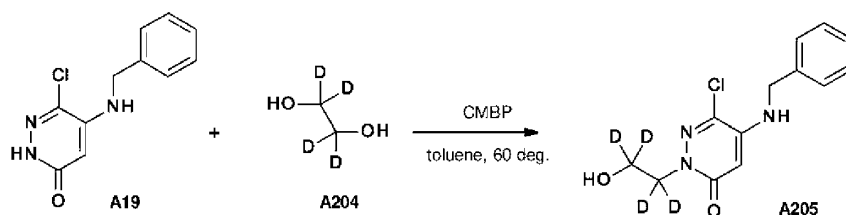


2-fluoro-N-(1-(2-hydroxyethyl-2-*d*)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide (Compound 99): To a solution of compound **59** (95 mg, 0.194 mmol, 1.00 eq) in DCM (8 mL) was added Dess-Martin Periodinane (CAS No.: 87413-09-0, 165 mg, 0.388 mmol, 2.00 eq). The mixture was stirred at room temperature over night. LCMS showed the compound **59** was consumed completely. To the reaction mixture was added saturated NaHCO₃ aq (10 mL), and the mixture was extracted with EtOAc (20 mL x 2). The combined organic phase was washed with brine and dried over Na₂SO₄. The filtrate was evaporated under reduced pressure. To a solution of the resulting residue in THF (10 mL) was added NaBD₄ (CAS No.: 15681-89-7, 40.6 mg, 0.971 mmol, 5.00 eq). The mixture was stirred at room temperature. After 20 min, saturated NaHCO₃ aq (10 mL) was added to the reaction mixture. The mixture was extracted with EtOAc (20 mL x 2). The combined organic phase was washed with brine and dried over Na₂SO₄. The filtrate was evaporated under reduced pressure. The residue was purified by reverse phase column chromatography (gradient: 5-95% MeCN in H₂O with 0.1% TFA) to afford the desired compound **99** (30 mg, 31% yield in 2 steps).

[0251]

Scheme 50

[Chem. 94]



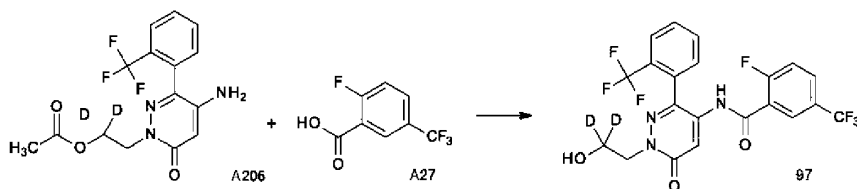
5-(benzylamino)-6-chloro-2-(2-hydroxyethyl-1,1,2,2-*d*4)pyridazin-3(2H)-one (Compound A205): To a suspension of compound **A19** (3.9 g, 16.5 mmol, 1.00 eq) and 1,1,2,2-tetradeuterioethane-1,2-diol (**A204**) (CAS No.: 2219-51-4, 2.2 g, 33.0 mmol, 2.00 eq) in toluene (50 mL) was added cyanomethylenetriphenylphosphorane (CMBP, CAS No.: 157141-27-0, 5.0 g, 21.0 mmol, 1.20 eq). The mixture was stirred at 60°C for 4 hrs. LCMS showed the compound **A19** was consumed completely. The reaction mixture was evaporated under reduced pressure. The residue was purified by normal phase column chromatography (gradient: 10-100%

Hexane/EtOAc, then 5% MeOH/EtOAc) to afford Compound **A205** (1.30 g, 4.60 mmol, 28% yield). MS (ESI) $m/z = 284.2$ $[M+H]^+$.

[0252]

Scheme 51

[Chem. 95]

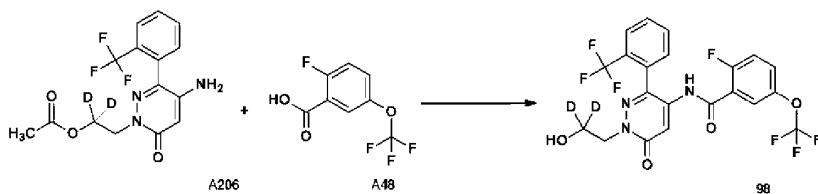


2-fluoro-N-(1-(2-hydroxyethyl-2,2- d_2)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide (Compound 97): The compound **97** was prepared in an analogous manner to Scheme 7 $\rightarrow$ Scheme 8 using **A206** in place of **A26**. Wherein, 2-(4-amino-6-oxo-3-(2-(trifluoromethyl)phenyl)pyridazin-1(6H)-yl)ethyl-1,1- d_2 acetate (**A206**) was prepared in an analogous manner to Scheme 4 $\rightarrow$ Scheme 5 $\rightarrow$ Scheme 6, where the reactions were carried out using NaBD₄ in place of NaBH₄.

[0253]

Scheme 52

[Chem. 96]

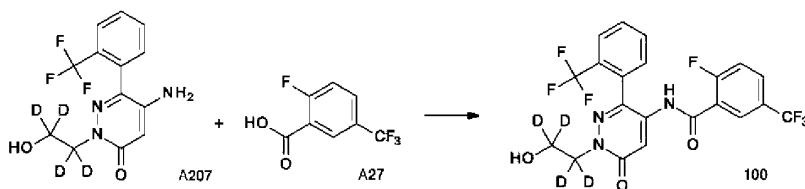


2-fluoro-N-(1-(2-hydroxyethyl-2,2- d_2)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethoxy)benzamide (Compound 98): The compound **98** was prepared in an analogous manner to Scheme 28 using **A206** in place of **A26**.

[0254]

Scheme 53

[Chem. 97]



2-fluoro-N-(1-(2-hydroxyethyl-1,1,2,2- d_4)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-

dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide (Compound 100): The compound **100** was prepared in an analogous manner to Scheme 7 → Scheme 8 using **A207** in place of **A26**.

Wherein, 5-amino-2-(2-hydroxyethyl-1,1,2,2-*d*₄)-6-[2-(trifluoromethyl)phenyl]pyridazin-3(2H)-one (**A207**) was prepared in an analogous manner to Scheme 3 → Scheme 6, where the reactions were carried out using **A205** in place of **A21**.

[0255]

Table 1 shows the synthesis of the compounds not described in Scheme 1 to 53.

[Table 1-1]

Cpd No.	Cpd Name	Scheme
2	5-chloro-2-methoxy-N-{1-(3-oxetanylmethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 2 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A46 and A58. Wherein, 5-amino-2-(oxetan-3-ylmethyl)-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (A58) was prepared in an analogous manner to Scheme 2 → Scheme 3 → Scheme 6, where the reactions were carried out using a corresponding alkylating reagent in place of compound A20 .
3	5-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxynicotinamide	The compound 3 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A40 and 5-chloro-2-methoxynicotinic acid (A59) (CAS No.: 1255147-31-9).
4	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 4 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A32 and A46 .
5	5-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 5 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A40 and A46 .
7	N-{1-(2-hydroxy-2-methylbutyl)-3-[2-(2-methyl-2-propanyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-methylbenzamide	The compound 7 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A60 and 2-methoxy-5-methylbenzoic acid (A61) (CAS No.: 25045-36-7). Wherein, 5-amino-6-(2-(tert-butyl)phenyl)-2-(2-hydroxy-2-methylbutyl)pyridazin-3(2H)-one (A60) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 and boronic acid in place of A31 .
8	5-chloro-N-[1-(2-hydroxy-2-methylbutyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 8 was prepared in an analogous manner to Scheme 29. Wherein, 5-amino-2-(2-hydroxy-2-methylbutyl)-6-(2-isopropylphenyl)pyridazin-3(2H)-one (A62) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
9	6-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]imidazol[1,2-a]pyridine-8-carboxamide	The compound 9 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A40 and 6-chloroimidazol[1,2-a]pyridine-8-carboxylic acid (A63) (CAS No.: 155735-02-7).

[Table 1-2]

Cpd No.	Cpd Name	Scheme
10	5-chloro-N-[1-(2-hydroxy-2-methylbutyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxynicotinamide	The compound 10 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A62 and A59 .
11	6-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-8-quinolinecarboxamide	The compound 11 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A40 and 6-chloroquinoline-8-carboxylic acid (A64) (CAS No.: 6456-78-6).
12	5-chloro-N-[3-(2-isopropylphenyl)-1-(methoxymethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 12 was prepared in an analogous manner to Scheme 29 using A65 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(methoxymethyl)pyridazin-3(2H)-one (A65) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
13	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1-(1,3-thiazol-5-ylmethyl)-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 13 was prepared in an analogous manner to Scheme 29 using A66 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(thiazol-5-ylmethyl)pyridazin-3(2H)-one (A66) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
15	5-chloro-N-[1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl]-2-methoxynicotinamide	The compound 15 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A47 and A59 .
16	5-chloro-N-[3-(2-isopropylphenyl)-1-(3-oxetanylmethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 16 was prepared in an analogous manner to Scheme 29 using A67 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(oxetan-3-ylmethyl)pyridazin-3(2H)-one (A67) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .

[Table 1-3]

Cpd No.	Cpd Name	Scheme
17	5-chloro-N-[1-(cyanomethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 17 was prepared in an analogous manner to Scheme 29 using A68 in place of A49 . Wherein, 2-(4-amino-3-(2-isopropylphenyl)-6-oxopyridazin-1(6H)-yl)acetonitrile (A68) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
18	5-chloro-N-{1-[2-(dimethylamino)-2-oxoethyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 18 was prepared in an analogous manner to Scheme 29 using A69 in place of A49 . Wherein, 2-(4-amino-3-(2-isopropylphenyl)-6-oxopyridazin-1(6H)-yl)-N,N-dimethylacetamide (A69) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
19	5-chloro-N-{3-(2-isopropylphenyl)-1-[(methoxymethoxy)methyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 19 was prepared in an analogous manner to Scheme 29 using A70 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-((methoxymethoxy)methyl)pyridazin-3(2H)-one (A70) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
20	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxynicotinamide	The compound 20 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A32 and A59 .
21	3-chloro-2,6-difluoro-N-[1-(2-hydroxy-2-methylbutyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide	The compound 21 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A62 and 3-chloro-2,6-difluorobenzoic acid (A71) (CAS No.: 225104-76-7).
22	5-chloro-N-{3-(2-isopropylphenyl)-6-oxo-1-[2-(1-pyrrolidinylethyl)-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 22 was prepared in an analogous manner to Scheme 29 using A72 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(2-(pyrrolidin-1-yl)ethyl)pyridazin-3(2H)-one (A72) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .

[Table 1-4]

Cpd No.	Cpd Name	Scheme
24	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1-[(2-propyn-1-yloxy)methyl]-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 24 was prepared in an analogous manner to Scheme 29 using A74 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-[(prop-2-yn-1-yloxy)methyl]pyridazin-3(2H)-one (A74) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
25	5-chloro-N-[1-(2-hydroxyethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 25 was prepared in an analogous manner to Scheme 26 using A75 in place of A26 . Wherein, 5-amino-2-(2-hydroxyethyl)-6-(2-isopropylphenyl)pyridazin-3(2H)-one (A75) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
26	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 26 was prepared in an analogous manner to Scheme 29 using A76 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)pyridazin-3(2H)-one (A76) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
27	5-chloro-N-[1-(2-hydroxy-3-methoxypropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 27 was prepared in an analogous manner to Scheme 29 using A77 in place of A49 . Wherein, 5-amino-2-(2-hydroxy-3-methoxypropyl)-6-(2-isopropylphenyl)pyridazin-3(2H)-one (A77) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
28	5-chloro-N-[1-(1-cyanoethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 28 was prepared in an analogous manner to Scheme 29 using A78 in place of A49 . Wherein, 2-(4-amino-3-(2-isopropylphenyl)-6-oxopyridazin-1(6H)-yl)propanenitrile (A78) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
29	5-chloro-N-[3-(2-isopropylphenyl)-1-(2-oxetanylmethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 29 was prepared in an analogous manner to Scheme 29 using A79 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(oxetan-2-ylmethyl)pyridazin-3(2H)-one (A79) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .

[Table 1-5]

Cpd No.	Cpd Name	Scheme
30	5-chloro-N-{3-(2-isopropylphenyl)-1-[2-(methylamino)-2-oxoethyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 30 was prepared in an analogous manner to Scheme 29 using A99 in place of A49 . Wherein, 2-(4-amino-3-(2-isopropylphenyl)-6-oxopyridazin-1(6H)-yl)-N-methylacetamide (A99) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
31	5-chloro-N-{3-(2-isopropylphenyl)-6-oxo-1-(3-pyrrolidinyl)-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 31 was prepared in an analogous manner to Scheme 48 using A80 in place of A102 . Wherein, tert-butyl 3-[4-[(5-chloro-2-methoxy-benzoyl)aminol-3-(2-isopropylphenyl)-6-oxo-pyridazin-1-yl]pyrrolidine-1-carboxylate (A80) was prepared using a corresponding alkylating reagent in place of compound A103 .
32	5-chloro-N-{3-(2-isopropylphenyl)-6-oxo-1-[(2-propyn-1-yloxy)methoxymethyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 32 was prepared in an analogous manner to Scheme 29 using A81 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(((prop-2-yn-1-yloxy)methoxy)methyl)pyridazin-3(2H)-one (A81) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
33	N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2,3-dihydro-1-benzofuran-7-carboxamide	The compound 33 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and 2,3-dihydrobenzofuran-7-carboxylic acid (A82) (CAS No.: 35700-40-4).
34	2-chloro-5-fluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 34 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and 2-chloro-5-fluorobenzoic acid (A83) (CAS No.: 394-30-9).
36	5-chloro-N-{3-(2-isopropylphenyl)-1-[2-(S-methylsulfonimidoylethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 36 was prepared in an analogous manner to Scheme 12 → Scheme 14, where the reactions were carried out using A46 in place of compound A35 .

[Table 1-6]

Cpd No.	Cpd Name	Scheme
37	5-chloro-N-[3-(2-isopropylphenyl)-1-(1-methoxy-2-propanyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 37 was prepared in an analogous manner to Scheme 29 using A84 in place of A49 . Wherein, 5-amino-6-(2-isopropylphenyl)-2-(1-methoxypropan-2-yl)pyridazin-3(2H)-one (A84) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
38	5-chloro-N-[1-(2-fluoro-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 38 was prepared in an analogous manner to Scheme 29 using A85 in place of A49 . Wherein, 5-amino-2-(2-fluoro-2-methylpropyl)-6-(2-isopropylphenyl)pyridazin-3(2H)-one (A85) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
39	5-chloro-N-[1-[2-(difluoromethoxy)ethyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 39 was prepared in an analogous manner to Scheme 29 using A86 in place of A49 . Wherein, 5-amino-2-(2-(difluoromethoxy)ethyl)-6-(2-isopropylphenyl)pyridazin-3(2H)-one (A86) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .
40	N-[3-(2-isopropylphenyl)-1-[2-(methylsulfonyl)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(2-methyl-2-propanyl)benzamide	The compound 40 was prepared in an analogous manner to Scheme 12 → Scheme 13, where the reactions were carried out using 5-(tert-butyl)-2-methoxybenzoic acid (A87) (CAS No.: 73469-54-2) in place of compound A35 .
41	N-[3-(2-isopropylphenyl)-1-[2-(methylsulfonyl)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide	The compound 41 was prepared in an analogous manner to Scheme 12 → Scheme 13, where the reactions were carried out using A52 in place of compound A35 .

[Table 1-7]

Cpd No.	Cpd Name	Scheme
42	N-{3-(2-isopropylphenyl)-1-[2-(S-methylsulfonimido)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide	The compound 42 was prepared in an analogous manner to Scheme 12 → Scheme 14, where the reactions were carried out using A52 in place of compound A35 .
43	N-{3-(2-isopropylphenyl)-1-[2-(S-methylsulfonimido)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(2-methyl-2-propanyl)benzamide	The compound 43 was prepared in an analogous manner to Scheme 12 → Scheme 14, where the reactions were carried out using A87 in place of compound A35 .
44	5-chloro-2-methoxy-N-{1-methyl-3-[3-methyl-2-(trifluoromethyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl}benzamide	The compound 44 was prepared in an analogous manner to Scheme 29 using A88 in place of A49 . Wherein, 5-amino-2-methyl-6-(3-methyl-2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (A88) was prepared in an analogous manner to Scheme 16 → Scheme 17, where the reactions were carried out using a corresponding boronic acid reagent in place of compound A31 .
45	5-chloro-2-fluoro-N-{1-methyl-3-[3-methyl-2-(trifluoromethyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl}benzamide	The compound 45 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A88 and 5-chloro-2-fluorobenzoic acid (A89) (CAS No.: 394-30-9).
46	2,5-difluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 46 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and 2,5-difluorobenzoic acid (A90) (CAS No.: 2991-28-8).

[Table 1-8]

Cpd No.	Cpd Name	Scheme
48	3-chloro-2,6-difluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 48 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and A71 .
49	N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-(trifluoromethoxy)benzamide	The compound 49 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and 2-(trifluoromethoxy)benzoic acid (A91) (CAS No.: 1979-29-9).
50	2-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 50 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and 2-chlorobenzoic acid (A92) (CAS No.: 118-91-2).
51	5-chloro-2-methoxy-N-{1-(methoxymethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 51 was prepared in an analogous manner to Scheme 29 using A93 in place of A49 . Wherein, 5-amino-2-(methoxymethyl)-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (A93) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 and a corresponding boronic acid reagent A22 .
52	5-chloro-2-methoxy-N-{6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 52 was prepared in an analogous manner to Scheme 25 using A99 in place of A47 . Wherein, 5-amino-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (A99) was prepared in an analogous manner to Scheme 10, where the reactions were carried out using a corresponding boronic acid reagent A22 in place of A31 .
53	6-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}imidazo[1,2-a]pyridine-8-carboxamide	The compound 53 was prepared in an analogous manner to Scheme 26, where the reaction was carried out using compound A26 and A63 .

[Table 1-9]

Cpd No.	Cpd Name	Scheme
54	6-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-8-quinolinecarboxamide	The compound 54 was prepared in an analogous manner to Scheme 26, where the reaction was carried out using compound A26 and A64 .
55	6-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}imidazole[1,2-a]pyridine-8-carboxamide	The compound 55 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and A63 .
56	6-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-8-quinolinecarboxamide	The compound 56 was prepared in an analogous manner to Scheme 25, where the reaction was carried out using compound A47 and A64 .
57	5-chloro-N-{1-[2-(dimethylamino)-2-oxoethyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 57 was prepared in an analogous manner to Scheme 29 using A94 in place of A49 . Wherein, 2-(4-amino-6-oxo-3-[2-(trifluoromethyl)phenyl]pyridazin-1(6H)-yl)-N,N-dimethylacetamide (A94) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 and a corresponding boronic acid reagent A22 .
58	5-chloro-2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 58 was prepared in an analogous manner to Scheme 26, where the reaction was carried out using compound A26 and A89 .
61	5-chloro-N-{1-[2-(dimethylamino)ethyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 61 was prepared in an analogous manner to Scheme 29 using A95 in place of A49 . Wherein, 5-amino-2-(2-(dimethylamino)ethyl)-6-(2-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (A95) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 and a corresponding boronic acid reagent A22 .

[Table 1-10]

Cpd No.	Cpd Name	Scheme
62	2-[4-{[2-fluoro-5-(trifluoromethyl)benzoyl]amino}-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl]ethyl acetate	The compound 62 was prepared in an analogous manner to Scheme 7, where the reaction was carried out using compound A26 and A27 .
64	2-fluoro-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	The compound 64 was prepared in an analogous manner to Scheme 29, where the reaction was carried out using compound A49 and A27 .
65	2-fluoro-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide	The compound 65 was prepared in an analogous manner to Scheme 29, where the reaction was carried out using compound A49 and A48 .
69	5-chloro-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide	The compound 69 was prepared in an analogous manner to Scheme 38, where the reaction was carried out using compound A40 and A89 .
71	5-(difluoromethyl)-2-fluoro-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 71 was prepared in an analogous manner to Scheme 23, where the reaction was carried out using compound A45 and A53 .
73	2-fluoro-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide	The compound 73 was prepared in an analogous manner to Scheme 23, where the reaction was carried out using compound A45 and A48 .
75	5-chloro-2-fluoro-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 75 was prepared in an analogous manner to Scheme 23, where the reaction was carried out using compound A45 and A89 .

[Table 1-11]

Cpd No.	Cpd Name	Scheme
76	5-(difluoromethoxy)-2-fluoro-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	The compound 76 was prepared in an analogous manner to Scheme 23, where the reaction was carried out using compound A45 and A54 .
77	5-chloro-N-[3-(2-isopropyl-3-pyridinyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	The compound 77 was prepared in an analogous manner to Scheme 23 using A96 in place of A45 . Wherein, 5-amino-6-(2-isopropylpyridin-3-yl)-2-methylpyridazin-3(2H)-one (A96) was prepared in an analogous manner to Scheme 16 → Scheme 17, where the reactions were carried out using a corresponding boronic acid reagent in place of compound A31 .
79	2-fluoro-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	The compound 79 was prepared in an analogous manner to Scheme 23, where the reaction was carried out using compound A45 and A27 .
80	2-fluoro-N-{1-methyl-3-[3-methyl-2-(trifluoromethyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	The compound 80 was prepared in an analogous manner to Scheme 23, where the reaction was carried out using compound A88 and A27 .
81	2-fluoro-N-[3-(2-isopropyl-3-pyridinyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(2-methyl-2-propanyl)benzamide	The compound 81 was prepared in an analogous manner to Scheme 23, where the reaction was carried out using compound A96 and 5-(tert-butyl)-2-fluorobenzoic acid A98 . Wherein, compound A98 was prepared in an analogous manner to Scheme 21 → Scheme 22 following Scheme 22-1 using compound AB184-2 .
84	2-fluoro-N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide	The compound 84 was prepared in an analogous manner to Scheme 39, where the reaction was carried out using compound A55 and AB199 .

[Table 1-12]

Cpd No.	Cpd Name	Scheme
88	2-fluoro-N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy) benzamide	The compound 88 was prepared in an analogous manner to Scheme 39, where the reaction was carried out using compound A55 and A48 .
91	2-fluoro-N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide	The compound 91 was prepared in an analogous manner to Scheme 39, where the reaction was carried out using compound A55 and A27 .
92	5-chloro-N-{1-[(3-hydroxy-3-oxetanyl)methyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	The compound 92 was prepared in an analogous manner to Scheme 29 using A97 in place of A49 . Wherein, 5-amino-2-[(3-hydroxyoxetan-3-yl)methyl]-6-(2-isopropylphenyl)pyridazin-3(2H)-one (A97) was prepared in an analogous manner to Scheme 18 → Scheme 19 → Scheme 20, where the reactions were carried out using a corresponding alkylating reagent in place of compound A41 .

[0256]

Table 2 shows the data measured in our LCMS and ^1H NMR conditions above. LCMS analysis was carried out by method of Reverse-phase LCMS (1) unless otherwise specified and ^1H NMR was taken by the method described above. The compounds shown in Table 2 were prepared in an analogous manner with the appropriate starting materials, and evaluated in our TREK-1 Thallium (TI^+) flux assay. The data were measured by Method 1 of TREK-1 Thallium flux assay as described below unless otherwise specified. It was found that each compound of present disclosure has a prominent TREK-1, TREK-2 or both TREK-1 and TREK-2 inhibitory activity.

[0257]

[Table 2-1]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 TL ⁺ Assay IC ₅₀ (uM)
1	5-chloro-2-methoxy-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 9.45 (s, 1H), 8.06 (d, 1H), 7.88-7.97 (m, 4H), 7.81 (d, 1H), 7.63 (d, 1H), 7.16 (d, 1H), 3.65 (s, 3H), 3.31 (s, 3H)	438.1 [M+H] ⁺	1.131	0.013
2	5-chloro-2-methoxy-N-{1-(3-oxetanylmethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 9.44 (s, 1H), 8.06 (d, 1H), 7.95 (m, 1H), 7.90 (m, 3H), 7.79-7.85 (m, 1H), 7.63 (d, 1H), 7.16 (d, 1H), 4.60 (m, 2H), 4.43-4.51 (m, 1H), 4.32-4.43 (m, 2H), 4.10-4.32 (m, 2H), 3.26 (s, 3H)	494.2 [M+H] ⁺	1.119	0.014
3	5-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxynicotinamide	(400MHz, CHLOROFORM-d) δ = 9.52 (s, 1H), 8.49 (d, 1H), 8.25 (s, 1H), 8.19 (d, 1H), 7.52-7.61 (m, 2H), 7.40 (m, 1H), 7.30 (d, 1H), 3.80 (s, 3H), 3.33 (s, 3H), 2.77 (m, 1H), 1.19 (d, 3H), 1.14 (d, 3H)	413.0 [M+H] ⁺	1.255	0.148
4	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 9.58 (s, 1H), 7.97 (d, 1H), 7.86 (s, 1H), 7.61-7.65 (m, 3H), 7.43 (br d, 1H), 7.39-7.40 (m, 1H), 7.15 (d, 1H), 4.16 (s, 3H), 2.69 (m, 1H), 1.09 (m, 6H)	398.1 [M+H] ⁺	1.168	0.065
5	5-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, DMSO-d ₆) δ = 9.61 (s, 1H), 7.97 (d, 1H), 7.92 (s, 1H), 7.60-7.66 (m, 3H), 7.39-7.46 (m, 2H), 7.15 (d, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 2.66-2.74 (m, 1H), 1.06-1.19 (m, 6H)	412.0 [M+H] ⁺	1.237	0.0074
6	5-chloro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.39-9.74 (m, 1H), 7.92-7.98 (m, 2H), 7.61-7.66 (m, 3H), 7.40-7.46 (m, 3H), 4.20 (d, 1H), 3.81-4.02 (m, 2H), 3.65 (s, 3H), 3.24-3.36 (m, 6H), 2.63-2.91 (m, 1H), 1.07-1.14 (m, 6H)	470.3 [M+H] ⁺	1.26	0.0054

[Table 2-2]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tr Assay IC ₅₀ (uM)
7	N-[1-(2-hydroxy-2-methylbutyl)-3-[2-(2-methyl-2-propanyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-methylbenzamide	(600MHz, DMSO-d ₆) δ = 9.66 (br s, 1H), 7.97 (d, 1H), 7.85 (s, 1H), 7.78 (d, 1H), 7.59 (m, 1H), 7.42 (m, 1H), 7.38 (br d, 1H), 7.28 (d, 1H), 6.98 (d, 1H), 4.08 (s, 2H), 3.14 (s, 3H), 2.28 (s, 3H), 1.23 (s, 9H), 1.18 (m, 2H), 1.04 (d, 3H), 0.85 (m, 3H)	478.4 [M+H] ⁺	1.342	0.010
8	5-chloro-N-[1-(2-hydroxy-2-methylbutyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.62 (br s, 1H), 8.32 (d, 1H), 8.20 (d, 1H), 7.51-7.61 (m, 2H), 7.36-7.44 (m, 2H), 7.30 (d, 1H), 6.76 (d, 1H), 4.81-4.73 (m, 1H), 4.49-4.11 (m, 2H) 3.15 (s, 3H), 2.77 (m, 1H), 1.50-1.55 (m, 2H), 1.10-1.20 (m, 9H), 0.97 (m, 3H)	484.1 [M+H] ⁺	1.301	0.0092
9	6-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]imidazo[1,2-a]pyridine-8-carboxamide	(400MHz, CHLOROFORM-d) δ = 12.09 (s, 1H), 8.29 (s, 1H), 8.25 (d, 1H), 8.14 (d, 1H), 7.50-7.62 (m, 2H), 7.46 (d, 1H), 7.35 (m, 1H), 7.29 (d, 1H), 6.98 (d, 1H), 3.78-3.88 (m, 3H), 2.77 (m, 1H), 1.17 (d, 3H), 1.04 (d, 3H)	422.0 [M+H] ⁺	1.197	0.063
10	5-chloro-N-[1-(2-hydroxy-2-methylbutyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxynicotinamide	(600MHz, DMSO-d ₆) δ = 9.50 (s, 1H), 8.46 (d, 1H), 8.38 (d, 1H), 7.93 (d, 1H), 7.63-7.66 (m, 2H), 7.39-7.47 (m, 2H), 4.46-4.70 (m, 1H), 4.14-4.38 (m, 1H), 3.86-4.07 (m, 1H), 3.29-3.36 (m, 3H), 2.64-2.87 (m, 1H), 1.37-1.48 (m, 2H), 1.12 (m, 6H), 1.04 (m, 3H), 0.82-0.88 (m, 3H)	485.4 [M+H] ⁺	1.34	0.124
11	6-chloro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-8-quinolinecarboxamide	(400MHz, CHLOROFORM-d) δ = 13.39 (s, 1H), 8.82 (d, 1H), 8.56 (s, 1H), 8.13 (m, 1H), 7.95 (d, 1H), 7.63-7.69 (m, 2H), 7.52-7.60 (m, 1H), 7.30-7.44 (m, 3H), 3.89 (s, 3H), 2.77-2.91 (m, 1H), 1.19 (d, 3H), 1.02 (d, 3H)	433.0 [M+H] ⁺	1.292	0.011
12	5-chloro-N-[3-(2-isopropylphenyl)-1-(methoxymethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.62 (s, 1H), 8.27 (s, 1H), 8.18 (d, 1H), 7.48-7.60 (m, 2H), 7.29-7.45 (m, 3H), 6.77 (d, 1H), 5.38-5.62 (m, 2H), 3.34-3.57 (m, 3H), 3.11-3.21 (m, 3H), 2.70-2.97 (m, 1H), 0.98-1.34 (m, 6H)	442.0 [M+H] ⁺	1.243	0.004

[Table 2-3]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (uM)
13	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1-(1,3-thiazol-5-ylmethyl)-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.73 (s, 1H), 8.94 (s, 1H), 8.04 (s, 1H), 8.00 (d, 1H), 7.61-7.68 (m, 4H), 7.48-7.51 (m, 1H), 7.45 (br d, 1H), 7.17 (d, 1H), 3.19 (s, 3H), 2.75-2.81 (m, 1H), 2.30 (s, 2H), 1.07-1.19 (m, 6H)	495.2 [M+H] ⁺	1.269	0.065
14	5-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.42 (s, 1H), 8.36 (s, 1H), 8.19 (d, 1H), 7.95 (d, 1H), 7.75-7.83 (m, 2H), 7.52 (d, 1H), 7.41 (m, 1H), 6.77 (d, 1H), 4.47 (d, 1H), 4.15 (d, 1H), 3.22 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H)	496.2 [M+H] ⁺	1.183	0.0075
15	5-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxynicotinamide	(400MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.48 (d, 1H), 8.30 (s, 1H), 8.20 (d, 1H), 7.97 (d, 1H), 7.77-7.84 (m, 2H), 7.50-7.54 (m, 1H), 4.46 (d, 1H), 4.14 (d, 1H), 3.38 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H)	497.2 [M+H] ⁺	1.193	0.139
16	5-chloro-N-[3-(2-isopropylphenyl)-1-(3-oxetanylmethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.57 (s, 1H), 8.17-8.29 (m, 2H), 7.49-7.60 (m, 2H), 7.27-7.47 (m, 3H), 6.75 (d, 1H), 4.76 (m, 2H), 4.38-4.66 (m, 4H), 3.48-3.71 (m, 1H), 3.15 (s, 3H), 2.63-2.82 (m, 1H), 1.07-1.22 (m, 6H)	468.0 [M+H] ⁺	1.207	0.052
17	5-chloro-N-[1-(cyanomethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.68 (s, 1H), 8.22-8.38 (m, 1H), 8.17 (d, 1H), 7.52-7.64 (m, 2H), 7.31-7.47 (m, 3H), 6.77 (d, 1H), 4.96-5.14 (m, 2H), 3.15 (s, 3H), 2.68-2.92 (m, 1H), 1.04-1.32 (m, 6H)	437.0 [M+H] ⁺	1.237	0.0047
18	5-chloro-N-{1-[2-(dimethylamino)-2-oxoethyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.60 (s, 1H), 8.14-8.28 (m, 2H), 7.44-7.60 (m, 2H), 7.29-7.42 (m, 3H), 6.75 (d, 1H), 5.03 (d, 1H), 4.93 (d, 1H), 3.14 (s, 3H), 3.06 (s, 3H), 2.97 (s, 3H), 2.79-2.92 (m, 1H), 1.15 (m, 6H)	483.1 [M+H] ⁺	1.16	0.048

[Table 2-4]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 TI ⁺ Assay IC ₅₀ (uM)
19	5-chloro-N-{3-(2-isopropylphenyl)-1-[(methoxymethoxy)methyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.59 (s, 1H), 8.26 (s, 1H), 8.19 (d, 1H), 7.51-7.59 (m, 2H), 7.30-7.42 (m, 3H), 6.75 (d, 1H), 5.48-5.63 (m, 2H), 4.80-4.89 (m, 2H), 3.32-3.47 (m, 3H), 3.14 (s, 3H), 2.74-2.84 (m, 1H), 1.11-1.20 (m, 6H)	472.0 [M+H] ⁺	1.253	0.0031
20	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxynicotinamide	(600MHz, DMSO-d ₆) δ = 13.06 (s, 1H), 9.47 (s, 1H), 8.46 (d, 1H), 8.37 (d, 1H), 7.85 (s, 1H), 7.63 (d, 1H), 7.63 (s, 1H), 7.44 (m, 1H), 7.39 (d, 1H), 3.30 (s, 3H), 2.68-2.73 (m, 1H), 1.11 (br d, 3H), 1.10 (br d, 3H)	399.2 [M+H] ⁺	1.182	0.527
21	3-chloro-2,6-difluoro-N-[1-(2-hydroxy-2-methylbutyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide	(600MHz, DMSO-d ₆) δ = 10.04 (s, 1H), 7.76 (br d, 1H), 7.60 (s, 1H), 7.44 (d, 1H), 7.43 (s, 1H), 7.21-7.28 (m, 3H), 4.29-4.82 (m, 1H), 3.71-4.29 (m, 2H), 2.74-2.80 (m, 1H), 1.38-1.47 (m, 2H), 1.18 (br s, 3H), 1.08 (br s, 3H), 1.05 (s, 3H), 0.85 (m, 3H)	490.3 [M+H] ⁺	1.242	0.231
22	5-chloro-N-{3-(2-isopropylphenyl)-6-oxo-1-[2-(1-pyrrolidinyl)ethyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.67 (s, 1H), 7.98 (s, 2H), 7.64-7.68 (m, 3H), 7.46 (br m, 1H), 7.41-7.44 (m, 1H), 7.17 (d, 1H), 4.14-4.69 (m, 2H), 3.59 (m, 2H), 3.18 (s, 3H), 3.00-3.15 (m, 4H), 2.76 (m, 1H), 2.03 (m, 2H), 1.85 (m, 2H), 1.11 (m, 6H)	495.4 [M+H] ⁺	0.987	0.200
23	N-[1-(2-aminoethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-chloro-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.65 (s, 1H), 7.98 (d, 1H), 7.97 (s, 1H), 7.86 (m, 2H), 7.63-7.67 (m, 3H), 7.45 (m, 1H), 7.40-7.43 (m, 1H), 7.17 (d, 1H), 4.27-4.37 (m, 2H), 3.27-3.34 (m, 2H), 3.14-3.23 (m, 3H), 2.75-2.80 (m, 1H), 1.10-1.12 (m, 6H)	441.3 [M+H] ⁺	0.939	0.063
24	5-chloro-N-{3-(2-isopropylphenyl)-6-oxo-1-[(2-propyn-1-yloxy)methyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.61 (s, 1H), 8.26 (s, 1H), 8.19 (d, 1H), 7.51-7.60 (m, 2H), 7.31-7.42 (m, 3H), 6.75 (d, 1H), 5.58 (s, 2H), 4.37 (m, 2H), 3.15 (s, 3H), 2.75-2.85 (m, 1H), 2.42 (m, 1H), 1.11-1.21 (m, 6H)	466.1 [M+H] ⁺	1.26	0.0029

[Table 2-5]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (μM)
25	5-chloro-N-[1-(2-hydroxyethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.62 (s, 1H), 8.30 (s, 1H), 8.18 (d, 1H), 7.51-7.62 (m, 2H), 7.30-7.43 (m, 3H), 6.75 (d, 1H), 4.35-4.46 (m, 2H), 3.96-4.06 (m, 2H), 3.52 (m, 1H), 3.15 (s, 3H), 2.72-2.85 (m, 1H), 1.16 (m, 6H)	442.0 [M+H] ⁺	1.137	0.011
26	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.69 (s, 1H), 8.35 (s, 1H), 8.19 (d, 1H), 7.52-7.63 (m, 2H), 7.26-7.44 (m, 2H), 6.77 (d, 1H), 6.42-6.14 (m, 1H), 4.83-4.61 (m, 1H), 4.46-4.25 (m, 1H), 3.15 (s, 3H), 2.68-2.80 (m, 1H), 1.40-1.35 (m, 3H), 1.24-1.41 (m, 6H)	524.1 [M+H] ⁺	1.337	0.005
27	5-chloro-N-[1-(2-hydroxy-3-methoxypropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.62 (s, 1H), 8.30 (s, 1H), 8.20 (d, 1H), 7.50-7.60 (m, 2H), 7.35-7.43 (m, 2H), 7.28-7.34 (m, 1H), 6.75 (d, 1H), 4.27-4.48 (m, 2H), 4.17-4.25 (m, 1H), 3.86-4.08 (m, 1H), 3.42-3.51 (m, 2H), 3.38 (m, 3H), 3.15 (s, 3H), 2.77 (m, 1H), 0.97-1.21 (m, 6H)	486.1 [M+H] ⁺	1.163	0.012
28	5-chloro-N-[1-(1-cyanoethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.70 (s, 1H), 7.96-7.99 (m, 2H), 7.64-7.68 (m, 2H), 7.45-7.49 (m, 2H), 7.16 (d, 1H), 6.14 (m, 1H), 3.48 (m, 1H), 3.18 (s, 3H), 2.64-2.84 (m, 1H), 1.63 (d, 3H), 1.12 (br m, 6H)	451.2 [M+H] ⁺	1.3	0.0063
29	5-chloro-N-[3-(2-isopropylphenyl)-1-(2-oxetanylmethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.61 (s, 1H), 7.75-8.09 (m, 2H), 7.52-7.73 (m, 2H), 7.24-7.50 (m, 3H), 7.15 (d, 1H), 4.00-4.48 (m, 1H), 3.33 (m, 1H), 3.17 (s, 3H), 2.89 (m, 2H), 2.59-2.75 (m, 2H), 2.08 (m, 2H), 1.06-1.14 (m, 6H)	468.3 [M+H] ⁺	1.241	0.0063
30	5-chloro-N-[3-(2-isopropylphenyl)-1-[2-(methylamino)-2-oxoethyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.66 (s, 1H), 7.96-8.01 (m, 2H), 7.60-7.66 (m, 3H), 7.43 (m, 1H), 7.39 (d, 1H), 7.16 (d, 1H), 4.62-4.87 (m, 1H), 4.28-4.62 (m, 1H), 3.18 (s, 3H), 2.70-2.83 (m, 1H), 2.60 (d, 3H), 1.09 (d, 6H)	469.2 [M+H] ⁺	1.138	0.015

[Table 2-6]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 T1+ Assay IC ₅₀ (uM)
31	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1-(3-pyrrolidinyl)-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.62 (s, 1H), 8.56-9.07 (m, 2H), 7.95-7.98 (m, 2H), 7.63-7.67 (m, 3H), 7.42-7.48 (m, 2H), 7.16 (d, 1H), 5.59 (br d, 1H), 3.60 (m, 1H), 3.34 (m, 3H), 3.19 (s, 3H), 2.62-2.77 (m, 1H), 2.32 (m, 1H), 2.19 (m, 1H), 1.07-1.18 (m, 6H)	467.3 [M+H] ⁺	0.946	0.137
32	5-chloro-N-[3-(2-isopropylphenyl)-6-oxo-1-[(2-propyn-1-yloxy)methoxy]methyl]-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.60 (s, 1H), 8.26 (s, 1H), 8.19 (d, 1H), 7.51-7.59 (m, 2H), 7.27-7.41 (m, 3H), 6.75 (d, 1H), 5.55-5.62 (m, 2H), 4.97-5.02 (m, 2H), 4.24-4.29 (m, 2H), 3.14 (s, 3H), 2.79 (m, 1H), 2.38-2.41 (m, 1H), 1.16 (m, 6H)	496.1 [M+H] ⁺	1.267	0.0063
33	N-[1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl]-2,3-dihydro-1-benzofuran-7-carboxamide	(400MHz, CHLOROFORM-d) δ = 9.09 (s, 1H), 8.28 (s, 1H), 7.84-7.95 (m, 2H), 7.65-7.81 (m, 2H), 7.44-7.59 (m, 1H), 7.28-7.41 (m, 1H), 6.96 (m, 1H), 4.59-4.75 (m, 1H), 4.35-4.50 (m, 1H), 3.92-4.20 (m, 2H), 2.96-3.17 (m, 2H), 1.07-1.33 (m, 6H)	474.4 [M+H] ⁺	1.104	0.810
34	2-chloro-5-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl]benzamide	(400MHz, CHLOROFORM-d) δ = 8.21 (s, 1H), 8.07 (s, 1H), 7.89 (d, 1H), 7.63-7.83 (m, 3H), 7.50 (d, 1H), 7.10-7.32 (m, 2H), 4.47 (d, 1H), 4.07-4.21 (m, 1H), 1.09-1.36 (m, 6H)	484.3 [M+H] ⁺	1.095	0.903
35	5-chloro-N-[1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.38 (s, 1H), 8.27 (s, 1H), 8.17 (d, 1H), 7.92-7.97 (m, 1H), 7.64-7.86 (m, 2H), 7.51-7.58 (m, 1H), 7.40 (m, 1H), 6.76 (d, 1H), 4.29-4.47 (m, 2H), 4.00 (m, 2H), 3.24 (m, 1H), 3.21 (s, 3H)	468.3 [M+H] ⁺	1.072	0.0066
36	5-chloro-N-[3-(2-isopropylphenyl)-1-[2-(S-methylsulfonimido)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400 MHz, DMSO-d ₆) δ = 9.63 (s, 1H), 7.97 (d, 1H), 7.93 (s, 1H), 7.66-7.61 (m, 3H), 7.47 – 7.39 (m, 2H), 7.15 (d, 1H), 4.57 – 4.38 (m, 2H), 3.82 (s, 1H), 3.47 (t, 2H), 3.17 (s, 3H), 2.95 (s, 3H), 2.72 (m, 1H), 1.10 (m, 6H)	503.1 [M+H] ⁺	0.78*	0.447**

[Table 2-7]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (uM)
37	5-chloro-N-[3-(2-isopropylphenyl)-1-(1-methoxy-2-propanyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400 MHz, DMSO-d ₆) δ = 9.61 (s, 1H), 7.96 (d, 1H), 7.89 (s, 1H), 7.67 – 7.58 (m, 3H), 7.48 – 7.34 (m, 2H), 7.15 (d, 1H), 5.37 – 5.24 (m, 1H), 3.63 – 3.52 (m, 1H), 3.42 (m, 1H), 3.20 (m, 3H), 3.18 (s, 3H), 2.78 – 2.63 (m, 1H), 1.22 – 1.16 (m, 3H), 1.16 – 1.06 (m, 6H)	470.1 [M+H] ⁺	0.99*	0.017**
38	5-chloro-N-[1-(2-fluoro-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400 MHz, DMSO-d ₆) δ = 9.62 (s, 1H), 7.97 (d, 1H), 7.94 (s, 1H), 7.66 – 7.59 (m, 3H), 7.46 – 7.38 (m, 2H), 7.15 (d, 1H), 4.42 (dd, 1H), 4.15 (dd, 1H), 3.17 (s, 3H), 2.71 (m, 1H), 1.37 (d, 3H), 1.31 (d, 3H), 1.09 (dd, 6H)	472.1 [M+H] ⁺	1*	0.018**
39	5-chloro-N-[1-(2-(difluoromethoxy)ethyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400 MHz, DMSO-d ₆) δ = 9.63 (s, 1H), 7.96 (d, 1H), 7.93 (s, 1H), 7.66 – 7.59 (m, 3H), 7.44 (m, 1H), 7.41 – 7.36 (m, 1H), 7.15 (d, 1H), 6.63 (t, 1H), 4.54 – 4.44 (m, 1H), 4.23 – 4.09 (m, 3H), 3.17 (s, 3H), 2.71 (m, 1H), 1.11 (d, 3H), 1.08 (d, 3H)	492.1 [M+H] ⁺	0.9*	0.012**
40	N-[3-(2-isopropylphenyl)-1-[2-(methylsulfonyl)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(2-methyl-2-propanyl)benzamide	(400 MHz, DMSO-d ₆) δ = 9.73 (s, 1H), 8.04 (d, 1H), 7.97 (s, 1H), 7.66 – 7.62 (m, 2H), 7.60 (dd, 1H), 7.47 – 7.37 (m, 2H), 7.01 (d, 1H), 4.56 (dt, 1H), 4.41 (dt, 1H), 3.65 – 3.50 (m, 2H), 3.13 (s, 3H), 3.05 (s, 3H), 2.74 (m, 1H), 1.26 (s, 9H), 1.12 (d, 3H), 1.08 (d, 3H)	526.1 [M+H] ⁺	0.96*	0.033**
41	N-[3-(2-isopropylphenyl)-1-[2-(methylsulfonyl)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide	(400 MHz, DMSO-d ₆) δ = 9.60 (s, 1H), 8.28 (d, 1H), 7.98 – 7.93 (m, 2H), 7.68 – 7.61 (m, 2H), 7.49 – 7.38 (m, 2H), 7.32 (d, 1H), 4.57 (dt, 1H), 4.42 (dt, 1H), 3.66 – 3.49 (m, 2H), 3.26 (s, 3H), 3.05 (s, 3H), 2.75 (m, 1H), 1.13 (d, 3H), 1.08 (d, 3H)	538.1 [M+H] ⁺	0.88*	0.016**

[Table 2-8]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 TI ⁺ Assay IC ₅₀ (uM)
42	N-{3-(2-isopropylphenyl)-1-[2-(S-methylsulfonimido)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide	(400 MHz, DMSO-d ₆) δ = 9.60 (s, 1H), 8.28 (d, 1H), 7.99 – 7.91 (m, 2H), 7.68 – 7.60 (m, 2H), 7.49 – 7.40 (m, 2H), 7.32 (d, 1H), 4.53 (dt, 1H), 4.43 (dt, 1H), 3.83 (s, 1H), 3.54 – 3.44 (m, 2H), 3.26 (s, 3H), 2.95 (s, 3H), 2.73 (m, 1H), 1.13 (d, 3H), 1.09 (d, 3H)	537.1 [M+H] ⁺	0.78**	0.070**
43	N-{3-(2-isopropylphenyl)-1-[2-(S-methylsulfonimido)ethyl]-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(2-methyl-2-propanyl)benzamide	(400 MHz, DMSO-d ₆) δ = 9.73 (s, 1H), 8.04 (d, 1H), 7.97 (s, 1H), 7.66 – 7.62 (m, 2H), 7.60 (dd, 1H), 7.47 – 7.38 (m, 2H), 7.01 (d, 1H), 4.57 – 4.47 (m, 1H), 4.43 (dt, 1H), 3.82 (s, 1H), 3.47 (t, 2H), 3.13 (s, 3H), 2.95 (s, 3H), 2.73 (m, 1H), 1.26 (s, 9H), 1.13 (d, 3H), 1.08 (d, 3H)	525.2 [M+H] ⁺	0.85*	0.041**
44	5-chloro-2-methoxy-N-{1-methyl-3-[3-methyl-2-(trifluoromethyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl}benzamide	(400MHz, CHLOROFORM-d) δ = 9.41 (br s, 1H), 8.40 - 8.07 (m, 2H), 7.71 - 7.52 (m, 2H), 7.40 (br dd, 1H), 7.36 - 7.28 (m, 1H), 6.77 (br d, 1H), 3.77 (s, 3H), 3.22 (s, 3H), 2.65 (br s, 3H)	452.2 [M+H] ⁺	1.164	0.013
45	5-chloro-2-fluoro-N-{1-methyl-3-[3-methyl-2-(trifluoromethyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl}benzamide	(400MHz, DMSO-d ₆) δ = 9.58 (br s, 1H), 7.70 - 7.53 (m, 5H), 7.46 - 7.27 (m, 2H), 3.64 (s, 3H), 2.52 (br s, 3H)	440.2 [M+H] ⁺	1.148	0.297
46	2,5-difluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 9.35 (d, 1H), 7.90 (d, 1H), 7.79-7.83 (m, 1H), 7.77 (d, 1H), 7.65-7.69 (m, 2H), 7.42-7.47 (m, 2H), 7.33 (m, 1H), 4.73 (br s, 1H), 3.81-4.36 (m, 2H), 1.11 (br s, 6H)	468.2 [M+H] ⁺	1.138	0.606

[Table 2-9]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (uM)
47	2-fluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	(600MHz, DMSO-d ₆) δ = 9.60 (br s, 1H), 7.88-7.92 (m, 2H), 7.74-7.81 (m, 3H), 7.67-7.69 (m, 2H), 7.52 (m, 1H), 4.52-4.87 (m, 1H), 3.92-4.30 (m, 2H), 1.11 (br s, 6H)	518.3 [M+H] ⁺	1.186	0.017
48	3-chloro-2,6-difluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 10.11 (s, 1H), 7.86 (d, 1H), 7.71-7.79 (m, 3H), 7.60 (s, 1H), 7.57 (d, 1H), 7.26 (m, 1H), 4.69 (br s, 1H), 3.81-4.32 (m, 2H), 1.11 (br s, 6H)	502.2 [M+H] ⁺	1.129	0.700
49	N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-(trifluoromethoxy)benzamide	(600MHz, DMSO-d ₆) δ = 9.74 (s, 1H), 7.86 (d, 1H), 7.75 (d, 1H), 7.72 (d, 1H), 7.58-7.65 (m, 3H), 7.51 (d, 1H), 7.46 (m, 1H), 7.42 (br d, 1H), 4.48-4.89 (m, 1H), 3.83-4.20 (m, 2H), 1.11 (br s, 6H)	516.3 [M+H] ⁺	1.156	0.593
50	2-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 9.88 (s, 1H), 7.84 (d, 1H), 7.75 (d, 1H), 7.68-7.72 (m, 1H), 7.60-7.63 (m, 2H), 7.44-7.48 (m, 2H), 7.37-7.41 (m, 2H), 4.52-4.97 (m, 1H), 3.75-4.34 (m, 2H), 1.11 (br s, 6H)	466.2 [M+H] ⁺	1.112	0.695
51	5-chloro-2-methoxy-N-{1-(methoxymethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 9.47 (s, 1H), 8.07 (d, 1H), 7.96 (d, 1H), 7.89-7.93 (m, 3H), 7.84 (d, 1H), 7.63 (br d, 1H), 7.16 (d, 1H), 4.97-5.62 (m, 2H), 3.26 (s, 3H), 2.52-2.56 (m, 3H)	467.9 [M] ⁺	1.189	0.0076
52	5-chloro-2-methoxy-N-{6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 13.14 (s, 1H), 9.40 (s, 1H), 8.05 (d, 1H), 7.87-7.96 (m, 3H), 7.82 (s, 1H), 7.79 (d, 1H), 7.63 (m, 1H), 7.15 (d, 1H), 3.25 (s, 3H)	423.9 [M] ⁺	1.112	0.117

[Table 2-10]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (uM)
53	6-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}imidazo[1,2-a]pyridine-8-carboxamide	(400MHz, DMSO-d ₆) δ = 12.08 (s, 1H), 9.08 (d, 1H), 7.86-8.05 (m, 6H), 7.74 (d, 1H), 6.98 (d, 1H), 4.83 (m, 1H), 4.02-4.20 (m, 2H), 3.69 (m, 2H)	478.0 [M+H] ⁺	1.038	0.090
54	6-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-8-quinolinecarboxamide	(400MHz, DMSO-d ₆) δ = 13.15 (s, 1H), 8.50-8.61 (m, 2H), 8.46 (d, 1H), 8.06-8.15 (m, 1H), 7.91-8.03 (m, 3H), 7.83 (d, 1H), 7.73 (m, 1H), 7.61 (m, 1H), 4.85 (br s, 1H), 4.00-4.22 (m, 2H), 3.69 (br m, 2H)	489.0 [M+H] ⁺	1.113	0.018
55	6-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}imidazo[1,2-a]pyridine-8-carboxamide	(600MHz, DMSO-d ₆) δ = 12.08 (s, 1H), 9.08 (d, 1H), 8.04 (d, 1H), 8.00 (d, 1H), 7.87-7.96 (m, 4H), 7.75 (d, 1H), 6.99 (s, 1H), 4.74 (s, 1H), 4.22 (d, 1H), 3.98 (d, 1H), 1.14 (s, 3H), 1.11 (s, 3H)	506.1 [M+H] ⁺	1.158	0.228
56	6-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-8-quinolinecarboxamide	(600MHz, DMSO-d ₆) δ = 13.14 (s, 1H), 8.59 (d, 1H), 8.53 (d, 1H), 8.46 (d, 1H), 8.09-8.12 (m, 1H), 8.04 (s, 1H), 7.94-7.98 (m, 2H), 7.84 (d, 1H), 7.74 (d, 1H), 7.61 (m, 1H), 4.74 (br s, 1H), 4.19 (d, 1H), 4.00 (d, 1H), 1.13 (s, 3H), 1.11 (s, 3H)	517.1 [M+H] ⁺	1.234	0.056
57	5-chloro-N-{1-[2-(dimethylamino)-2-oxoethyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.48 (s, 1H), 8.05 (d, 1H), 7.87-7.96 (m, 4H), 7.76 (d, 1H), 7.63 (m, 1H), 7.16 (d, 1H), 4.58-5.23 (m, 2H), 3.26 (s, 3H), 3.01 (s, 3H), 2.83 (s, 3H)	509.1 [M+H] ⁺	1.128	0.044
58	5-chloro-2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(400MHz, DMSO-d ₆) δ = 9.52 (s, 1H), 7.90 (d, 1H), 7.60-7.84 (m, 6H), 7.33 (m, 1H), 4.82 (m, 1H), 4.00-4.18 (m, 2H), 3.68 (m, 2H)	456.1 [M+H] ⁺	1.05	0.128

[Table 2-11]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 TL+ Assay IC ₅₀ (uM)
59	2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	(400MHz, DMSO-d ₆) δ = 9.66 (s, 1H), 7.87-7.99 (m, 3H), 7.62-7.80 (m, 4H), 7.52 (t, 1H), 4.83 (t, 1H), 4.12 (t, 2H), 3.66-3.70 (m, 2H)	490.2 [M+H] ⁺	1.085	0.030
60	2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide	(400MHz, DMSO-d ₆) δ = 9.55 (s, 1H), 7.89 (d, 1H), 7.57-7.80 (m, 6H), 7.43 (m, 1H), 4.82 (m, 1H), 4.00-4.18 (m, 2H), 3.67 (m, 2H)	506.1 [M+H] ⁺	1.167	0.029
61	5-chloro-N-{1-[2-(dimethylamino)ethyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(600MHz, DMSO-d ₆) δ = 9.50 (s, 1H), 8.08 (d, 1H), 7.90-7.99 (m, 4H), 7.78 (d, 1H), 7.65 (m, 1H), 7.17 (d, 1H), 4.20-4.60 (m, 4H), 3.27 (s, 3H), 2.83 (s, 6H)	495.1 [M+H] ⁺	0.945	0.103
62	2-[4-{[2-fluoro-5-(trifluoromethyl)benzoylamino]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1(6H)-pyridazinyl]ethyl acetate	(600MHz, DMSO-d ₆) δ = 9.68 (br s, 1H), 7.95-7.99 (m, 1H), 7.89-7.93 (m, 2H), 7.73-7.81 (m, 2H), 7.63-7.69 (m, 2H), 7.52 (m, 1H), 4.34 (m, 2H), 3.10 (m, 2H), 1.93 (s, 3H)	532.1 [M+H] ⁺	1.218	0.015
63	5-chloro-2-methoxy-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(600MHz, DMSO-d ₆) δ = 9.46 (s, 1H), 8.06 (d, 1H), 7.87-7.96 (m, 4H), 7.80 (br d, 1H), 7.63 (br d, 1H), 7.15 (d, 1H), 3.64 (m, 2H), 3.43 (m, 2H), 3.26 (s, 3H), 3.22 (s, 3H)	482.1 [M+H] ⁺	1.178	0.0089
64	2-fluoro-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	(600MHz, DMSO-d ₆) δ = 9.67 (s, 1H), 7.96 (br s, 1H), 7.89-7.93 (m, 2H), 7.77-7.81 (m, 1H), 7.75 (d, 1H), 7.69 (d, 1H), 7.64 (s, 1H), 7.52 (m, 1H), 3.66 (br m, 2H), 3.33-3.37 (m, 2H), 3.22 (s, 3H)	504.1 [M+H] ⁺	1.177	0.019

[Table 2-12]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 TL ⁺ Assay IC ₅₀ (uM)
65	2-fluoro-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide	(600MHz, DMSO-d ₆) δ = 9.47-9.60 (m, 1H), 7.84-7.98 (m, 1H), 7.70-7.82 (m, 2H), 7.57-7.68 (m, 4H), 7.34-7.49 (m, 1H), 3.65 (m, 2H), 3.45 (m, 2H), 3.22 (s, 3H)	520.1 [M+H] ⁺	1.195	0.016
66	2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	(400MHz, DMSO-d ₆) δ = 9.64 (br s, 1H), 7.64-7.98 (m, 7H), 7.51 (m, 1H), 4.80-4.90 (m, 1H), 4.00-4.12 (m, 3H), 1.05 (br d, 3H)	504.2 [M+H] ⁺	1.109	0.016
67	2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	(400MHz, DMSO-d ₆) δ = 9.64 (br s, 1H), 7.86-7.98 (m, 3H), 7.64-7.83 (m, 4H), 7.44-7.56 (m, 1H), 4.78-4.93 (m, 1H), 3.89-4.14 (m, 3H), 1.05 (br d, 3H)	504.2 [M+H] ⁺	1.113	0.026
68	N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide	(400MHz, DMSO-d ₆) δ = 9.43 (s, 1H), 8.20 (d, 1H), 8.05 (d, 1H), 7.86-7.97 (m, 4H), 7.79 (d, 1H), 7.32 (d, 1H), 4.79-4.84 (m, 1H), 4.11 (m, 2H), 3.67 (m, 2H), 3.33 (s, 3H)	502.2 [M+H] ⁺	1.099	0.0031
69	5-chloro-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide	(400MHz, DMSO-d ₆) δ = 8.98 (br s, 1H), 9.02 - 8.94 (m, 1H), 7.71 (dd, 1H), 7.69 - 7.63 (m, 2H), 7.53 - 7.49 (m, 2H), 7.37 - 7.31 (m, 2H), 3.67 (s, 3H), 2.79 - 2.69 (m, 1H), 1.12 (br d, 6H)	400.2 [M+H] ⁺	1.200	0.046
70	5-(difluoromethyl)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide	(400MHz, DMSO-d ₆) δ = 8.95 (br d, 1H), 7.97 (br d, 1H), 7.81 (br s, 1H), 7.69 (s, 1H), 7.56 - 7.48 (m, 2H), 7.47 - 7.39 (m, 1H), 7.33 (br d, 2H), 7.26 - 6.93 (m, 1H), 3.67 (s, 3H), 2.77 - 2.71 (m, 1H), 1.12 (br d, 6H)	416.3 [M+H] ⁺	1.154	0.057

[Table 2-13]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 TI ⁺ Assay IC ₅₀ (uM)
71	5-(difluoromethyl)-2-fluoro-N-({1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(400 MHz, DMSO-d ₆) δ = 9.52 (br s, 1H), 7.88 (d, 1H), 7.71 - 7.84 (m, 4H), 7.63 - 7.68 (m, 2H), 7.38 (t, 1H), 7.05 (t, 1H), 3.64 (s, 3H)	442.2 [M+H] ⁺	1.081	0.734
72	2-fluoro-N-({3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide	(400MHz, DMSO-d ₆) δ = 9.03 (s, 1H), 7.68 - 7.60 (m, 3H), 7.53 - 7.47 (m, 2H), 7.47 - 7.41 (m, 1H), 7.34 - 7.28 (m, 2H), 3.67 (s, 3H), 2.74 (m, 1H), 1.12 (br d, 6H)	450.2 [M+H] ⁺	1.218	0.021
73	2-fluoro-N-({1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide	(400MHz, DMSO-d ₆) δ = 9.52 (br s, 1H), 7.89 (d, 1H), 7.81 - 7.72 (m, 2H), 7.69 - 7.64 (m, 2H), 7.63 - 7.56 (m, 2H), 7.42 (t, 1H), 3.65 (s, 3H)	476.2 [M+H] ⁺	1.148	0.158
74	5-(difluoromethoxy)-2-fluoro-N-({3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl}benzamide	(400MHz, DMSO-d ₆) δ = 8.83 (br s, 1H), 7.69 (s, 1H), 7.55 - 7.51 (m, 3H), 7.45 - 7.40 (m, 1H), 7.39 - 7.32 (m, 3H), 7.32 - 7.05 (m, 1H), 3.67 (s, 3H), 2.73 (m, 1H), 1.12 (d, 6H)	432.2 [M+H] ⁺	1.161	0.0072
75	5-chloro-2-fluoro-N-({1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(400 MHz, DMSO-d ₆) δ = 8.79 (br s, 1H), 7.89 (d, 1 H), 7.70 - 7.82 (m, 2 H), 7.58 - 7.69 (m, 4 H), 7.32 (t, 1 H), 3.65 (s, 3 H)	426.2 [M+H] ⁺	1.116	0.295
76	5-(difluoromethoxy)-2-fluoro-N-({1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide	(400 MHz, DMSO-d ₆) δ = 9.45 (s, 1H), 7.85 - 7.91 (m, 2H), 7.69 - 7.79 (m, 3H), 7.61 - 7.66 (m, 4H), 3.63 (s, 3 H)	458.2 [M+H] ⁺	1.095	0.095
77	5-chloro-N-({3-(2-isopropyl-3-pyridinyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.45 (s, 1H), 8.84 (dd, 1H), 8.27 (s, 1H), 8.21 (d, 1H), 7.66 (dd, 1H), 7.42 (dd, 1H), 7.36 (dd, 1H), 6.78 (d, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 2.94 (m, 1H), 1.23 (d, 6H)	413.3 [M+H] ⁺	0.978	0.960

[Table 2-14]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (uM)
78	2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide	(400MHz, DMSO-d ₆) δ = 9.19 (br s, 1H), 7.98 (m, 2H), 7.65 (s, 1H), 7.57 - 7.46 (m, 3H), 7.35 - 7.27 (m, 2H), 3.67 (s, 3H), 2.81 - 2.71 (m, 1H), 1.13 (br d, 6H)	434.2 [M+H] ⁺	1.199	0.012
79	2-fluoro-N-[1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide	(400MHz, CHLOROFORM-d) δ = 8.45 (dd, 1H), 8.16 (s, 1H), 7.98 - 7.89 (m, 2H), 7.80 - 7.74 (m, 2H), 7.53 - 7.48 (m, 1H), 7.16 - 7.07 (m, 1H), 7.11 (dd, 1H), 3.82 (s, 3H)	460.2 [M+H] ⁺	1.124	0.147
80	2-fluoro-N-[1-methyl-3-[3-methyl-2-(trifluoromethyl)phenyl]-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide	(400MHz, CHLOROFORM-d) δ = 8.45 (dd, 1H), 8.14 (s, 1H), 8.00 (br d, 1H), 7.81 - 7.73 (m, 1H), 7.66 - 7.54 (m, 2H), 7.25 (s, 1H), 7.14 (dd, 1H), 3.81 (s, 3H), 2.64 (q, 3H)	474.2 [M+H] ⁺	1.150	0.203
81	2-fluoro-N-[3-(2-isopropyl-3-pyridinyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(2-methyl-2-propanyl)benzamide	(400MHz, CHLOROFORM-d) δ = 8.83 (dd, 1H), 8.20 (s, 1H), 8.18 - 8.08 (m, 2H), 7.61 (dd, 1H), 7.51 (m, 1H), 7.35 - 7.30 (m, 1H), 6.91 (dd, 1H), 3.86 - 3.78 (m, 3H), 2.97 - 2.80 (m, 1H), 1.32 - 1.31 (m, 9H), 1.23 (d, 6H)	423.4 [M+H] ⁺	0.986	0.293
82	2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide	(400MHz, CHLOROFORM-d) δ = 8.33 - 8.16 (m, 2H), 8.01 (br s, 1H), 7.64 - 7.47 (m, 2H), 7.43 - 7.31 (m, 2H), 7.24 (br d, 1H), 7.09 - 7.00 (m, 1H), 4.66 (s, 1H), 4.46 (d, 1H), 4.22 (d, 1H), 2.74 (m, 1H), 1.28 (br d, 6H), 1.18 (m, 6H)	508.3 [M+H] ⁺	1.214	0.0057
83	2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide	(400MHz, CHLOROFORM-d) δ = 8.16 (s, 1H), 7.85 (s, 1H), 7.62 (t, 1H), 7.55 - 7.45 (m, 2H), 7.36 (dt, 1H), 7.28 (s, 1H), 6.70 (d, 1H), 3.81 (s, 3H), 3.54 (s, 3H), 2.90 - 2.74 (m, 1H), 1.17 (m, 6H)	464.3 [M+H] ⁺	1.149	0.0072

[Table 2-15]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 T1+ Assay IC ₅₀ (uM)
84	2-fluoro-N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide	(400MHz, CHLOROFORM-d) δ = 8.14 (s, 1H), 7.85 (s, 1H), 7.61 (t, 1H), 7.55 - 7.46 (m, 2H), 7.34 (dt, 1H), 7.29 (s, 1H), 6.70 (d, 1H), 4.49 (m, 1H), 4.34 - 4.22 (m, 1H), 3.82 - 3.75 (m, 2H), 3.55 (s, 3H), 3.35 (s, 3H), 2.83 (m, 1H), 1.19 (d, 3H), 1.15 (d, 3H)	508.3 [M+H] ⁺	1.164	0.0044
85	N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide	(400MHz, CHLOROFORM-d) δ = 9.53 (s, 1H), 8.52 (d, 1H), 8.26 (s, 1H), 7.70 (dd, 1H), 7.61 - 7.52 (m, 2H), 7.40 (dt, 1H), 7.34 - 7.30 (m, 1H), 6.92 (d, 1H), 4.49 (m, 1H), 4.29 (m, 1H), 3.84 - 3.73 (m, 2H), 3.34 (s, 3H), 3.23 (s, 3H), 2.87 - 2.76 (m, 1H), 1.19 (d, 3H), 1.14 (d, 3H)	490.3 [M+H] ⁺	1.220	0.0019
86	5-(difluoromethoxy)-2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide	(400MHz, CHLOROFORM-d) δ = 8.27 (s, 1H), 8.23 (s, 1H), 7.88 (dd, 1H), 7.64 - 7.49 (m, 2H), 7.38 (t, 1H), 7.23 (br d, 2H), 6.99 (dd, 1H), 6.80 - 6.29 (m, 1H), 4.73 (s, 1H), 4.45 (d, 1H), 4.20 (d, 1H), 2.72 (m, 1H), 1.27 (m, 6H), 1.16 (m, 6H)	490.3 [M+H] ⁺	1.161	0.0077
87	N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide	(400MHz, CHLOROFORM-d) δ = 9.60 (s, 1H), 8.54 (d, 1H), 8.35 (s, 1H), 7.72 (dd, 1H), 7.65 - 7.53 (m, 2H), 7.42 (dt, 1H), 7.32 (dd, 1H), 6.93 (d, 1H), 4.82 (s, 1H), 4.43 (d, 1H), 4.20 (d, 1H), 3.23 (s, 3H), 2.78 (m, 1H), 1.29 (s, 3H), 1.26 - 1.25 (m, 3H), 1.16 (m, 6H)	504.3 [M+H] ⁺	1.208	0.0028
88	2-fluoro-N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide	(400 MHz, DMSO-d ₆) δ = 9.11 - 9.04 (m, 1H), 7.68 - 7.60 (m, 3H), 7.54 - 7.47 (m, 2H), 7.47 - 7.40 (m, 1H), 7.35 - 7.29 (m, 2H), 4.49 - 4.36 (m, 1H), 4.15 - 4.02 (m, 1H), 3.70 - 3.65 (m, 2H), 3.22 (s, 3H), 2.69 - 2.68 (m, 1H), 1.15 - 1.10 (m, 6H)	494.2 [M+H] ⁺	1.231	0.008

[Table 2-16]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (uM)
89	2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide	(400MHz, CHLOROFORM-d) δ = 8.45 (dd, 1H), 8.26 - 8.19 (m, 2H), 7.81 - 7.73 (m, 1H), 7.63 - 7.52 (m, 2H), 7.40 (dt, 1H), 7.26 - 7.23 (m, 1H), 7.13 (dd, 1H), 4.68 (s, 1H), 4.46 (d, 1H), 4.29 - 4.16 (m, 1H), 2.82 - 2.66 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.19 (d, 3H), 1.17 (d, 3H)	492.3 [M+H] ⁺	1.199	0.012
90	2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide	(400 MHz, CHLOROFORM-d) δ = 8.27 - 8.19 (m, 1H), 7.98 - 7.88 (m, 1H), 7.67 - 7.59 (m, 1H), 7.57 - 7.49 (m, 2H), 7.40 - 7.34 (m, 1H), 7.26 - 7.25 (m, 1H), 6.70 (d, 1H), 4.73 - 4.66 (m, 1H), 4.46 - 4.38 (m, 1H), 4.22 (d, 1H), 3.57 - 3.51 (m, 3H), 2.85 - 2.71 (m, 1H), 1.28 (d, 6H), 1.17 (m, 6H)	522.3 [M+H] ⁺	1.152	0.016
91	2-fluoro-N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide	(400 MHz, DMSO-d ₆) δ = 9.12 - 9.00 (m, 1H), 7.84 - 7.75 (m, 2H), 7.48 - 7.44 (m, 1H), 7.38 - 7.27 (m, 3H), 7.17 - 7.09 (m, 2H), 4.30 - 4.13 (m, 1H), 3.99 - 3.81 (m, 1H), 3.53 - 3.46 (m, 2H), 3.04 (s, 3H), 2.64 - 2.55 (m, 1H), 0.97 - 0.92 (m, 6H)	478.3 [M+H] ⁺	1.205	0.0079
92	5-chloro-N-[1-[(3-hydroxy-3-oxetanyl)methyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide	(400MHz, CHLOROFORM-d) δ = 9.69 (s, 1H), 8.34 (s, 1H), 8.20 (d, 1H), 7.68 - 7.51 (m, 2H), 7.42 (m, 2H), 7.29 (dd, 1H), 6.77 (d, 1H), 5.84 (s, 1H), 4.82 - 4.73 (m, 2H), 4.71 - 4.62 (m, 2H), 4.58 - 4.53 (m, 2H), 3.16 (s, 3H), 2.73 (m, 1H), 1.19 (d, 3H), 1.15 (d, 3H)	484.3 [M+H] ⁺	1.127	0.018
93	2-fluoro-N-[1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide	(400 MHz, CHLOROFORM-d) δ = 8.28 - 8.20 (m, 2H), 8.00 (dd, 1H), 7.62 - 7.52 (m, 2H), 7.41 - 7.33 (m, 2H), 7.25 (d, 1H), 7.07 - 7.00 (m, 1H), 4.40 - 4.32 (m, 1H), 4.31 - 4.21 (m, 2H), 3.95 - 3.67 (m, 1H), 2.80 - 2.65 (m, 1H), 1.27 (m, 3H), 1.20 - 1.16 (m, 6H)	494.3 [M+H] ⁺	1.166	0.013

[Table 2-17]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Tl ⁺ Assay IC ₅₀ (uM)
94	2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	(400 MHz, CHLOROFORM-d) δ = 8.44 (dd, 1H), 8.25 - 8.17 (m, 2H), 7.80 - 7.74 (m, 1H), 7.62 - 7.52 (m, 2H), 7.39 (t, 1H), 7.27 - 7.24 (m, 1H), 7.17 - 7.10 (m, 1H), 4.41 - 4.24 (m, 3H), 3.86 - 3.61 (m, 1H), 2.79 - 2.71 (m, 1H), 1.29 - 1.25 (m, 3H), 1.21 - 1.15 (m, 6H)	478.2 [M+H] ⁺	1.145	0.016
95	2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide	(400 MHz, CHLOROFORM-d) δ = 8.27 - 8.20 (m, 2H), 8.02 - 7.95 (m, 1H), 7.62 - 7.51 (m, 2H), 7.42 - 7.32 (m, 2H), 7.27 - 7.22 (m, 1H), 7.08 - 7.00 (m, 1H), 4.43 - 4.32 (m, 2H), 4.30 - 4.20 (m, 2H), 2.83 - 2.65 (m, 1H), 1.27 (m, 3H), 1.20 - 1.16 (m, 6H)	494.2 [M+H] ⁺	1.166	0.0068
96	2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide	(400 MHz, CHLOROFORM-d) δ = 8.44 (dd, 1H), 8.26 - 8.18 (m, 2H), 7.79 - 7.73 (m, 1H), 7.63 - 7.52 (m, 2H), 7.39 (t, 1H), 7.25 (s, 1H), 7.13 (dd, 1H), 4.39 - 4.33 (m, 2H), 4.30 - 4.21 (m, 2H), 2.79 - 2.71 (m, 1H), 1.28 (m, 3H), 1.20 - 1.16 (m, 6H)	478.3 [M+H] ⁺	1.144	0.0092
97	2-fluoro-N-(1-(2-hydroxyethyl)-2,2-d ₂ -6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide	(400MHz, DMSO-d ₆) δ = 9.66 (s, 1H), 7.98 - 7.83 (m, 3H), 7.80 - 7.63 (m, 4H), 7.52 (m, 1H), 4.84 - 4.74 (m, 1H), 4.18 - 4.00 (m, 2H)	492.1 [M+H] ⁺	1.069	0.020
98	2-fluoro-N-(1-(2-hydroxyethyl)-2,2-d ₂ -6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethoxy)benzamide	(400MHz, DMSO-d ₆) δ = 9.55 (s, 1H), 7.89 (d, 1H), 7.80 - 7.55 (m, 6H), 7.43 (m, 1H), 4.81 - 4.77 (m, 1H), 4.11 (s, 2H)	508.2 [M+H] ⁺	1.091	0.027

[Table 2-18]

Cpd No.	Cpd Name	¹ H NMR	ESI-MS	LCMS Retention Time (min)	human TREK-1 Th ⁺ Assay IC ₅₀ (uM)
99	2-fluoro-N-(1-(2-hydroxyethyl-2- <i>d</i>)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide	(400MHz, DMSO- <i>d</i> ₆) δ = 9.68 (s, 1H), 7.87-7.99 (m, 3H), 7.62-7.81 (m, 4H), 7.52 (m, 1H), 4.12 (br d, 2H), 3.67 (br t, 1H)	491.2 [M+H] ⁺	1.095	0.023
100	2-fluoro-N-(1-(2-hydroxyethyl-1,1,2,2- <i>d</i>)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide	(400MHz, DMSO- <i>d</i> ₆) δ = 9.70 - 9.63 (m, 1H), 7.99 - 7.87 (m, 3H), 7.80 - 7.62 (m, 4H), 7.52 (m, 1H), 4.84 - 4.77 (m, 1H)	494.2 [M+H] ⁺	1.070	0.022

*: The data was measured by Reversed-phase LCMS Method (5) as described above.

** : The data was measured by TREK-1 Thallium flux assay Method 2 as described below.

[0258]

Example 1: In vitro TREK-1 and TREK-2 Inhibitor Activity

Measurement conditions of TREK-1 and TREK-2 Inhibitor Activity are as below.

TREK-1 Thallium flux assay

Method 1;

CHO-K1 cells stably expressing hTREK-1 were cultured in T225 flask. The cells were loaded with FluxOR dye and plated in 384 well plate at the experiment day. Test compounds or control compound (tert-butyl (3-((4-(benzyloxy)-2-methylphenyl)carbamoyl)-4-chlorophenyl)carbamate) or 0.3% DMSO (vehicle control) were added directly to the cell plates and incubated for 10 min, and then treated with thallium stimulus buffer to initiate thallium flux. To measure the efficacy and potency of test compounds, the change in fluorescence intensity (ΔRatio) and % inhibition were calculated using the following equations:

$$\Delta\text{Ratio} = (\text{fluorescence intensity at 25 seconds after thallium addition}) / (\text{average of fluorescent intensity before thallium addition})$$

$$\% \text{ inhibition} = \{1 - (\Delta\text{Ratio of test compound} - \Delta\text{Ratio of } 10 \mu\text{M control compound}) / (\Delta\text{Ratio of } 0.3\% \text{ DMSO} - \Delta\text{Ratio of } 10 \mu\text{M control compound})\} \times 100$$

% inhibition vs compound concentration were plotted in XLfit and calculated IC₅₀.

[0259]

Method 2;

CHO-K1 cells stably expressing human TREK-1 (hTREK-1) were cultured in T225 flask. The cells were loaded with FluxOR dye and plated in 384 well plate at the experiment day. Test compounds or control compound (tert-butyl (3-((4-(benzyloxy)-2-methylphenyl)carbamoyl)-4-chlorophenyl)carbamate) or 0.3% DMSO (vehicle control) which were prepared on separate plates were added to the cell plates and incubated for 10 min, and then the cells with test compounds or control compound (tert-butyl (3-((4-(benzyloxy)-2-methylphenyl)carbamoyl)-4-chlorophenyl)carbamate) or 0.3% DMSO (vehicle control) were treated with thallium stimulus buffer to initiate thallium flux. To measure the efficacy and potency of test compounds, the change in fluorescence intensity (Δ Ratio) and % inhibition were calculated using the following equations:

$$\Delta\text{Ratio} = (\text{fluorescence intensity at 25 seconds after thallium addition}) / (\text{average of fluorescent intensity before thallium addition})$$

$$\% \text{ inhibition} = \{1 - (\Delta\text{Ratio of test compound} - \Delta\text{Ratio of } 10 \mu\text{M control compound}) / (\Delta\text{Ratio of } 0.3\% \text{ DMSO} - \Delta\text{Ratio of } 10 \mu\text{M control compound})\} \times 100$$

% inhibition vs compound concentration were plotted in XLfit and calculated IC₅₀.

It was found that each compound of present disclosure has a prominent TREK-1 inhibitory activity.

[0260]

TREK-2 Thallium flux assay

HEK293 cells stably expressing human TREK-2 (hTREK-2) are plated in 384-well plates, cultured overnight, loaded with Thallos dye the following day. Test compounds or control compound (tert-butyl (3-((4-(benzyloxy)-2-methylphenyl)carbamoyl)-4-chlorophenyl)carbamate) or 0.3% DMSO (vehicle control) which are prepared on separate plates are added to the cell plates and incubated for 10 min, and then the cells are treated with thallium stimulus buffer to initiate thallium flux. To measure the efficacy and potency of test compounds, the change in fluorescence intensity (Δ Ratio) and % inhibition are calculated using the following equations:

$$\Delta\text{Ratio} = (\text{fluorescence intensity at 25 seconds after thallium addition}) / (\text{average of fluorescent intensity before thallium addition})$$

$$\% \text{ inhibition} = \{1 - (\Delta\text{Ratio of test compound} - \Delta\text{Ratio of } 10 \mu\text{M control compound}) / (\Delta\text{Ratio of } 0.3\% \text{ DMSO} - \Delta\text{Ratio of } 10 \mu\text{M control compound})\} \times 100$$

[0261]

Patch clamp technique

hTREK-1 and mTREK-1 patch clamp assay

CHO-K1 cells stably expressing hTREK-1 or CHO-K1 cells transiently expressing mouse TREK-1 (mTREK-1) were plated on glass coverslips, and voltage clamped in the whole-

cell configuration of the patch clamp technique. Cells were voltage clamped at a holding potential of -80 mV and the stepped to 0 mV for 500 msec. The voltage was subsequently ramped from -120mV to +80 mV over a 500 msec duration. This step-ramp protocol was repeated every 10 sec. The bathing solution contained the following: 135 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 5 mM D-Glucose, 10 mM HEPES, 10 mM sucrose (adjusted to pH 7.4 with NaOH, 300 mosmol/kg H₂O). The pipette solution contained the following: 135 mM KCl, 2 mM MgCl₂, 1 mM EGTA, 10 mM HEPES, 2 mM Na₂ATP (adjusted to pH 7.35 with KOH, 285 mosmol/kg H₂O). Test compounds were dissolved into the bathing solution. The effects of test compound on the currents were calculated at 0 mV using the following equations:

$$\% \text{ inhibition} = (1 - \text{post current} / \text{pre current}) \times 100$$

% inhibition vs compound concentrations were plotted in GraphPad Prism and calculated IC₅₀.

It was found that each compound of present disclosure has a prominent TREK-1 inhibitory activity.

[0262]

hTREK-2 patch clamp assay

HEK293 cells stably expressing human TREK-2 are plated on glass coverslips, and voltage clamped in the whole-cell configuration of the patch clamp technique. Cells are voltage clamped at a holding potential of -80 mV and the stepped to 0 mV for 500 msec. The voltage is subsequently ramped from -120mV to +80 mV over a 500 msec duration. This step-ramp protocol is repeated every 10 sec. The bathing solution contained the following: 135 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 5 mM D-Glucose, 10 mM HEPES, 10 mM sucrose (adjusted to pH 7.4 with NaOH, 300 mosmol/kg H₂O). The pipette solution contained the following: 135 mM KCl, 2 mM MgCl₂, 1 mM EGTA, 10 mM HEPES, 2 mM Na₂ATP (adjusted to pH 7.35 with KOH, 285 mosmol/kg H₂O). Test compounds are dissolved into the bathing solution. Experiments are terminated with the addition of the control compound (tert-butyl (3-((4-(benzyloxy)-2-methylphenyl)carbamoyl)-4-chlorophenyl)carbamate) so that maximal inhibition can be determined. The effects of test compound on the currents can be calculated at 0 mV using the following equations:

$$\% \text{ inhibition} = \{1 - (\text{post current} - \text{current in the presence of } 10 \mu\text{M control compound}) / (\text{pre current} - \text{current in the presence of } 10 \mu\text{M control compound})\} \times 100$$

[0263]

In some embodiments, the disclosed compounds inhibited TREK-1 channel response as a decrease in thallium fluorescence in thallium flux assay or a decrease in current measured at 0 mV in patch clamp electrophysiology assays.

The disclosed compounds may inhibit TREK-1 and/or TREK-2 via an inhibit mechanism or through an allosteric modulation mechanism.

The compounds shown in Table 2 were prepared in an analogous manner with the appropriate starting materials, and evaluated in our TREK-1 Thallium (Tl^+) flux assay. The data were measured by Method 1 of TREK-1 Thallium flux assay as described above unless otherwise specified.

[0264]

Example 2. In vivo pharmacology test

Forced swim test

Drugs: Test compounds were formulated in 10% Tween 80 / 90% sterile water vehicle. Following vigorous vortexing, the formulated compound was placed in an ultrasonic water bath for 1 hour. Test compounds were formulated at a concentration that allowed for an oral (p.o.) administration of 10 mL dosing solution/kg body weight.

Animals: Adult male BALB/cCrSlc mice (Japan SLC) at six-week-old were used. They were housed in an animal care facility certified by the Japan Health Sciences Foundation under a 12-hour light/dark cycle (lights on: 7 a.m.; lights off: 7 p.m.) and had free access to food and water. Animals were acclimated to the housing facility for at least six days before being tested and the behavioral testing was performed during the light phase. All experiments were approved by the Institutional Animals Care and Use Committee of Ono Pharmaceutical Co., Ltd.

Apparatus: For the forced swim test, a clear plastic cylinder (10 cm diameter x 25 cm height) containing 10 cm water in depth warmed $24 \pm 2^\circ\text{C}$ was used.

Procedure: Plastic animal cages (29 cm × 44 cm × 20 cm, 8 animals for each) were moved from the animal facility to the soundproof room in the morning of the test. After acclimation for 5 hours, the vehicle solution or test compounds was administered orally an hour before the forced swim procedure. Imipramine (60 mg/kg, p.o.) was administered as a positive control.

Behavioral analysis: The total immobility time in the above cylinder was recorded for six minutes using a video camera, and used as an index of antidepressant-like behaviors.

Data Analysis: Statistical analyses were performed using EXSUS ver 8.1 (CAC Croit Corporation). The total immobility time of the vehicle solution and compound groups were analyzed. The vehicle and compound-treated groups were analyzed by one-way ANOVA followed by Dunnett's test. The vehicle and imipramine-treated group were analyzed by Student t-test. A p-value ≤ 0.05 is considered to represent a significant difference.

Results: Compound 6 at 10 mg/kg, Compound 14 at 10 mg/kg, Compound 35 at 10 mg/kg, Compound 59 at 3 mg/kg and Compound 73 at 10 mg/kg significantly reduced the immobility time. Data are illustrated in Figure 1.

Conclusions: Systemic administration of Compound 6, Compound 14, Compound 35, Compound 59 and Compound 73 caused reduction of immobility time in the forced swim test, a preclinical rodent model of depression-like behavior.

[0265]

MK-801 induced novel object recognition test

Drugs: Test compounds formulated in 20% Kolliphor HS 15/propylene glycol (7:3) / 80% sterile water vehicle. Following vigorous vortexing, the formulated compound was placed in an ultrasonic water bath for 1 hour. The compound formulates at a concentration that allowed for an oral (p.o.) administration of 10 mL dosing solution/kg body weight. MK-801 hydrogen maleate was obtained from Sigma-Aldrich, dissolved in sterile saline, and dosed intraperitoneally in a volume of 1 mL/kg body weight (0.2 mg/kg).

Animals: Adult male C57BL/6J mice (Charles River Japan) at six-week-old were used. They were housed in an animal care facility certified by the Japan Health Sciences Foundation under a 12-hour light/dark cycle (lights on: 7 a.m.; lights off: 7 p.m.) and had free access to food and water. Animals were acclimated to the housing facility for a minimum of six days before being tested and the behavioral testing was performed during the light phase. All experiments were approved by the Institutional Animals Care and Use Committee of Ono Pharmaceutical Co., Ltd.

Apparatus: For the novel object recognition test an opaque Plastic chamber (35 cm x 40 cm x 18 cm) was used. At opposite ends of the chamber test objects could be placed. A video camera was mounted above the apparatus for recording the behavior.

Procedure: Habituation. At least one day prior to behavioral testing, animals were habituated to the empty testing chamber, i.e. in the absence of any objects, for ten minutes.

Training. One hour after administration of vehicle, the compound (p.o.) or clozapine (1 mg/kg, p.o.), and 30 minutes after administration of saline or MK-801, animals were placed into the testing chamber that contained two identical objects (LEGO (registered Trademark) blocks) for a session duration of 10 minutes. Afterwards, animals were returned to their home cage.

Recognition. Ninety minutes after the end of the training session, animals were reintroduced to the test chamber where one of the two identical objects have been replaced by a novel object (glass vial) for a total of 10 minutes.

Behavioral analysis: An observer blinded to treatment condition and novel object location used the video recordings to score the interaction of the animal with the two objects offline. The duration an animal explored each object was determined as the total time an animal is facing the object with its nose being ≤ 2 cm away from the object and some discernible whisker movement being present. From these data, a Discrimination Index is calculated as follows:

Discrimination Index = $100 \times (\text{time exploring Novel object} - \text{time exploring Familiar object}) / (\text{time exploring Novel object} + \text{time exploring Familiar object})$.

Data Analysis: Statistical analyses can be performed using EXSUS ver 8.1 (CAC Croit Corporation). The vehicle and compound-treated groups were analyzed by one-way ANOVA followed by Dunnett's test. The vehicle and vehicle-MK-801, and vehicle-MK-801 and clozapine

groups can be analyzed by Student t-test. A p-value ≤ 0.05 is considered to represent a significant difference.

Results: Compound 59 at 3 mg/kg significantly reduced Discrimination Index. Data are illustrated in Figure 2.

Conclusions: Systemic administration of Compound 59 caused amelioration in the MK-801-induced novel object recognition test, a preclinical rodent model of cognitive disrupted behavior. [0266]

Novel suppressed feeding test

Drugs: Test compounds formulated in 20% Kolliphor HS 15/propylene glycol (7:3) / 80% sterile water vehicle. Following vigorous vortexing, the formulated compound was placed in an ultrasonic water bath for 1 hour. The compound formulates at a concentration that allowed for an oral (p.o.) administration of 10 mL dosing solution/kg body weight.

Animals: Adult male Slc:ICR mice (Japan SLC Inc.) at six-week-old were housed in an animal care facility certified by the Japan Health Sciences Foundation under a 12-hour light/dark cycle (lights on: 7 a.m.; lights off: 7 p.m.), acclimated at least for six days before the test. The animals had free access to water, and were fasted only for 24 hours before the test. All experiments were approved by the Institutional Animals Care and Use Committee of Ono Pharmaceutical Co., Ltd.

Apparatus: For the novel suppressed feeding test, an opaque Plastic open field (60 cm in diameter) under 200 Lux was used. A video camera was mounted above the apparatus for recording the behavior.

Procedure: Animals were moved to the testing facility and acclimated for 5 hours prior to the test. One hour after administration of vehicle, the compound (p.o.) or scopolamine (0.03 mg/kg, i.p.) as a positive control, animals were placed into the open field, in which a food pellet is placed in the center.

Behavioral analysis: The latency to initiate a feeding behavior was recorded, and used as an index of early onset antidepressant-like behaviors. The test was stopped immediately after the first feeding episode and the cut-off time was 5 minutes.

Data Analysis: Statistical analyses can be performed using EXSUS ver 8.1 (CAC Croit Corporation). The vehicle and compound-treated groups were analyzed by one-way ANOVA followed by Dunnett's test. The vehicle and scopolamine-treated group were analyzed by Student t-test. A p-value ≤ 0.05 is considered to represent a significant difference.

Results & Conclusions: Systemic administration of the compounds of the present disclosure caused amelioration of latency time in the novel suppressed feeding test, a preclinical rodent model of depression-like behavior.

[0267]

It is understood that the foregoing detailed description and accompanying examples are

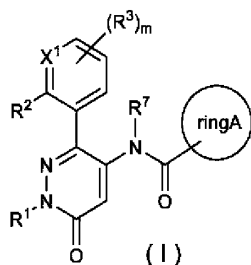
merely illustrative and are not to be taken as limitations upon the scope of the disclosure, which is defined solely by the appended claims and their equivalents.

CLAIMS

[Claim 1]

A compound of formula (I):

[Chem. 1]

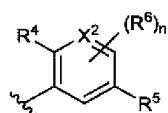


or a pharmaceutically acceptable salt thereof;

wherein

ring A is

[Chem. 2]



or 8 to 10-membered bicyclic which may be substituted by 1 to 6 halogen atoms;

R^1 is selected from the group consisting of (1) a hydrogen atom, (2) C1-8 alkyl, (3) C1-8 haloalkyl, (4) C2-8 alkenyl, (5) C2-8 haloalkenyl, (6) C2-8 alkynyl, (7) C2-8 haloalkynyl and (8) 4 to 6-membered saturated monocyclic heterocycle, wherein 1 or 2 carbon atoms in each of the groups (2) to (7) may be independently replaced by (1) NR^8 , (2) an oxygen atom or (3) a sulfur atom which may be oxidized;

and each of the groups (2) to (8) in R^1 may be substituted by 1 to 6 R^{1-1} s;

R^{1-1} is selected from the group consisting of (1) a deuterium atom, (2) a halogen atom, (3) a hydroxy group, (4) C1-4 alkyl, (5) C1-4 haloalkyl, (6) C1-4 alkoxy, (7) C1-4 haloalkoxy, (8) $-CO-NR^{1-2}R^{1-3}$, (9) $-O-CO-R^{1-4}$, (10) $-SO_2-R^{1-5}$, (11) $-S(=O)(=NR^{1-6})-R^{1-7}$, (12) $-NR^{1-8}R^{1-9}$, (13) cyano and (14) 3 to 6-membered heterocycle;

when there are 2 to 6 R^{1-1} s, a plurality of R^{1-1} s may be the same as or different from each other; R^{1-2} , R^{1-3} , R^{1-4} , R^{1-5} , R^{1-6} , R^{1-7} , R^{1-8} and R^{1-9} is each independently selected from the group consisting of (1) a hydrogen atom, (2) C1-4 alkyl and (3) C1-4 haloalkyl;

 R^2 is (1) C1-4 alkyl or (2) C1-4 haloalkyl;

R^3 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl and (4) C1-4 haloalkyl;

when there are 2 or 3 R^3 s, a plurality of R^3 s may be the same as or different from each other;

R^4 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkoxy and (3) C1-4

haloalkoxy;

R^5 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy and (6) C1-4 haloalkoxy;

R^6 is (1) a hydrogen atom or (2) a halogen atom;

when there are 2 R^6 s, a plurality of R^6 s may be the same as or different from each other;

R^7 is (1) a hydrogen atom or (2) C1-4 alkyl;

R^8 is (1) a hydrogen atom or (2) C1-4 alkyl;

R^9 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl and (4) C1-4 haloalkyl;

R^{10} is (1) a hydrogen atom or (2) a halogen atom;

X^1 is (1) CR^9 or (2) N;

X^2 is (1) CR^{10} or (2) N;

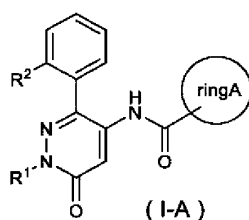
m is an integer of 1 to 3;

n is an integer of 1 or 2.

[Claim 2]

The compound according to claim 1, which is a compound of formula (I-A):

[Chem. 3]

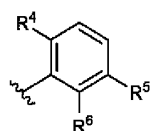


wherein all symbols are as defined in claim 1;
or a pharmaceutically acceptable salt thereof.

[Claim 3]

The compound according to claim 1 or claim 2,
wherein ring A is

[Chem. 4]



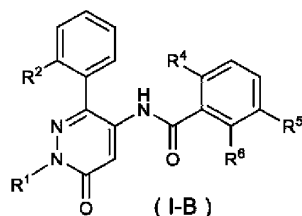
;

and the other symbols are as defined in claim 1;
or a pharmaceutically acceptable salt thereof.

[Claim 4]

The compound according to any one of claims 1 to 3, which is a compound of formula (I-B):

[Chem. 5]



wherein all symbols are as defined in claim 1;
or a pharmaceutically acceptable salt thereof.

[Claim 5]

The compound according to any one of claims 1 to 4,
wherein R^1 is C1-4 alkyl which may be substituted by 1 to 6 R^{1-1A} s;
 R^{1-1A} is selected from the group consisting of (1) a deuterium atom, (2) a hydroxy group, (3) methyl, (4) methoxy, (5) cyano and (6) oxetane;
when there are 2 to 6 R^{1-1A} s, a plurality of R^{1-1A} s may be the same as or different from each other;
and the other symbols are as defined in claim 1;
or a pharmaceutically acceptable salt thereof.

[Claim 6]

The compound according to claim 1, wherein the compound is

- (1) 5-chloro-2-methoxy-N-{1-methyl-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide;
- (2) 5-chloro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxybenzamide;
- (3) 5-chloro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide;
- (4) 5-chloro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxybenzamide;
- (5) 2-fluoro-N-{1-(2-hydroxy-2-methylpropyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (6) 2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-

- pyridazinyl}-5-(trifluoromethyl)benzamide;
- (7) 2-fluoro-N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;
- (8) 5-chloro-2-methoxy-N-{1-(2-methoxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}benzamide;
- (9) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (10) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;
- (11) N-{1-(2-hydroxyethyl)-6-oxo-3-[2-(trifluoromethyl)phenyl]-1,6-dihydro-4-pyridazinyl}-2-methoxy-5-(trifluoromethyl)benzamide;
- (12) 5-(difluoromethyl)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;
- (13) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide;
- (14) 5-(difluoromethoxy)-2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;
- (15) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide;
- (16) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethoxy)benzamide;
- (17) 2-fluoro-N-[3-(2-isopropylphenyl)-1-methyl-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide;
- (18) N-[3-(2-isopropylphenyl)-1-(2-methoxyethyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide;
- (19) 5-(difluoromethoxy)-2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzamide;
- (20) N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-2-methoxy-5-(trifluoromethyl)benzamide;
- (21) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-5-(trifluoromethyl)benzamide;
- (22) 2-fluoro-N-[1-(2-hydroxy-2-methylpropyl)-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]-6-methoxy-3-(trifluoromethyl)benzamide;
- (23) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;
- (24) 2-fluoro-N-{1-[(2R)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-

pyridazinyl}-5-(trifluoromethyl)benzamide;

(25) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethoxy)benzamide;

(26) 2-fluoro-N-{1-[(2S)-2-hydroxypropyl]-3-(2-isopropylphenyl)-6-oxo-1,6-dihydro-4-pyridazinyl}-5-(trifluoromethyl)benzamide;

(27) 2-fluoro-N-(1-(2-hydroxyethyl-2,2-*d*₂)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide;

(28) 2-fluoro-N-(1-(2-hydroxyethyl-2,2-*d*₂)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethoxy)benzamide;

(29) 2-fluoro-N-(1-(2-hydroxyethyl-2-*d*)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide or

(30) 2-fluoro-N-(1-(2-hydroxyethyl-1,1,2,2-*d*₄)-6-oxo-3-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazin-4-yl)-5-(trifluoromethyl)benzamide;

or a pharmaceutically acceptable salt thereof.

[Claim 7]

A pharmaceutical composition comprising a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[Claim 8]

The pharmaceutical composition according to claim 7, which is a TREK-1, TREK-2 or both TREK-1 and TREK-2 inhibitor.

[Claim 9]

The pharmaceutical composition according to claim 7, which is a preventive and/or therapeutic agent for a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction.

[Claim 10]

The pharmaceutical composition according to claim 9, wherein the disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction is a neurological and/or psychiatric disorder.

[Claim 11]

The pharmaceutical composition according to claim 10, wherein the neurological and/or psychiatric disorder is selected from the group consisting of depression, schizophrenia, anxiety

disorders, bipolar disorder, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, 22q11.2 deletion syndrome, neuropathic pain and cerebral infarction.

[Claim 12]

A method for preventing and/or treating a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction, comprising administering an effective amount of the compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof to a mammal.

[Claim 13]

A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof for use in prevention and/or treatment of a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction.

[Claim 14]

Use of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof for manufacturing of a preventive and/or therapeutic agent for a disorder associated with TREK-1, TREK-2 or both TREK-1 and TREK-2 dysfunction.

[Claim 15]

A kit comprising a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, and one or more of:

- (a) at least one agent known to decrease TREK-1 channel activity;
- (b) at least one agent known to decrease TREK-2 channel activity;
- (c) at least one agent known to prevent and/or treat a disorder associated with TREK channel dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal;
- (d) instructions for preventing and/or treating a disorder associated with TREK channel dysfunction in which inhibitors of TREK-1, TREK-2 or both TREK-1 and TREK-2 would offer therapeutic benefit in a mammal; and
- (e) instructions for administering the compound in connection with cognitive behavioral therapy.