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(54) **Title**: TRPV4 ANTAGONISTS

(57) **Abstract**: The present invention relates to diazabicyclo[2.2.1]hept-2-yl analogs, pharmaceutical compositions containing them and their use as TRPV4 antagonists.

TRPV4 ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to diazabicyclo[2.2.1]hept-2-yl analogs, pharmaceutical compositions containing them and their use as TRPV4 antagonists.

BACKGROUND OF THE INVENTION

Heart failure results in the decreased ability of the left ventricle to pump blood into the peripheral circulation as indicated by a reduced ejection fraction. This increases the end diastolic pressure and pulmonary blood pressure, placing the septal barrier at risk, which serves to separate the circulatory aqueous environment and the alveolar airspaces of the lung. Increased pulmonary pressure results in the flow of fluid from the pulmonary circulation into the alveolar space resulting in lung edema/congestion, as is observed in patients with congestive heart failure.

TRPV4 is a member of the Transient Receptor Potential (TRP) superfamily of cation channels (Plant TD, Strotmann R. 2007. *Handb Exp Pharmacol* **179**: 189-205) and is activated by heat, demonstrating spontaneous activity at physiological temperatures (Guler et al. 2002. *J Neurosci* **22**: 6408-6414). TRPV4 is also activated by physical cell stress (Strotmann et al. 2000. *Nat Cell Biol* **2**: 695-702), through phospholipase A2 activation and production of arachidonic acid and epoxyeicosatrienoic acids (Vriens et al. 2004. *Proc Natl Acad Sci U S A* **101**: 396-401). TRPV4 is expressed in the lung (Delany et al. 2001. *Physiol. Genomics* **4**: 165-174) and has been shown to mediated Ca^{2+} entry in isolated endothelial cells (Vriens et al. 2005. *Circ Res* **97**: 908-15). Endothelial cells are responsible for forming the capillary vessels that mediate oxygen/carbon dioxide exchange, contributing to the septal barrier in the lung. Activation of TRPV4 channels results in contraction of endothelial cells in culture and cardiovascular collapse *in vivo*, at least partially due to the enhanced filtration at the septal barrier resulting in lung edema and hemorrage (Alvarez et al. 2006. *Circ Res* **99**: 988-95). Indeed filtration at the septal barrier is increased in response to increased vascular and/or airway pressures and this response is dependent on the activity of TRPV4 channels (Jian et al. 2007 *Am J Respir Cell Mol Biol* doi:10.1165/rcmb.2007-0192OC; Hamanaka et al. 2007. *Am J Physiol* **293**: L923-32). Overall this suggests a clinical benefit of inhibiting TRPV4 function in the treatment of heart failure associated lung congestion, and in other pathological conditions with symptoms of lung edema/congestion, including a number of respiratory disorders.

In addition, TRPV4 channels have recently been implicated in urinary bladder function (Birder L, et al. 2007. *J Pharmacol Exp Ther* **323**: 227-235.; Gevaert et al. 2007 *J Clin Invest*. **117**: 3453-62) and are likely to provide therapeutic benefit for conditions of bladder overactivity, characterized by an increased urge to urinate and an enhancement of micturition frequency. The etiology is complex but generally results from dysfunctions of bladder based myogenic and/or neurogenic mechanisms, alterations in control of bladder contractility and/or firing of bladder neurons. TRPV4 channels expressed within bladder

smooth muscle cells (Birder L, et al. 2007. *J Pharmacol Exp Ther* **323**: 227-235) are likely to act as sensors of bladder pressure/stretch/filling, contributing to bladder contraction and hyperactivity. In addition, TRPV4 expression in urothelial cells of the bladder regulate the release of transmitters, (Birder L, et al. 2007. *J Pharmacol Exp Ther* **323**: 227-235; Gevaert et al. 2007 *J Clin Invest*. **117**: 3453-62) that are known to sensitize sensory afferent nerves controlling bladder activity. TRPV4 is also likely to be expressed directly on afferent nerves providing a direct neuronal stimulation of the bladder (Facer et al. 2007. *BMC Neurol*. **7**: 11). These data suggest a clinically beneficial effect of inhibiting TRPV4, located on multiple cell types, on urinary bladder function that is likely to be effective in bladder disorders such as overactive bladder, interstitial cystitis and painful bladder syndrome.

In addition TRPV4 has been recently implicated in a number of other physiological/pathophysiological processes in which TRPV4 antagonists are likely to provide significant clinical benefit these include various aspects of pain (Todaka et al. 2004. *J Biol Chem* **279:** 35133-35138; Grant et al. 2007. *J Physiol* **578:** 715-733; Alessandri-Haber et al. 2006. *J Neurosci* **26**: 3864-3874), cardiovascular disease (Earley et al. 2005. *Circ Res* **97**: 1270-9; Yang et al. 2006. *Am. J Physiol.* **290**:L1267-L1276), and osteoarthritis (Muramatsu et al. 2007. *J. Biol. Chem.* **282**: 32158-67).

SUMMARY OF THE INVENTION

In one aspect this invention provides for diazabicyclo[2.2.1]hept-2-yl analogs, pharmaceutically acceptable salts thereof, and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of the compounds of Formula (I) as TRPV4 antagonists.

In another aspect, this invention provides for the use of the compounds of Formula (I) for treating and preventing conditions associated with TRPV4 imbalance.

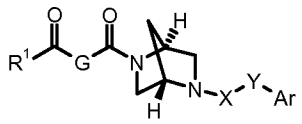
In yet another aspect, this invention provides for the use of the compounds of Formula (I) for the treatment or prevention of atherosclerosis, disorders related to intestinal edema, post-surgical abdominal edema, local and systemic edema, fluid retention, hypertension, inflammation, bone loss associated with immobilization and congestive heart failure, pulmonary disorders, sinusitis/rhinitis, asthma, overactive bladder, pain, cardiovascular disease, renal dysfunction and osteoarthritis.

The TRPV4 antagonist may be administered alone or in conjunction with one or more other therapeutic agents, eg. agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotension II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, beta blocker, aldosterone antagonists, iontropes, NSAIDS, nitric oxide donors, calcium channel modulators, muscarinic antagonists, steroidal anti-inflammatory drugs, bronchodilators, Leukotriene antagonist, HMG-CoA reductase inhibitors, dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists and type-5 phosphodiesterase inhibitors.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

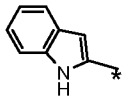
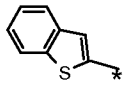
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):

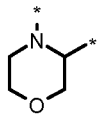
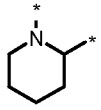
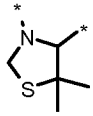


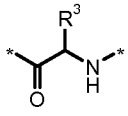
(I)

wherein:

R^1 is:  or  ; both of which may be unsubstituted or substituted with one, two, or three substituents chosen from C_{1-3} alkyl, OCF_3, OC_{1-3} alkyl, halogen, CF_3, or CN;

Ar is phenyl which may be unsubstituted or substituted with one to four substituents chosen from: halogen, C_{1-3} alkyl, CN, NO_2, NH_2, N_3, OC_{1-3}alkyl, OCF_3, CF_3, or phenyl;

G is  ,  ,  ,  , or  ;

X is  ;

R^3 is H, C_{1-4} alkyl which maybe unsubstituted or substituted with OH, OC_1-C_4 alkyl; and
Y is SO_2 or CH_2
or a pharmaceutically acceptable salt thereof.

"Alkyl" refers to a monovalent saturated hydrocarbon chain having the specified number of member atoms. For example, C_{1-4} alkyl refers to an alkyl group having from 1 to 4 member atoms. Alkyl groups may be straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl includes methyl, ethyl, propyl (n-propyl and isopropyl), and butyl (n-butyl, isobutyl, and t-butyl).

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine, and fluoro, chloro, bromo, and iodo, respectively.

"Substituted" in reference to a group indicates that one or more hydrogen atom attached to a member atom within the group is replaced with a substituent selected from the group of defined substituents. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with the permitted

valence of the substituted atom and the substituent and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation such as by rearrangement, cyclization, or elimination and that is sufficiently robust to survive isolation from a reaction mixture). When it is stated that a group may contain one or more substituents, one or more (as appropriate) member atoms within the group may be substituted. In addition, a single member atom within the group may be substituted with more than one substituent as long as such substitution is in accordance with the permitted valence of the atom. Suitable substituents are defined herein for each substituted or optionally substituted group.

With regard to stereoisomers, the compounds of Formula (I) may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

As used herein, “pharmaceutically acceptable” refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The skilled artisan will appreciate that pharmaceutically acceptable salts of the compounds according to Formula (I) may be prepared. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

In certain embodiments, compounds according to Formula (I) may contain an acidic functional group and are, therefore, capable of forming pharmaceutically acceptable base addition salts by treatment with a suitable base. Examples of such bases include a) hydroxides, carbonates, and bicarbonates of sodium, potassium, lithium, calcium, magnesium, aluminium, and zinc; and b) primary, secondary, and tertiary amines including aliphatic amines, aromatic amines, aliphatic diamines, and hydroxy alkylamines such as methylamine, ethylamine, 2-hydroxyethylamine, diethylamine, triethylamine, ethylenediamine, ethanolamine, diethanolamine, and cyclohexylamine.

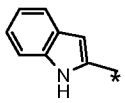
In certain embodiments, compounds according to Formula (I) may contain a basic functional group and are therefore capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and organic acids. Representative pharmaceutically acceptable acids include hydrogen chloride, hydrogen bromide, nitric acid, sulfuric acid, sulfonic acid, phosphoric acid, acetic acid, hydroxyacetic acid, phenylacetic acid, propionic acid, butyric acid, valeric acid, maleic acid, acrylic acid, fumaric acid, malic acid, malonic acid, tartaric acid, citric acid, salicylic acid, benzoic acid, tannic acid, formic acid, stearic acid, lactic acid, ascorbic acid, *p*-toluenesulfonic acid, oleic acid, lauric acid, and the like.

As used herein, the term “a compound of Formula (I)” or “the compound of Formula (I)” refers to one or more compounds according to Formula (I). The compound of Formula (I) may exist in solid or liquid form. In the solid state, it may exist in crystalline or noncrystalline form, or as a mixture thereof. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline compounds wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve non-aqueous solvents such as, but not limited to, ethanol, isopropanol, DMSO, acetic acid, ethanolamine, or ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

The skilled artisan will further appreciate that certain compounds of the invention that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." The invention includes all such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

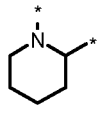
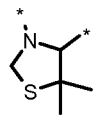
Representative Embodiments

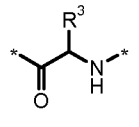
In one embodiment:

R^1 is  unsubstituted or substituted by halo;

Ar is phenyl which may be unsubstituted or substituted with one or two substituents chosen from: halogen, C_{1-3} alkyl, CF_3, or OC_{1-3}alkyl;

G is

 , or  ;

X is  ;

R^3 is hydrogen; and
Y is SO_2;
Or a pharmaceutically acceptable salt thereof.

Specific examples of compounds of the present invention include the following:

2-Chloro-N-[2-((1S,4S)-5-{[(4R)-3-(1H-indol-2-ylcarbonyl)-5,5-dimethyl-1,3-thiazolidin-4-yl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide;

2-Chloro-N-[2-((1S,4S)-5-{[(2S)-1-(1H-indol-2-ylcarbonyl)-2-piperidinyl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide; and

2-Chloro-N-{2-[(1S,4S)-5-({(4R)-3-[(5-fluoro-1H-indol-2-yl)carbonyl]-5,5-dimethyl-1,3-thiazolidin-4-yl}carbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-oxoethyl}-5-(trifluoromethyl)benzenesulfonamide;
or a pharmaceutically acceptable salt thereof.

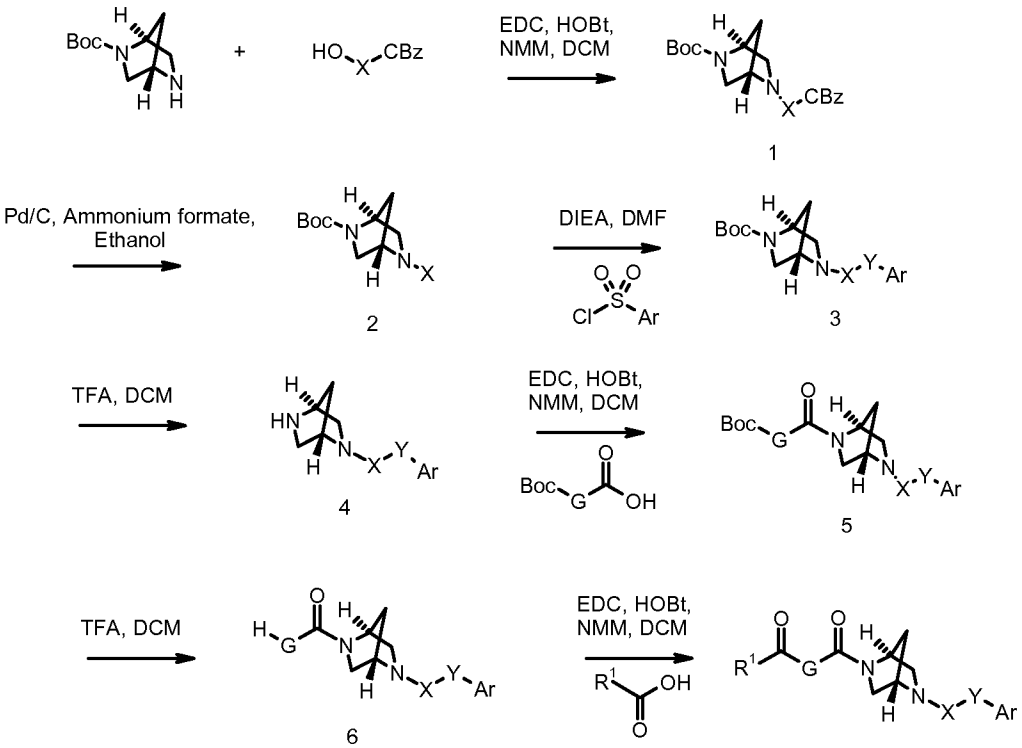
Compound Preparation

The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999). In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound or is a desired substituent in a target compound.

The synthesis of the compounds of the general Formula (I) and pharmaceutically acceptable derivatives and salts thereof may be accomplished as outlined below in Scheme 1. In the following description, the groups are as defined above for compounds of Formula (I) unless otherwise indicated. Starting materials are commercially available or are made from commercially available starting materials using methods known to those skilled in the art.

The compounds of Formula (I) and pharmaceutically acceptable derivatives and salts thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups are as defined above for compounds of Formula (I) unless otherwise indicated.

Scheme 1



The compounds of Formula (I) can be prepared using reactions described in Scheme 1. The free secondary amine of *N*-Boc-(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane can be coupled to a carboxylic acid such as, but not limited to, *N*-{[(phenylmethyl)oxy]carbonyl}glycine under conditions common to the art such as EDC in the presence of a base such as *N*-methylmorpholine or triethylamine, and a coupling modifier such as HOBt to provide the amide intermediate **1**. Subsequent CBz deprotection under standard conditions such as by treatment with Pd/C in the presence of ammonium formate and EtOH provides the amine intermediate **2**. Treatment of intermediate **2** with an appropriate electrophilic reagent such as appropriately substituted sulfonyl chloride in the presence of an amine base such as triethylamine under conditions common to the art yielding intermediate **3**. Subsequent Boc deprotection of intermediate **3** can be accomplished under conditions common to the art such as treatment with an acid such as hydrochloric acid in 1,4-dioxane and methanol or TFA in dichloromethane to

provide the intermediate **4**. Treatment of intermediate **4** with an appropriate carboxylic acid under conditions common to the art such as EDC in the presence of a base such as *N*-methylmorpholine and a coupling modifier such as HOBt provides the BOC-protected amide intermediate **5**. Removal of the BOC protecting group of intermediate **5** can be accomplished under conditions common to the art such as treatment with an acid such as hydrochloric acid in 1,4-dioxane and methanol or TFA in dichloromethane yielding intermediate **6**. Subsequent treatment of intermediate **6** with an appropriate carboxylic acid under conditions common to the art such as EDC in the presence of a base such as *N*-methylmorpholine and a coupling modifier such as HOBt provides the compound of Formula (I).

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography, H.P.L.C. or SCF of a stereoisomeric mixture. Pure stereoisomer of the agent may also be prepared from the corresponding optically pure intermediate or by resolution, such as H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Biological Activity

As stated above, the compounds according to Formula I are TRPV4 antagonists, and are useful in the treatment or prevention of atherosclerosis, disorders related to intestinal edema, post-surgical abdominal edema, local and systemic edema, fluid retention, hypertension, inflammation, bone loss associated with immobilization and congestive heart failure, pulmonary disorders, sinusitis/rhinitis, asthma, overactive bladder, pain, cardiovascular disease, renal dysfunction and osteoarthritis.

The biological activity of the compounds according to Formula I can be determined using any suitable assay for determining the activity of a candidate compound as a TRPV4 antagonist, as well as tissue and in vivo models.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests.

Ligand-gated assay:

TRP channel activation/opening results in an influx of divalent and monovalent cations including calcium. The resulting changes in intracellular calcium are monitored using a calcium selective fluorescent dye Fluo4 (MDS Analytical Technologies). Dye loaded cells are initially exposed to test compound to verify a lack of agonist activity. Cells are subsequently activated by addition of an agonist and inhibition of the agonist–induced activation is recorded. Human embryonic kidney 293 cells stably expressing the macrophage scavenger receptor class II (HEK-293-MSR-II) and transduced with 1% BacMam (J.P. Condreay, S.M. Witherspoon, W.C. Clay and T.A. Kost, Proc Natl Acad Sci 96 (1999), pp. 127–132) virus expressing the human TRPV4 gene are plated at 15000 cells/well in a volume of 50 uL in a 384 well poly-D lysine coated plate. Cells are incubated for 24 hours at 37 degrees and 5% CO_2. Media is then aspirated using a Tecan Plate-washer and replaced with 20 uL of dye loading buffer: HBSS, 500 uM Brilliant Black

(MDS Analytical Technologies), 2 uM Fluo-4 (MDS Analytical Technologies). Dye loaded plates are then incubated in the dark at room temperature for 1-1.5 hours. 10 uL of test compound diluted in HBSS + 0.01% Chaps is added to the plate, incubated for 10 min at room temperature in the dark and then 10 uL of agonist is added at a final conc. equal to the agonist EC80. Calcium release is measured using the FLIPRtetra (MDS Analytical Technologies).

All examples described herein possessed TRPV4 biological activity with IC_{50}s ranges from 1 nM – 10 uM.

Hypotonicity assay:

TRP channel activation/opening results in an influx of divalent and monovalent cations including calcium. The resulting changes in intracellular calcium are monitored using a calcium selective fluorescent dye Fluo4 (InvitrogenTM). Dye loaded cells are initially exposed to test compound to verify a lack of agonist activity. Cells are subsequently activated by addition of a hypotonic buffer and inhibition of the hypotonicity–induced activation is recorded.

50 uL of HEK293 cells stably transformed with human TRPV4 are plated at 30K cells per well in 384 well poly-D-lysine coated plates. The following day, the media is removed and replaced with 50 uL of dye loading buffer (Fluo-4 from Invitrogen diluted 1:500 in DMEM/F12) then the cells are incubated for 1.5 hours at room temperature in the dark. Dye is then removed and replaced with 50 uL of 310mOsm isotonic buffer (130 mM NaCl, 2.5 mM KCl, 1 mg/mL D-glucose, 10 mM Hepes, 1.2 mM $MgCl_2$, 1.5 mM $CaCl_2$, 0.25% DMSO, pH 7.4) and incubated in dark at room temp for an additional hour. Test compounds are diluted in isotonic buffer to a final DMSO concentration of 0.25%. Using the Molecular Devices FLIPR instrument, 25 uL of diluted compound is added 30 seconds after start. At 8 minutes, 25 uL of 110-115 mOsm hypotonic buffer (2.5 mM KCl, 1 mg/mL D-glucose, 10 mM Hepes, 1.2 mM $MgCl_2$, 1.5 mM $CaCl_2$, 0.25% DMSO, 80 mM mannitol, pH 7.4) is added. Signal is recorded for a total of 20 minutes with reads every 4.5 seconds.

Alternatively, the following assay may be used.

BHK/AC9_DMEM/F12conditioned (Baby Hamster Kidney) cells are transduced with 2% BacMam virus expressing the human TRPV4 gene and are plated at 10K cells per well in a volume of 50uL in 384 well poly-D-lysine coated plates. Cells are incubated for 18-24 hours at 37 degrees and 5% CO_2. The following day, the media is aspirated using a Tecan Plate-washer and replaced with 20uL of dye loading buffer: HBSS buffer, 2.5mM Probenecid , 500 uM Brilliant Black, 2 uM Fluo-4. The dye loaded cells are incubated for 1-1.5 hours at room temperature in the dark. 10 uL of test compound diluted in HBSS/H_2O (~1:2.3) + 0.01% Chaps is added to the plate, incubated for 10 min at room temperature in the dark, and then 10uL of hypotonic buffer (H_2O + 1.5mM $CaCl_2$ + ~68mM NaCl; 140mOsm stock/260mOsm FAC) is used to test the inhibition of the hypotonicity–induced activation. Reaction is measured on a heated stage (37 degrees) using the FLIPRtetra (MDS Analytical Technologies).

Methods of Use

The compounds of the invention are TRPV4 antagonists, and are useful in the treatment or prevention of atherosclerosis, disorders related to intestinal edema, post-surgical abdominal edema, local and systemic edema, fluid retention, hypertension, inflammation, bone loss associated with immobilization, congestive heart failure, pulmonary disorders, sinusitis/rhinitis, asthma, overactive bladder, pain, cardiovascular disease, renal dysfunction and osteoarthritis. Accordingly, in another aspect the invention is directed to methods of treating such conditions.

The methods of treatment of the invention comprise administering a safe and effective amount of a compound according to Formula I or a pharmaceutically-acceptable salt thereof to a patient in need thereof.

As used herein, "treat" in reference to a condition means: (1) to ameliorate or prevent the condition or one or more of the biological manifestations of the condition, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the condition or (b) one or more of the biological manifestations of the condition, (3) to alleviate one or more of the symptoms or effects associated with the condition, or (4) to slow the progression of the condition or one or more of the biological manifestations of the condition.

As indicated above, "treatment" of a condition includes prevention of the condition. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological manifestation thereof.

As used herein, "safe and effective amount" in reference to a compound of the invention or other pharmaceutically-active agent means an amount of the compound sufficient to treat the patient's condition but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be routinely determined by the skilled artisan.

As used herein, "patient" refers to a human or other animal.

The compounds of the invention may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration, rectal administration, and administration by inhalation. Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or

infusion. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. Topical administration includes application to the skin as well as intraocular, otic, intravaginal, and intranasal administration.

The compounds of the invention may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

Typical daily dosages may vary depending upon the particular route of administration chosen. Typical dosages for oral administration range from 1 mg to 1000 mg per person per dose.

Additionally, the compounds of the invention may be administered as prodrugs. As used herein, a "prodrug" of a compound of the invention is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of the invention in vivo. Administration of a compound of the invention as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of the compound in vivo; (b) modify the duration of action of the compound in vivo; (C) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome or overcome a side effect or other difficulty encountered with the compound. Typical functional derivatives used to prepare prodrugs include modifications of the compound that are chemically or enzymatically cleaved in vivo. Such modifications, which include the preparation of phosphates, amides, esters, thioesters, carbonates, and carbamates, are well known to those skilled in the art.

Compositions

The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. Accordingly, in another aspect the invention is directed to pharmaceutical compositions comprising a compound of the invention and one or more pharmaceutically-acceptable excipient.

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of the invention can be extracted and then given to the patient such as with powders or syrups. Alternatively, the

pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a safe and effective amount of a compound of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically contain from 1 mg to 1000 mg.

The pharmaceutical compositions of the invention typically contain one compound of the invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. For example, in certain embodiments the pharmaceutical compositions of the invention contain two compounds of the invention. In addition, the pharmaceutical compositions of the invention may optionally further comprise one or more additional pharmaceutically active compounds.

As used herein, "pharmaceutically-acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must of course be of sufficiently high purity to render it pharmaceutically-acceptable.

The compound of the invention and the pharmaceutically-acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as dry powders, aerosols, suspensions, and solutions; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: Diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers,

sweetners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a safe and effective amount of a compound of the invention and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesuim stearate, calcium stearate, and talc.

The compounds may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotension II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, beta blocker, aldosterone antagonists, iontropes, NSAIDS, nitric oxide donors, calcium channel modulators, muscarinic antagonists, steroidal anti-inflammatory drugs, bronchodilators, Leukotriene antagonist, HMG-CoA reductase inhibitors, dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists and type-5 phosphodiesterase inhibitors.

EXAMPLES

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

In the Examples:

Chemical shifts are expressed in parts per million (ppm) units. Coupling constants (*J*) are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), m (multiplet), br (broad).

Flash column chromatography was performed on silica gel.

The naming program used is ACD Name Pro 6.02.

The following abbreviations and terms had the indicated meanings throughout:

BOC (*tert*-butyloxycarbonyl);

CBz (carbobenzoxy);

DMF (*N*,*N*-dimethylformamide);

DIEA (*N,N*-diisopropylethylamine);

DCM (dichloromethane);

DMSO (dimethylsulfoxide);

EDCI (1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide);

EDC (1-[3-dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride);

Fmoc (9-fluorenylmethoxycarbonyl);

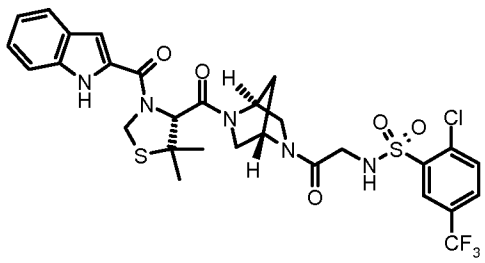
HOBT (1-hydroxybenzotriazole);

HOOBt (Hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine);

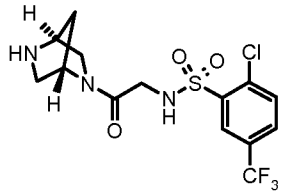
NMM (*N*-methyl morpholine);

TFA (trifluoroacetic acid);

Example 1



2-Chloro-*N*-[2-((1*S*,4*S*)-5-{[(4*R*)-3-(1*H*-indol-2-ylcarbonyl)-5,5-dimethyl-1,3-thiazolidin-4-yl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide



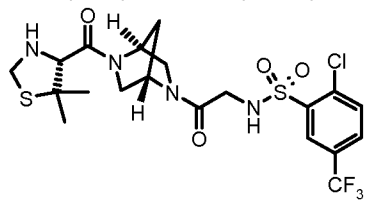
2-Chloro-*N*-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-oxoethyl}-5-(trifluoromethyl)benzenesulfonamide

To a 500 mL flask was added 1,1-dimethylethyl (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.0 g, 25.2 mmol), *N*-{[(phenylmethyl)oxy]carbonyl}glycine (7.91 g, 37.8 mmol), 1*H*-1,2,3-benzotriazol-1-ol hydrate (5.79 g, 37.8 mmol) and DCM (250 mL). Next EDC (14.45 g, 76 mmol) was added followed by 4-methylmorpholine (13.86 mL, 126 mmol). The reaction was stirred overnight, then diluted with DCM, washed with saturated Na_2CO_3, 1N HCl, $NaHCO_3$, and brine. The organic layer was passed through a phase separator and concentrated to afford the crude bis-protected amine as an off white solid.

To the residue was added ethanol (100 mL), 10% palladium on carbon (4.03 g), and ammonium formate (15.90 g, 252 mmol). The reaction mixture was stirred at room temperature overnight, then filtered over celite eluting with ethanol and concentrated to afford the crude mono-protected amine.

The residue was dissolved in DCM (250 mL). To the mixture was added TEA (14.06 mL, 101 mmol), followed by 2-chloro-5-(trifluoromethyl)benzenesulfonyl chloride (8.45 g, 30.3 mmol). The mixture was stirred overnight at room temperature and then diluted with water. The organic layer was separated and washed with 1N HCl, then $NaHCO_3$. The organic layer was then passed over a phase separator and concentrated to afford the crude sulfonamide product.

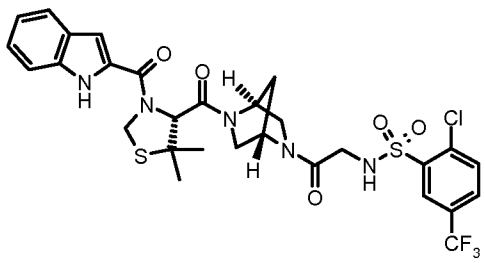
To this residue was added DCM (50 mL) followed by TFA (25 mL, 324 mmol). The reaction was stirred for 1h, and then concentrated under reduced pressure. The residue was then dissolved in a minimum amount of methanol, and purified over an SCX column eluting with methanol, then 2N-NH_3/methanol to release the product. Concentration of the ammonia-methanol solution afforded 6 g (60% yield) of the title compound as an off white solid. LCMS (m/z): 398.0 (M+H).



2-Chloro-*N*-[2-((1*S*,4*S*)-5-{[(4*R*)-5,5-dimethyl-1,3-thiazolidin-4-yl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide

To a 8 mL vial was added 2-chloro-*N*-{2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-oxoethyl}-5-(trifluoromethyl)benzenesulfonamide (300 mg, 0.754 mmol), 1*H*-1,2,3-benzotriazol-1-ol hydrate (173 mg, 1.131 mmol), DCM (4 mL), and (4*R*)-3-{[(1,1-dimethylethyl)oxy]carbonyl}-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (296 mg, 1.13 mmol). Next EDC (432 mg, 2.262 mmol) was added followed by 4-methylmorpholine (0.332 mL, 3.02 mmol). The mixture stirred overnight at room temperature and then diluted with saturated Na_2CO_3 and stirring continued for 30 min. The mixture was then poured into a phase separator and the DCM was collected and concentrated to afford the boc-amine product.

To the residue was added DCM (4 mL) followed by TFA (3 mL). The mixture was stirred for 1h and then concentrated under reduced pressure. The residue was then dissolved in a minimum amount of methanol, and purified over an SCX column eluting with methanol, then 2N-NH_3/methanol to release the product. Concentration of the ammonia-methanol solution afforded 375 mg (92% yield) of the title compound as an off white solid. LCMS (m/z): 541.1 (M+H).



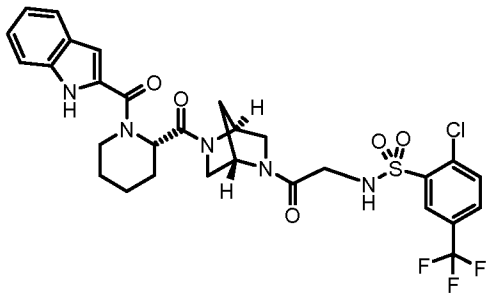
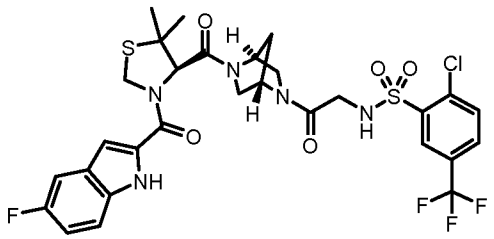
2-Chloro-*N*-[2-((1*S*,4*S*)-5-{[(4*R*)-3-(1*H*-indol-2-ylcarbonyl)-5,5-dimethyl-1,3-thiazolidin-4-yl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide

To a 3 mL vial was added 2-chloro-*N*-[2-((1*S*,4*S*)-5-{[(4*R*)-5,5-dimethyl-1,3-thiazolidin-4-yl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide (150 mg, 0.277 mmol), HOBT (46.8 mg, 0.347 mmol), 1*H*-indole-2-carboxylic acid (56 mg, 0.347 mmol) and DCM (2 mL). Next, EDC (159 mg, 0.832 mmol) was added followed by 4-methylmorpholine (0.122 mL, 1.109 mmol). The mixture stirred overnight at room temperature. The reaction mixture was then diluted with methanol, concentrated under reduced pressure, then re-dissolved in methanol, filtered and purified by reverse phase HPLC 30-80% ACN/Water (0.1% TFA) over 14 min. to give the title compound 10 mg (5.3%) as an off white solid. LCMS (m/z): 684.0 (M+H). 1H NMR (400 MHz, DMSO-d_6) δ 1.31 - 1.41 (m, 3 H), 1.54 - 1.69 (m, 3 H), 1.79 - 1.99 (m, 1 H), 3.15 – 3.30 (m, 2 H), 3.67 - 5.33 (m, 9 H), 6.84 - 7.03 (m, 3 H), 7.30 - 7.50 (m, 1 H), 7.51 - 7.76 (m, 1 H), 7.78 - 8.10 (m, 2H), 8.13 - 8.72 (m, 3 H), 11.33 - 12.05 (m, 1 H).

Examples 2-3

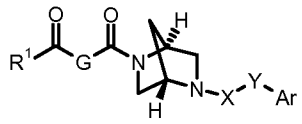
The compounds in Table 2 were prepared by a method similar to the one described for the preparation of 2-chloro-*N*-[2-((1*S*,4*S*)-5-{[(4*R*)-3-(1*H*-indol-2-ylcarbonyl)-5,5-dimethyl-1,3-thiazolidin-4-yl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide or Scheme 2. As is appreciated by those skilled in the art, these analogous examples may involve variations in synthetic procedure.

Table 1

Ex #	Structure	Name	MS $[M+H]^+$
2		2-chloro-N-[2-((1S,4S)-5-{[(2S)-1-(1H-indol-2-ylcarbonyl)-2-piperidinyl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide	674.0 (M+Na)
3		2-chloro-N-{2-[(1S,4S)-5-({(4R)-3-[(5-fluoro-1H-indol-2-yl)carbonyl]-5,5-dimethyl-1,3-thiazolidin-4-yl}carbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-oxoethyl}-5-(trifluoromethyl)benzenesulfonamide	702.0

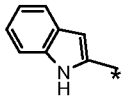
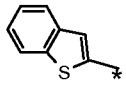
Claims:

1. A compound of Formula I:



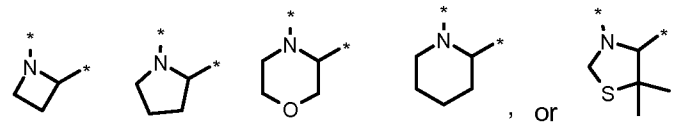
(I)

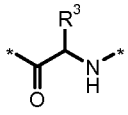
wherein:

R^1 is:  or  both of which may be unsubstituted or substituted with one, two, or three substituents chosen from C_1-$_3$ alkyl, OCF_3, OC_1-$_3$ alkyl, halogen, CF_3, or CN;

Ar is phenyl which may be unsubstituted or substituted with one to four substituents chosen from: halogen, C_1-$_3$ alkyl, CN, NO_2, NH_2, N_3, OC_1-$_3$alkyl, OCF_3, CF_3, or phenyl;

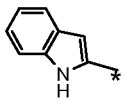
G is

 ;

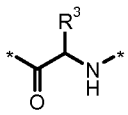
X is  ;

R^3 is H, C_1-$_4$ alkyl which maybe unsubstituted or substituted with OH, OC_1-C_4 alkyl; and
Y is SO_2 or CH_2
or a pharmaceutically acceptable salt thereof.

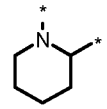
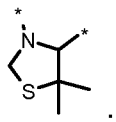
2. A compound of claim 1 wherein:

R^1 is  unsubstituted or substituted by halo;

Ar is phenyl which may be unsubstituted or substituted with one or two substituents chosen from: halogen, C_1-$_3$ alkyl, CF_3, or OC_1-$_3$alkyl;

X is  ;

G is


, or 
;

R^3 is hydrogen; and
Y is SO_2;
or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 chosen from:
2-Chloro-N-[2-((1S,4S)-5-{[(4R)-3-(1H-indol-2-ylcarbonyl)-5,5-dimethyl-1,3-thiazolidin-4-yl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide;

2-Chloro-N-[2-((1S,4S)-5-{[(2S)-1-(1H-indol-2-ylcarbonyl)-2-piperidinyl]carbonyl}-2,5-diazabicyclo[2.2.1]hept-2-yl)-2-oxoethyl]-5-(trifluoromethyl)benzenesulfonamide; and

2-Chloro-N-{2-[(1S,4S)-5-({(4R)-3-[(5-fluoro-1H-indol-2-yl)carbonyl]-5,5-dimethyl-1,3-thiazolidin-4-yl}carbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-oxoethyl}-5-(trifluoromethyl)benzenesulfonamide;
or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound of Formula (I) of claims 1–3 and a pharmaceutically acceptable carrier or excipient.

5. A method of treating congestive heart failure, overactive bladder, pain, cardiovascular disease, or osteoarthritis, which comprises administering to a patient in need thereof, a compound of Formula I of claims 1-3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/40615

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/58; A61K 31/21, 31/50 (2009.01)
USPC - 514/247-248, 511
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/247-248, 511

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/19, 214.03, 216, 247-249, 252.15, 255.05, 281, 365, 511 (text search - see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB); Google Patent; Google
Search terms used: TRPV4, transient receptor potential, diazabicyclo[2.2.1]hept-2-yl, carbonyl, sulfonyl, indole, benzothiophene, carboxamide, piperidinyl, antagonist, cardiovascular

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/070865 A2 (CASILLAS et al.) 21 June 2007 (21.06.2007) pg 3, ln 9-25; pg 6, ln 19; pg 8, ln 7-24; pg 9, ln 27-32; pg 45, ln 16-19; pg 69, ln 17-25; pg 72, ln 5-9	1-3
Y	US 6,677,336 B2 (ZABLOCKI et al.) 13 January 2004 (13.01.2004) col 21, ln 19-31, ln 36-62	1-3

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 2009 (15.05.2009)	29 MAY 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/40615

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-5
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.