

TRPM3 MODULATORS FOR TREATMENT OF PAIN

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to United States Provisional patent application no.
5 63/518,020, filed August 7, 2023, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

Disclosed are methods and uses of TRPM3 modulators and their salts for treating pain-
related disorders. Also disclosed are pharmaceutical compositions comprising TRPM3 modulators,
10 including oral solid molded fast-dispersing dosage forms.

BACKGROUND OF THE INVENTION

Transient receptor potential melastatin 3 (TRPM3) represents a promising pharmacological
target. TRPM3 is expressed in a large subset of small-diameter sensory neurons from dorsal root
15 and trigeminal ganglia, and is involved in heat sensing. The neurosteroid pregnenolone sulfate is a
potent known activator of TRPM3. The neurosteroid pregnenolone sulfate evoked pain in wild type
mice but not in knock-out TRPM3 mice. It was also recently shown that complete Freund's adjuvant
(CFA) induced inflammation and inflammatory pain are eliminated in TRPM3 knock-out mice.

TRPM3 is a calcium channel expressed in the trigeminovascular system, where it drives
20 neurogenic inflammation and sensitization/activation of nociceptors. TRPM3 antagonism normalizes
nociceptor function and, therefore, TRPM3 antagonists could be used as analgesic drugs to
counteract pain, such as inflammatory pain and migraine pain. Additionally, TRPM3 gene
mutations/variants are associated with migraine risk and pain sensitivity in humans.

A few TRPM3 antagonists are known in the art. However, there is still a great medical need
25 for novel, alternative and/or better therapeutics for the prevention or treatment of TRPM3
mediated disorders, more in particular for pain such as inflammatory pain and migraine pain.
Therapeutics with good potency on a certain type of pain, fast onset of action, low level or no side-
effects (such as no possibilities for addiction as with opiates, no toxicity) and/or good or better
pharmacokinetic or -dynamic properties are highly needed. Additionally, these therapeutics need to
30 be delivered in a fast-acting form which can be tolerated by individuals experiencing pain or
migraine. Migraine sufferers often have difficulty consuming traditional oral dosages due to nausea
and aversion to consuming food or liquids during an attack. In an aspect, the present disclosure

provides for oral solid molded fast-dispersing and dissolving dosage forms of TRPM3 modulators. Such forms can advantageously be taken without the need for water or the need to swallow a pill.

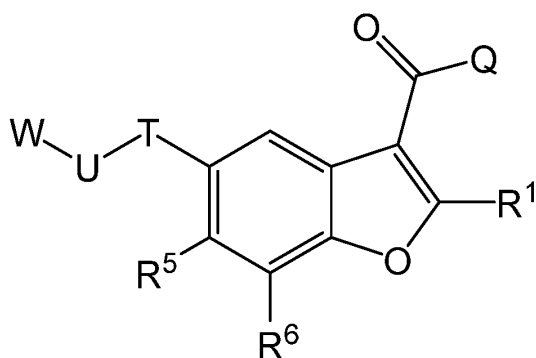
SUMMARY OF THE INVENTION

5 Provided are pharmaceutical compositions including a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

Also provided are methods of treating pain in a patient in need thereof, including
10 inflammatory pain and migraine pain, including administering to the patient a pharmaceutical composition including a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

In an embodiment, provided for is a pharmaceutical composition comprising a
15 pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

In an embodiment, the TRPM3 modulator is a compound according to Formula I:



, or a pharmaceutically acceptable salt

20 thereof, wherein:

R¹ is -H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, cyclopropyl, or -(C=O)NH₂;

Q is -O-R² or -N-R^{3a}R^{3b};

R² is -H, or C₁-C₃ alkyl optionally substituted with one or more of -NH₂, carbonyl, carboxylic acid, hydroxyl, C₃-C₇ cycloalkyl, or C₃-C₇ heterocycloalkyl;

25 R^{3a} is -H, C₃-C₇ cycloalkyl, C₃-C₇ heterocycloalkyl, phenyl, C₅-C₇ heteroaryl, C₁-C₆ alkyl, or C₁-C₆ heteroalkyl, optionally substituted with one or more of carbonyl, halogen, cyano, C₁-C₅ alkyl or C₁-C₅

heteroalkyl, said C₁-C₅ alkyl or C₁-C₅ heteroalkyl optionally substituted with one or more of -NH₂, carbonyl, carboxylic acid, hydroxyl, cyano, or halogen; and R^{3b} is -H or C₁-C₃ alkyl; or

R^{3a} and R^{3b} together form a C₃-C₇ cycloalkyl or C₅-C₇ heteroaryl, optionally substituted with one or more of -NH₂, carbonyl, carboxylic acid, hydroxyl, cyano, halogen, C₁-C₃ alkyl, or C₁-C₃

5 haloalkyl;

wherein T is -O- and U is CR^{4a}R^{4b}, or T is CR^{4a}R^{4b} and U is -O-;

R^{4a} and R^{4b} are independently -H or C₁-C₃ alkyl;

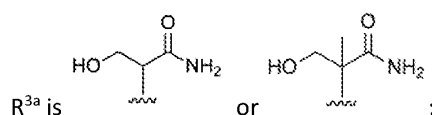
W is C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ heterocycloalkyl, phenyl, or C₅-C₁₀ heteroaryl, optionally substituted with halogen, carbonyl, hydroxyl, C₁-C₃ alkyl or C₁-C₃ heteroalkyl, said C₁-C₃ alkyl or C₁-C₃ heteroalkyl optionally substituted with one or more of halogen, carbonyl, hydroxyl, azetidine, oxetane, or cyclopropyl; and

R⁵ and R⁶ are independently -H, halogen, cyano, C₁-C₃ alkyl, or C₁-C₃ haloalkyl.

In an embodiment, the TRPM3 modulator is a compound according to Formula I, wherein:

R¹ is -CH₃ optionally substituted with F;

15 Q is -N-R^{3a}R^{3b};



R^{3b} is -H;

R⁵ and R⁶ are -H;

T is -O- and U is -CH₂-;

20 W is a 5-membered heteroaryl selected from the group consisting of oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, and imidazolyl, or a 6-membered heteroaryl selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, wherein the 5-membered heteroaryl and 6-membered heteroaryl are optionally substituted with -F, -Cl, C₁-C₃ alkyl optionally substituted with -F, or C₁-C₃ alkoxy optionally substituted with -F.

25 In an embodiment, the TRPM3 modulator is a compound selected from the group consisting of:

(S)-N-(1-amino-2-methyl-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;

(S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide; and

30 (S)-N-(1-amino-2-methyl-3-hydroxy-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide.

In an embodiment, the TRPM3 modulator is a compound selected from those presented in Table 1 herein.

In an embodiment, the pharmaceutical composition further comprises gelatin as a carrier.

In an embodiment, the gelatin carrier comprises fish gelatin.

5 In an embodiment, the pharmaceutical composition further comprises a filler.

In an embodiment, the filler comprises a sugar alcohol. In an embodiment, the filler is mannitol.

10 In an embodiment, the pharmaceutical composition further comprises from about 70-80 weight% of the TRPM3 modulator, about 10-20 weight% gelatin, about 10-20 weight% of filler, and optionally 0.1-5.0 weight% of a flavorant.

In an embodiment, the pharmaceutical composition is in the form of a unit dosage form, and comprises about 100 mg to about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

15 In an embodiment, the pharmaceutical composition comprises about 100 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the pharmaceutical composition comprises about 150 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the pharmaceutical composition comprises about 200 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

20 In an embodiment, the pharmaceutical composition comprises about 250 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the pharmaceutical composition comprises about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

25 In an embodiment, the pharmaceutical composition is capable of disintegrating or dispersing within an interval selected from 1 to 60 seconds, 1 to 30 seconds, 1 to 10 seconds, and 2 to 8 seconds, after being placed in contact with a fluid. In an embodiment, the fluid comprises saliva.

30 In an embodiment, provided for is a method of treating pain in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

In an embodiment, provided for is a use of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator,

or a pharmaceutically acceptable salt thereof for the treatment of pain, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

In an embodiment, provided for is a use of a pharmaceutical composition for the manufacture of a medicament for the treatment of pain, wherein the pharmaceutical composition
5 comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, and wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

In an embodiment, the oral solid molded fast-dispersing dosage form is administered orally to the patient to dissolve in the oral cavity of the patient.

10 In an embodiment, the oral solid molded fast-dispersing dosage form is administered without coadministration of water or other fluid.

In an embodiment, the administered pharmaceutical composition further comprises gelatin as a carrier.

In an embodiment, the administered pharmaceutical composition further comprises
15 mannitol as a filler.

In an embodiment, the administered pharmaceutical composition comprises from about 70-80 weight% of the TRPM3 modulator, about 10-20 weight% fish gelatin, about 10-20 weight% of a filler, and 0.1-5.0 weight% of a flavorant.

In an embodiment, the administered pharmaceutical composition is in the form of a unit
20 dosage form comprising about 100 mg to about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the administered pharmaceutical composition comprises about 100 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the administered pharmaceutical composition comprises about 150 mg
25 of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the administered pharmaceutical composition comprises about 200 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the administered pharmaceutical composition comprises about 250 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

30 In an embodiment, the administered pharmaceutical composition comprises about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

In an embodiment, the administered pharmaceutical composition is capable of disintegrating or dispersing within an interval selected from 1 to 60 seconds, 1 to 30 seconds, 1 to 10

seconds, and 2 to 8 seconds, after being placed in contact with a fluid. In an embodiment, the fluid comprises saliva.

Various further embodiments should be evident based upon the following disclosure.

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DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure. 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 to which this disclosure belongs. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting.

As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present invention.

The articles "a" and "an" refer to one or to more than one (i.e., to at least one) of the grammatical object of the article unless the context clearly indicates otherwise. By way of example, "an element" means one element or more than one element.

The term "about" refers to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" can mean a range of up to 1%, 5%, 10% or 20% (i.e., $\pm 10\%$ or $\pm 20\%$) depending on the context of the application. For example, about 3 mg can include any number between 2.7 mg and 3.3 mg (for 10%) or between 2.4 mg and 3.6 mg (for 20%). Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" should be assumed to be within an acceptable error range for that particular value or composition.

The term "administering" refers to the physical introduction of a composition including a therapeutic agent to a subject, using any of the various methods and delivery systems known to

those skilled in the art. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods and can be a therapeutically effective dose or a subtherapeutic dose.

5 The term "AUC" (area under the curve) refers to a total amount of drug absorbed or exposed to a subject. Generally, AUC may be obtained from mathematical method in a plot of drug concentration in the subject over time until the concentration is negligible. The term "AUC" could also refer to partial AUC at specified time intervals.

10 The term " C_{max} " refers to a maximum concentration of a drug in blood, serum, a specified compartment or test area of a subject between administration of a first dose and administration of a second dose. The term C_{max} could also refer to dose normalized ratios, if specified.

The term "dosing interval," refers to the amount of time that elapses between multiple doses of a formulation disclosed herein being administered to a subject. Dosing interval can thus be indicated as ranges.

15 The term "dosing frequency" refers to the frequency of administering doses of a formulation disclosed herein in a given time. Dosing frequency can be indicated as the number of doses per a given time, *e.g.*, once a week or once in two weeks.

20 The terms "in combination with" and "in conjunction with" refer to administration of one treatment modality in addition to another treatment modality. As such, "in combination with" or "in conjunction with" refers to administration of one treatment modality before, during, or after administration of the other treatment modality to the subject.

25 The term "pharmaceutically acceptable salt" refers to a salt form of one or more of the compounds described herein which are typically presented to increase the solubility of the compound in the gastric or gastroenteric juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids, where applicable. Suitable salts include, for example, those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids and bases well known in the pharmaceutical art.

30 The terms "subject" and "patient" refer any human or nonhuman animal. The term "nonhuman animal" includes, but is not limited to, vertebrates such as nonhuman primates, sheep, dogs, and rodents such as mice, rats and guinea pigs. In some embodiments, the subject is a human. The terms, "subject" and "patient" are used interchangeably herein.

The terms “effective amount”, “therapeutically effective amount”, “therapeutically effective dosage” and “therapeutically effective dose” of an agent (also sometimes referred to herein as a “drug”) refers to any amount of the agent that, when used alone or in combination with another agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or relief from impairment or disability due to the disease affliction. The therapeutically effective amount of an agent can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in in vitro assays.

A “TRPM3 modulator” targets the TRPM3 protein to modulate its activity. A TRPM3 modulator may be an “antagonist” or inhibitor of the TRPM3 ion channel. An “antagonist” refers to a compound capable of producing, depending on the circumstance, a functional antagonism of the TRPM3 ion channel, including competitive antagonists, non- competitive antagonists, desensitizing agonists, and partial agonists.

The term “ T_{max} ” refers to a time or period after administration of a drug when the maximum concentration (C_{max}) is reached in blood, serum, a specified compartment or test area of a subject.

The term “treatment” refers to any treatment of a condition or disease in a subject and may include: (i) preventing the disease or condition from occurring in the subject which may be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease or condition, *i.e.*, arresting its development; relieving the disease or condition, *i.e.*, causing regression of the condition; (iii) ameliorating or relieving the conditions caused by the disease, *i.e.*, symptoms of the disease; (iv) preventing recurrence or attacks of a known disease or condition such that the frequency of recurrence or attacks is lessened; and/or (v) preventing, to some degree, the severity of recurrence or attacks of a known disease or condition. Treatment could be used in combination with other standard therapies or alone. Treatment or “therapy” of a subject also includes any type of intervention or process performed on, or the administration of an agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication or condition, or biochemical indicia associated with a disease.

With respect to pain, “treatment” is an approach for obtaining beneficial or desired results with a subject. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: improvement in any aspect of pain including lessening severity, alleviation of pain intensity, and other associated symptoms, reducing frequency of

recurrence, increasing the quality of life of those suffering from pain, decreasing dose of other medications required to treat pain and reducing the number of pain days per month.

In an embodiment, provided is a pharmaceutical composition including a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

As used herein, the term “alkyl” or refers to straight and branched carbon chains. The term may be preceded by a range of carbon atoms (e.g., C₁-C₁₀ alkyl) which means that the straight or branched chain may include from 1 to 10 carbon atoms, not accounting for those which may also be present in a substituent to the carbon chain at any position. It should be appreciated that while a range of atom numbers is given for the purposes of defining embodiments of the present invention, a small number of additional atoms outside of the range (such as one, two, three, or four) may be contemplated in other embodiments of the present invention. Alkyl groups may also contain one or more (e.g., one, two, or three) unsaturations such as double or triple bonds, which may be alternatively referred to as alkenyl or alkynyl groups, respectively. Alkyl groups may generally be substituted at one or more positions to replace a hydrogen atom with a different atom or constituent atom of another group. One example of a substituted alkyl group is “hydroxyalkyl” which contains one or more hydroxyl (-OH) substituents. As would be apparent from the context, in some cases “alkyl” is also intended to encompass internal linking groups which bridge two substituents. Such internal alkyl linking groups may be alternatively referred to as alkylene groups, which are bivalent saturated aliphatic radicals such as in the context of linking groups. An example of an alkylene group is methylene, i.e., -CH₂-.

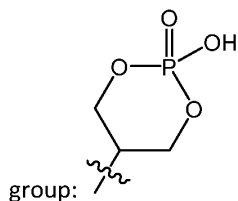
As used herein, the term “haloalkyl” refers to an “alkyl” as defined above with one or more halogen substituents. A “haloalkyl” may generally be substituted with halogens such as -F, -Cl, -Br, or -I. In some embodiments, the “haloalkyl” has one or more -F or -Cl substituents. Also contemplated are “haloalkyls” having a mono, di, or tri-substituted terminal carbon atom, such as in the groups -CF₃, -CF₂H, and -CFH₂. A “haloalkyl” may contain such halogen substituents at one or more positions, such as at one positions, two positions, or three positions.

As used herein, the term “heteroalkyl” refers to straight and branched carbon chains including at least one heteroatom independently selected from S, N, or O. For example, “C₂-C₁₀ heteroalkyl” means linear or branched chain of two to ten atoms where at least one of the atoms is a heteroatom (such as S, N, or O) while the other atoms are carbon. Branched groups may include one or more C or heteroatoms (e.g., methyl, ethyl, propyl, carbonyl, hydroxyl, amine, etc.). In some embodiments, a heteroalkyl may contain one, two, three, or four heteroatoms. It should be

appreciated that while a range of atom numbers is given for the purposes of defining embodiments of the present invention, a small number of additional atoms outside of the range (such as one, two, three, or four) may be contemplated in other embodiments of the present invention. Heteroalkyl groups may also contain one or more (e.g., one, two, or three) unsaturations such as double or triple bonds, which may be alternatively referred to as heteroalkenyl or heteroalkynyl groups, respectively. Heteroalkyl groups may generally be substituted at one or more positions to replace a hydrogen atom or lone electron pair with a different atom or constituent atom of another group. One specific type of heteroalkyl is an "alkoxy" group containing one or more oxygen atoms in the chain. As would be apparent from the context, in some cases "heteroalkyl" is also intended to encompass internal linking groups which bridge two substituents.

As used herein, the term "cycloalkyl" refers to one or more rings of carbon atoms. For example, "C₄-C₇ cycloalkyl" means one or more rings having between 4 to 7 carbon atoms total (by way of non-limiting example, cyclobutyl having 4 carbon atoms, cyclohexyl having 6 carbon atoms, norbornane having 7 carbon atoms as a bridged ring system, and spiro[2.3]hexane having 6 carbon atoms as a spiro system). It should be appreciated that while a range of atom numbers is given for the purposes of defining embodiments of the present invention, a small number additional atoms outside of the range (such as one, two, three, or four) may be contemplated in other embodiments of the present invention. Cycloalkyl groups may also contain one or more (e.g., one, two, or three) unsaturations such as double bonds. Cycloalkyl groups may generally be substituted at one or more positions to replace a hydrogen atom with a different atom or constituent atom of another group. As would be apparent from the context, in some cases "cycloalkyl" is also intended to encompass internal linking groups which bridge two substituents.

As used herein, the term "heterocycloalkyl" refers to one or more rings including at least one heteroatom independently selected from S, N, or O. For example, C₄-C₇ heterocycloalkyl means one or more rings having between 4 and 7 atoms total, where at least one atom is a heteroatom other than C, such as S, N, or O. In some embodiments, a heterocycloalkyl may contain one, two, three, or four heteroatoms. It should be appreciated that while a range of atom numbers is given for the purposes of defining embodiments of the present invention, a small number additional atoms outside of the range (such as one, two, three, or four) may be contemplated in other embodiments of the present invention. Heterocycloalkyl groups may also contain phosphorous such as in the



. Heterocycloalkyl groups may also contain one or more (e.g., one, two, or

three) unsaturations such as double bonds. Heterocycloalkyl groups may generally be substituted at one or more positions to replace a hydrogen atom or lone electron pair with a different atom or constituent atom of another group. As would be apparent from the context, in some cases “heterocycloalkyl” is also intended to encompass internal linking groups which bridge two substituents.

As used herein, the term “heteroaryl” means an aromatic ring system including at least one heteroatom independently selected from S, N, or O. Included are unsaturated, aromatic monocyclic rings and unsaturated, polycyclic rings. For example, C₅-C₁₀ heteroaryl means one or more rings having between 5 and 10 atoms total, where at least one atom is a heteroatom other than C, such as S, N, or O. In some embodiments, a heteroaryl may contain one, two, three, or four heteroatoms. It should be appreciated that while a range of atom numbers is given for the purposes of defining embodiments of the present invention, a small number additional atoms outside of the range (such as one, two, three, or four) may be contemplated in other embodiments of the present invention. Heteroaryl groups may generally be substituted at one or more positions to replace a hydrogen atom or lone electron pair with a different atom or constituent atom of another group. As would be apparent from the context, in some cases “heteroaryl” is also intended to encompass internal linking groups which bridge two substituents.

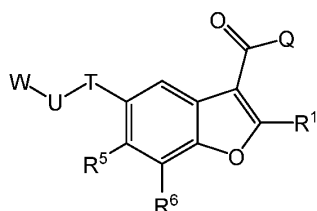
As used herein, the term “compound” includes all enantiomeric forms, diastereomeric forms, stereoisomers, salts, solvates, and esters thereof. Also encompassed are all isotopic variants having natural or enriched isotopic content such as deuterated compounds or other isotopically enriched forms.

In various embodiments, a number of atoms in a particular group or substituent is denoted by a range (e.g. C₁-C₁₀ alkyl). It is specifically intended that each and every individual numbers of atoms in the range are contemplated, as are each and every sub-combination of numbers within the ranges. For example “C₁-C₁₀” in the context of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, heteroaryl, and others would include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ groups, as well as sub-combinations such as C₁-C₉, C₁-C₈, C₁-C₇, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₂-C₁₀, C₂-C₉, C₂-C₈, C₂-C₇, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₃-C₁₀, C₃-C₉, C₃-C₈, C₃-C₇, C₃-C₆, C₃-C₅, C₃-C₄, C₄-C₁₀, C₄-C₉, C₄-C₈, C₄-C₇, C₄-C₆, C₄-C₅, C₅-C₁₀, C₅-C₉, C₅-C₈, C₅-C₇, C₅-C₆, C₆-C₁₀, C₆-C₉, C₆-C₈, C₆-C₇, C₇-C₁₀, C₇-C₉, C₇-C₈, C₈-C₁₀, C₈-C₉, and C₉-C₁₀. Other ranges given herein likewise include the individual numbers and all sub-combinations.

Examples of TRPM3 modulators are disclosed in International Application No. PCT/EP2021/082853 filed November 24, 2023 and published as WO 2022/112345 A1 on June 2, 2022, and International Application No. PCT/EP2021/082865 filed November 24, 2023 and published as WO 2022/112352 A1 on June 2, 2022, all of which applications and publications are incorporated

herein in their entireties by reference. Examples of TRPM3 modulators are also disclosed in International Application No. PCT/EP2023/06399 filed May 25, 2023, International Application No. PCT/EP2023/063994 filed May 25, 2023, International Application No. PCT/EP2023/063996 filed May 25, 2023, International Application No. PCT/EP2023/063997 filed May 25, 2023, International Application No. PCT/US2023/067443 filed May 25, 2023, International Application No. PCT/US2023/067446 filed May 25, 2023, and International Application No. PCT/US2023/067448 filed May 25, 2023, all of which applications are incorporated herein in their entireties by reference. It should be appreciated that, among other teachings, these disclosures contain synthetic methodologies upon which a person of skill in the art could rely upon to prepare the TRPM3 modulators disclosed herein.

In an embodiment, the TRPM3 modulator is a compound according to Formula I:



, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is -H, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, cyclopropyl, or $-(C=O)NH_2$;

Q is $-O-R^2$ or $-N-R^{3a}R^{3b}$;

R^2 is -H, or C_1 - C_3 alkyl optionally substituted with one or more of $-NH_2$, carbonyl, carboxylic acid, hydroxyl, C_3 - C_7 cycloalkyl, or C_3 - C_7 heterocycloalkyl;

R^{3a} is -H, C_3 - C_7 cycloalkyl, C_3 - C_7 heterocycloalkyl, phenyl, C_5 - C_7 heteroaryl, C_1 - C_6 alkyl, or C_1 - C_6 heteroalkyl, optionally substituted with one or more of carbonyl, halogen, cyano, C_1 - C_5 alkyl or C_1 - C_5 heteroalkyl, said C_1 - C_5 alkyl or C_1 - C_5 heteroalkyl optionally substituted with one or more of $-NH_2$, carbonyl, carboxylic acid, hydroxyl, cyano, or halogen; and R^{3b} is -H or C_1 - C_3 alkyl; or

R^{3a} and R^{3b} together form a C_3 - C_7 cycloalkyl or C_5 - C_7 heteroaryl, optionally substituted with one or more of $-NH_2$, carbonyl, carboxylic acid, hydroxyl, cyano, halogen, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl;

wherein T is $-O-$ and U is $CR^{4a}R^{4b}$, or T is $CR^{4a}R^{4b}$ and U is $-O-$;

R^{4a} and R^{4b} are independently -H or C_1 - C_3 alkyl;

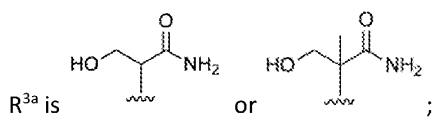
W is C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} heterocycloalkyl, phenyl, or C_5 - C_{10} heteroaryl, optionally substituted with halogen, carbonyl, hydroxyl, C_1 - C_3 alkyl or C_1 - C_3 heteroalkyl, said C_1 - C_3 alkyl or C_1 - C_3 heteroalkyl optionally substituted with one or more of halogen, carbonyl, hydroxyl, azetidine, oxetane, or cyclopropyl; and

R^5 and R^6 are independently -H, halogen, cyano, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl.

In another embodiment of Formula I, or a pharmaceutically acceptable salt thereof:

R¹ is -CH₃ optionally substituted with F;

Q is -N-R^{3a}R^{3b};



R^{3b} is -H;

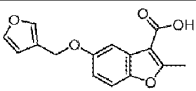
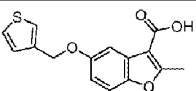
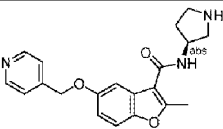
5 T is -O- and U is -CH₂-;

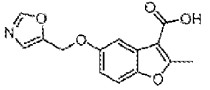
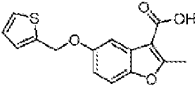
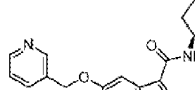
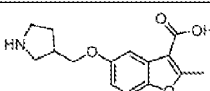
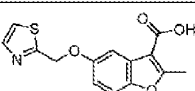
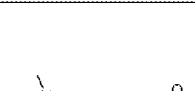
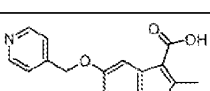
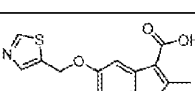
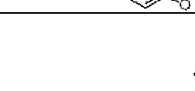
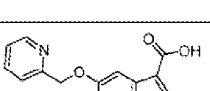
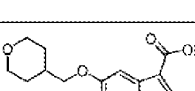
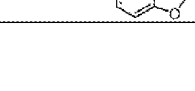
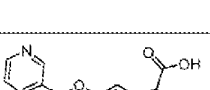
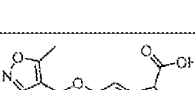
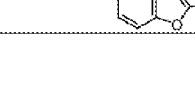
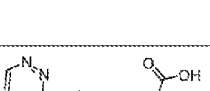
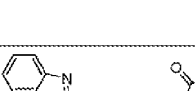
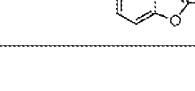
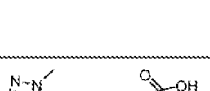
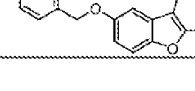
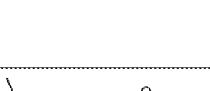
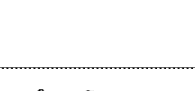
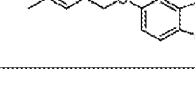
W is a 5-membered heteroaryl selected from the group consisting of oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, and imidazolyl, or a 6-membered heteroaryl selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, wherein the 5-membered heteroaryl and 6-membered heteroaryl are optionally substituted with -F, -Cl, C₁-C₃ alkyl optionally substituted with -

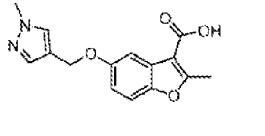
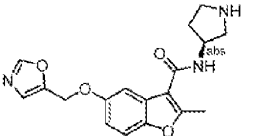
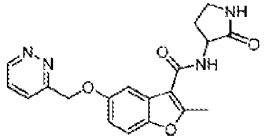
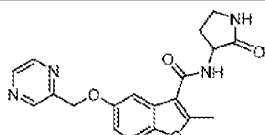
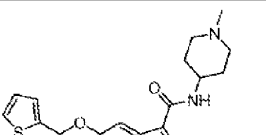
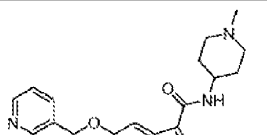
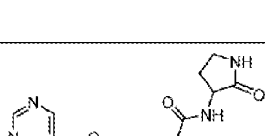
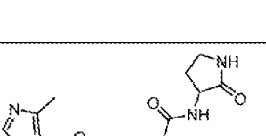
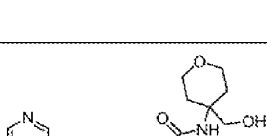
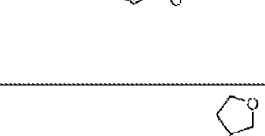
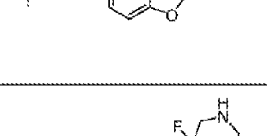
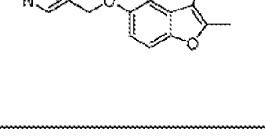
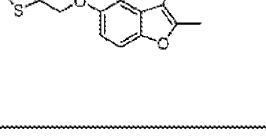
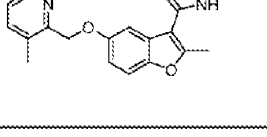
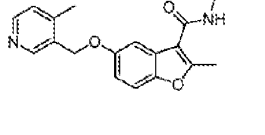
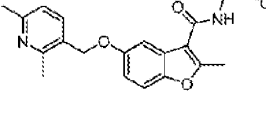
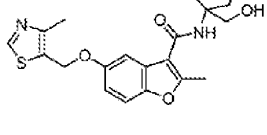
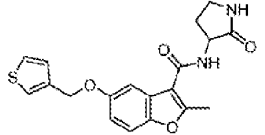
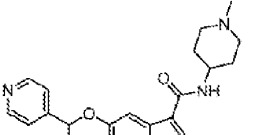
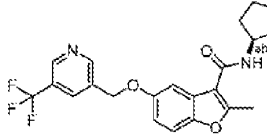
10 F, or C₁-C₃ alkoxy optionally substituted with -F.

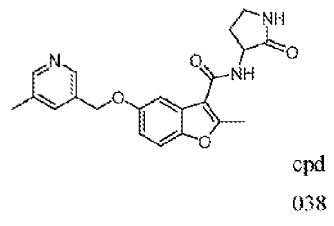
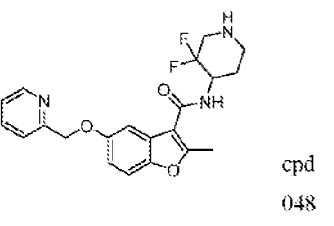
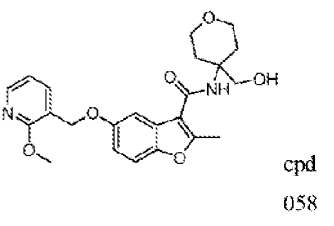
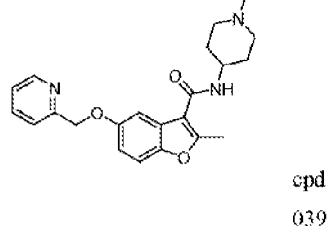
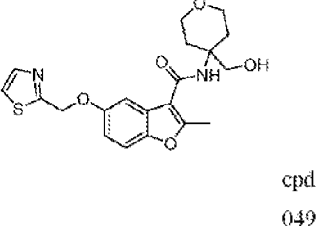
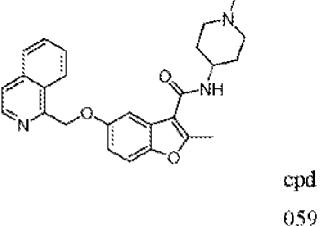
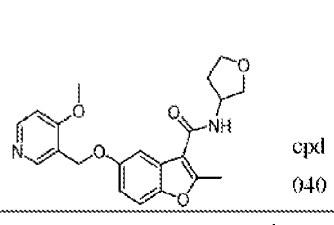
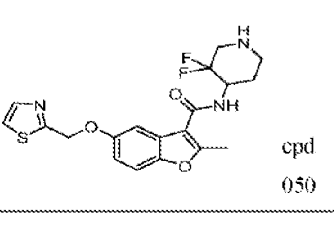
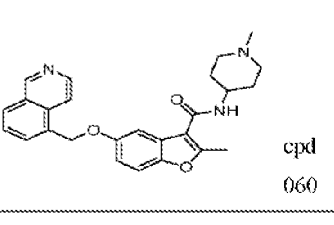
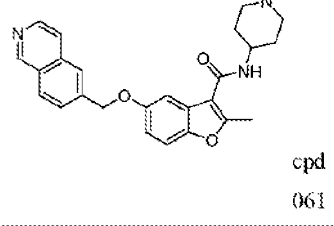
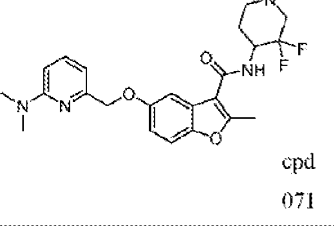
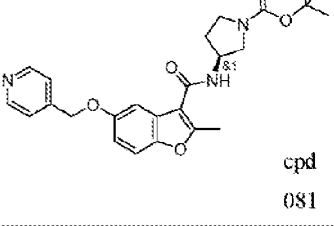
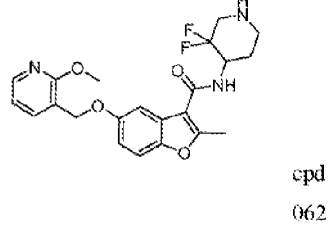
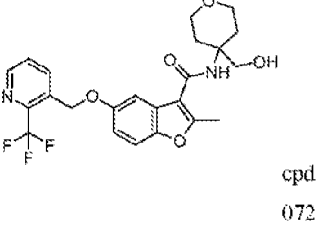
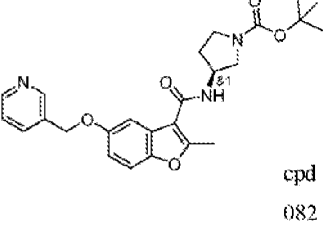
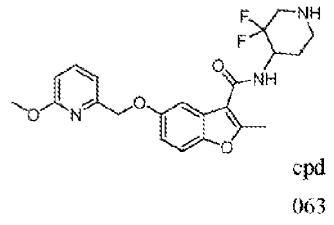
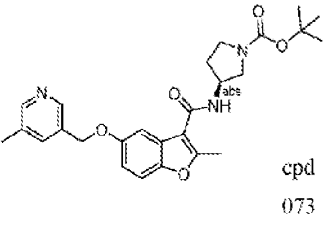
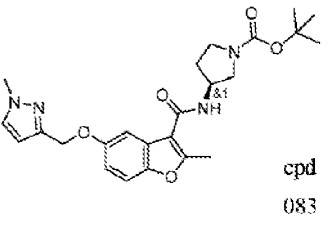
In an embodiment, the TRPM3 modulator may be represented by any of the following structures of Table 1:

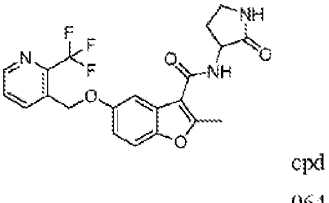
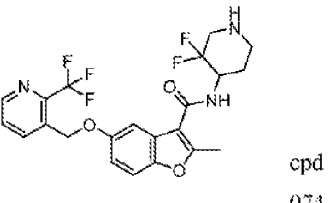
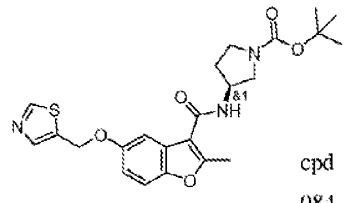
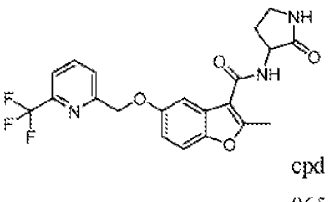
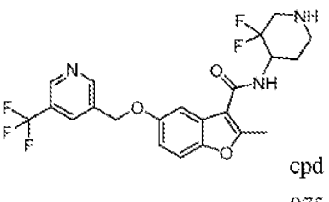
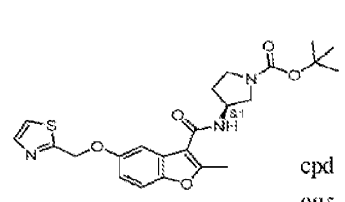
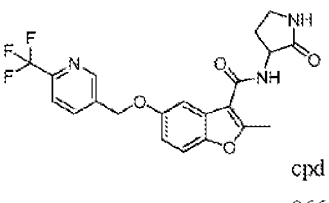
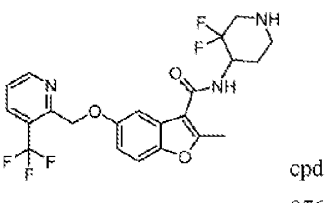
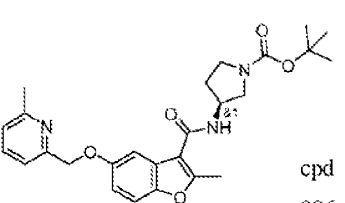
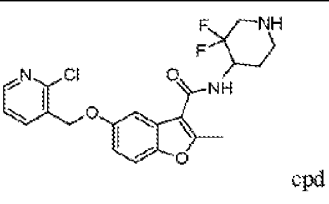
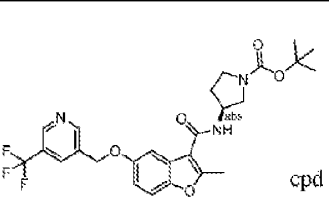
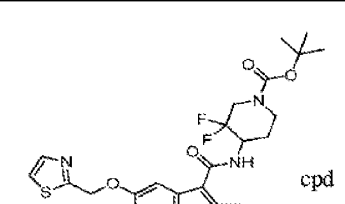
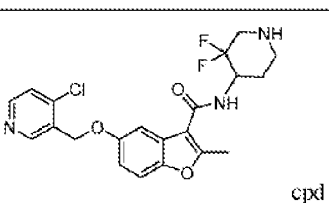
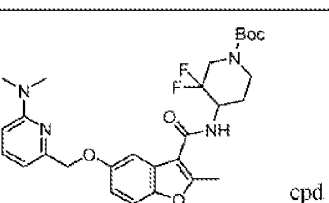
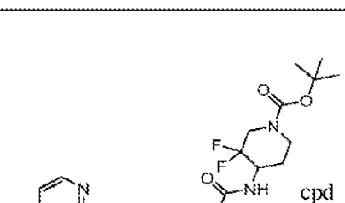
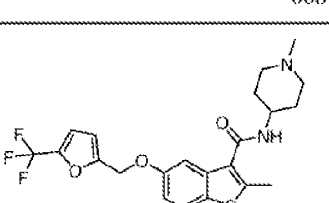
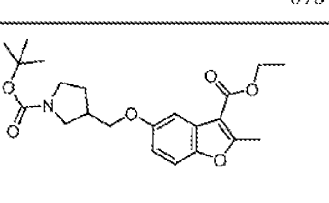
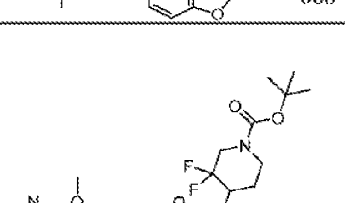
Table 1: Exemplary TRPM3 Modulators.

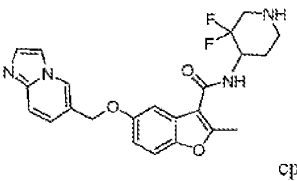
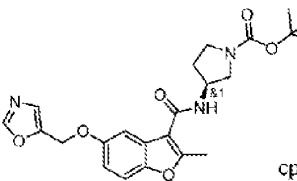
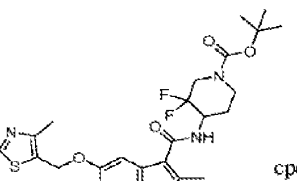
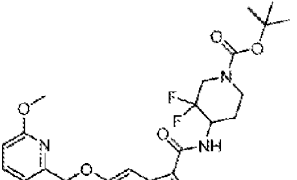
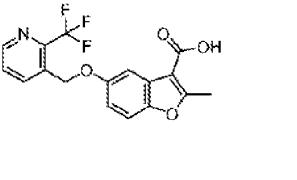
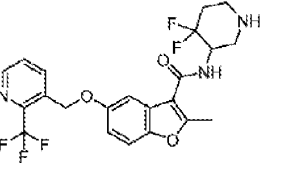
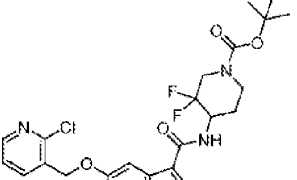
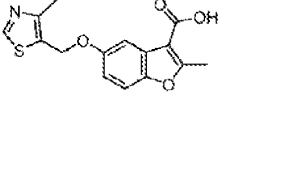
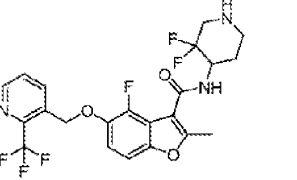
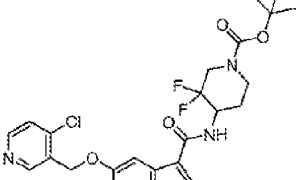
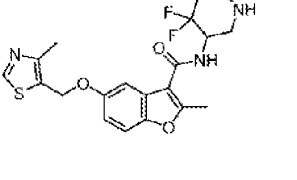
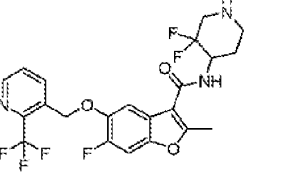
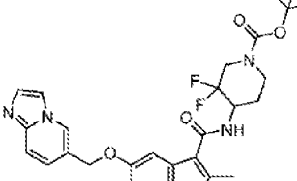
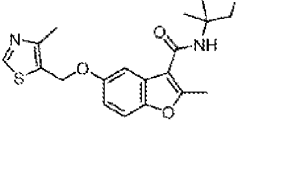
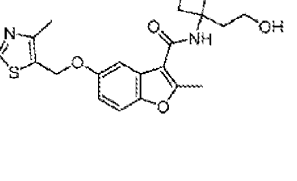
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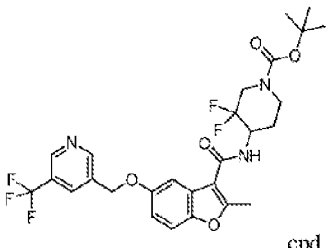
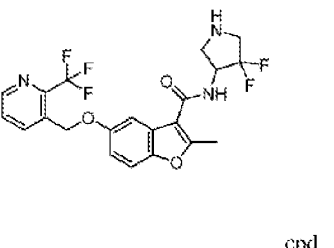
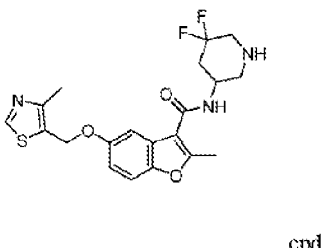
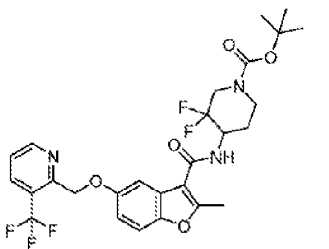
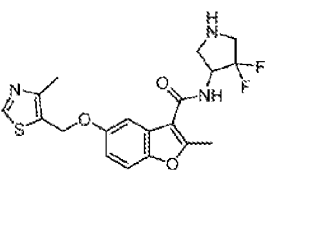
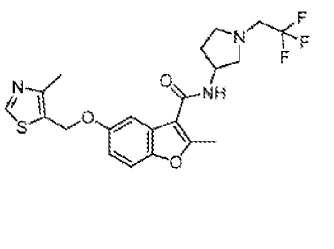
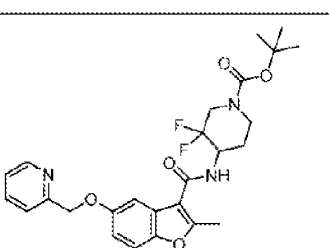
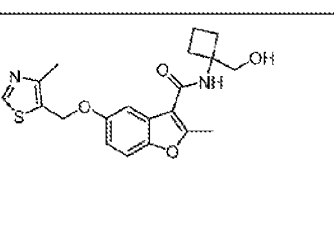
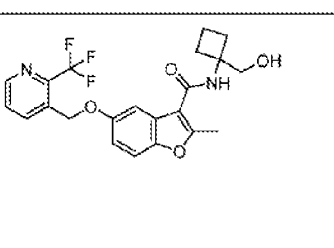
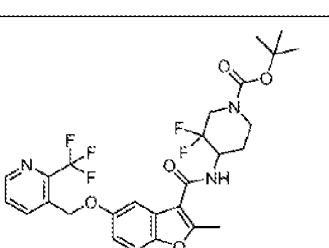
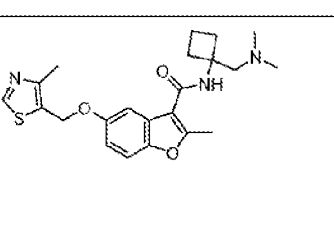
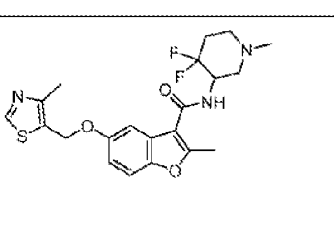
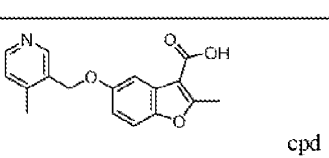
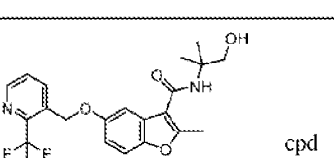
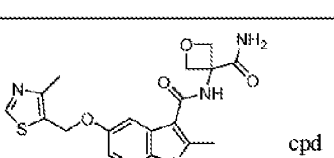
		
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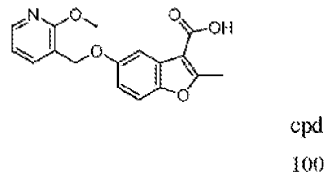
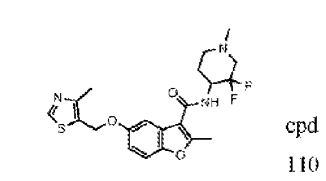
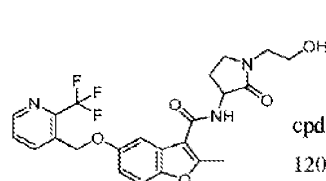
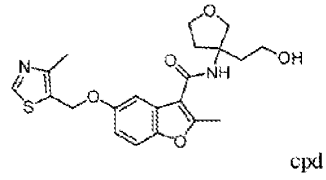
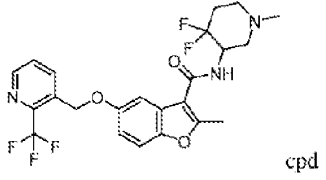
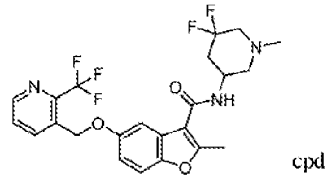
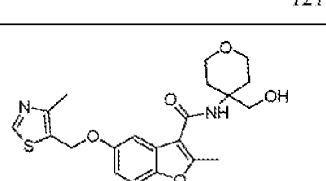
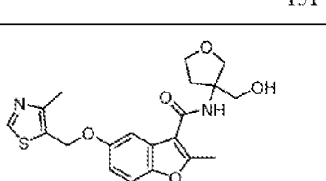
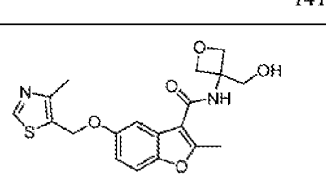
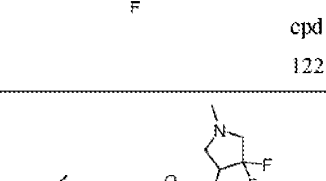
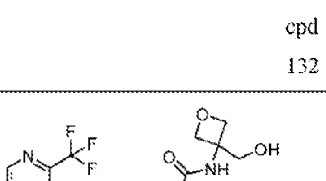
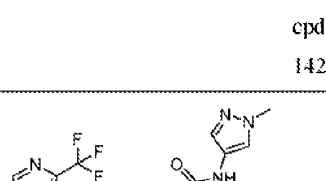
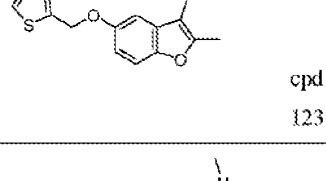
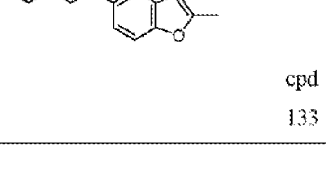
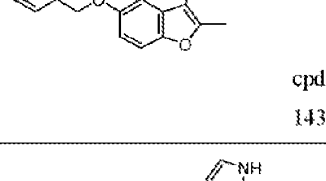
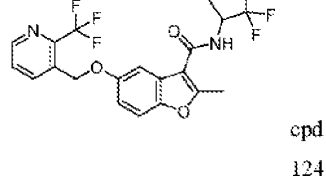
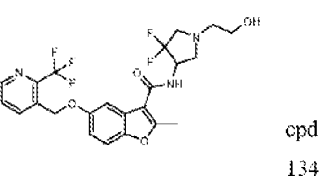
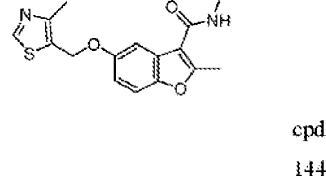
		
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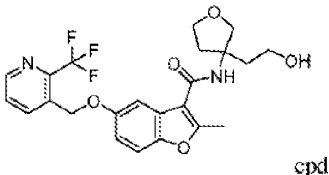
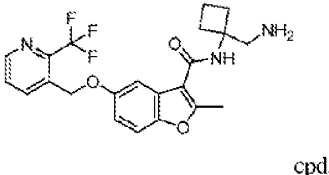
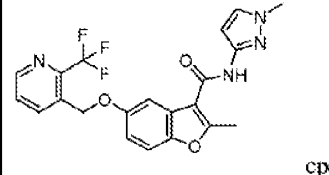
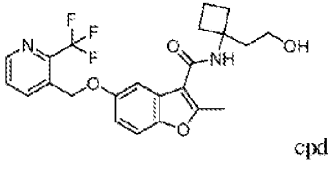
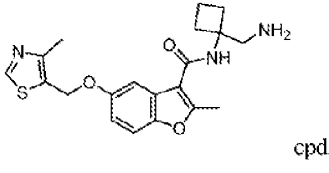
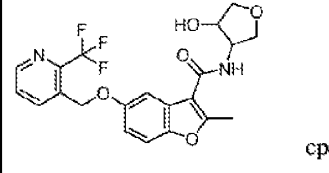
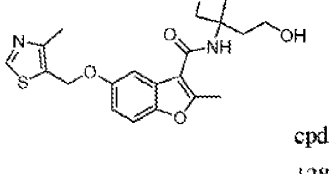
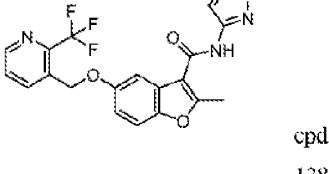
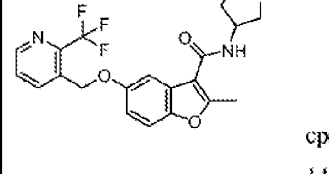
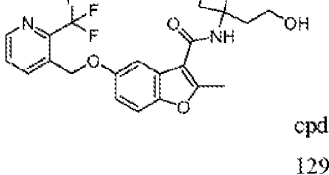
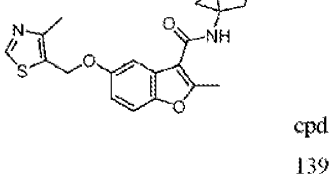
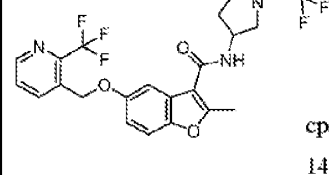
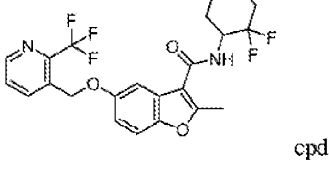
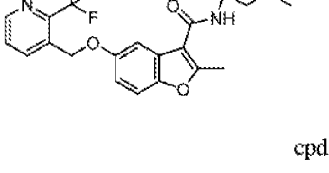
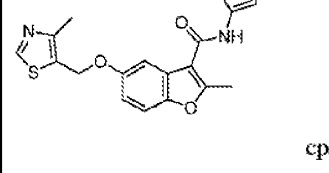
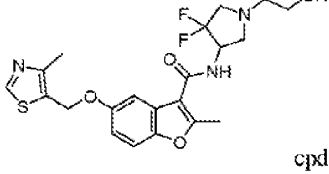
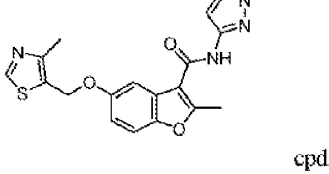
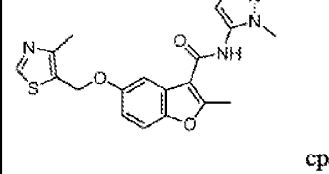
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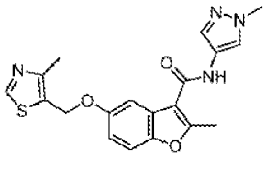
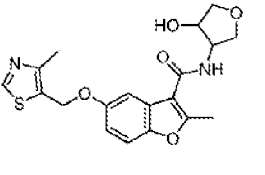
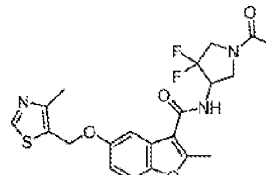
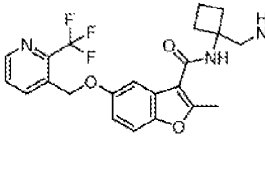
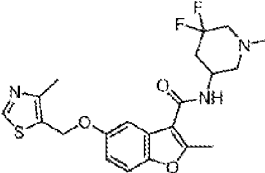
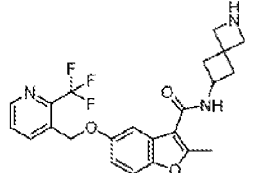
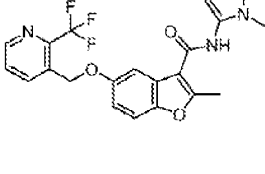
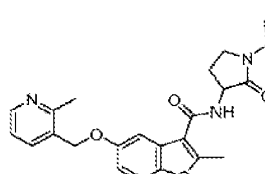
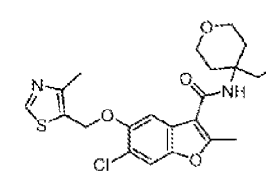
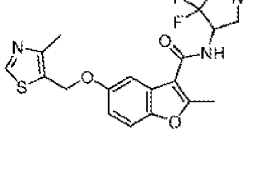
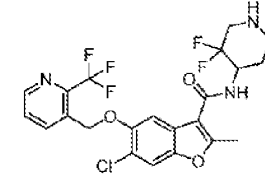
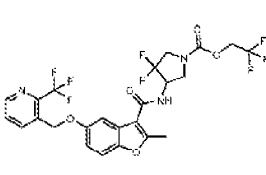
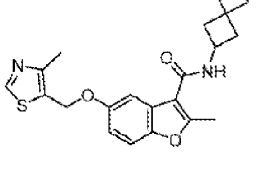
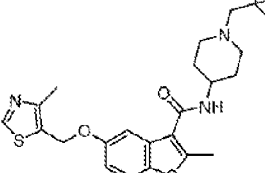
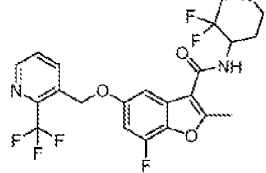
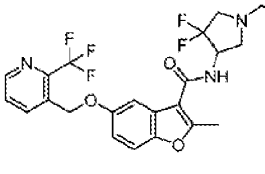
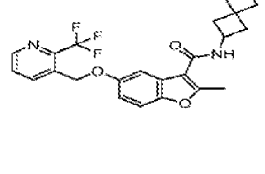
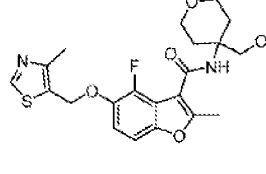
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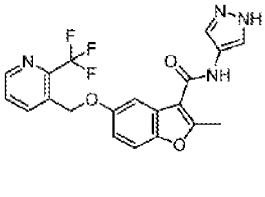
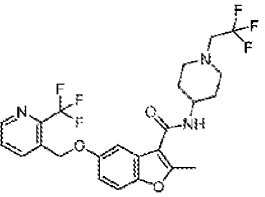
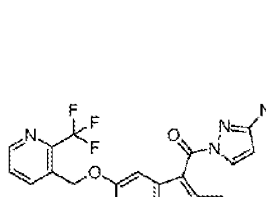
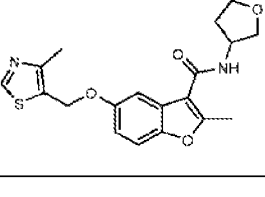
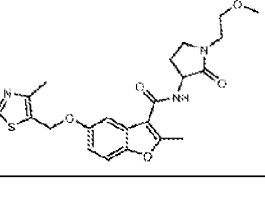
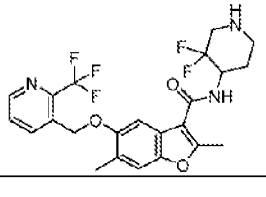
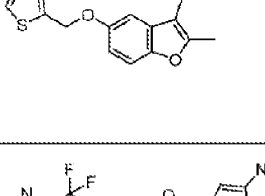
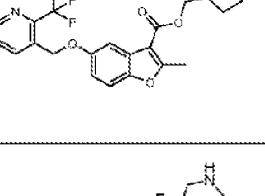
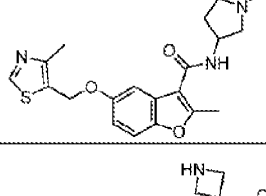
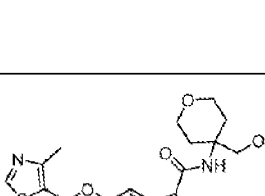
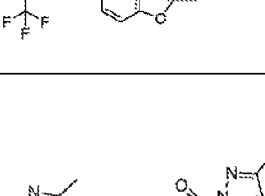
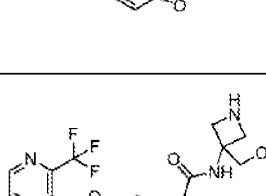
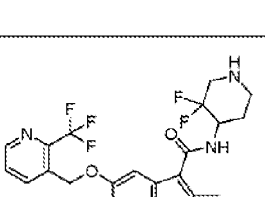
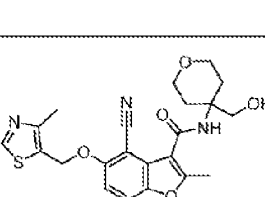
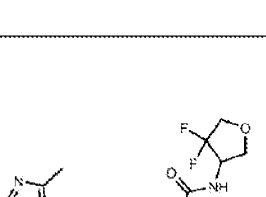
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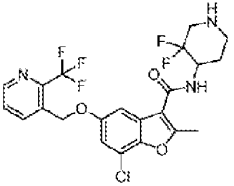
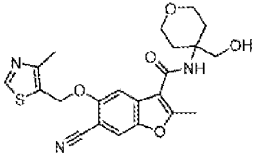
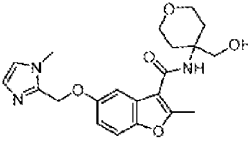
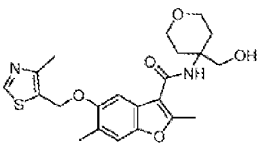
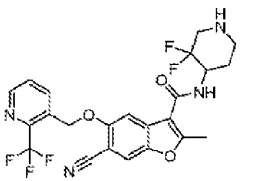
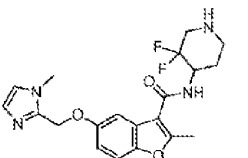
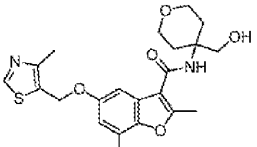
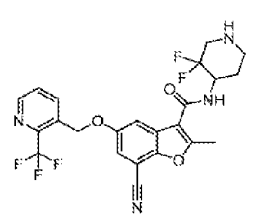
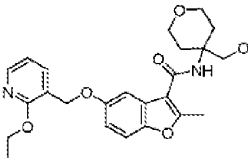
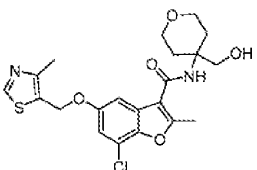
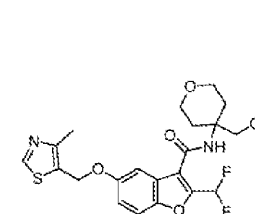
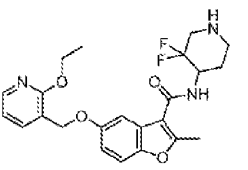
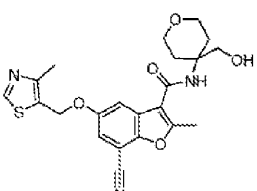
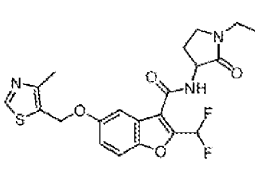
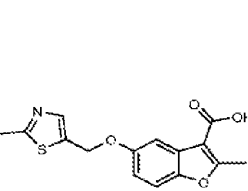
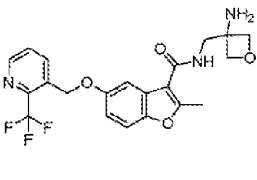
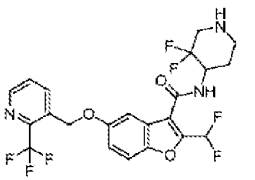
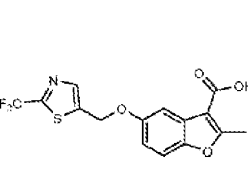
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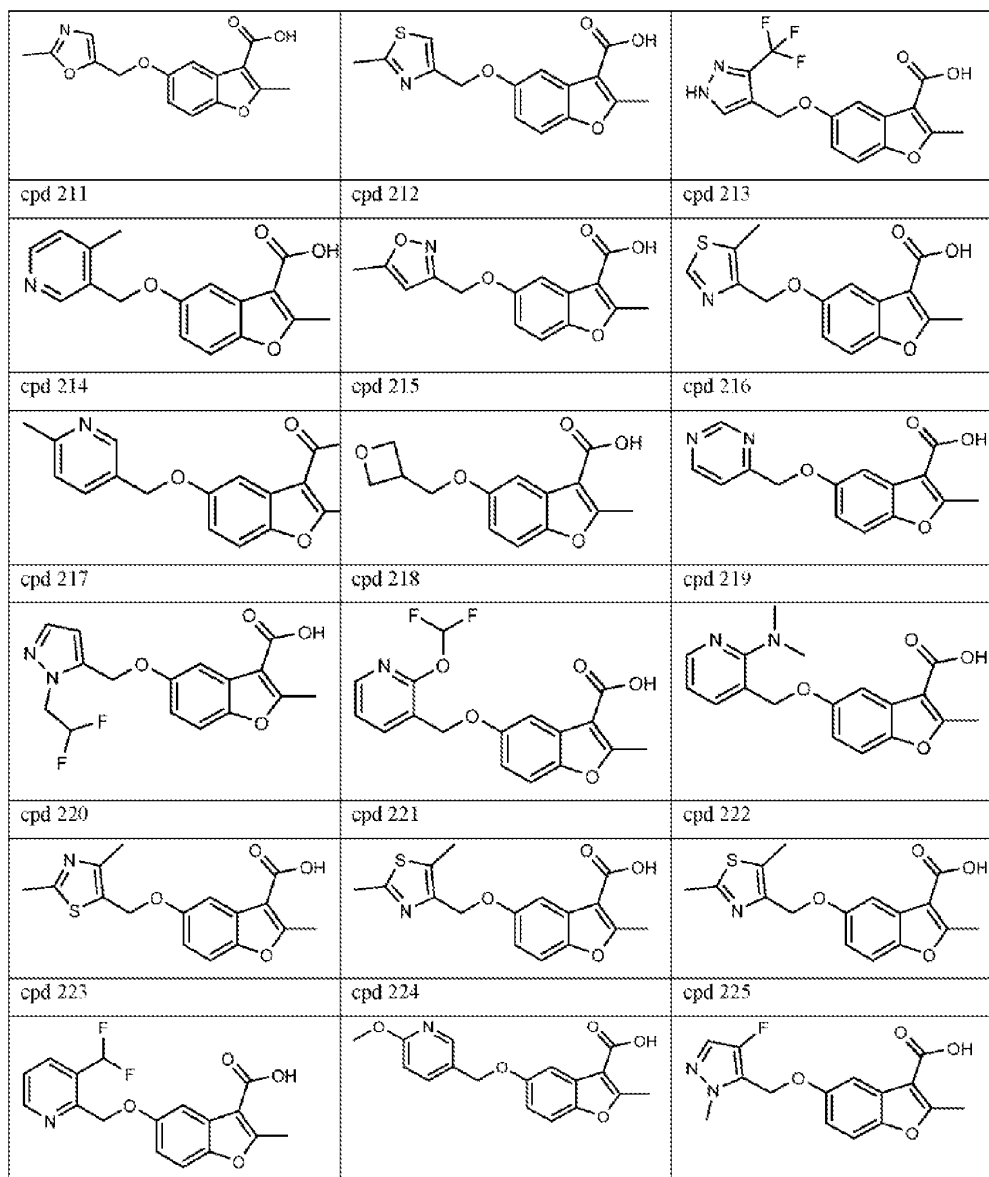
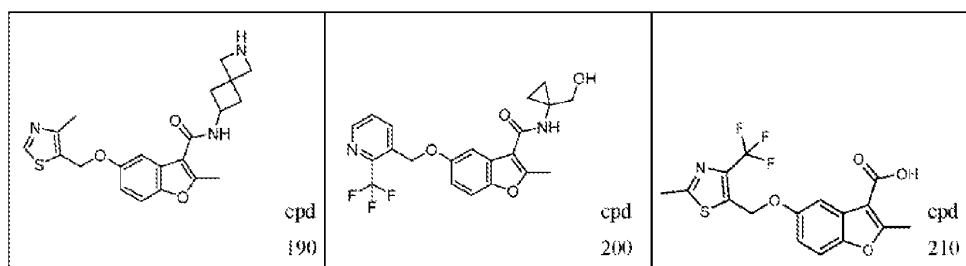
		
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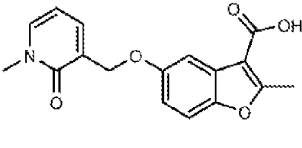
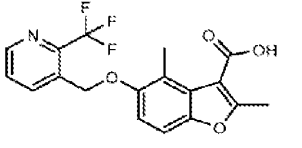
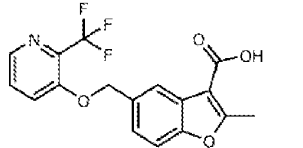
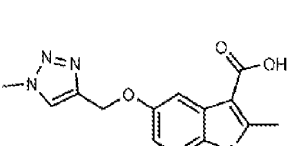
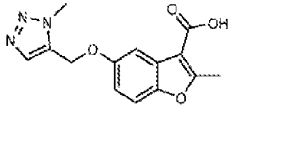
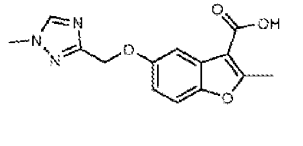
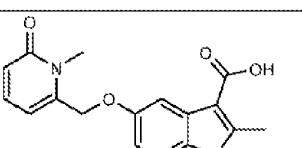
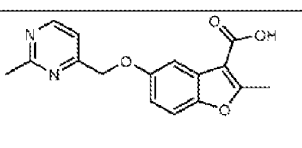
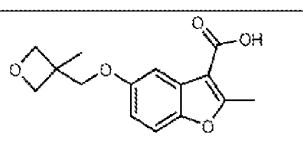
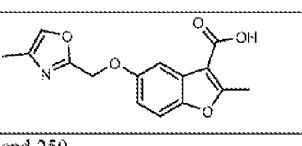
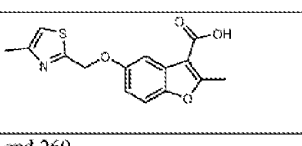
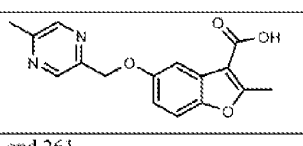
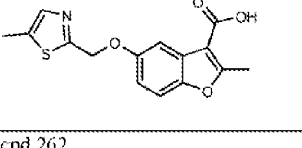
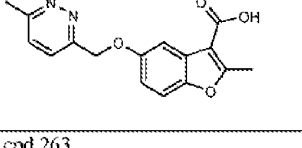
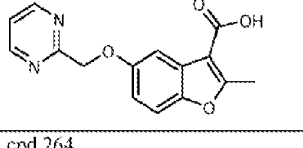
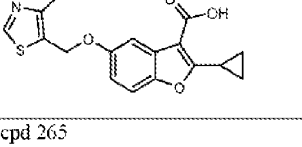
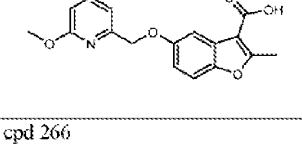
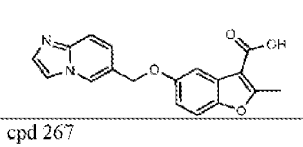
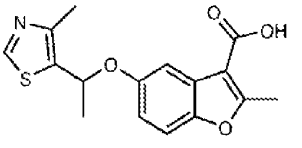
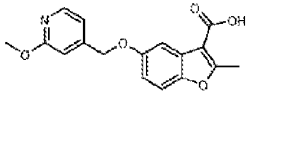
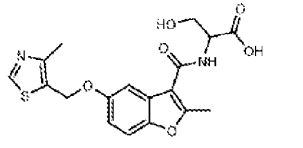
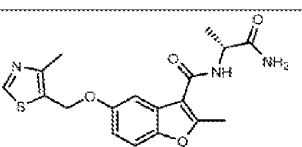
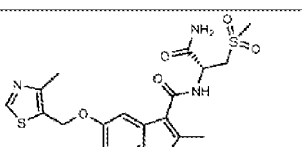
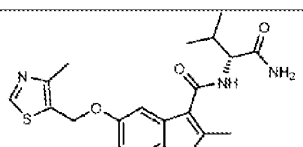
		
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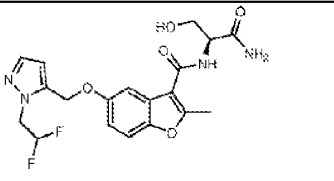
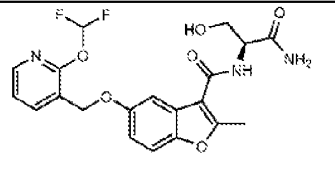
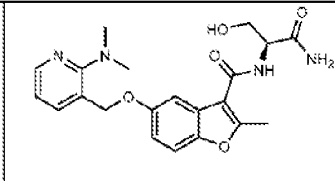
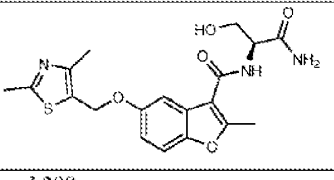
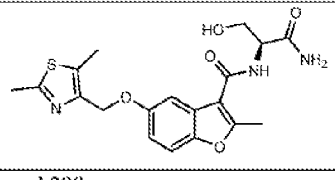
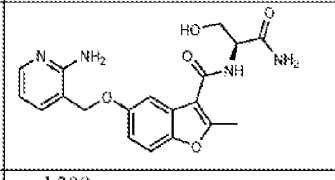
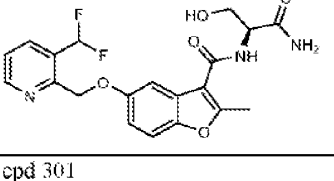
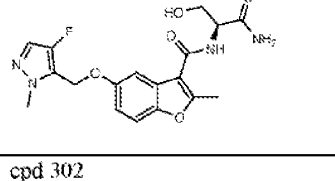
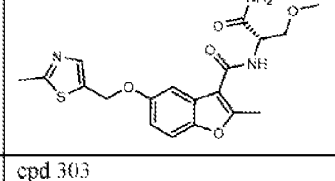
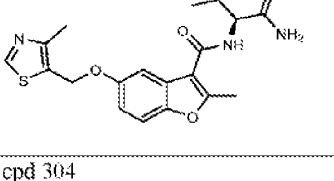
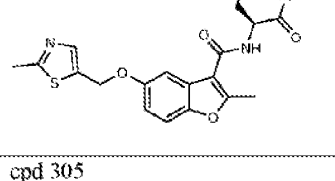
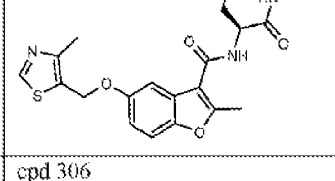
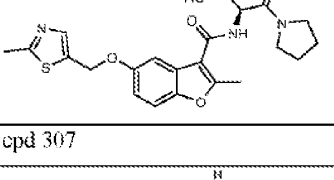
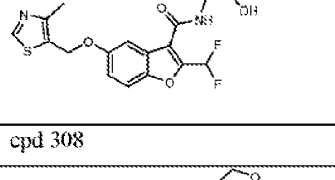
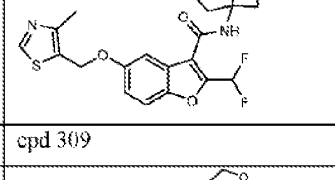
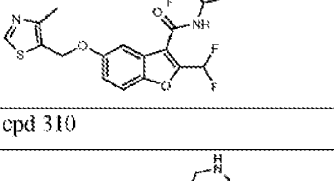
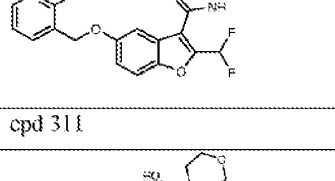
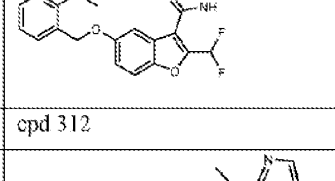
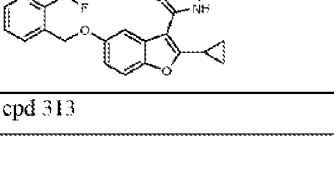
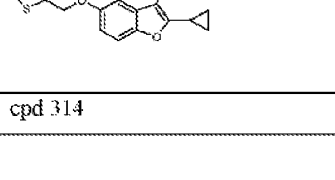
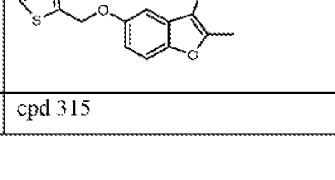
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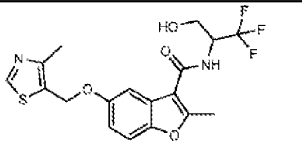
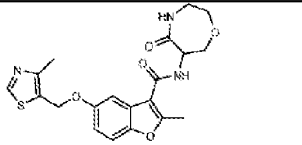
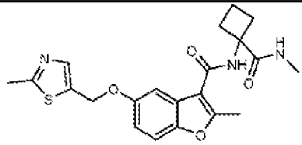
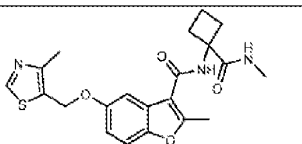
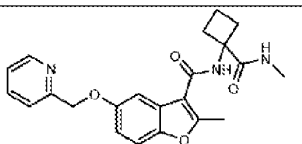
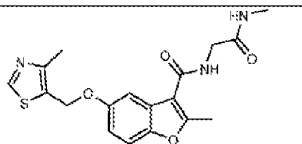
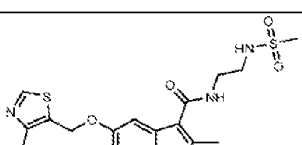
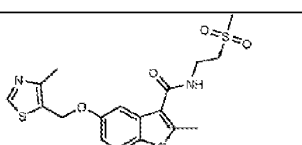
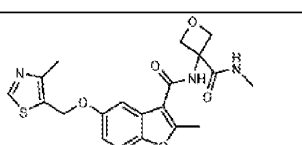
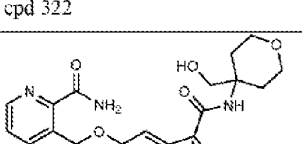
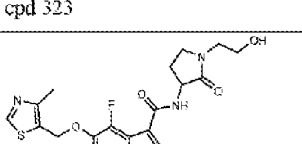
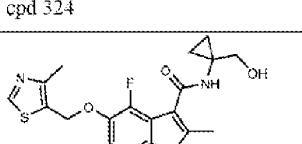
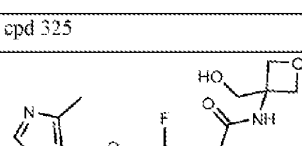
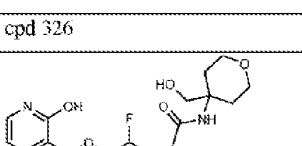
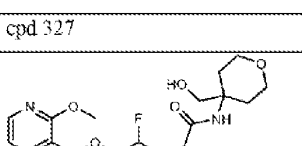
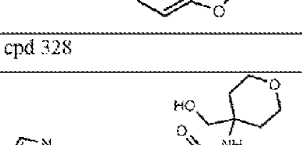
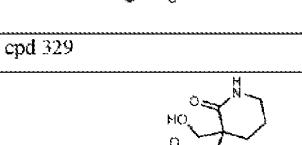
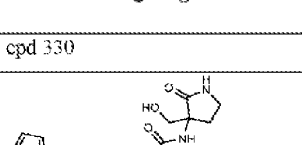
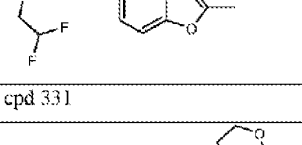
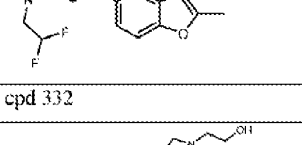
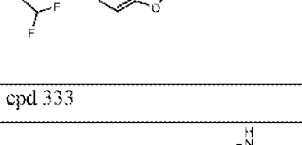


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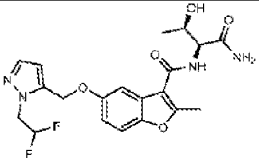
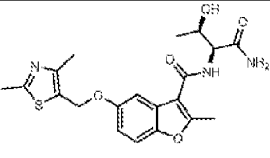
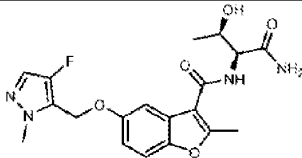
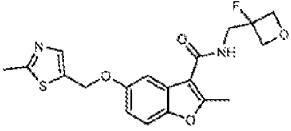
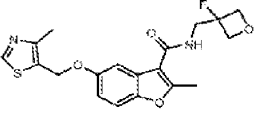
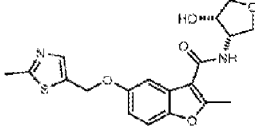
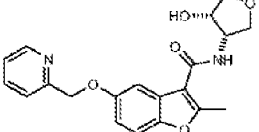
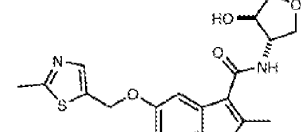
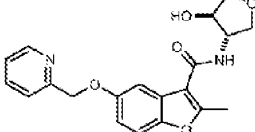
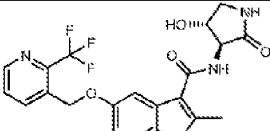
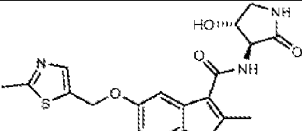
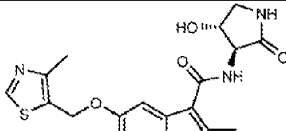
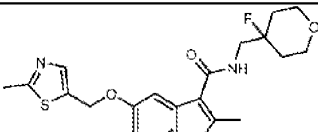
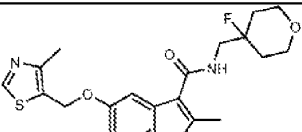
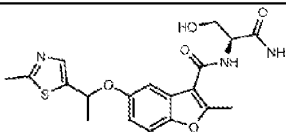
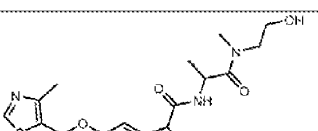
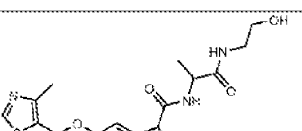
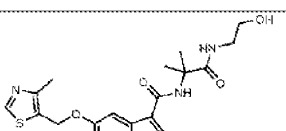
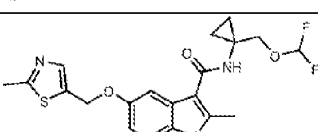
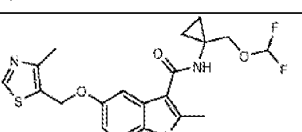
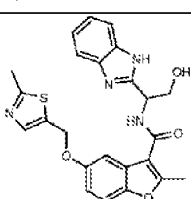
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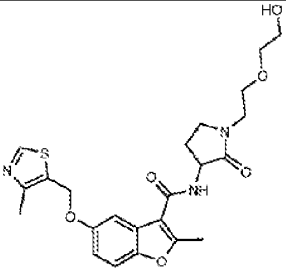
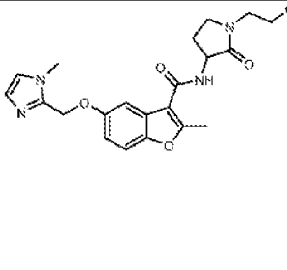
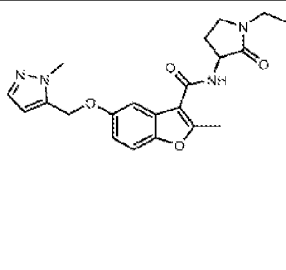
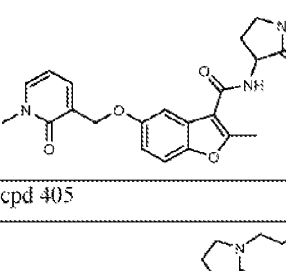
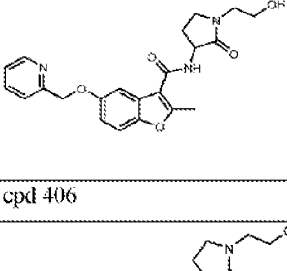
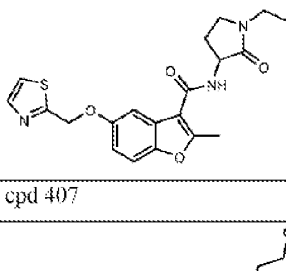
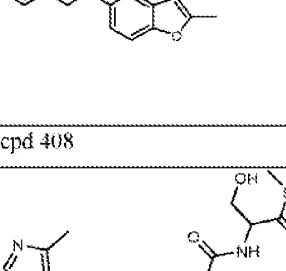
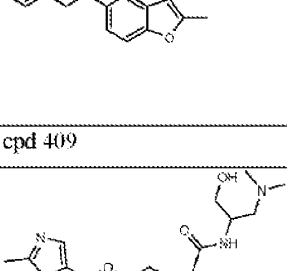
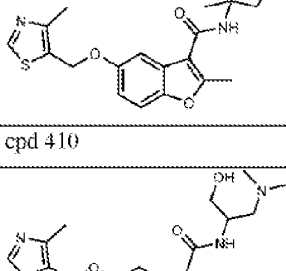
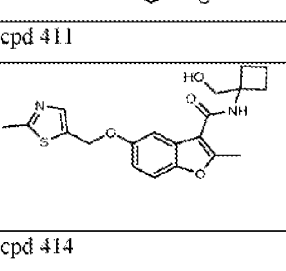
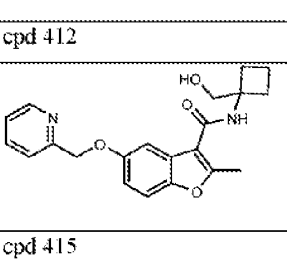
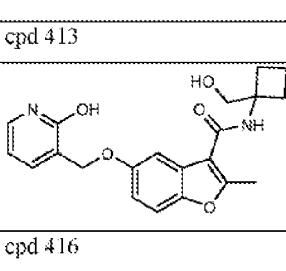
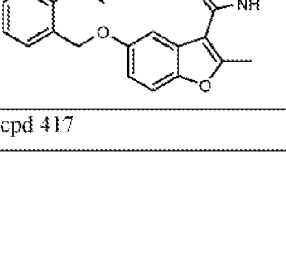
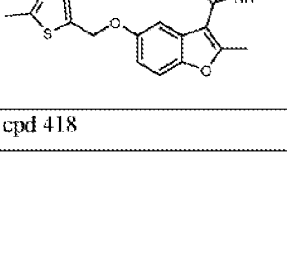
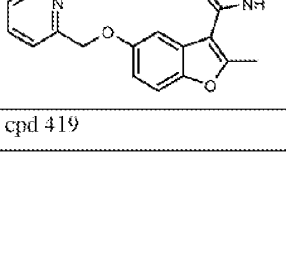
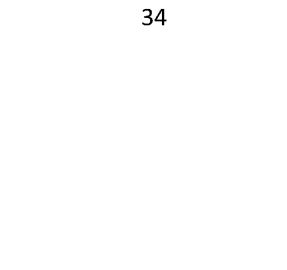
		
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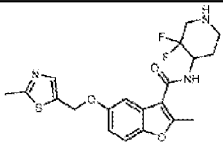
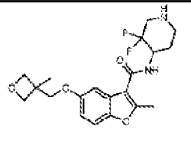
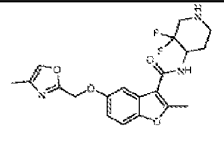
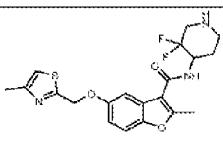
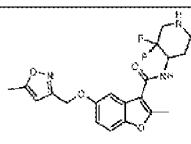
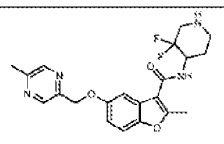
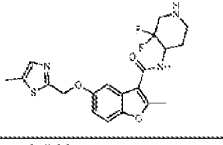
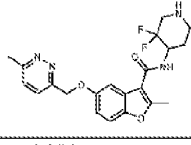
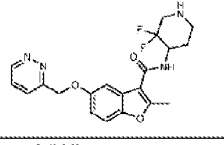
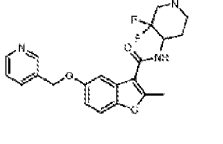
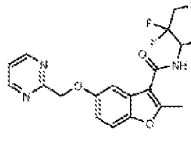
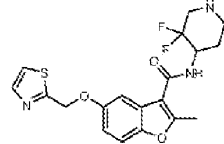
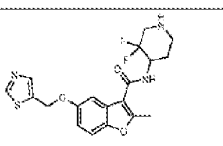
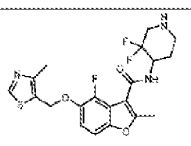
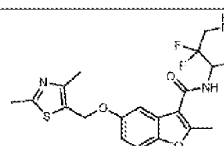
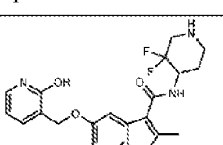
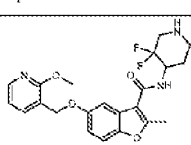
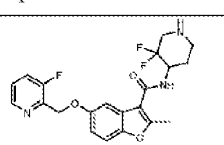
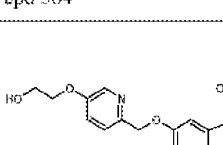
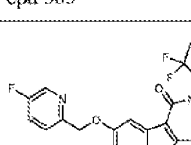
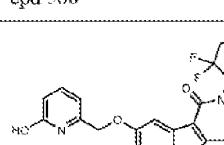
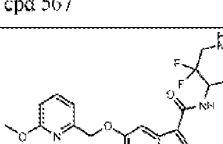
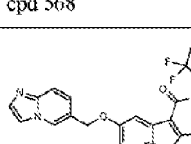
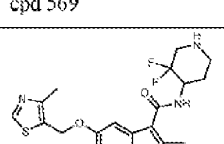
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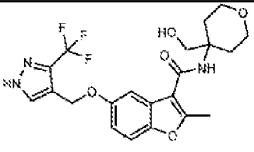
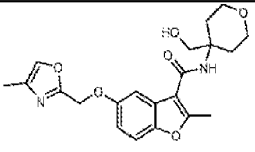
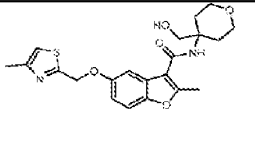
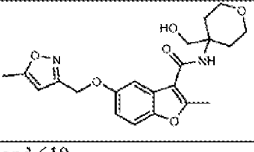
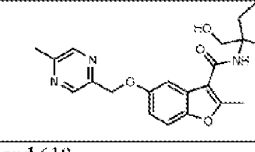
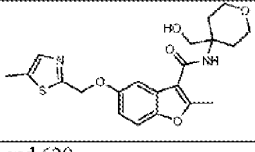
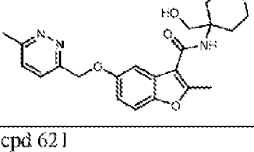
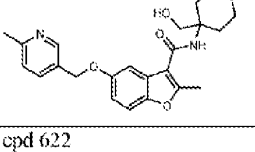
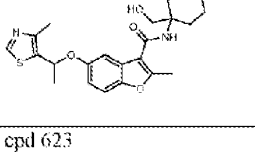
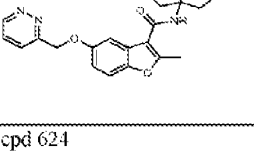
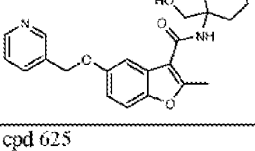
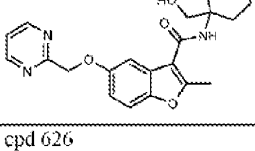
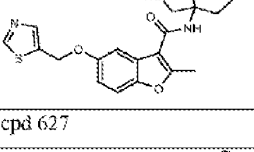
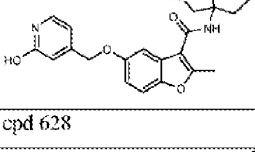
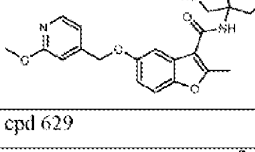
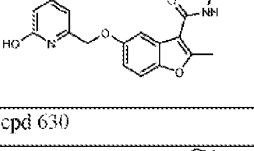
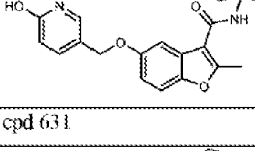
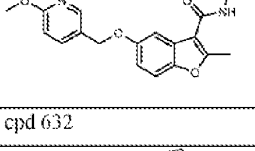
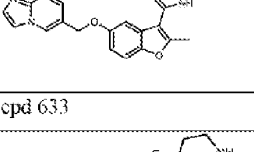
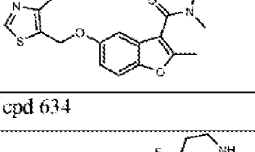
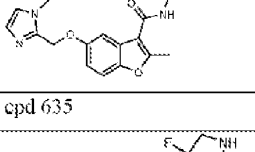
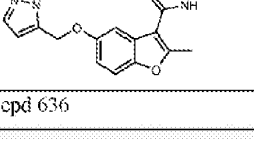
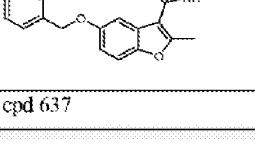
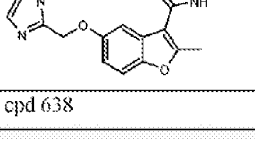
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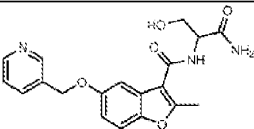
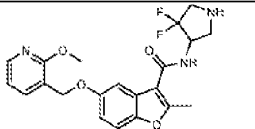
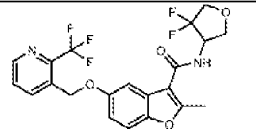
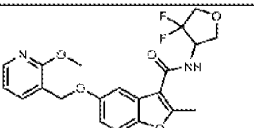
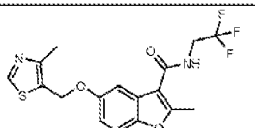
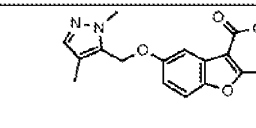
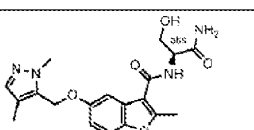
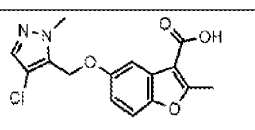
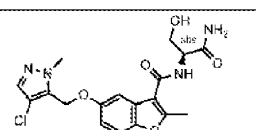
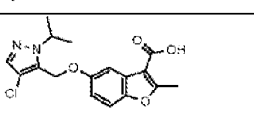
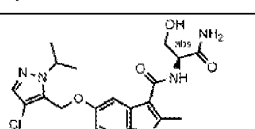
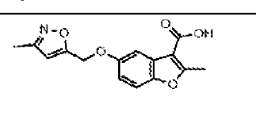
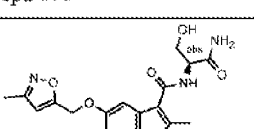
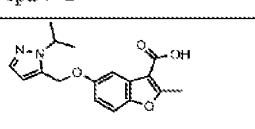
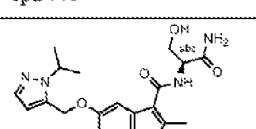
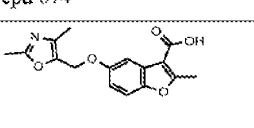
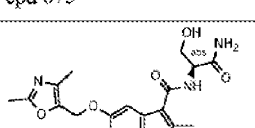
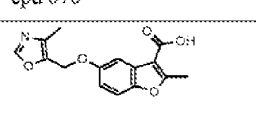
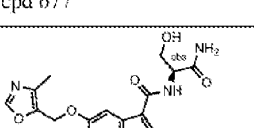
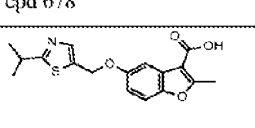
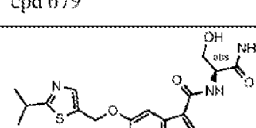
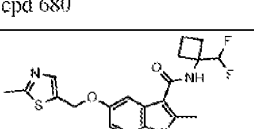
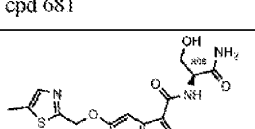
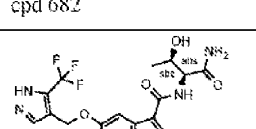
		
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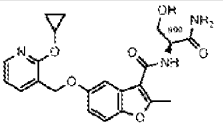
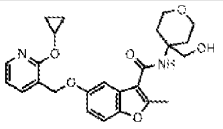
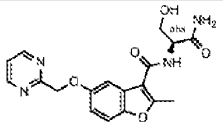
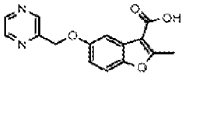
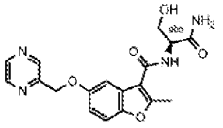
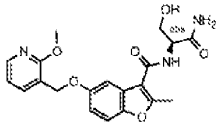
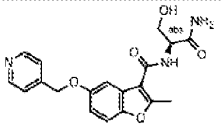
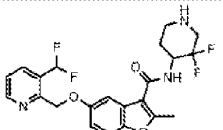
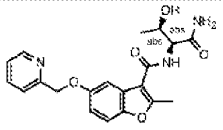
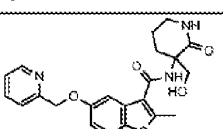
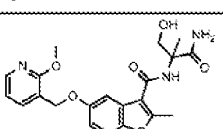
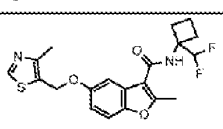
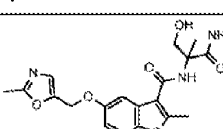
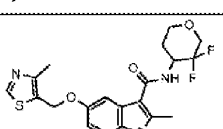
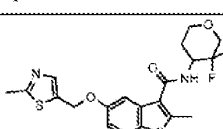
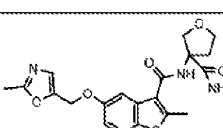
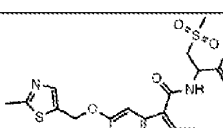
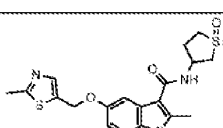
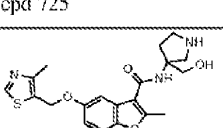
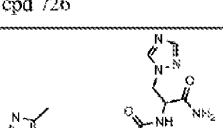
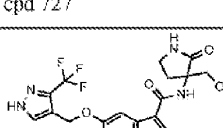
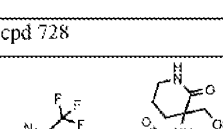
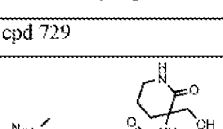
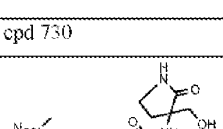
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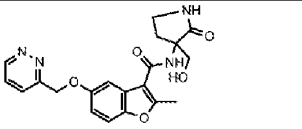
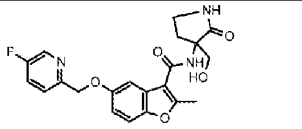
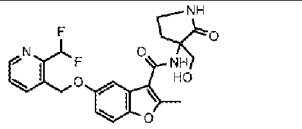
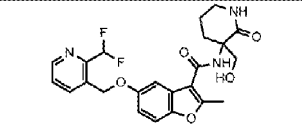
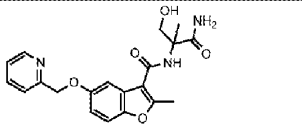
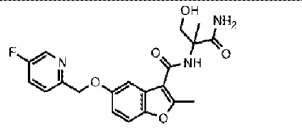
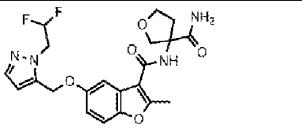
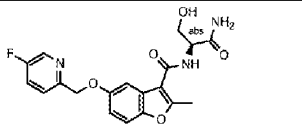
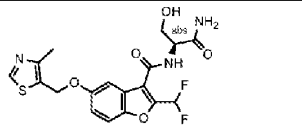
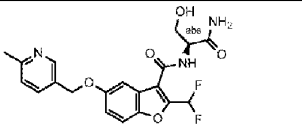
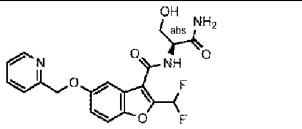
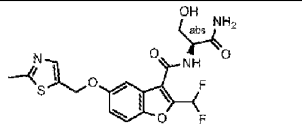
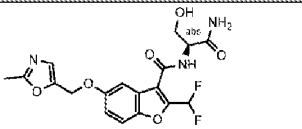
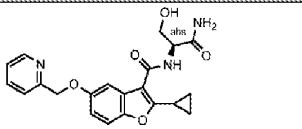
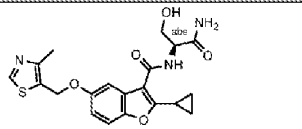
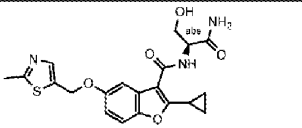
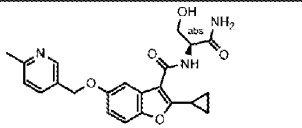
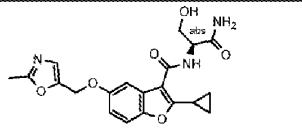
		
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cpd 743	cpd 744	cpd 745
		
cpd 746	cpd 747	cpd 748
		
cpd 749	cpd 750	cpd 751

In a further embodiment, the TRPM3 modulator is a compound selected from the group consisting of:

- 5 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-(trifluoromethyl)thiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methyl-4-(trifluoromethyl)thiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- 10 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methyloxazol-5-yl)methoxy)benzofuran-3-carboxamide;

- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylpyridin-3-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-4-yl)methoxy)benzofuran-3-carboxamide;
- 5 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((3-(trifluoromethyl)-1H-pyrazol-4-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((4-methylpyridin-3-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((4-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- 10 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((5-methylisoxazol-3-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((5-methylthiazol-4-yl)methoxy)benzofuran-3-carboxamide;
- 15 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((6-methylpyridin-3-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(pyridazin-3-ylmethoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(pyrimidin-4-ylmethoxy)benzofuran-3-carboxamide;
- 20 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2-(difluoromethoxy)pyridin-3-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- 25 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2,4-dimethylthiazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2,5-dimethylthiazol-4-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((3-(difluoromethyl)pyridin-2-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- 30 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((4-fluoro-1-methyl-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((1-methyl-1H-imidazol-2-yl)methoxy)benzofuran-3-carboxamide;

- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((1-methyl-1H-pyrazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- 5 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((4-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- 10 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2-(difluoromethyl)pyridin-3-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2,4-dimethylthiazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2-hydroxypyridin-3-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- 15 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((4-fluoro-1-methyl-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((2-methylpyridin-3-yl)methoxy)benzofuran-3-carboxamide;
- 20 (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((4-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- 25 (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((6-methylpyridin-3-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-5-((1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-5 3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-5-((4-fluoro-1-methyl-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- 30 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(pyridin-3-ylmethoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((1,4-dimethyl-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;

- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((4-chloro-1-methyl-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((4-chloro-1-isopropyl-1H-pyrazol-5-yl) methoxy)-2-methylbenzofuran-3-carboxamide;
- 5 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((3-methylisoxazol-5-yl)methyl)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((1-isopropyl-1H-pyrazol-5-yl) methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2, 4-dimethyloxazol-5-yl) methoxy)-2-
- 10 methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((4-methyloxazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2-isopropylthiazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- 15 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((5-methylthiazol-2-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((1-methyl-1H-pyrazol-3-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-
- 20 yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((1-(cyclopropylmethyl)-1H-pyrazol-5-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methoxy)benzofuran-3-carboxamide;
- 25 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((4-(trifluoromethyl)thiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(thiazol-2-ylmethoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(thiazol-5-ylmethoxy)benzofuran-3-
- 30 carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((1-methyl-1H-pyrazol-4-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((5-methylpyridin-2-yl)methoxy)benzofuran-3-carboxamide;

- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylpyrimidin-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(pyrimidin-2-ylmethoxy)benzofuran-3-carboxamide;
- 5 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(pyrazin-2-ylmethoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((2-methoxypyridin-3-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-(pyridin-4-ylmethoxy)benzofuran-3-carboxamide;
- 10 (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-5-((2-methoxypyridin-3-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((2-methyloxazol-5-yl)methoxy)benzofuran-3-carboxamide;
- 15 (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-5-((5-fluoropyridin-2-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-5-((5-fluoropyridin-2-yl)methoxy)-2-methylbenzofuran-3-carboxamide;
- 20 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((4-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((6-methylpyridin-3-yl)methoxy)benzofuran-3-carboxamide;
- 25 (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-(difluoromethyl)-5-(pyridin-2-ylmethoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide; and
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((2-methyloxazol-5-yl)methoxy)benzofuran-3-carboxamide,
- 30 or a physiologically acceptable salt thereof.

In a further embodiment, the TRPM3 modulator is a compound selected from the group consisting of:

(S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;

(S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide; and

- 5 (S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide.

10 The pharmaceutical composition may further include gelatin as a carrier. The gelatin may comprise fish gelatin. The pharmaceutical composition may further include a filler. The filler may comprise a sugar alcohol (i.e., a polyol). The sugar alcohol may comprise mannitol.

In an aspect, the pharmaceutical composition may include from about 70-80 weight% of the TRPM3 modulator, about 10-20 weight% gelatin, about 10-20 weight% of a filler, and 0.1-5.0 weight% of a flavorant. In an aspect, the flavorant may comprise aspartame. In an aspect, the pharmaceutical composition may further include a preservative. In an embodiment, the preservative
15 comprises a paraben, such as methyl paraben and/or propyl paraben.

The pharmaceutical compositions are typically formulated as unit dosages for administration to the subject. These unit dosages typically comprise an amount of the active ingredient intended to be therapeutically safe and effective. The pharmaceutical composition may include about 100 mg to about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof (i.e., a unit
20 dosage of about 100 mg to about 300 mg), for example, about 100 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof, about 150 mg of TRPM3 modulator or a pharmaceutically acceptable salt thereof, about 200 mg of TRPM3 modulator or a pharmaceutically acceptable salt thereof, about 250 mg of TRPM3 modulator or a pharmaceutically acceptable salt thereof, or about 300 mg of TRPM3 modulator or a pharmaceutically acceptable salt thereof.

25 The pharmaceutical composition may be capable of disintegrating or dispersing within an interval selected from 1 to 60 seconds, 1 to 30 seconds, 1 to 10 seconds, and 2 to 8 seconds, after being placed in contact with a fluid. The fluid may include saliva.

In another embodiment, a method of treating pain in a patient in need thereof is provided. The method includes administering to the patient a pharmaceutical composition including a
30 pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

The starting materials useful for making the pharmaceutical compositions of the present invention are readily commercially available or can be prepared by those skilled in the art.

The pharmaceutical compositions of the present invention can be prepared in any suitable dosage form including, for example, such as tablets, capsules, nasal sprays, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Preferably, the dosage form is an orally dissolvable dosage form.

The pharmaceutical compositions of the present invention typically also include other pharmaceutically acceptable carriers (also referred to as excipients) such as, for example, binders, lubricants, diluents, coatings, disintegrants, barrier layer components, glidants, coloring agents, solubility enhancers, gelling agents, fillers, proteins, co-factors, emulsifiers, solubilizing agents, suspending agents, flavorants, preservatives and mixtures thereof. The choice of excipients depends on the desired characteristics of the compositions and on the nature of other pharmacologically active compounds in the formulation. Suitable excipients are known to those skilled in the art (see Handbook of Pharmaceutical Excipients, fifth edition, 2005 edited by Rowe et al., McGraw Hill).

Examples of pharmaceutically acceptable carriers that may be used in preparing the pharmaceutical compositions of the present invention may include, but are not limited to, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropyl methyl-cellulose, sodium carboxymethylcellulose, polyvinyl-pyrrolidone (PVP), talc, calcium sulphate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, pyrogen-free water and combinations thereof. If desired, disintegrating agents may be combined as well, and exemplary disintegrating agents may be, but not limited to, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. In an aspect of the invention, the flavoring agent is selected from mint, peppermint, berries, cherries, menthol and sodium chloride flavoring agents, and combinations thereof. In an aspect of the invention, the sweetener is selected from sugar, sucralose, aspartame, acesulfame, neotame, and combinations thereof.

In general, the pharmaceutical compositions of the present invention may be manufactured in conventional methods known in the art, for example, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes and the like.

In one aspect of the invention the pharmaceutical compositions are prepared in oral solid molded fast-dispersing dosage form, such as described in US Patent No. 9,192,580, issued November 24, 2015.

5 The phrase "fast-dispersing dosage form" refers to compositions which disintegrate or disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds, after being placed in contact with a fluid. The fluid is preferably that found in the oral cavity, *i.e.*, saliva, as with oral administration.

10 In a preferred embodiment, the compositions of the invention are solid fast-dispersing dosage forms including a solid network of the active ingredient, a TRPM3 modulator, and a water-soluble or water-dispersible carrier containing fish gelatin. Accordingly, the carrier is inert towards the active ingredient. The network is obtained by subliming solvent from a composition in the solid state, the composition including the active ingredient and a solution of the carrier in the solvent. The dosage forms according to the invention can be prepared according to the process disclosed in Gregory et al., U.K. Patent No. 1,548,022 using fish gelatin as the carrier. Accordingly, an initial
15 composition (or admixture) including the active ingredient and a solution of the fish gelatin carrier in a solvent is prepared followed by sublimation. The sublimation is preferably carried out by freeze drying the composition. The composition can be contained in a mold during the freeze-drying process to produce a solid form in any desired shape. The mold can be cooled using liquid nitrogen or solid carbon dioxide in a preliminary step prior to the deposition of the composition therein.
20 After freezing the mold and composition, they are next subjected to reduced pressure and, if desired, controlled application of heat to aid in sublimation of solvent. The reduced pressure applied in the process can be below about 4 mm Hg, preferably below about 0.3 mm Hg. The freeze dried compositions can then be removed from the mold if desired or stored therein until later use.

25 When the process is used with active ingredients and fish gelatin as the carrier, a solid fast-dispersing dosage form is produced having the advantages associated with the use of fish gelatin described herein. Generally, fish gelatin is categorized as being from cold water and warm water fish sources and as being of the gelling or non-gelling variety. The non-gelling variety of fish gelatin, in comparison to gelling fish gelatin and bovine gelatin, contains lower proline and hydroxyproline amino acid content, which are known to be associated with cross-linking properties and gelling
30 ability. Non-gelling fish gelatin can remain at solution concentrations of up to about 40% as well as in temperatures as low as 20° C. In one aspect of the invention, the fish gelatin used in accordance with the invention is preferably obtained from cold water fish sources and is the non-gelling type of fish gelatin. More preferably, in one aspect of the invention, the non-hydrolyzed form of non-gelling

fish gelatin is used. In an alternative embodiment, spray-dried non-hydrolyzed non-gelling fish gelatin can be used. Fish gelatins suitable for use in the invention are commercially available.

The compositions according to the invention can also contain, in addition to the active ingredient and fish gelatin carrier, other matrix forming agents and secondary components. Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as other gelatins, dextrans and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

Other materials which may also be incorporated into the fast-dissolving compositions of the present invention include sugar alcohols or sugars such as mannitol, dextrose, lactose, galactose, and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicates; and amino acids having from 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine. One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification (freezing). The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension. This is especially helpful in the case of active agents that are not sufficiently soluble in water and must, therefore, be suspended rather than dissolved. Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, coloring agents, flavoring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the fast-dissolving compositions. Suitable coloring agents include red, black and yellow iron oxides and FD & C dyes such as FD&C Blue No. 2 and FD&C Red No. 40 available from Ellis & Everard. Suitable flavoring agents include mint, raspberry, licorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavors and combinations of these. Suitable pH modifiers include the edible acids and bases, such as citric acid, tartaric acid, phosphoric acid, hydrochloric acid, maleic acid and sodium hydroxide. Suitable sweeteners include, for example, sucralose, aspartame, acesulfame K and thaumatin. Suitable taste-masking agents include, for example, sodium bicarbonate, ion exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

Typical routes of administering the pharmaceutical compositions of the invention include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. Pharmaceutical

compositions according to certain embodiments of the present invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient may take the form of one or more dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). Preferably, the pharmaceutical compositions are delivered orally in an orally dissolving dosage form. Such orally dissolving dosage forms may be placed on or below the tongue for dissolution. In some cases, at least some of the TRPM3 modulator may be absorbed sublingually.

Solid compositions are normally formulated in dosage units (i.e., unit dosages) providing from about 1 to about 1000 mg of the active ingredient per dose. Some examples of solid dosage units are 0.1 mg, 1 mg, 10 mg, 37.5 mg, 75 mg, 100 mg, 150 mg, 300 mg, 500 mg, 600 mg and 1000 mg. Typical dose ranges in accordance with the present invention include from about 10-600 mg, 25-300 mg, 100-300 mg, 25-150 mg, 50-100 mg, 60-90 mg, and 70-80 mg. Liquid compositions are generally in a unit dosage range of 1-100 mg/mL. Some examples of liquid dosage units are 0.1 mg/mL, 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL.

In some embodiments, a method may include administering to a subject one or more additional agent(s) simultaneously or sequentially with the TRPM3 modulator. In some embodiments, an additional agent may be a medication known in the art. In some embodiments, a therapeutic effect may be greater as compared to use of the TRPM3 modulator or one or more additional agent(s) alone. Accordingly, a synergistic effect between the TRPM3 modulator and the one or more additional agents may be achieved. In some embodiments, the one or more additional agent(s) may be taken by a subject prophylactically.

In one aspect, the invention also provides kits for use in the instant methods. Kits can include one or more containers including a pharmaceutical composition described herein and instructions for use in accordance with any of the methods described herein. Generally, these instructions include a description of administration of the pharmaceutical composition to treat, ameliorate or prevent pain, or other TRPM3-mediated disorder, according to any of the methods described herein. The kit may, for example, include a description of selecting an individual suitable for treatment based on identifying whether that individual has pain or whether the individual is at risk of having pain. The instructions are typically provided in the form of a package insert, or label, in accordance with the requirements of the regulatory having authority over the jurisdiction where the pharmaceutical composition is to be provided to patients.

In accordance with the present invention, administration of the pharmaceutical compositions including the TRPM3 modulator to a subject may promote a reduction in severity (which can include reducing need for and/or amount of (*e.g.*, exposure to) other drugs and/or therapies generally used for this condition.

5 In addition, administration of the pharmaceutical compositions including the TRPM3 modulator to a subject may promote a lessening or improvement of one or more symptoms of pain, or a reduction in the duration of a symptom, as compared to not administering a treatment.

In addition, administration of the pharmaceutical compositions including the TRPM3 modulator to a subject may promote a reduction in the frequency of pain incidents in an individual
10 (as compared to the level before treatment) in a certain time period, *e.g.*, per month. For example, the frequency of pain incidents may be reduced by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, or 70% in the individual as compared to the level before treatment.

In addition, administration of the pharmaceutical compositions including the TRPM3 modulator to a subject may promote a delay in the development of pain, *i.e.*, to defer, hinder, slow,
15 retard, stabilize, and/or postpone progression of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individuals being treated.

In addition, administration of the pharmaceutical compositions including the TRPM3 modulator to a subject may delay the development or progression of pain, *i.e.*, delay of the initial manifestations and/or ensuing progression of the disorder. Development of the disorder can be
20 detectable and assessed using standard clinical techniques as well-known in the art. However, development also refers to progression that may be undetectable.

EXAMPLES

Preparation of Dosage Forms

Dosage forms of compounds of Formula I are prepared as oral solid molded fast-dispersing
25 dosage forms at unit-dosage strengths of 25 mg, 75 mg, 150 mg for analytical evaluation and unit dosage strengths from about 100 mg to about 300 mg for pre-clinical and clinical evaluation. The dosage forms have a composition according to Table 2 below. Certain dosage forms omit a flavorant and/or preservative or may contain additional inactive components and exemplary weight percentage ranges may vary accordingly.

30 Table 2: Solid Dosage Forms

Component	Example	Exemplary weight percentage
TRPM3 Modulator	Formula I (<i>e.g.</i> , Cmpd. 1 – 751)	70 – 80%
gelatin	gelatin (<i>e.g.</i> , fish gelatin)	10 – 20%

filler	sugar alcohol (e.g., mannitol)	10 – 20%
flavorant	sweetener (e.g., aspartame) and/or other flavorant	0.1 – 5%
preservative	parabens (e.g., methyl and ethyl parabens)	0.1 – 5%
Other excipients	pH modifiers, antioxidants, permeation enhancers, stabilizers	0.1 – 5%

The fast-dispersing solid dosage forms can dissolve completely or near completely in saliva in a time period shorter than 60 seconds, and in many cases shorter than 10 seconds. While various preparation methods are contemplated, an exemplary preparation is described. A fish gelatin carrier, or other gelatin carrier which is inert toward the TRPM3 modulator, is selected as described herein. The carrier, TRPM3 modulator, and various excipients (see Table 2, including one or more of filler, flavorant, preservative, and other excipients) are dissolved in a solvent as an admixture. The solvent can be water or any other suitable solvents, and a water solvent may include co-solvents such as an alcohol. Once dissolved, the admixture is then sublimed to produce the solid dosage form. Sublimation may be carried out by freeze-drying or alternative processes which accomplish sublimation of the solvent. To produce shaped solid dosage forms, the sublimation may be performed in a mold as described herein. The produced fast dispersing solid dosage forms are evaluated for stability and advantageous release profile characteristics.

Evaluation of Dosage Forms

Solid dosage forms are evaluated for short-term stability with analytical techniques including HPLC/UPLC assay with UV detection. Evaluated dosage forms may omit optional components such as flavoring/sweetening agents. The excipients (i.e., solid dosage form components other than the TRPM3 modulator) are approved in major jurisdictions, including the U.S., E.U., and Japan.

Solid dosage forms are prepared initially at batch sizes of 100g – 300g for stability studies and optimization. The dosage forms target a minimum unit size, with proportional unit size to unit dosage. Formulation components may also include pH modifiers, antioxidants, stabilizers, or other excipients. A target pH range is identified for optimum stability and/or oromucosal absorption. Physiologically based pharmacokinetic model (PBPK) studies are also employed to model sublingual drug uptake. Antioxidants and permeation enhancers are included to optimize stability and uptake.

Stability is assessed under various temperature, light, humidity, and other stability test conditions. Stability is assessed in analytical studies and animal studies on a short term (e.g., up to 3

month)_timeframe. Animal studies are performed using product immediately after normal preparation and after extended mix hold times (24 – 48 h). Analytical studies are performed to analyze particle size and morphology in normal preparation and extended mix hold times. Further analytical studies include HPLC/UPLC with UV detection for stability under stability test conditions.

- 5 Dissolution and release characteristics are likewise evaluated using observational and analytical techniques. For chiral TRPM3 modulators, chiral chromatography methods are employed as necessary. Stability is further evaluated using powder X-ray diffraction spectroscopy (i.e., XRD) using an appropriate X-ray energy such as Cu K α .

- 10 Exemplary stability test conditions are: 40 °C/75% humidity (RH) and 25°C/60% humidity (RH). Table 2 below depicts stability testing intervals to evaluate stability of the solid dosage forms on an accelerated 3-month timeframe. Longer-time contingency stability measurements are performed to evaluate longer-term stability under accelerated conditions.

Table 2: Stability Testing

Storage Condition	Interval				
	Initial	2 weeks	1 Month	3 Months	Contingency
25°C/60% RH	(X)*	-	X (XRD)	X (XRD)	(X)
40°C/75% RH	-	X (XRD)	X (XRD)	X (XRD)	(X)

X = appearance, disintegration and assay / related substances, dissolution

- 15 XRD = X-Ray Diffraction testing

- Throughout this application, various publications are referenced by author name and date, by patent number, by patent application number, or by patent publication number. The disclosures of these publications are hereby incorporated in their entireties by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention.

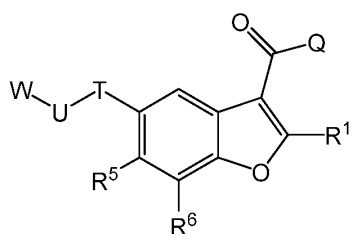
- Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. For example, pharmaceutically acceptable salts other than those specifically disclosed in the description and Examples herein can be employed. Furthermore, it is intended that specific items within lists of items, or subset groups of items within larger groups of items, can be combined with other specific items, subset groups of items or larger groups of items whether or not there is a specific disclosure herein identifying such a combination.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.

2. The pharmaceutical composition of claim 1, wherein the TRPM3 modulator is a compound according to Formula I:



, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is -H, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, cyclopropyl, or $-(C=O)NH_2$;

Q is $-O-R^2$ or $-N-R^{3a}R^{3b}$;

R^2 is -H, or C_1 - C_3 alkyl optionally substituted with one or more of $-NH_2$, carbonyl, carboxylic acid, hydroxyl, C_3 - C_7 cycloalkyl, or C_3 - C_7 heterocycloalkyl;

R^{3a} is -H, C_3 - C_7 cycloalkyl, C_3 - C_7 heterocycloalkyl, phenyl, C_5 - C_7 heteroaryl, C_1 - C_6 alkyl, or C_1 - C_6 heteroalkyl, optionally substituted with one or more of carbonyl, halogen, cyano, C_1 - C_5 alkyl or C_1 - C_5 heteroalkyl, said C_1 - C_5 alkyl or C_1 - C_5 heteroalkyl optionally substituted with one or more of $-NH_2$, carbonyl, carboxylic acid, hydroxyl, cyano, or halogen; and R^{3b} is -H or C_1 - C_3 alkyl; or

R^{3a} and R^{3b} together form a C_3 - C_7 cycloalkyl or C_5 - C_7 heteroaryl, optionally substituted with one or more of $-NH_2$, carbonyl, carboxylic acid, hydroxyl, cyano, halogen, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl;

wherein T is -O- and U is $CR^{4a}R^{4b}$, or T is $CR^{4a}R^{4b}$ and U is -O-;

R^{4a} and R^{4b} are independently -H or C_1 - C_3 alkyl;

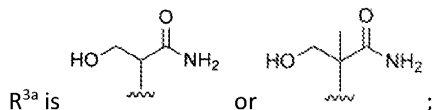
W is C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} heterocycloalkyl, phenyl, or C_5 - C_{10} heteroaryl, optionally substituted with halogen, carbonyl, hydroxyl, C_1 - C_3 alkyl or C_1 - C_3 heteroalkyl, said C_1 - C_3 alkyl or C_1 - C_3 heteroalkyl optionally substituted with one or more of halogen, carbonyl, hydroxyl, azetidine, oxetane, or cyclopropyl; and

R^5 and R^6 are independently -H, halogen, cyano, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl.

3. The pharmaceutical composition of claim 2, wherein:

R^1 is $-\text{CH}_3$ optionally substituted with F;

Q is $-\text{N}-R^{3a}R^{3b}$;



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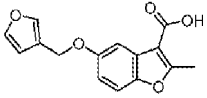
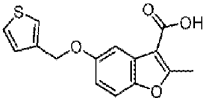
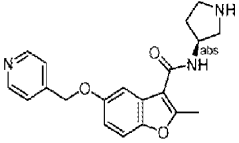
R^{3b} is $-\text{H}$;

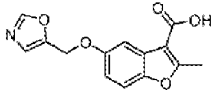
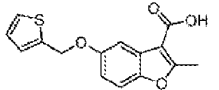
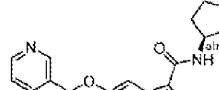
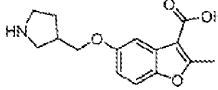
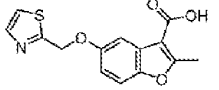
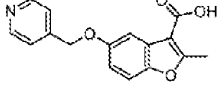
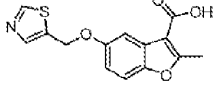
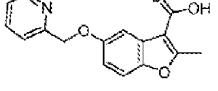
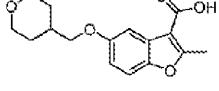
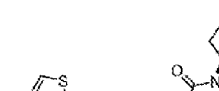
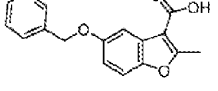
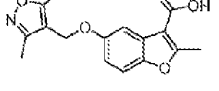
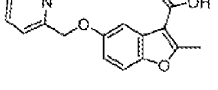
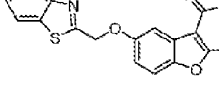
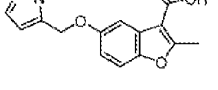
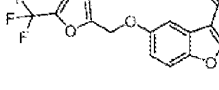
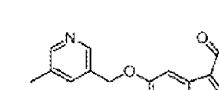
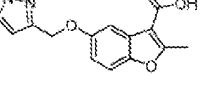
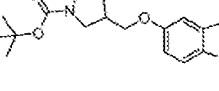
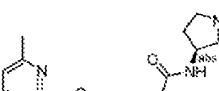
T is $-\text{O}-$ and U is $-\text{CH}_2-$; and

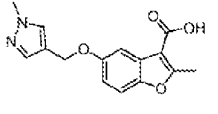
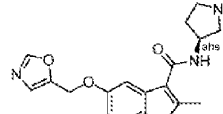
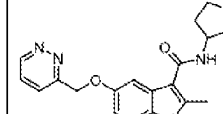
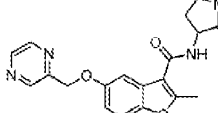
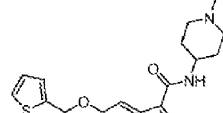
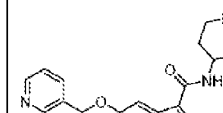
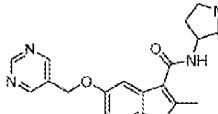
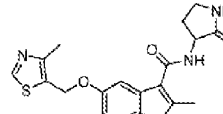
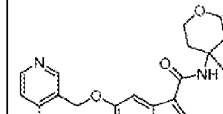
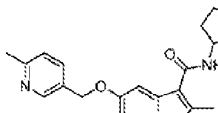
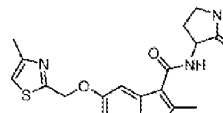
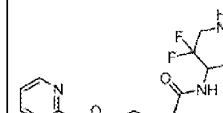
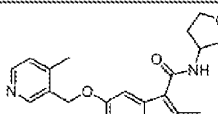
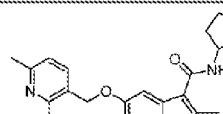
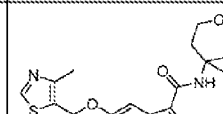
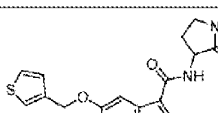
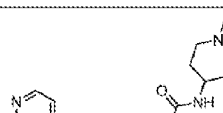
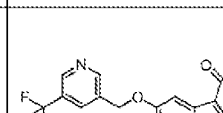
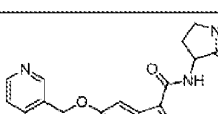
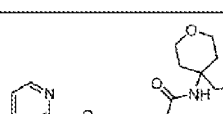
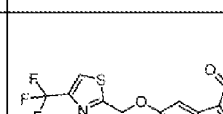
W is a 5-membered heteroaryl selected from the group consisting of oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, and imidazolyl, or a 6-membered heteroaryl selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, wherein the 5-membered heteroaryl and 6-membered heteroaryl are optionally substituted with $-\text{F}$, $-\text{Cl}$, $\text{C}_1\text{-C}_3$ alkyl optionally substituted with $-\text{F}$, or $\text{C}_1\text{-C}_3$ alkoxy optionally substituted with $-\text{F}$.

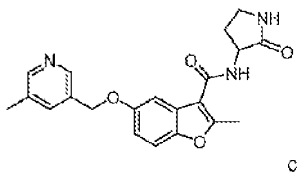
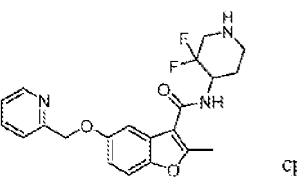
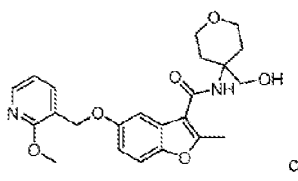
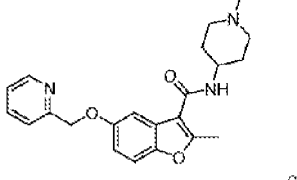
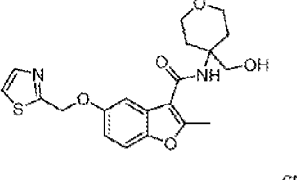
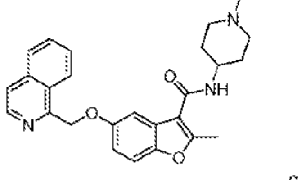
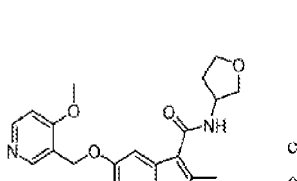
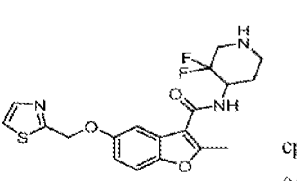
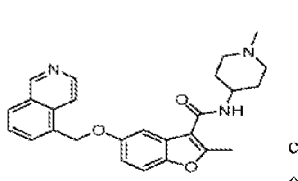
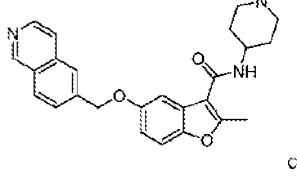
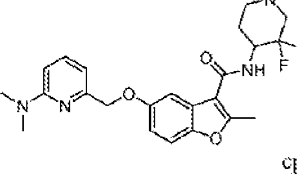
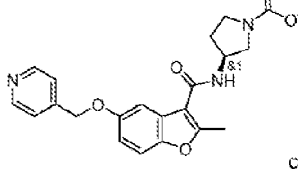
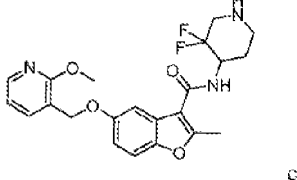
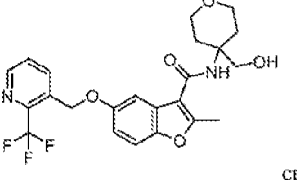
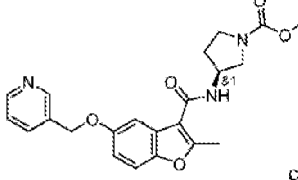
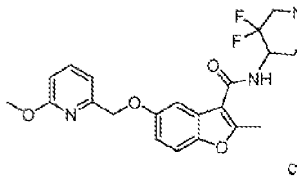
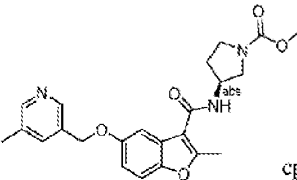
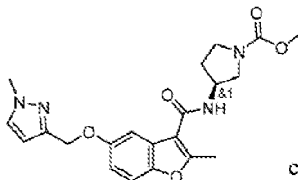
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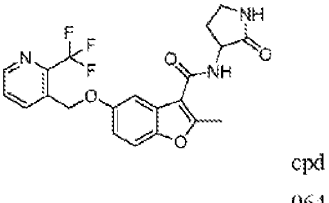
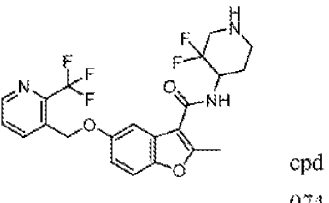
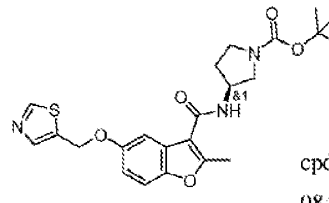
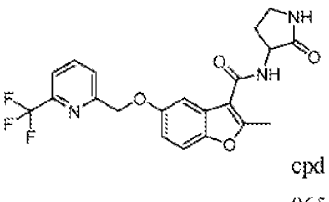
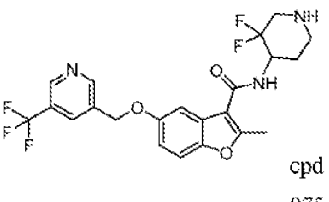
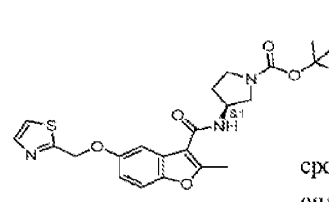
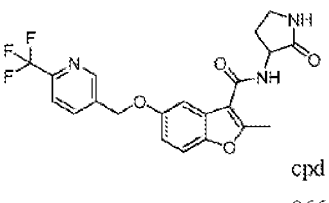
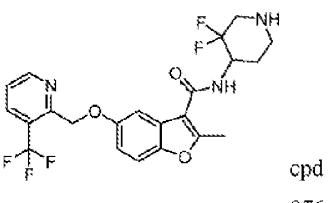
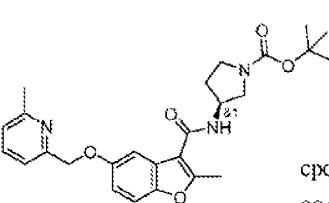
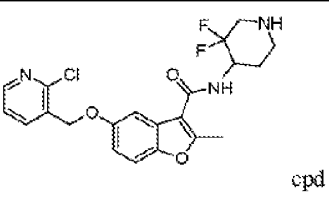
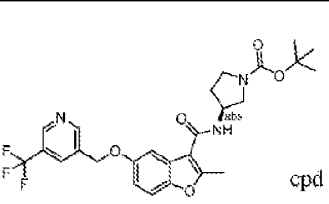
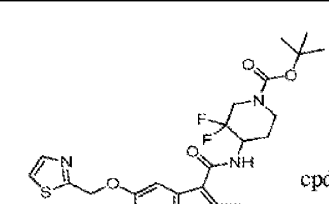
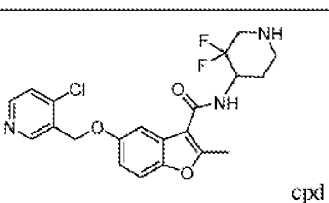
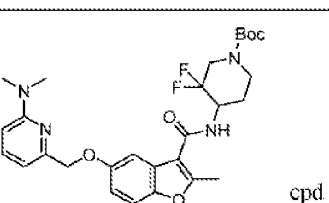
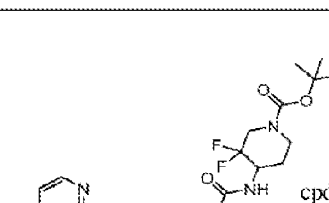
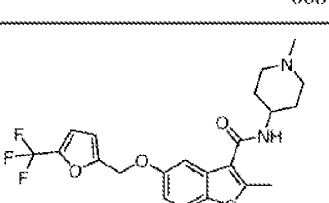
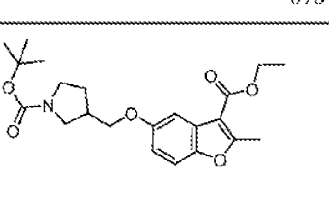
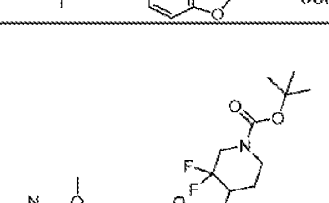
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the TRPM3 modulator is represented by any of the following structures:

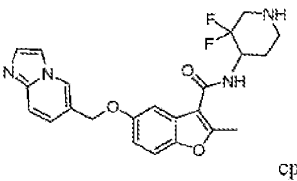
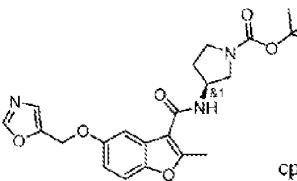
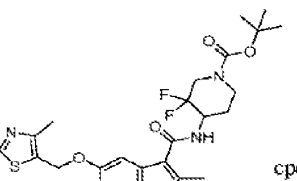
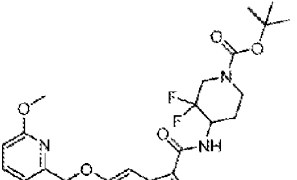
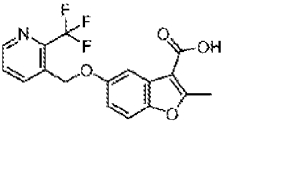
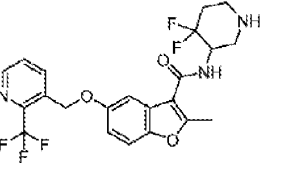
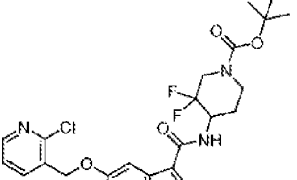
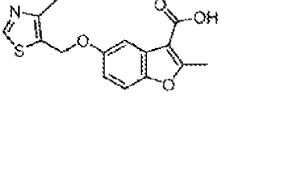
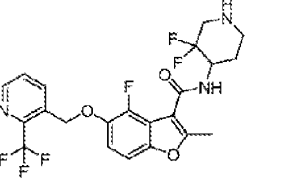
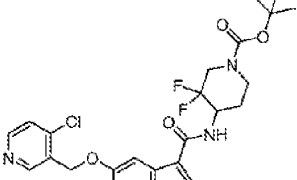
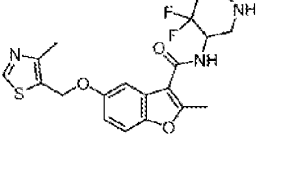
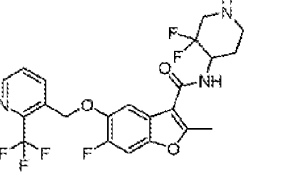
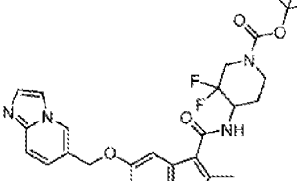
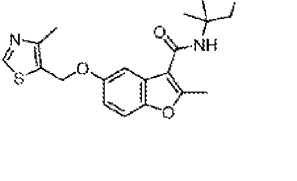
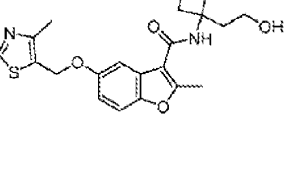
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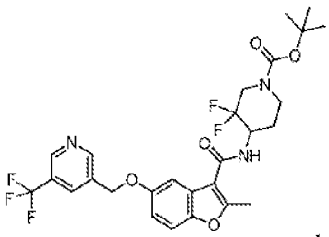
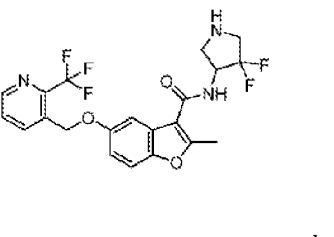
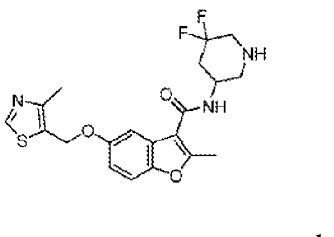
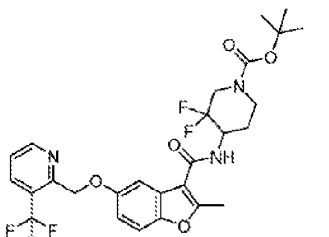
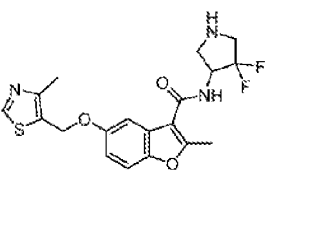
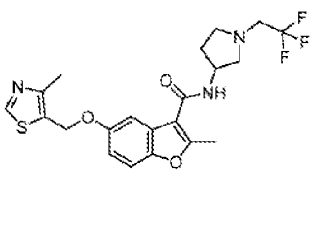
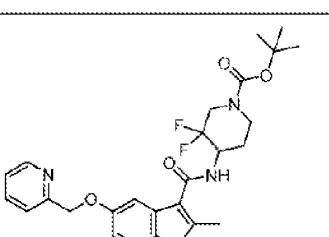
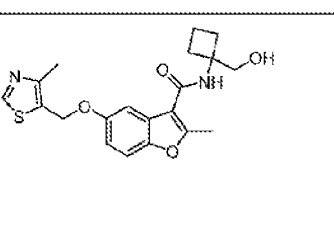
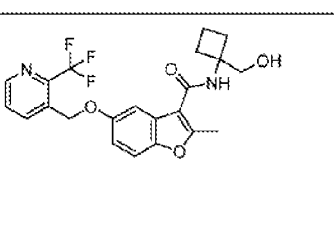
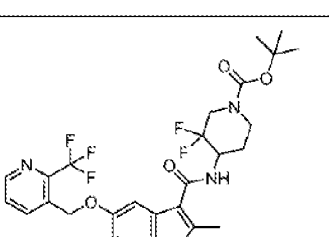
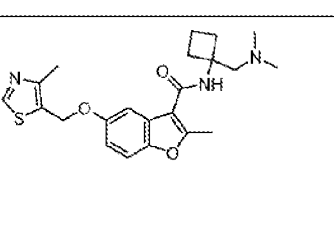
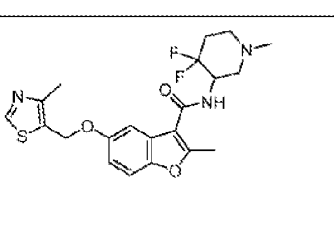
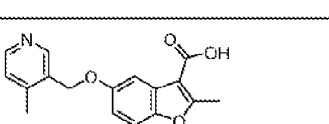
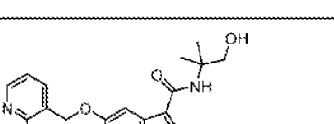
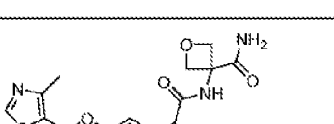
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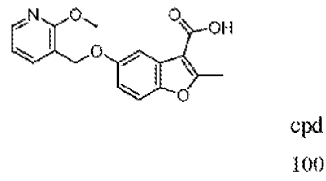
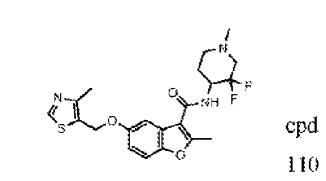
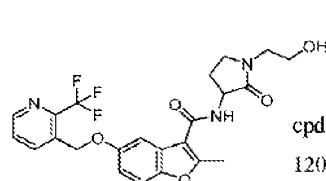
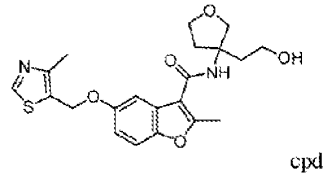
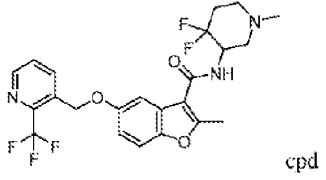
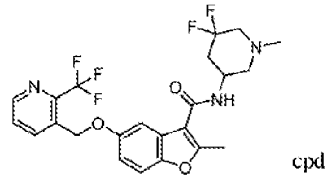
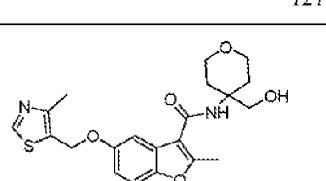
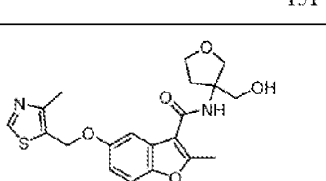
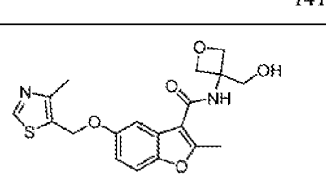
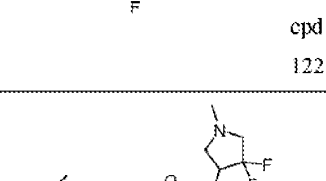
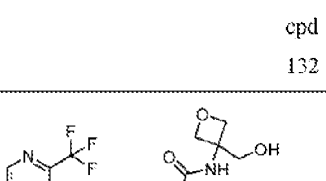
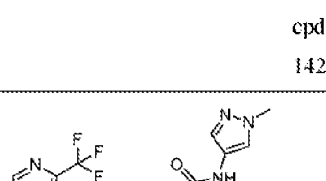
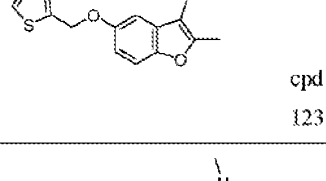
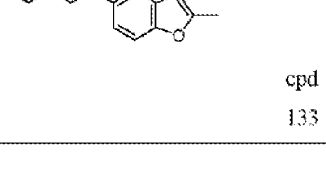
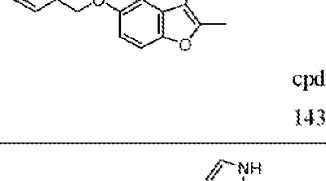
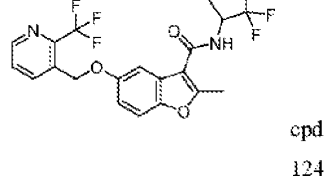
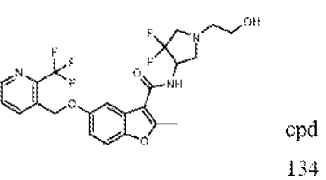
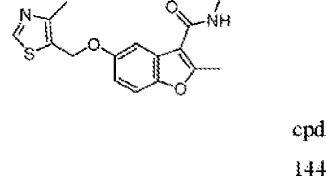
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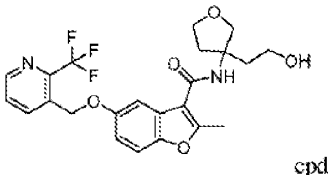
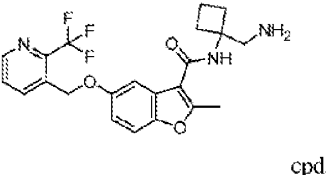
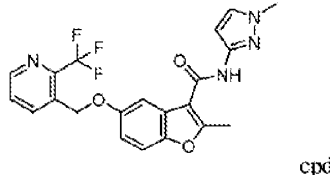
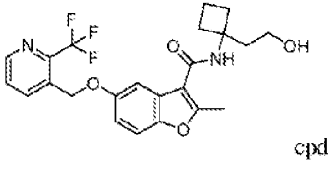
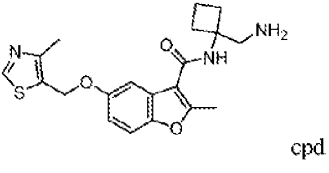
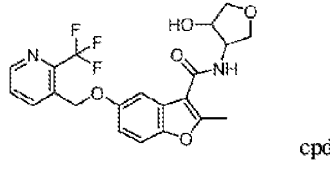
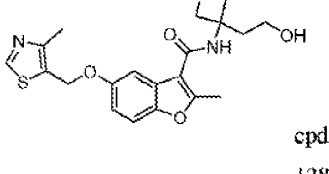
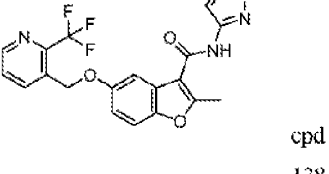
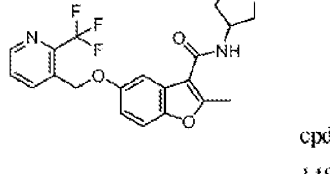
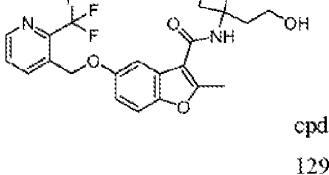
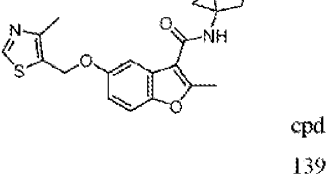
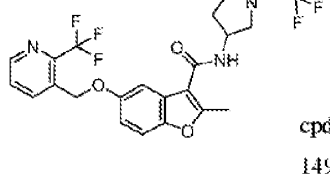
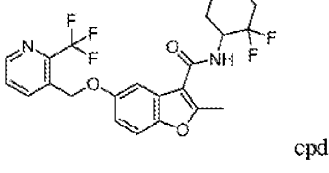
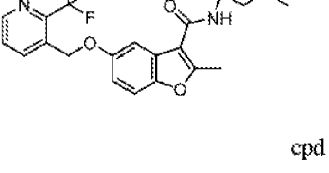
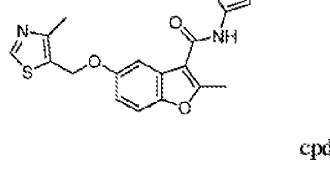
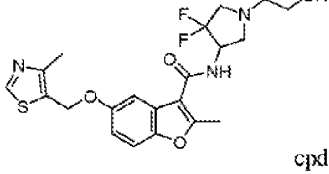
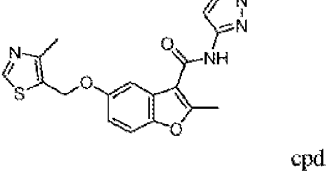
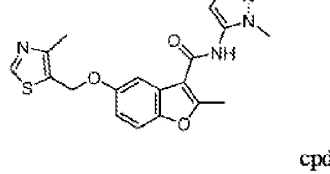
		
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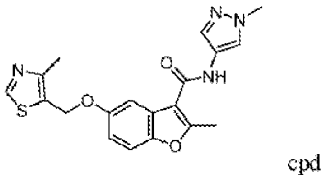
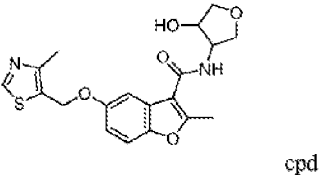
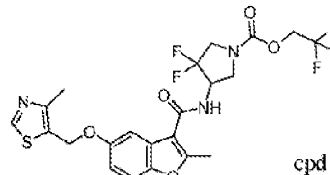
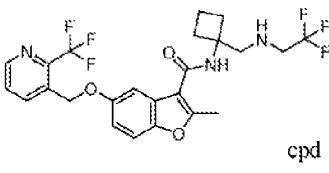
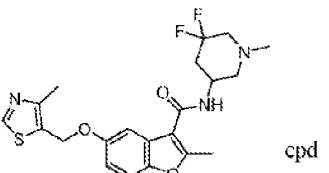
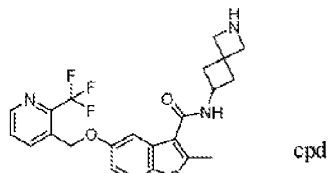
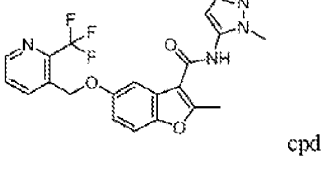
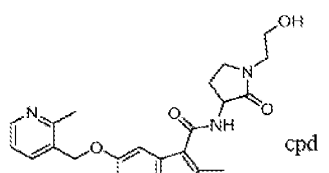
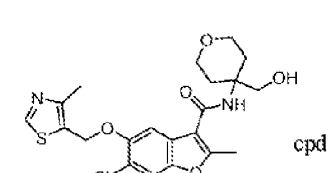
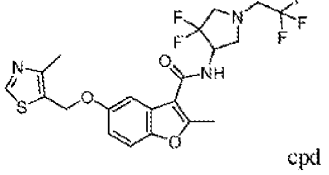
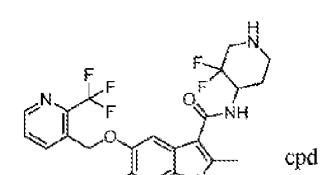
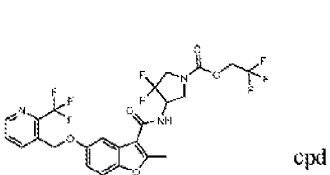
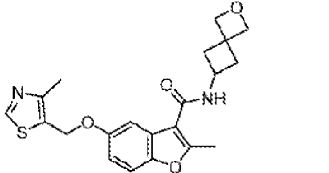
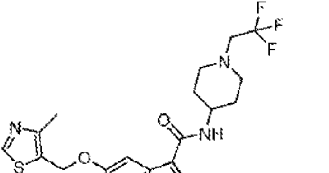
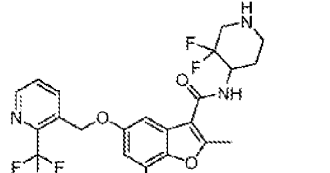
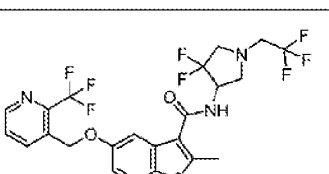
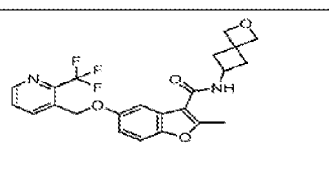
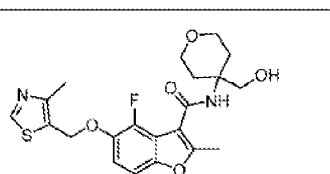
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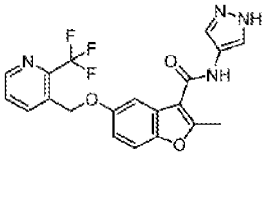
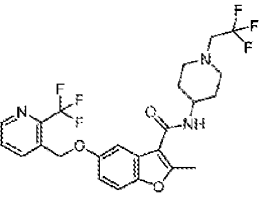
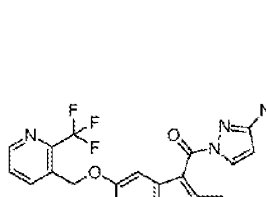
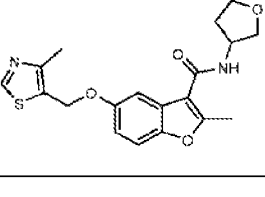
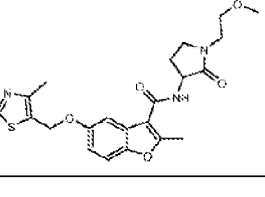
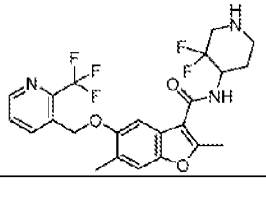
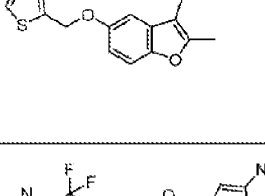
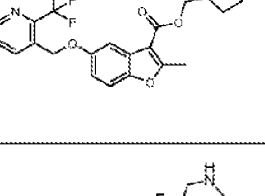
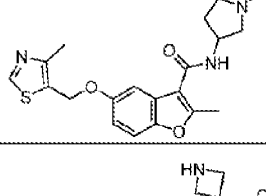
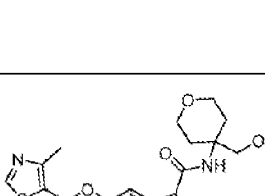
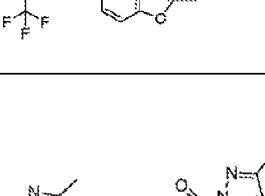
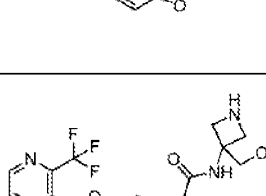
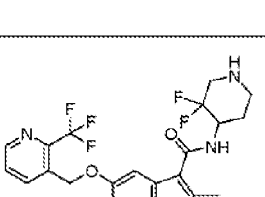
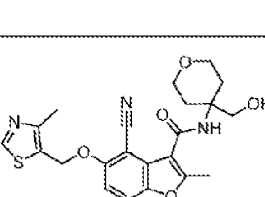
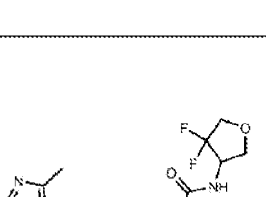
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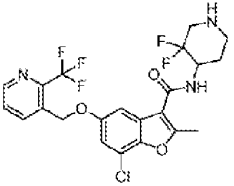
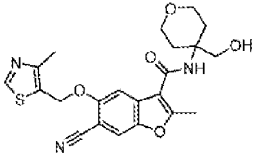
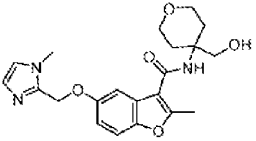
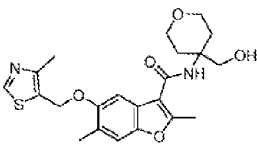
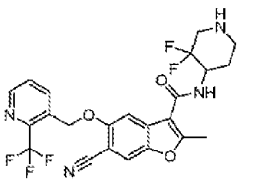
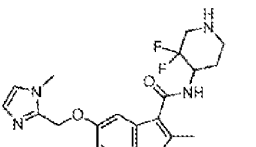
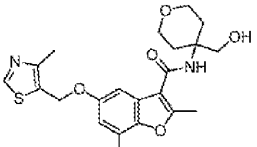
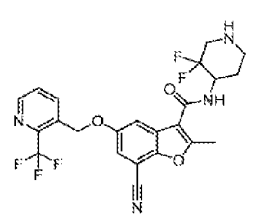
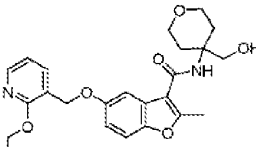
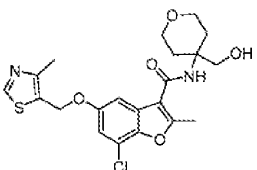
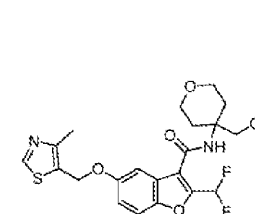
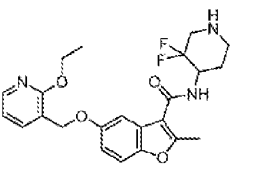
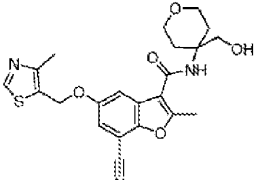
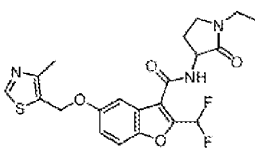
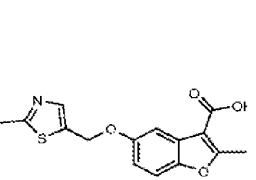
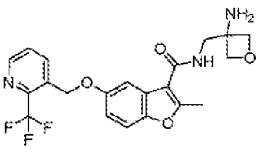
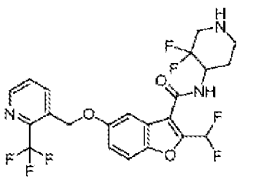
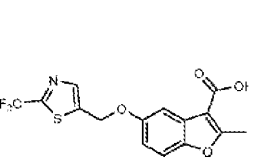
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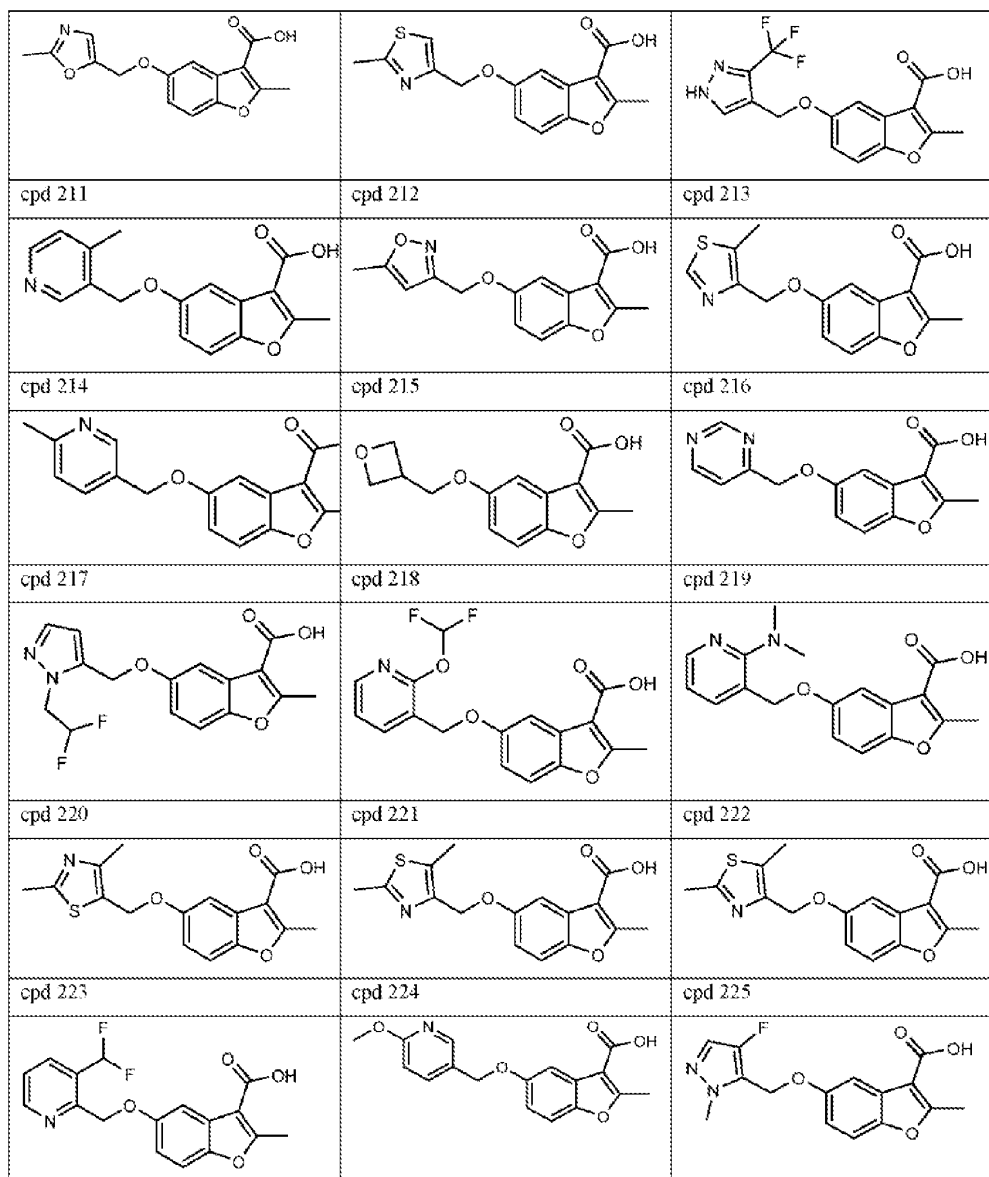
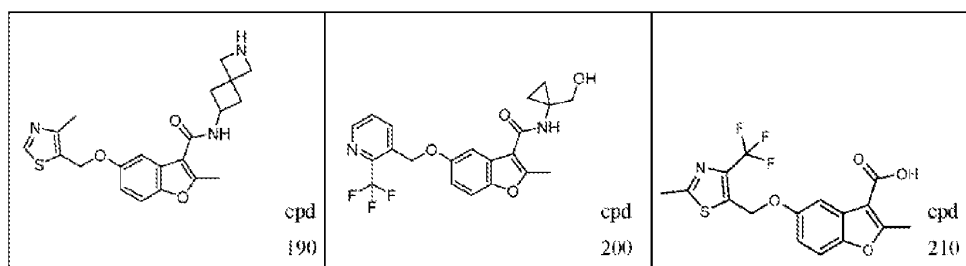
		
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cpd 125	cpd 135	cpd 145

 cpd 126	 cpd 136	 cpd 146
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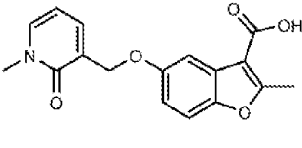
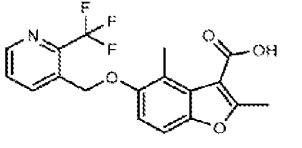
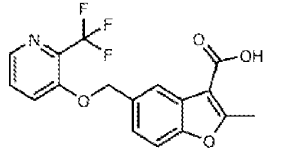
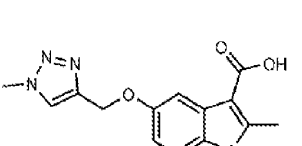
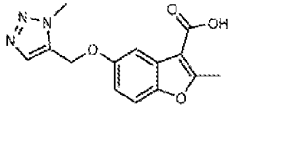
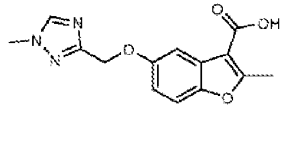
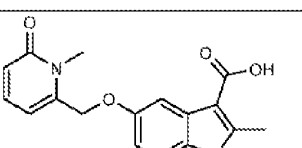
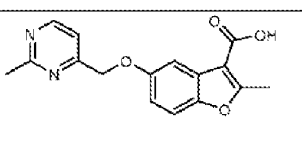
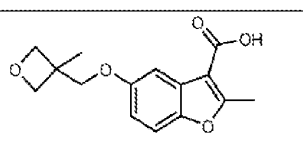
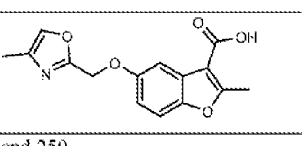
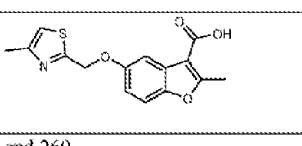
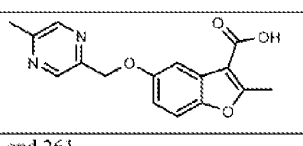
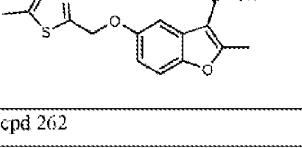
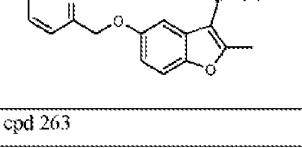
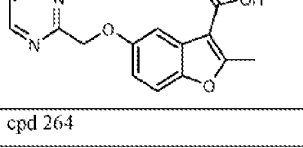
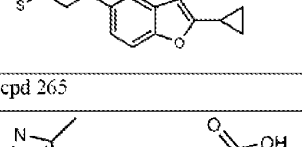
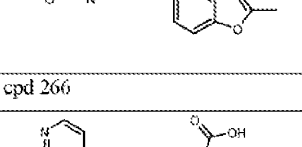
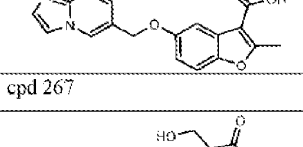
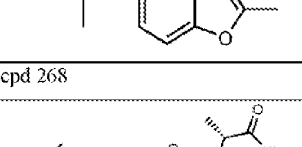
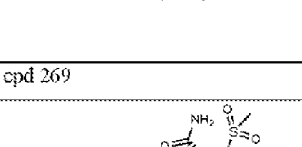
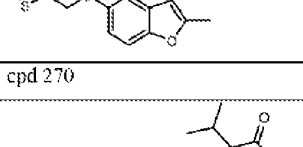
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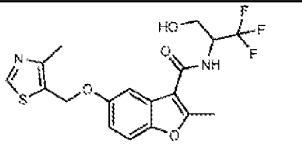
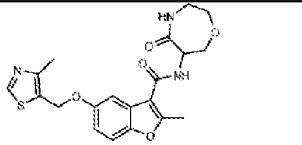
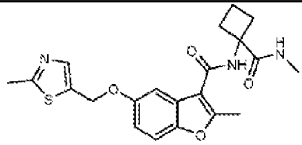
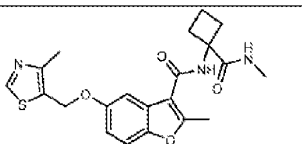
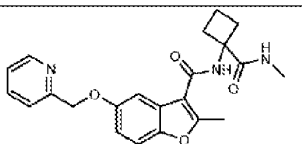
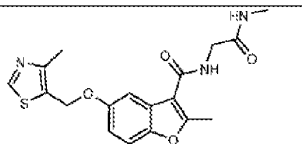
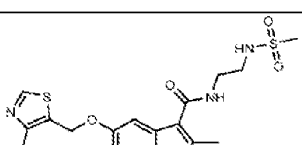
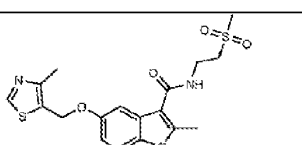
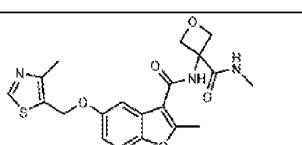
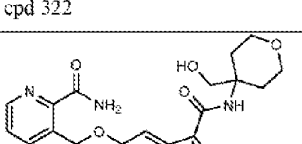
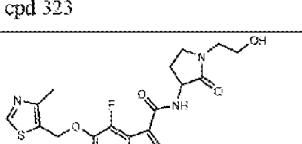
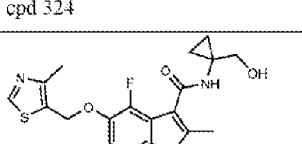
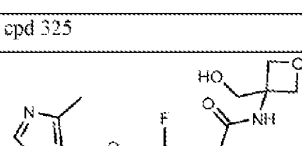
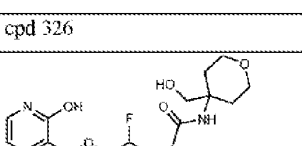
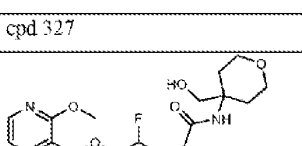
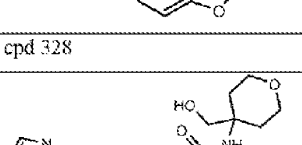
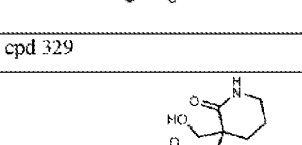
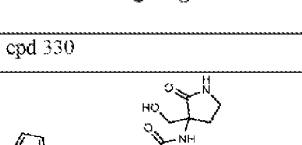
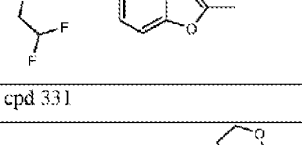
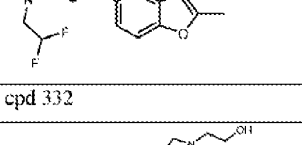
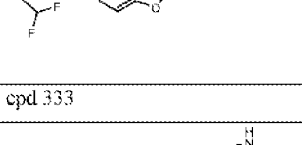


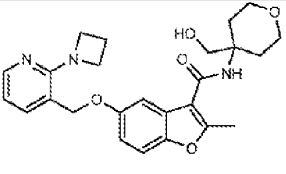
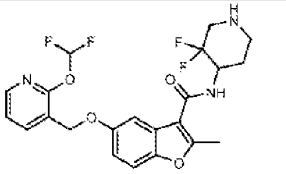
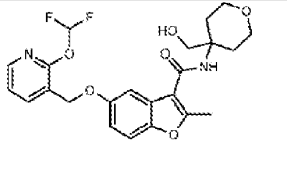
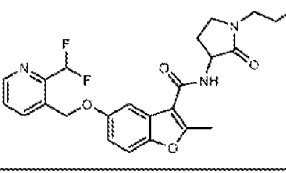
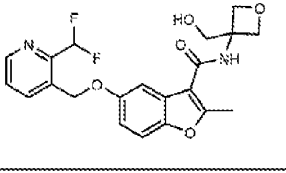
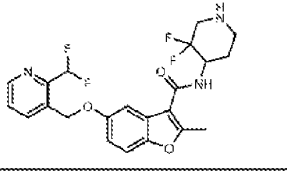
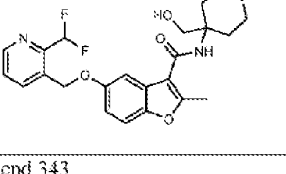
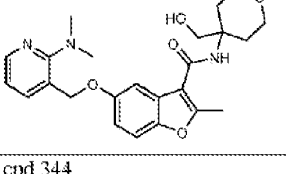
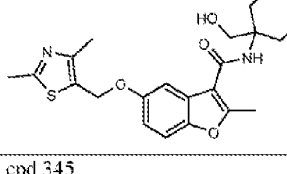
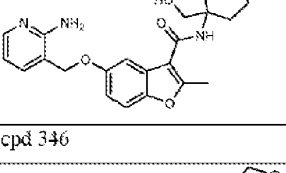
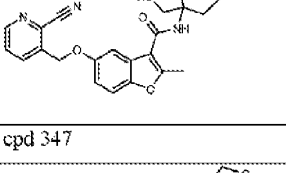
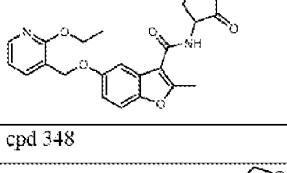
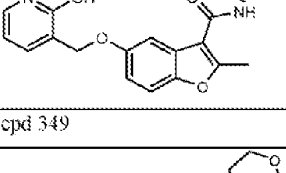
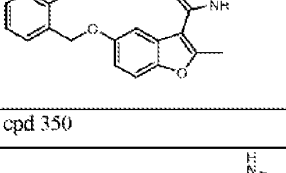
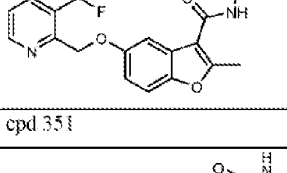
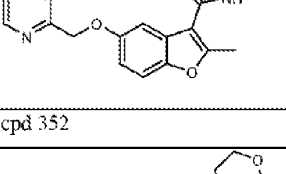
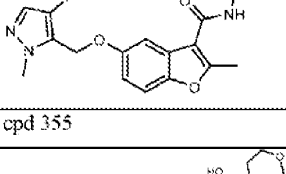
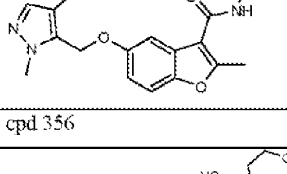
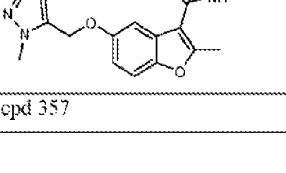
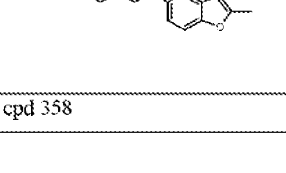
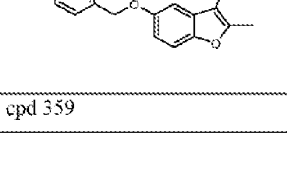
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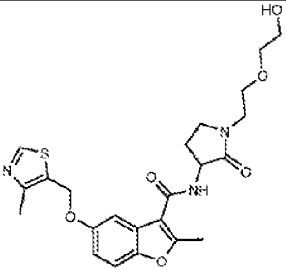
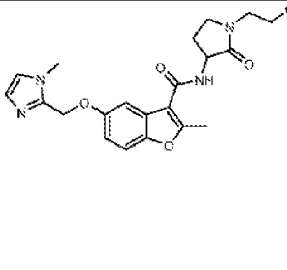
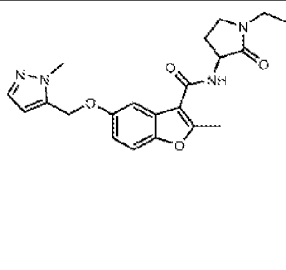
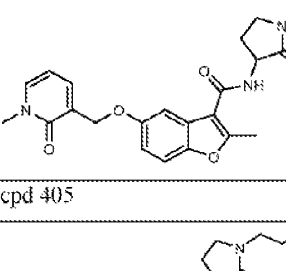
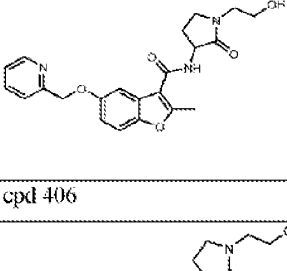
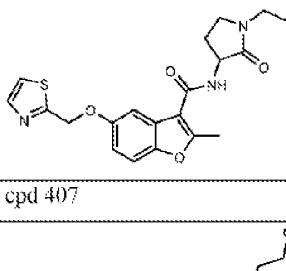
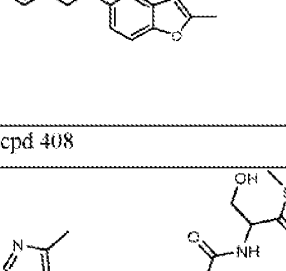
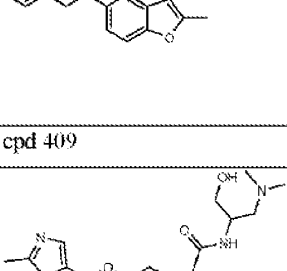
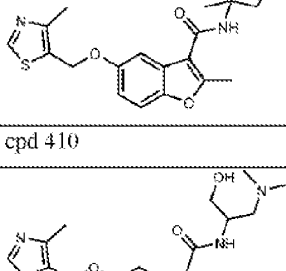
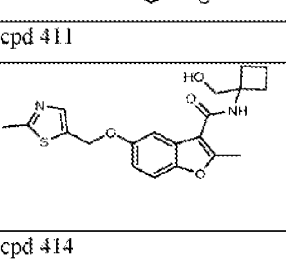
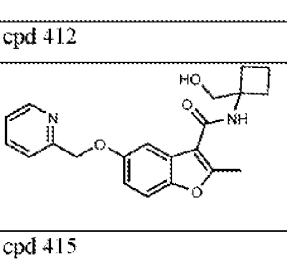
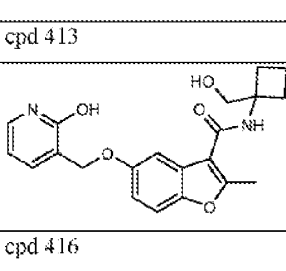
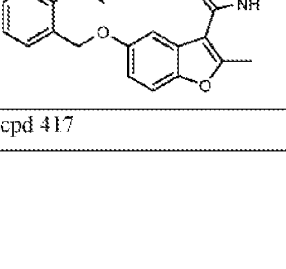
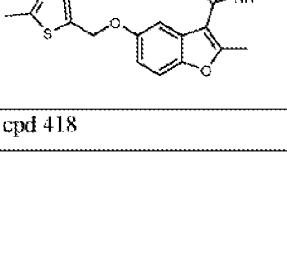
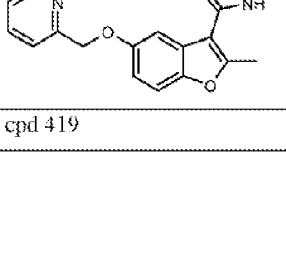
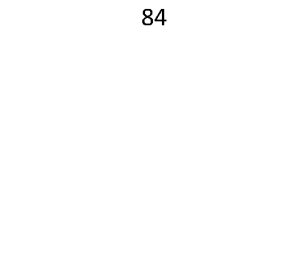
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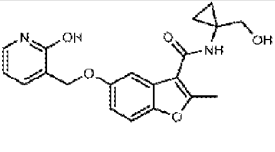
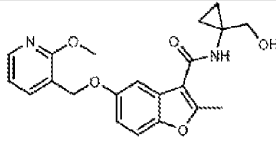
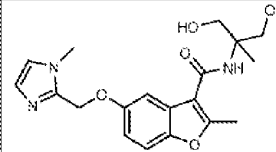
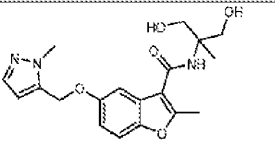
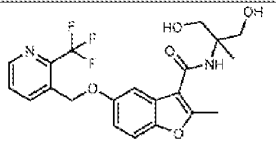
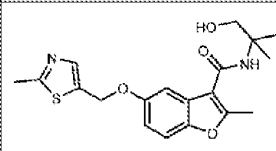
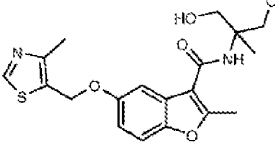
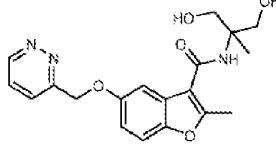
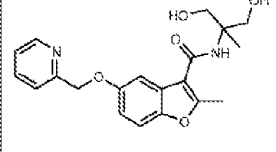
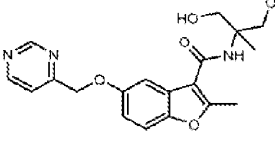
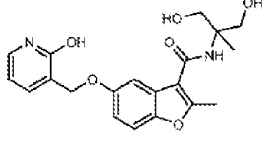
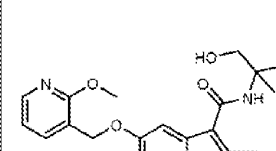
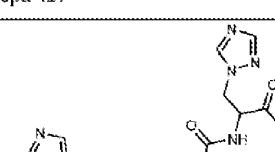
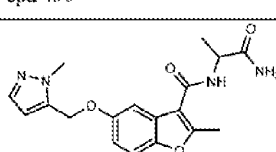
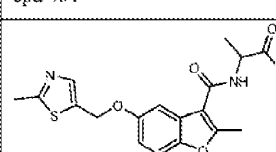
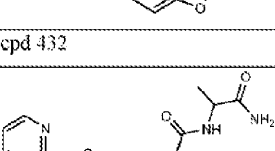
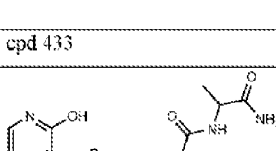
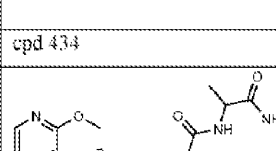
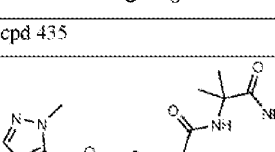
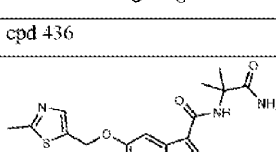
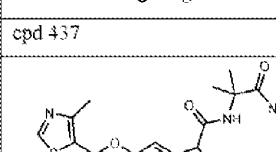
		
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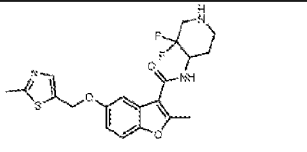
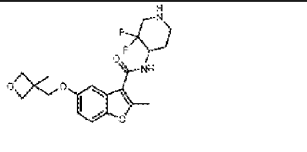
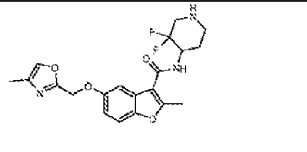
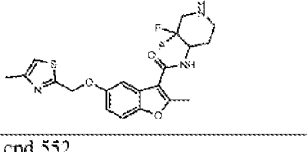
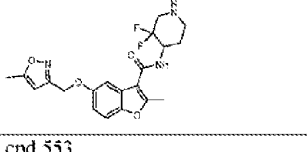
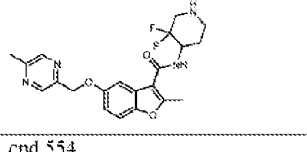
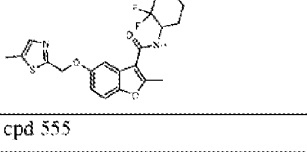
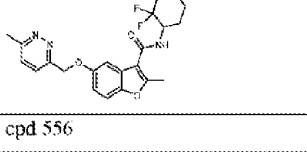
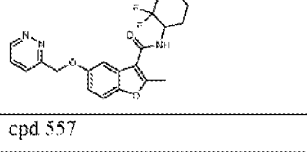
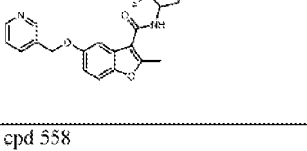
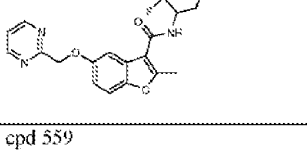
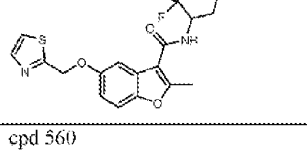
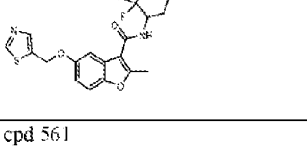
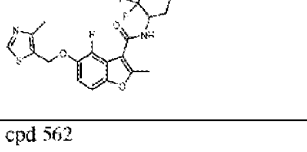
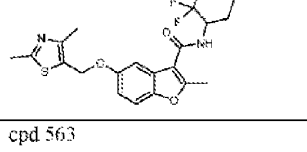
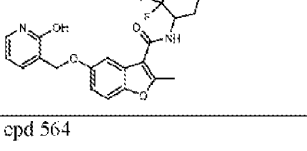
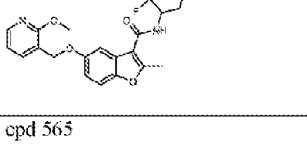
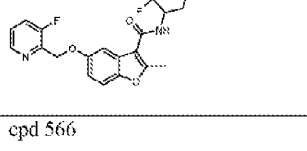
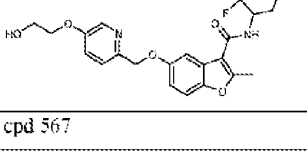
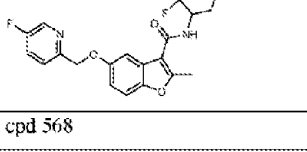
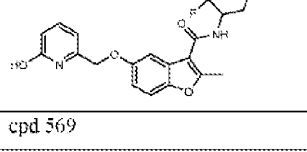
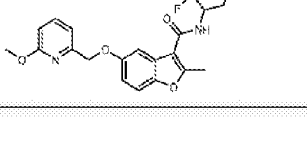
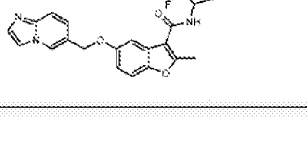
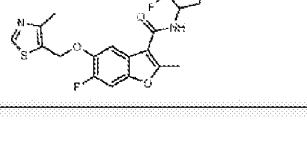
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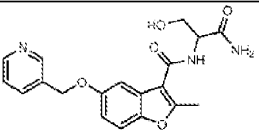
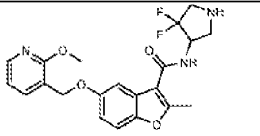
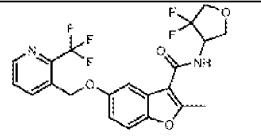
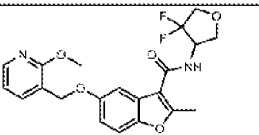
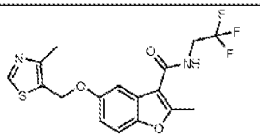
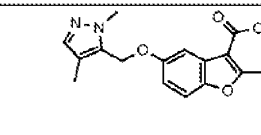
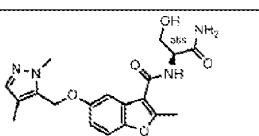
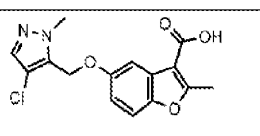
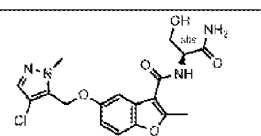
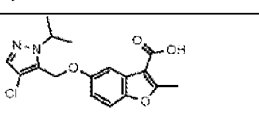
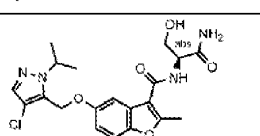
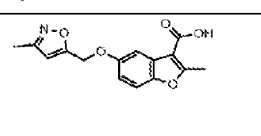
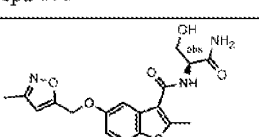
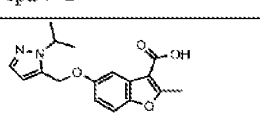
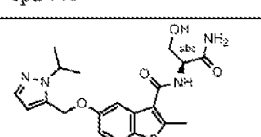
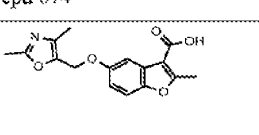
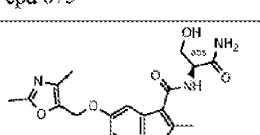
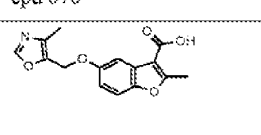
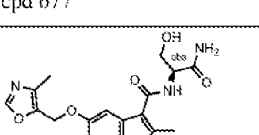
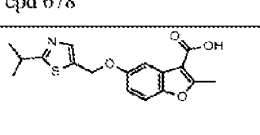
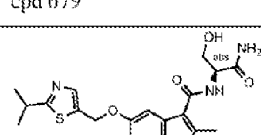
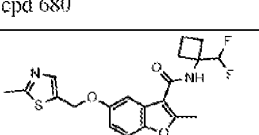
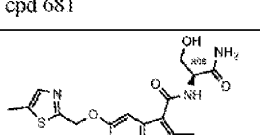
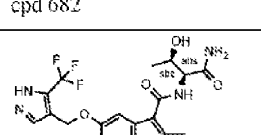
		
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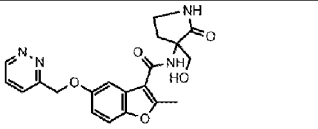
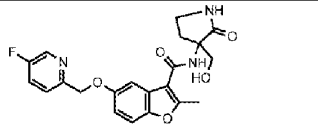
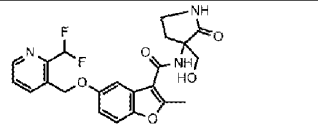
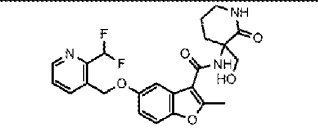
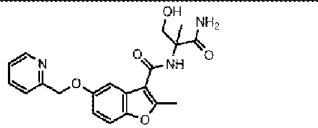
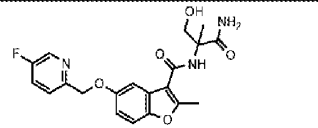
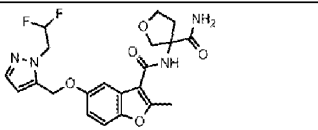
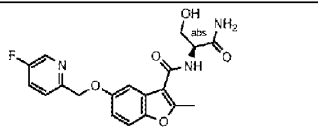
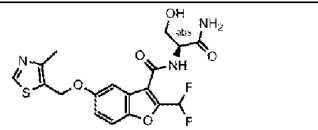
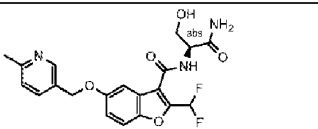
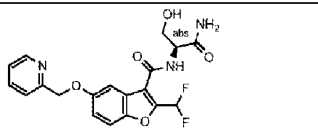
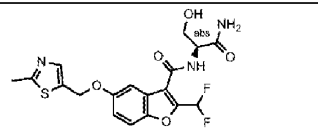
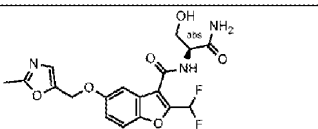
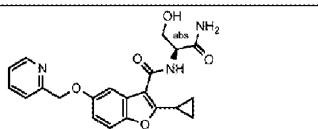
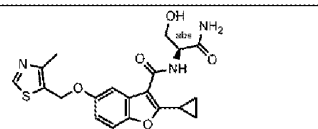
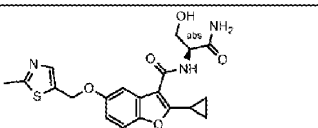
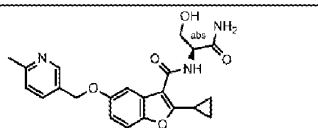
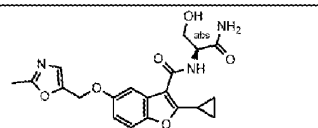
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cpd 650	cpd 651	cpd 652
cpd 653	cpd 654	cpd 655
cpd 656	cpd 657	cpd 658
cpd 659	cpd 660	cpd 661

		
cpd 662	cpd 663	cpd 664
		
cpd 665	cpd 666	cpd 667
		
cpd 668	cpd 669	cpd 670
		
cpd 671	cpd 672	cpd 673
		
cpd 674	cpd 675	cpd 676
		
cpd 677	cpd 678	cpd 679
		
cpd 680	cpd 681	cpd 682
		
cpd 683	cpd 684	cpd 685

cpd 686	cpd 687	cpd 688
cpd 689	cpd 690	cpd 691
cpd 692	cpd 693	cpd 694
cpd 695	cpd 696	cpd 697
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cpd 701	cpd 702	cpd 703
cpd 704	cpd 705	cpd 706
cpd 707	cpd 708	cpd 709

cpd 710	cpd 711	cpd 712
cpd 713	cpd 714	cpd 715
cpd 716	cpd 717	cpd 718
cpd 719	cpd 720	cpd 721
cpd 722	cpd 723	cpd 724
cpd 725	cpd 726	cpd 727
cpd 728	cpd 729	cpd 730
cpd 731	cpd 732	cpd 733

3.

		
cpd 734	cpd 735	cpd 736
		
cpd 737	cpd 738	cpd 739
		
cpd 740	cpd 741	cpd 742
		
cpd 743	cpd 744	cpd 745
		
cpd 746	cpd 747	cpd 748
		
cpd 749	cpd 750	cpd 751

5. The pharmaceutical composition of claim 3, wherein the TRPM3 modulator is a compound selected from the group consisting of:

- 5 (S)-N-(1-amino-2-methyl-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide;
- (S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide; and
- (S)-N-(1-amino-2-methyl-3-hydroxy-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((2-methylthiazol-5-yl)methoxy)benzofuran-3-carboxamide.

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6. The pharmaceutical composition of any one of claims 1 to 5, further comprising gelatin as a carrier.

7.The pharmaceutical composition of claim 6, wherein the gelatin comprises fish gelatin.

8.The pharmaceutical composition of any one of claims 1 to 7, further comprising a filler.

5 9.The pharmaceutical composition of claim 8, wherein the filler comprises mannitol.

10.The pharmaceutical composition of any one of claims 1 to 9, comprising from about 70-80 weight% of the TRPM3 modulator, about 10-20 weight% gelatin, about 10-20 weight% of filler, and optionally 0.1-5.0 weight% of a flavorant.

10

11.The pharmaceutical composition of any one of claims 1 to 10, in the form of a unit dosage form comprising about 100 mg to about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

15

12.The pharmaceutical composition of claim 11, comprising about 100 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

13.The pharmaceutical composition of claim 11, comprising about 150 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

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14.The pharmaceutical composition of claim 11, comprising about 200 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

15.The pharmaceutical composition of claim 11, comprising about 250 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

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16.The pharmaceutical composition of claim 11, comprising about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

30

17.The pharmaceutical composition of any one of claims 1 to 16, wherein the pharmaceutical composition is capable of disintegrating or dispersing within an interval selected from 1 to 60 seconds, 1 to 30 seconds, 1 to 10 seconds, and 2 to 8 seconds, after being placed in contact with a fluid.

18. The pharmaceutical composition of claim 17, wherein the fluid comprises saliva.
19. The use of a pharmaceutical composition of any one of claims 1 to 18 for the treatment of pain.
- 5 20. The use of a pharmaceutical composition of any one of claims 1 to 18 for the manufacture of a medicament for the treatment of pain.
- 10 21. A method of treating pain in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a TRPM3 modulator, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in a form of an oral solid molded fast-dispersing dosage form.
- 15 22. The method of claim 21, wherein the oral solid molded fast-dispersing dosage form is administered orally to the patient to dissolve in the oral cavity of the patient.
23. The method of claim 21, wherein the oral solid molded fast-dispersing dosage form is administered without coadministration of water or other fluid.
- 20 24. The method of claim 21, wherein the pharmaceutical composition further comprises gelatin as a carrier.
- 25 25. The method of any one of claims 21 to 24, wherein the pharmaceutical composition further comprises mannitol as a filler.
- 26 26. The method of any one of claims 21 to 25, wherein the pharmaceutical composition comprises from about 70-80 weight% of the TRPM3 modulator, about 10-20 weight% fish gelatin, about 10-20 weight% of a filler, and 0.1-5.0 weight% of a flavorant.
- 30 27. The method of any one of claims 21 to 26, in the form of a unit dosage form comprising about 100 mg to about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.
28. The method of claim 27, comprising about 100 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

29. The method of claim 27, comprising about 150 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

5 30. The method of claim 27, comprising about 200 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

31. The method of claim 27, comprising about 250 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

10 32. The method of claim 27, comprising about 300 mg of the TRPM3 modulator or a pharmaceutically acceptable salt thereof.

33. The method of any one of claims 21 to 32, wherein the pharmaceutical composition is capable of disintegrating or dispersing within an interval selected from 1 to 60 seconds, 1 to 30 seconds, 1 to 10
15 seconds, and 2 to 8 seconds, after being placed in contact with a fluid.

34. The method of claim 33, wherein the fluid comprises saliva.

35. The method of any one of claims 21 to 34, wherein the TRPM3 modulator is any one of
20 compounds 1 to 751 as described in the specification.

34. The method of any one of claims 21 to 34, wherein the TRPM3 modulator is a compound selected from the group consisting of:

(S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-
25 yl)methoxy)benzofuran-3-carboxamide;
(S)-N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)benzofuran-
3-carboxamide; and
(S)-N-(1-amino-3-hydroxy-2-methyl-1-oxopropan-2-yl)-2-(difluoromethyl)-5-((2-methylthiazol-5-
yl)methoxy)benzofuran-3-carboxamide.

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