(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2012 (27.12.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/176105 A1

(51) **International Patent Classification**:
A61K 31/404 (2006.01) *A61K 31/47* (2006.01)
A61K 31/407 (2006.01) *A61K 31/4985* (2006.01)
A61K 31/41 (2006.01) *A61P 11/00* (2006.01)
A61K 31/429 (2006.01)

(21) **International Application Number**:
PCT/IB2012/053049

(22) **International Filing Date**:
18 June 2012 (18.06.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
1813/MUM/2011 22 June 2011 (22.06.2011) IN

(71) **Applicant** *(for all designated States except US)*: **GLENMARK PHARMACEUTICALS SA** [CH/CH]; Chemin de la Combeta 5, CH-2300 La Chaux-de-Fonds (CH).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **KHAIRATKAR-JOSHI, Neelima** [IN/IN]; C-101, Devprayag CHS, Bhakti Mandir Road, Hari Niwas, Panchpakhadi, Thane (W) 400602 (IN). **KULKARNI, Abhay** [IN/IN]; Flat No. 703, Indra Vihar Society, Sector-20, Plot No. 20/21, Koparkhairne, Navi Mumbai 400709 (IN). **BHOSALE, Vikram Mansingh** [IN/IN]; D/18, Shivaji Nagar, G. D. Mahajani Road, Siwree, Mumbai 400015 (IN). **WALE, Dinesh Pradeep** [IN/IN]; At post-Mangrule, Taluka -Tuljapur, District-Osmanabad, Osmanabad 413601 (IN). **KADAM, Anil Hari** [IN/IN]; At- Mokal- Ohal, Post- Umbare, Tal- Rahuri, Dist- Ahmednagar, Ahmednagar 414105 (IN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2012/176105 A1

(54) **Title**: PHARMACEUTICAL COMPOSITION COMPRISING A TRPA1 ANTAGONIST AND A LEUKOTRIENE RECEPTOR ANTAGONIST

(57) **Abstract**: The present patent application relates to a pharmaceutical composition comprising a transient receptor potential ankyrin-1 receptor ("TRPA1") antagonist and a leukotriene receptor antagonist.

PHARMACEUTICAL COMPOSITION COMPRISING A TRPA1 ANTAGONIST AND A LEUKOTRIENE RECEPTOR ANTAGONIST

PRIORITY DOCUMENT

This patent application claims priority to Indian Provisional Patent Application number 1813/MUM/2011 (filed on Jun. 22, 2011), the contents of which are incorporated by reference herein.

TECHNICAL FIELD

The present patent application relates to a pharmaceutical composition comprising a transient receptor potential ankyrin-1 receptor ("TRPA1") antagonist and a leukotriene receptor antagonist. Particularly, the application provides a pharmaceutical composition comprising a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar with respect to TRPA1 activity and a leukotriene receptor antagonist; a process for preparing such composition; and its use in treating a respiratory disorder in a subject.

BACKGROUND

Respiratory disorders related to airway inflammation include a number of severe lung diseases such as asthma and chronic obstructive pulmonary disease ("COPD"). The airways of asthmatic patients are infiltrated by inflammatory leukocytes, of which the eosinophil is believed to be the most prominent component. Inflammatory sensitization of airway neurons is believed to increase nasal and cough sensitivity, heighten the sense of irritation, and promote fluid secretion, airway narrowing, and bronchoconstriction.

TRPA1 receptor activation in the airways by exogenous noxious stimuli, including cold temperatures (generally, less than about 17°C), pungent natural compounds (e.g., mustard, cinnamon and garlic), tobacco smoke, tear gas and environmental irritants as well as by endogenous biochemical mediators released during inflammation, is supposed to be one of the mechanisms for neurogenic

inflammation in the airways. Neurogenic inflammation is an important component of chronic airway diseases like COPD and asthma.

PCT Application Publication Nos. viz., WO 2004/055054, WO 2005/089206, WO 2007/073505, WO 2008/0949099, WO 2009/089082, WO 2009/002933 WO 2009/158719, WO 2009/144548, WO 2010/004390, WO 2010/109287, WO 2010/109334, WO 2010/109329, WO 2010/109328, WO 2010/125469 and WO 2010/004390 describe various transient receptor potential ("TRP") receptor modulators.

Leukotriene receptor antagonists are believed to act at the leukotriene receptors in tissues such as the bronchial smooth muscles and block the actions of leukotrienes at the receptor site. Leukotriene receptor antagonists (such as montelukast and zafirlukast) are used to treat certain respiratory disorders.

Montelukast sodium is chemically [R - (E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid, monosodium salt. Montelukast sodium is commercially available as SINGULAIR® as 10mg tablets, 4mg and 5mg chewable tablets and as 4mg oral granules (marketed by Merck and Co., Inc.) in the United States. Montelukast sodium is indicated for the prophylaxis and chronic treatment of asthma, for the prevention of exercise-induced bronchoconstriction and for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis and perennial allergic rhinitis).

Zafirlukast is chemically, 4-(5-cyclopentyloxy-carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide. Zafirlukast is commercially available as ACCOLATE® as 10mg and 20mg oral tablets (marketed by AstraZeneca Pharmaceuticals LP) in the United States. Zafirlukast is indicated for the prophylaxis and chronic treatment of asthma.

There still exists a need for an effective therapeutic treatment for respiratory disorders like asthma and COPD.

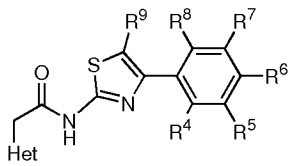
SUMMARY

The present invention relates to a pharmaceutical composition comprising a TRPA1 antagonist and a leukotriene receptor antagonist.

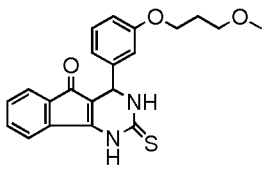
The inventors have surprisingly found that a TRPA1 antagonist and a leukotriene receptor antagonist (particularly, montelukast or its pharmaceutically acceptable salt) act synergistically in the treatment of respiratory disorders, and are more effective and provide better therapeutic value than treatment with either active ingredient alone.

In an embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist. Preferably, the TRPA1 antagonist of the present invention has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 500 nanomolar, or more preferably less than 250 nanomolar, as measured by a method described herein.

In another embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar having structure of formulae: (XII) or (D)

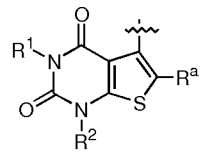


(XII)

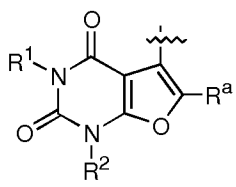


(D)

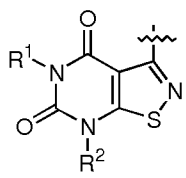
or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of



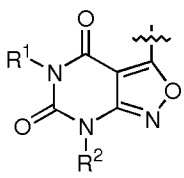
,



,



,

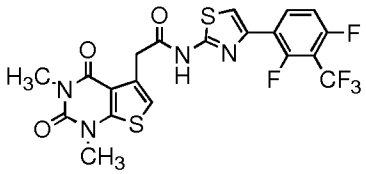


;

R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl and a leukotriene receptor antagonist.

In yet another embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

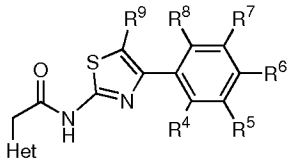
and a leukotriene receptor antagonist.

The leukotriene receptor antagonist, as contemplated herein, includes montelukast, zafirlukast, pranlukast, tipelukast, masilukast, iralukast, cinalukast, tomelukast, verlukast, pobilukast, sulukast, SKF-106203, L-648051, DS-4574, CGP-57698, YM-158, AS-35, KP-496, MEN-91507, KP-496, MK-571 and CR-3465 or salts thereof. The salt may be present in the form of their isomers, polymorphs, and solvates, including hydrates, all of which are included in the scope of the invention. Preferably, the leukotriene receptor antagonist includes montelukast, zafirlukast or salts thereof.

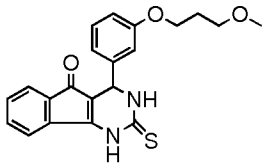
In another embodiment, there is provided a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist in a weight ratio ranging from about 1:0.005 to about 1:10, and preferably from about 1:0.05 to about 1:5 respectively.

In an embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1

receptor activity of less than 1 micromolar and a leukotriene receptor antagonist. In an aspect of this embodiment, the TRPA1 antagonist has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar having structure of formulae: (XII) or (D)

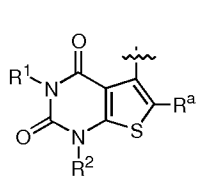
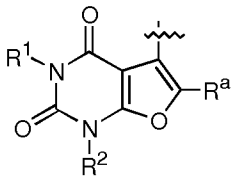
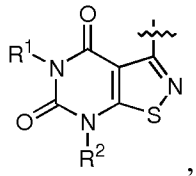
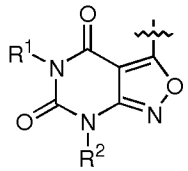


(XII)



(D)

or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of


,

,

,

;

R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

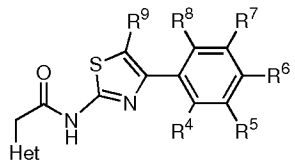
R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

The respiratory disorder, in the context of present invention, includes but is not limited to airway inflammation, asthma, emphysema, bronchitis, COPD, sinusitis, rhinitis, cough, respiratory depression, reactive airways dysfunction syndrome (RADS), acute respiratory distress syndrome (ARDS), irritant induced asthma, occupational asthma, sensory hyper-reactivity, multiple chemical sensitivity, and aid in smoking cessation therapy.

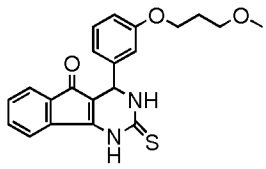
In a further embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, said method comprising administering the subject a pharmaceutical composition comprising synergistically effective

amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and montelukast or its salt.

In a further embodiment, the present invention relates to use of synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist in the preparation of a pharmaceutical composition of the present invention for the treatment of a respiratory disorder in a subject. In an aspect of this embodiment, the TRPA1 antagonist has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar having structure of formulae: (XII) or (D)

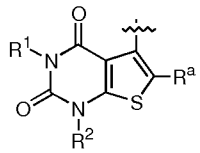
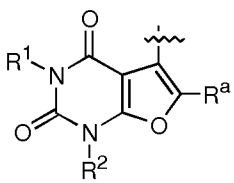
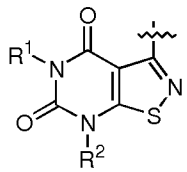
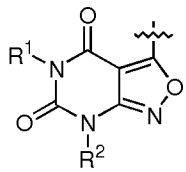


(XII)



(D)

or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of


,

,

,

;

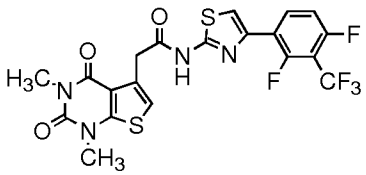
R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

In a further embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1

micromolar and a leukotriene receptor antagonist for the treatment of respiratory disorders in a subject.

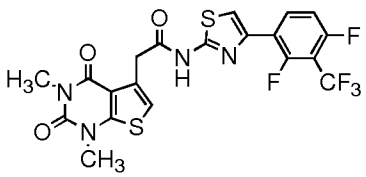
In an embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and a leukotriene receptor antagonist. The TRPA1 antagonist and the leukotriene receptor antagonist are preferably administered orally. In one aspect, the TRPA1 antagonist and the leukotriene receptor antagonist are incorporated into a single pharmaceutical composition (e.g., an oral dosage form). In another aspect, there is provided a kit containing a unit dose formulation comprising the TRPA1 antagonist and another unit dose formulation comprising the leukotriene receptor antagonist.

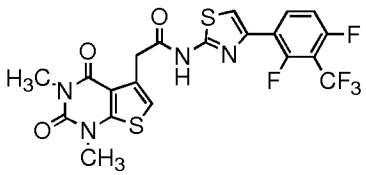
In an embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

and montelukast or its salt, wherein the composition is a fixed dose combination.

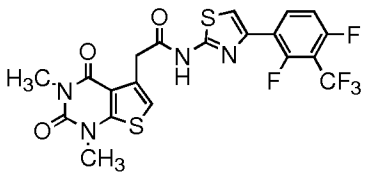
In an embodiment, the present invention relates to a method of treating a respiratory disorder by reducing eosinophils count and/or increasing FEV1 value in a subject, said method comprising administering to the subject the pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

and a leukotriene receptor antagonist. Preferably, the leukotriene receptor antagonist is montelukast sodium, and the composition is a fixed dose combination. In an aspect, the respiratory disorder is asthma

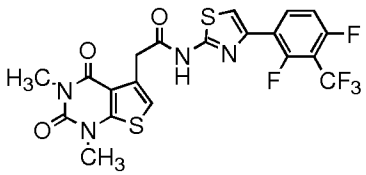
In an embodiment, the present invention relates to a method of reducing eosinophils count and/or increasing FEV1 value in a subject having a respiratory disorder, said method comprising administering to the subject the pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

and a leukotriene receptor antagonist, thereby reducing said eosinophil count and/or increasing FEV1 value in said subject.

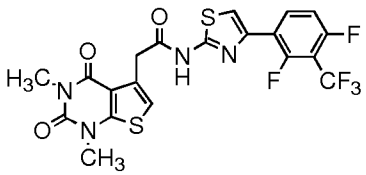
In another embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

and montelukast sodium present in a weight ratio from about 1:0.005 to about 1:5, wherein the composition is a fixed dose combination.

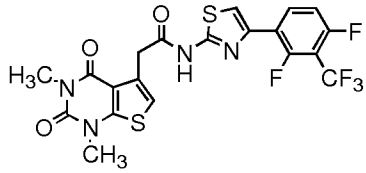
In a further embodiment, the present invention relates to use of synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and montelukast sodium present in a weight ratio from about 1:0.005 to about 1:5 in the preparation of a pharmaceutical composition for the treatment of a respiratory disorder in a subject, wherein the composition is a fixed dose combination.

In an embodiment, the present invention relates to a pharmaceutical composition for oral administration comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and montelukast sodium, wherein the composition is a fixed dose combination. Preferably, the TRPA1 antagonist and montelukast sodium are present in a weight ratio from about 1:0.05 to about 1:5 in the composition.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a bar graph showing the effect of Compound 52 and montelukast on ovalbumin induced eosinophilia in ovalbumin sensitized female Balb/C mice.

DETAILED DESCRIPTION

Definitions

The terms used herein are defined as follows. The terms used herein are defined as follows. If a definition set forth in the present application and a definition set forth earlier in a provisional application from which priority is

claimed are in conflict, the definition in the present application shall control the meaning of the terms.

The term "effective amount" or "therapeutically effective amount" denotes an amount of an active ingredient that, when administered to a subject for treating a respiratory disorder, produces an intended therapeutic benefit in a subject. The effective amount of a TRPA1 antagonist as described herein ranges from about 10μg/kg to about 20mg/kg, and preferably from about 50μg/kg to about 15mg/kg. The therapeutically effective amount of montelukast or its salt to be administered per day ranges from about 0.1 mg to about 50 mg, and preferably from about 1 mg to about 30 mg. The therapeutically effective amount of zafirlukast or its salt to be administered per day ranges from about 1 mg to about 100 mg, and preferably from about 5 mg to about 50 mg. The therapeutically effective ranges of actives are given as above, although larger or smaller amount are not excluded if they fall within the scope of the definition of this paragraph.

The IC_{50} value is believed to be measure of the effectiveness of a compound in inhibiting biological or biochemical function. This quantitative measure generally indicates molar concentration of a particular compound (or substance) is needed to inhibit a given biological process by half. In other words, it is the half maximal (50%) inhibitory concentration (IC) of the compound. The IC_{50} of a drug compound (or active substance) can be determined by constructing a concentration-response curve so as to examine the effect of different concentrations of antagonist on reversing agonist activity. IC_{50} values can be calculated for a given antagonist by determining the concentration needed to inhibit half of the maximum biological response of the agonist. IC_{50} values can be used to compare the potency of two antagonists.

The term “active ingredient” (used interchangeably with “active” or “active substance” or “drug”) as used herein includes a TRPA1 antagonist, a leukotriene receptor antagonist or a pharmaceutically acceptable salt thereof. Preferably, the active ingredient includes a TRPA1 antagonist having a human IC_{50} value of less than 1μM, montelukast or its salt, and zafirlukast or its salt.

By “salt” or “pharmaceutically acceptable salt”, it is meant those salts and esters which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit to risk ratio, and effective for their intended use. Representative acid additions salts include the hydrochloride, hydrobromide, sulphate, bisulphate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, mesylate, citrate, maleate, fumarate, succinate, tartrate, ascorbate, glucoheptonate, lactobionate, and lauryl sulphate salts. Representative alkali or alkaline earth metal salts include the sodium, calcium, potassium and magnesium salts.

The term “treating” or “treatment” as used herein also covers the prophylaxis, mitigation, prevention, amelioration, or suppression of a disorder modulated by the TRPA1 receptor, or the leukotriene receptor, or by a combination of the two in a mammal.

The respiratory disorder includes but is not limited to airway inflammation, asthma, emphysema, bronchitis, COPD, sinusitis, rhinitis, cough, respiratory depression, reactive airways dysfunction syndrome (RADS), acute respiratory distress syndrome (ARDS), irritant induced asthma, occupational asthma, sensory hyper-reactivity, multiple chemical sensitivity, and aid in smoking cessation therapy. Preferably, the respiratory disorder is asthma, COPD or rhinitis.

The term "subject" includes mammals like human and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife). Preferably, the subject is a human.

By “pharmaceutically acceptable excipients”, it is meant any of the components of a pharmaceutical composition other than the actives and which are approved by regulatory authorities or are generally regarded as safe for human or animal use.

The term "synergistic" or “synergy”, as used herein, refers to a combination exhibiting an effect greater than would be expected from the sum of the effects of the individual components of the combination alone. The term "synergistic" or

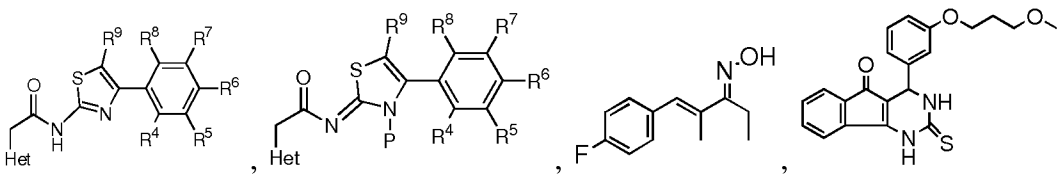
"synergy" with regard to the combination of a TRPA1 antagonist with a leukotriene receptor antagonist which is used in the treatment of a respiratory disorder (for example, in the form of a pharmaceutical composition, a combination product or a kit according to the invention) refers to an efficacy for the treatment of the respiratory disorder that is greater than would be expected from the sum of their individuals effects. The advantages for the synergistic combinations of the present invention include, but are not limited to, lowering the required dose of one or more of the active compounds of the combination, reducing the side effects of one or more of the active compounds of the combination and/or rendering one or more of the active compounds more tolerable to the subject in need of treatment of the respiratory disorder.

Combinations

The present invention relates to a pharmaceutical composition comprising: a TRPA1 antagonist, and a leukotriene receptor antagonist.

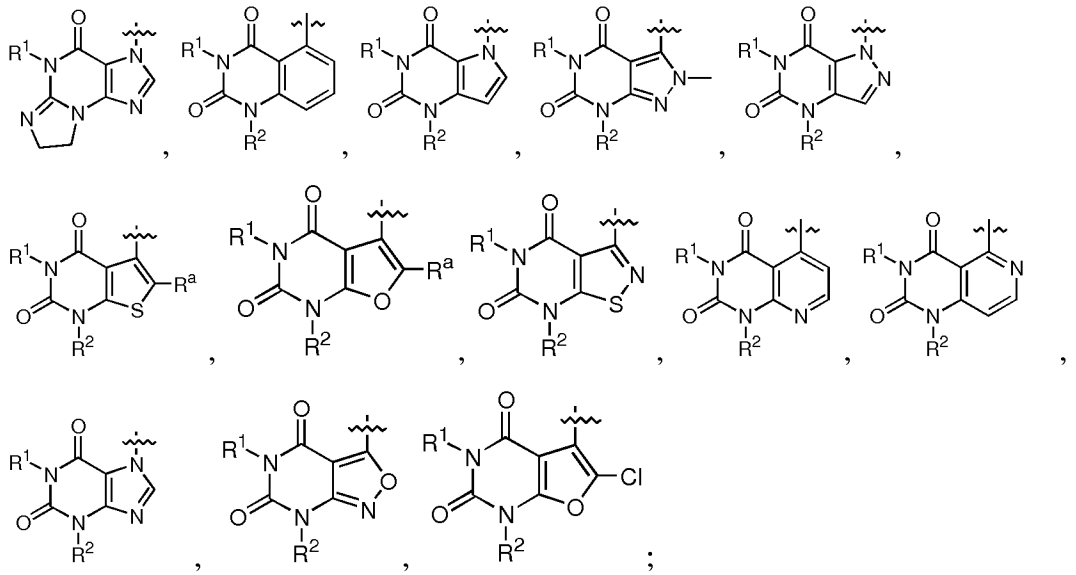
In another embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist. Preferably, the TRPA1 antagonist of the present invention has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 500 nanomolar, or more preferably less than 250 nanomolar, as measured by a method described herein.

In an aspect, TRPA1 antagonists useful in the context of the invention, are selected from one of the following formulae: (A) or (B) or (C) or (D)

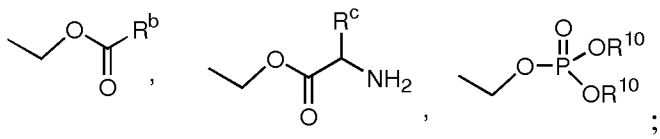


(A) (B) (C) (D)

or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of



P is selected from



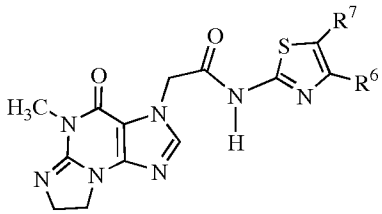
R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

R^b and R^c independently selected from hydrogen, substituted or unsubstituted alkyl arylalkyl, amino acid and heterocyclic ring;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl;

R^{10} is selected from hydrogen, alkyl, arylalkyl and pharmaceutically acceptable cation.

In one aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2009144548. Accordingly, a TRPA1 antagonist useful in the context of the invention has the formula (I):



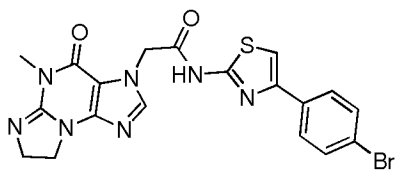
(I)

or a pharmaceutically acceptable salt thereof, wherein,

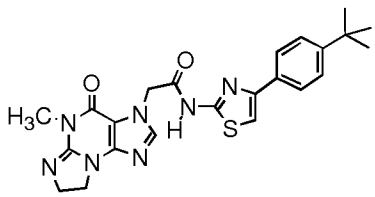
R^6 represents hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring and substituted or unsubstituted heterocyclylalkyl;

R^7 independently represents hydrogen or alkyl.

Few representative TRPA1 antagonists useful in the methods of the invention are mentioned below:



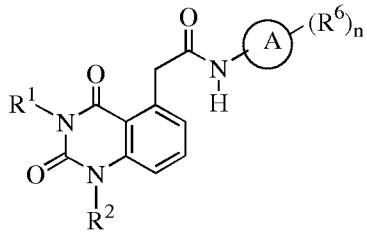
Compound 1



Compound 2

The preparation of above said compounds is described in WO2009144548.

In another aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2010004390. Accordingly, TRPA1 antagonist useful in the context of the invention has the formula (II):



(II)

or pharmaceutically acceptable salts thereof,

wherein,

at each occurrence $R^1$and R^2 is independently selected from hydrogen, hydroxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, $(CR^xR^y)_nOR^x$, COR^x, $COOR^x$, $CONR^xR^y$, $SO_2NR^xR^y$, NR^xR^y, $NR^x(CR^xR^y)_nOR^x$, $NR^x(CR^xR^y)_nCN$ $(CH_2)_nNR^xR^y$, $(CH_2)_nCHR^xR^y$, $(CR^xR^y)NR^xR^y$, $NR^x(CR^xR^y)_nCONR^xR^y$, $(CH_2)_nNHCOR^x$ and $(CH_2)_nNH(CH_2)_nSO_2R^x$, $(CH_2)_nNHSO_2R^x$;

R^x and R^y are independently selected from hydrogen, hydroxyl, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring and substituted or unsubstituted heterocyclylalkyl;

R^x and R^y may be joined together to form an optionally substituted 3 to 7 membered saturated, unsaturated or partially saturated cyclic ring, which may optionally include at least two heteroatoms selected from O, NR^aor S;

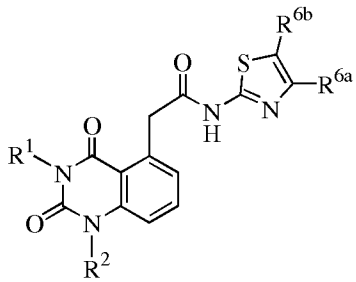
ring A is selected from phenyl, pyridinyl, pyrazolyl, thiazolyl and thiadiazolyl;

each occurrence of R^6 is independently hydrogen, cyano, nitro, $-NR^xR^y$, halogen, hydroxyl, haloalkyl, haloalkoxy, cycloalkylalkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring and substituted or unsubstituted heterocyclylalkyl,

R^x and R^y are independently selected from hydrogen, hydroxyl, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl;

at each occurrence of 'n' is independently selected from 1 to 5.

According to one aspect, specifically provided are compounds of the formula (IIa)



(IIa)

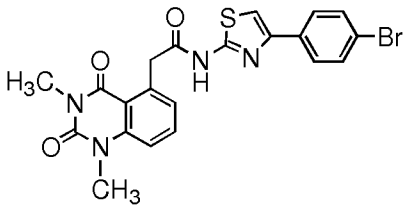
or pharmaceutically acceptable salts thereof,

wherein,

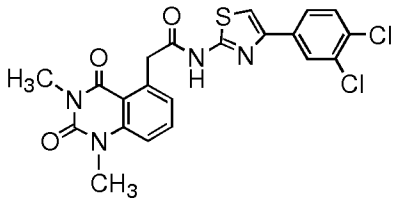
R^1 and R^2 are as defined above for the compound of formula (II);

R^{6a} and R^{6b} are independently selected from hydrogen, cyano, nitro, -NR^xR^y, halogen, hydroxyl, haloalkyl, haloalkoxy, cycloalkylalkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring and substituted or unsubstituted heterocyclylalkyl, -$C(O)OR^x$, -OR^x, -$C(O)NR^xR^y$, -$C(O)R^x$, -SO_2R^x, -SO_2-NR^xR^y.

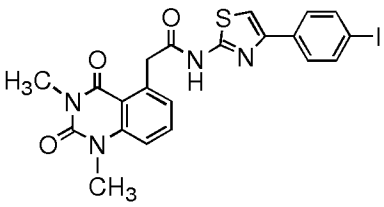
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



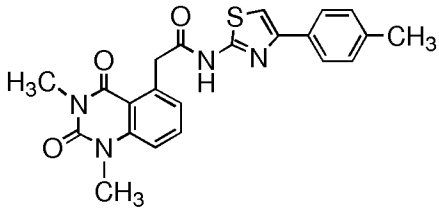
Compound 3



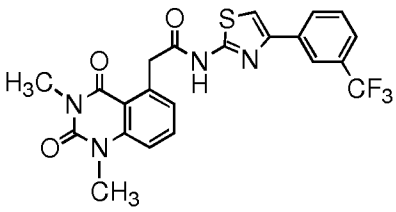
Compound 4



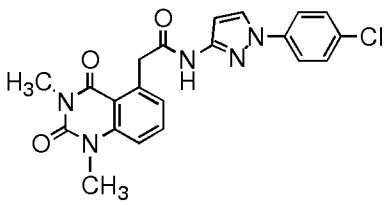
Compound 5



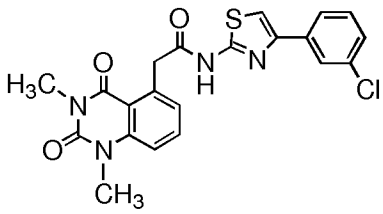
Compound 6



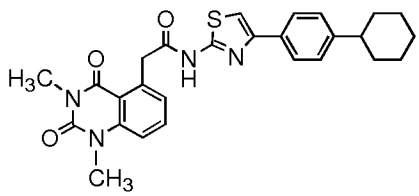
Compound 7



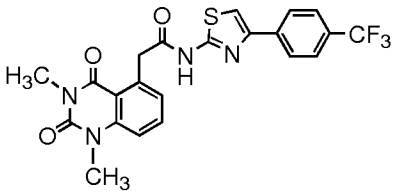
Compound 8



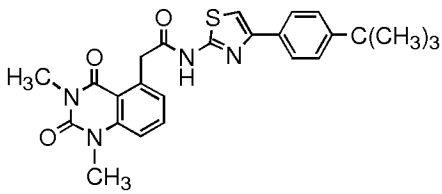
Compound 9



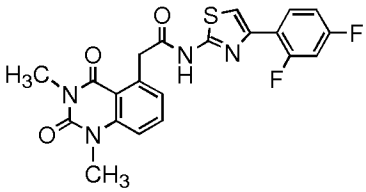
Compound 10



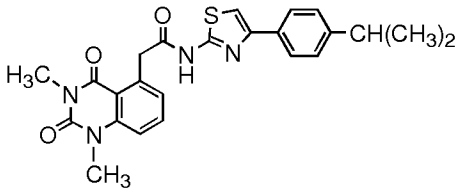
Compound 11



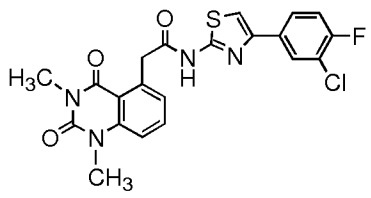
Compound 12



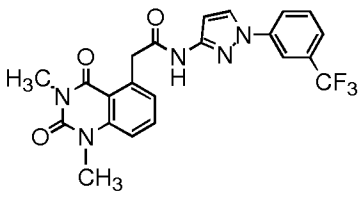
Compound 13



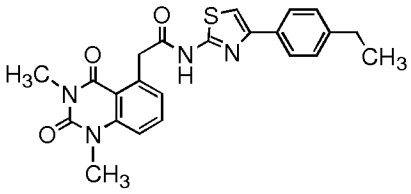
Compound 14



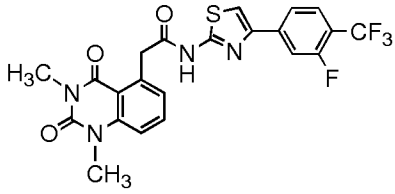
Compound 15



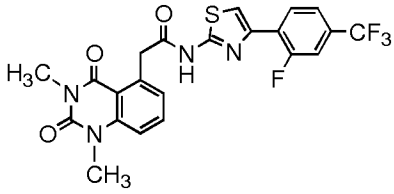
Compound 16



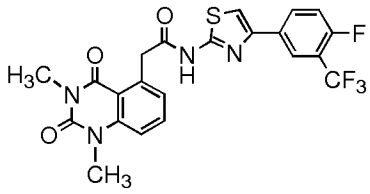
Compound 17



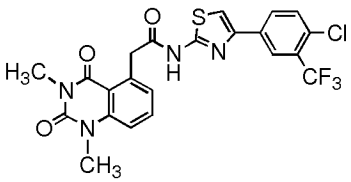
Compound 18



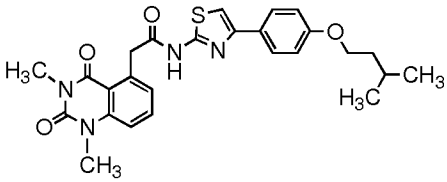
Compound 19



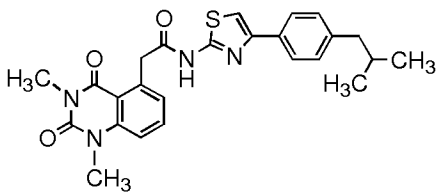
Compound 20



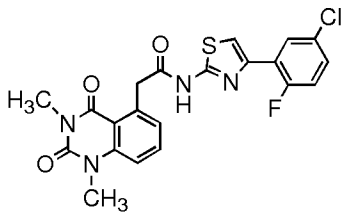
Compound 21



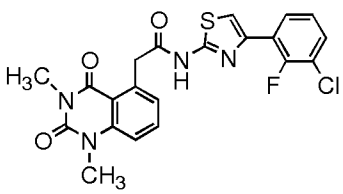
Compound 22



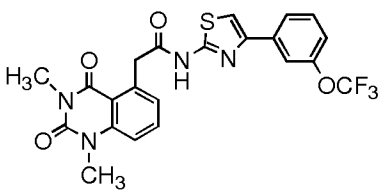
Compound 23



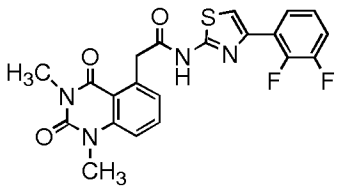
Compound 24



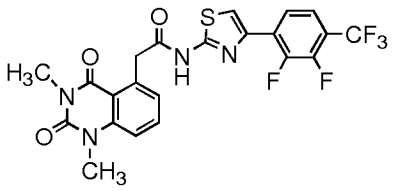
Compound 25



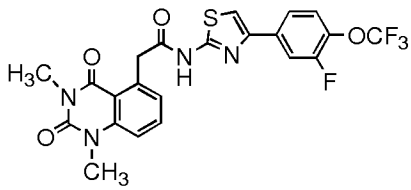
Compound 26



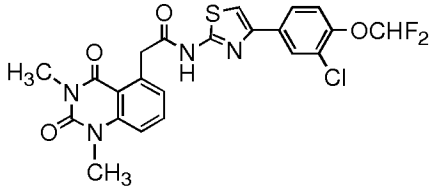
Compound 27



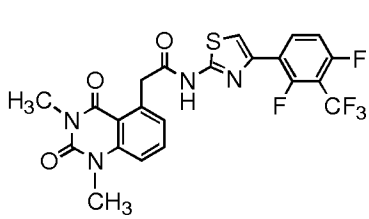
Compound 28



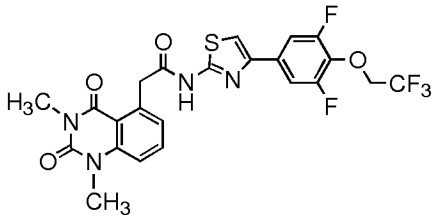
Compound 29



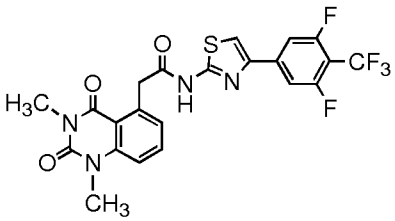
Compound 30



Compound 31



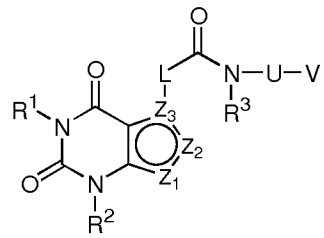
Compound 32



Compound 33

The preparation of above said compounds is described in WO2010004390.

In one aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2010109287. Accordingly, TRPA1 antagonist useful in the context of the invention has the formula (III):



(III)

or a pharmaceutically acceptable salt thereof,

wherein,

Z_1 is NR^a or CR^a;

Z_2 is NR^b or CR^b;

Z_3 is N or C;

with the proviso that when Z_2 is CR^b then both Z_1 and Z_3 are not nitrogen at the same time;

at each occurrence, R^a and R^b which may be same or different, are independently selected from hydrogen, hydroxyl, cyano, halogen, substituted or unsubstituted alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, $-(CR^xR^y)_nOR^x$, $-COR^x$, $-COOR^x$, $-CONR^xR^y$, $-S(O)_mNR^xR^y$, $-NR^xR^y$, $-NR^x(CR^xR^y)_nOR^x$, $-(CH_2)_nNR^xR^y$, $-(CH_2)_nCHR^xR^y$, $-(CH_2)NR^xR^y$, $-NR^x(CR^xR^y)_nCONR^xR^y$, $-(CH_2)_nNHCOR^x$, $-(CH_2)_nNH(CH_2)_nSO_2R^x$ and $(CH_2)_nNHSO_2R^x$;

alternatively either of R^a or R^b is absent;

R^1 and R^2, which may be same or different, are independently selected from hydrogen, hydroxyl, substituted or unsubstituted alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, arylalkyl, $(CR^xR^y)_nOR^x$, COR^x, $COOR^x$, $CONR^xR^y$, $(CH_2)_nNR^xR^y$, $(CH_2)_nCHR^xR^y$, $(CH_2)NR^xR^y$ and $(CH_2)_nNHCOR^x$;

R^3 is selected from hydrogen, substituted or unsubstituted alkyl, alkenyl, haloalkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl;

L is a linker selected from $-(CR^xR^y)_n-$, $-O-(CR^xR^y)_n-$, $-C(O)-$, $-NR^x-$, $-S(O)_mNR^x-$, $-NR^x(CR^xR^y)_n-$ and $-S(O)_mNR^x(CR^xR^y)_n$;

U is selected from substituted or unsubstituted aryl, substituted or unsubstituted five membered heterocycles selected from the group consisting of thiazole, isothiazole, oxazole, isoxazole, thiadiazole, oxadiazole, pyrazole, imidazole, furan, thiophene, pyroles, 1,2,3-triazoles and 1,2,4-triazole; and substituted or unsubstituted six membered heterocycles selected from the group consisting of pyrimidine, pyridine and pyridazine;

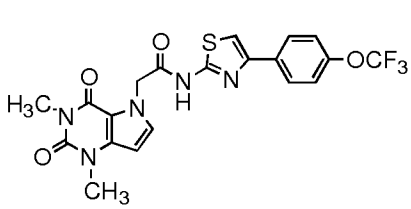
V is selected from hydrogen, cyano, nitro, $-NR^xR^y$, halogen, hydroxyl, substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,

cycloalkenyl, haloalkyl, haloalkoxy, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl, $-C(O)OR^x$, $-OR^x$, $-C(O)NR^xR^y$, $-C(O)R^x$ and $-SO_2NR^xR^y$; or U and V together may form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, that may optionally include one or more heteroatoms selected from O, S and N;

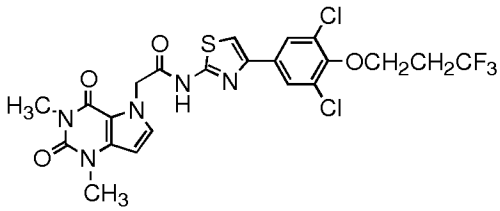
at each occurrence, R^x and R^y are independently selected from the group consisting of hydrogen, hydroxyl, halogen, substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl; and

at each occurrence 'm' and 'n' are independently selected from 0 to 2, both inclusive.

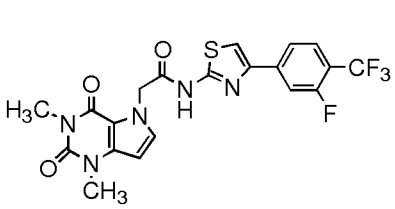
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



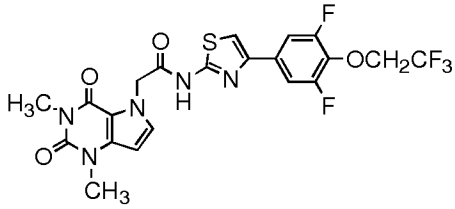
Compound 34



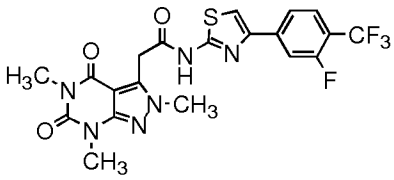
Compound 35



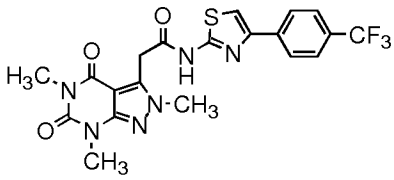
Compound 36



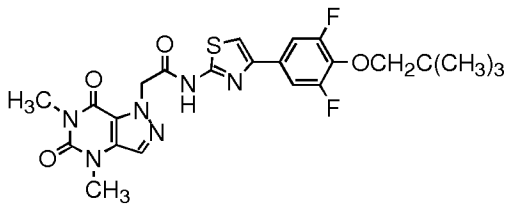
Compound 37



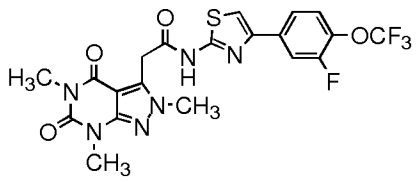
Compound 38



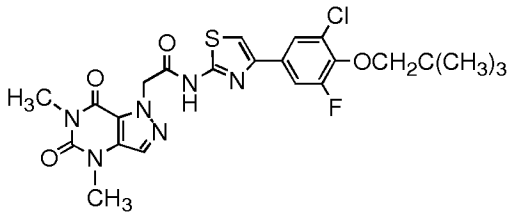
Compound 39



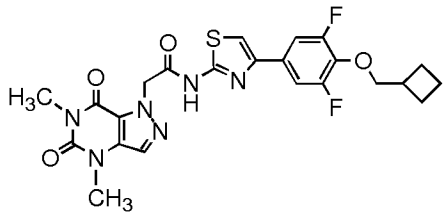
Compound 40



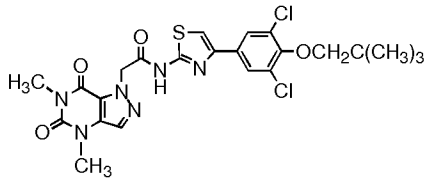
Compound 41



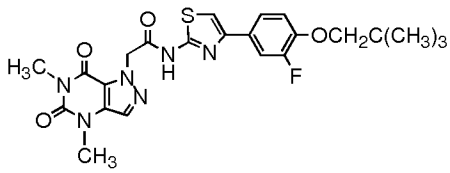
Compound 42



Compound 43



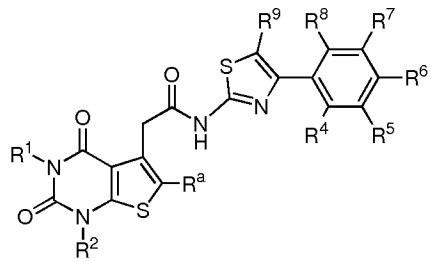
Compound 44



Compound 45

The preparation of above said compounds is described in WO2010109287.

In one aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO 2010109334. Accordingly, TRPA1 antagonists useful in the context of the invention has the formula (IV)



(IV)

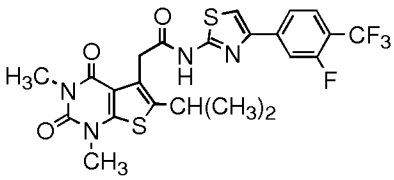
or a pharmaceutically-acceptable salt thereof.

wherein,

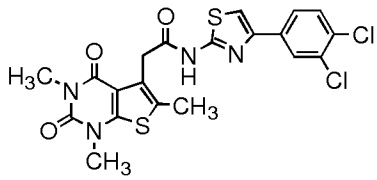
R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or $(C_1$-$C_4)$alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

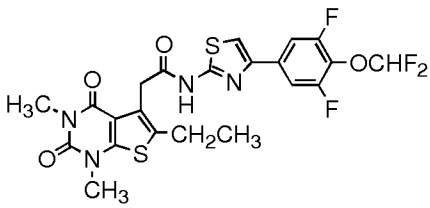
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



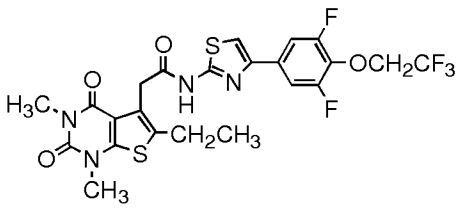
Compound 46



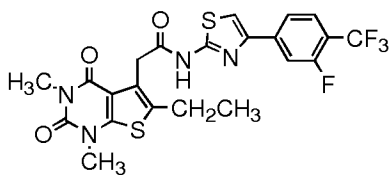
Compound 47



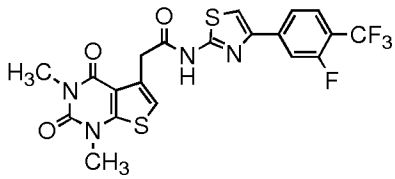
Compound 48



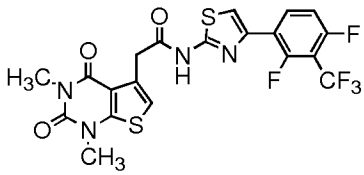
Compound 49



Compound 50



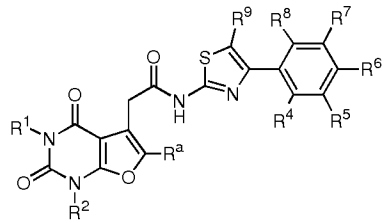
Compound 51



Compound 52

The preparation of above said compounds is described in WO2010109334.

In one aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2010109329. Accordingly, TRPA1 antagonists useful in the context of the invention has the formula (V)



(V)

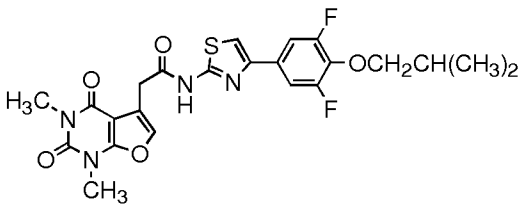
or a pharmaceutically acceptable salt thereof,

wherein,

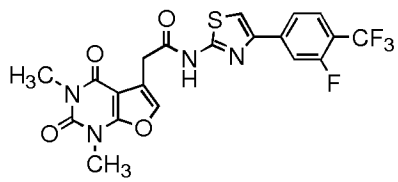
R^1, R^2 and R^a which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl; and

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

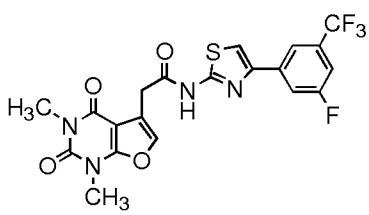
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



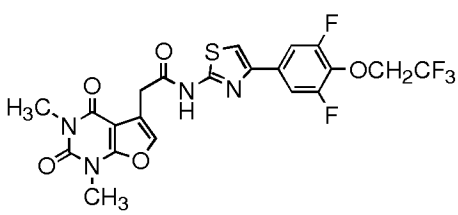
Compound 53



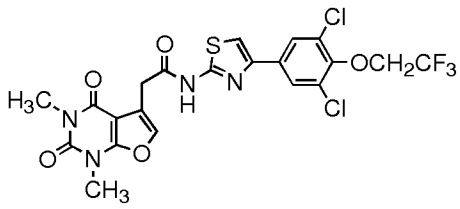
Compound 54



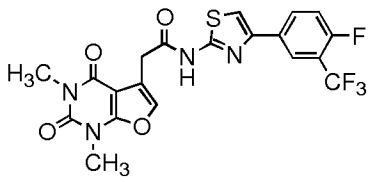
Compound 55



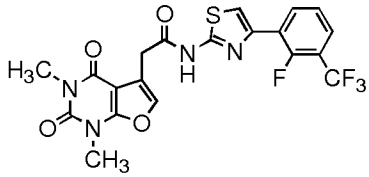
Compound 56



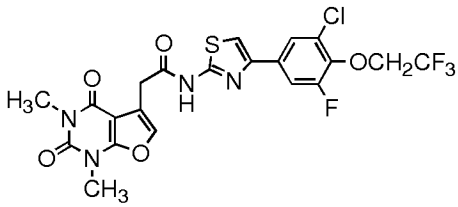
Compound 57



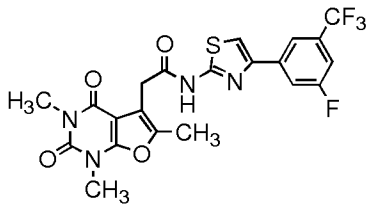
Compound 58



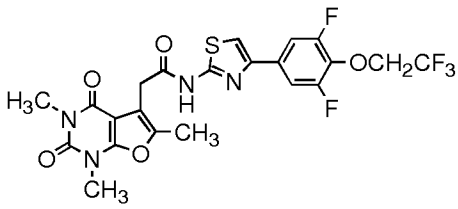
Compound 59



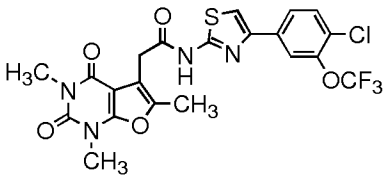
Compound 60



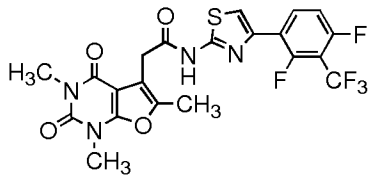
Compound 61



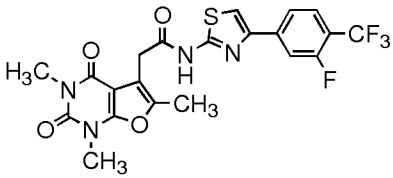
Compound 62



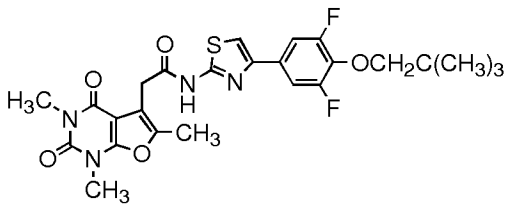
Compound 63



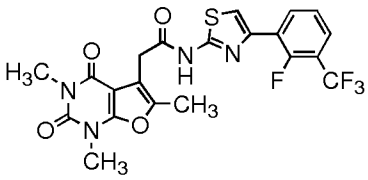
Compound 64



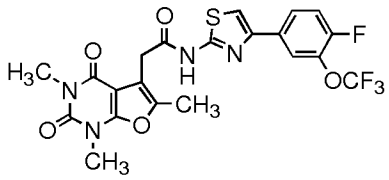
Compound 65



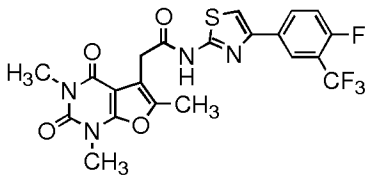
Compound 66



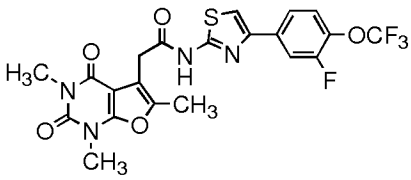
Compound 67



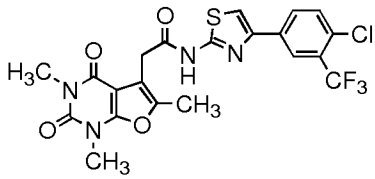
Compound 68



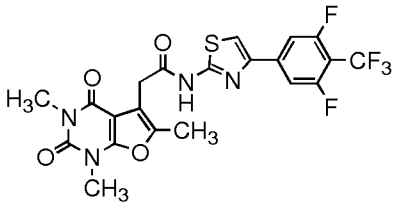
Compound 69



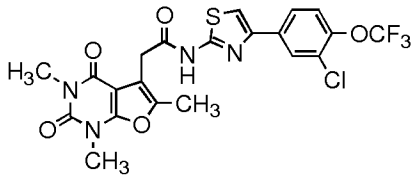
Compound 70



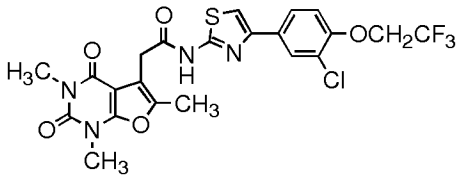
Compound 71



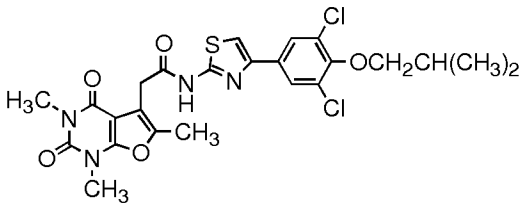
Compound 72



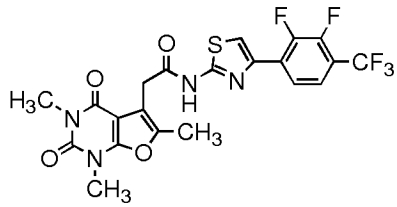
Compound 73



Compound 74



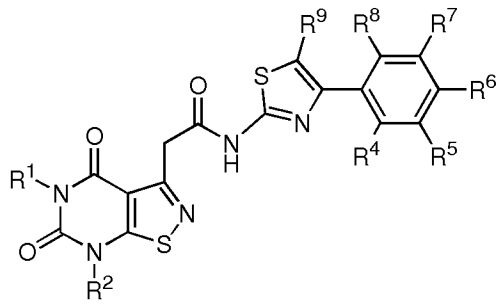
Compound 75



Compound 76

The preparation of above said compounds is described in WO2010109329.

In one aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2010109328. Accordingly, TRPA1 antagonists useful in the context of the invention has the formula (VI)



(VI),

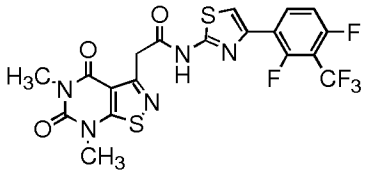
or a pharmaceutically-acceptable salt thereof.

wherein,

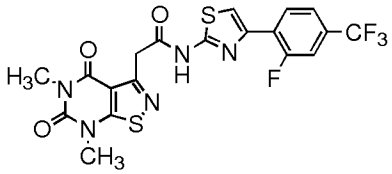
R^1 and R^2, which may be the same or different, are each independently hydrogen or (C_1-C_4)alkyl; and

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

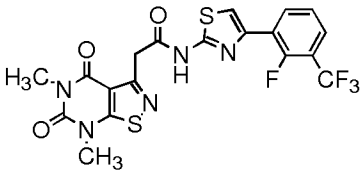
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



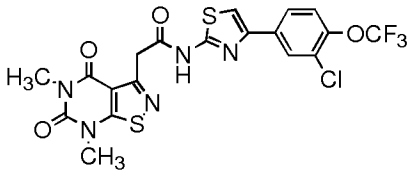
Compound 77



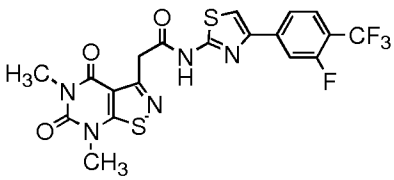
Compound 78



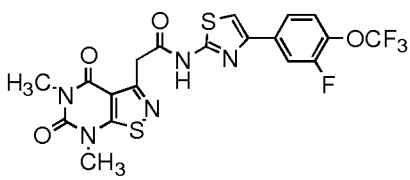
Compound 79



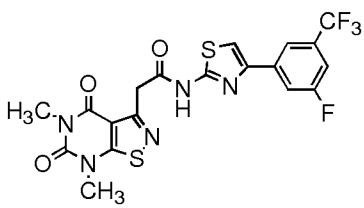
Compound 80



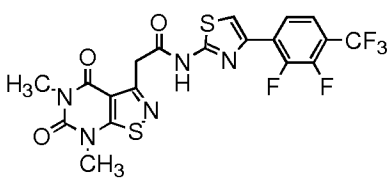
Compound 81



Compound 82



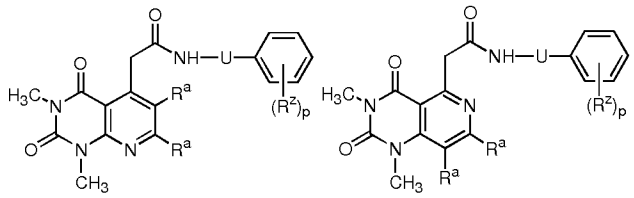
Compound 83



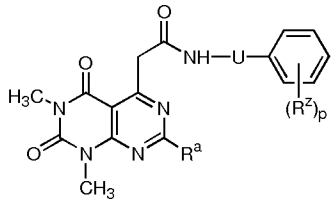
Compound 84

The preparation of above said compounds is described in WO2010109328.

In one aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2010125469. Accordingly, TRPA1 antagonists useful in the context of the invention have the formulas (VIIa, VIIb and VIIc):



(VIIa) (VIIb)



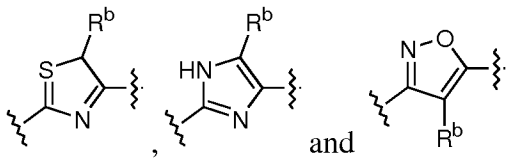
(VIIc)

or pharmaceutically acceptable salt thereof,

wherein,

at each occurrence, R^a is selected from hydrogen, cyano, halogen, substituted or unsubstituted alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, cycloalkyl and cycloalkylalkyl;

U is substituted or unsubstituted five membered heterocycle, for example selected from the group consisting of



;

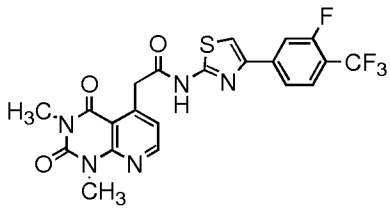
at each occurrence, R^b is independently selected from hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl;

at each occurrence, R^z is independently selected from halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring, heterocyclylalkyl, $COOR^x$, $CONR^xR^y$, $S(O)_mNR^xR^y$, $NR^x(CR^xR^y)_nOR^x$, $(CH_2)_nNR^xR^y$, $NR^x(CR^xR^y)_nCONR^xR^y$, $(CH_2)_nNHCOR^x$, $(CH_2)_nNH(CH_2)_nSO_2R^x$ and $(CH_2)_nNHSO_2R^x$;

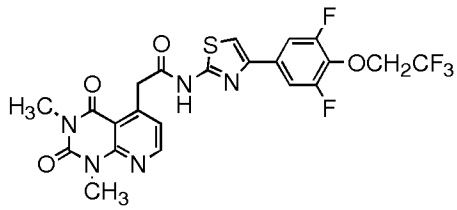
at each occurrence, R^x and$R^y$are independently selected from hydrogen, hydroxyl, halogen, substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl;

at each occurrence, 'm' and 'n' are independently selected from 0 to 2, both inclusive; and 'p' is independently selected from 0 to 5, both inclusive.

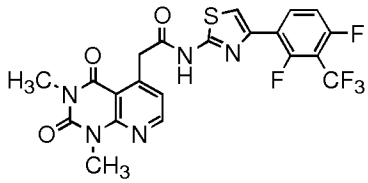
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



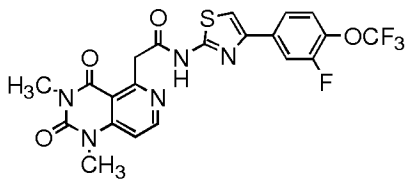
Compound 85



Compound 86



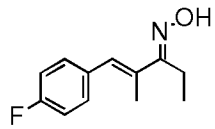
Compound 87



Compound 88

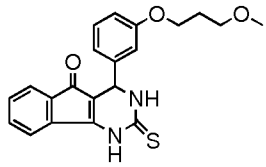
The preparation of above said compounds is described in WO2010125469.

In one aspect, the TRPA1 antagonist useful in the context of the invention is Compound 89:



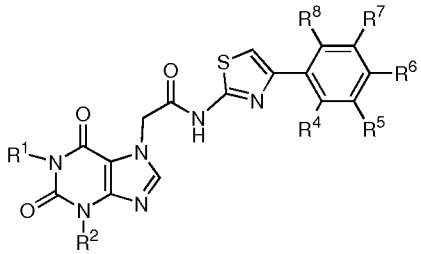
Compound 89

In one embodiment, the TRPA1 antagonist useful in the context of the invention is Compound 90:



Compound 90

In an embodiment, TRPA1 antagonists useful in the context of the invention has the formula



(VIII)

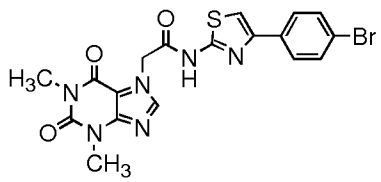
or a pharmaceutically-acceptable salt thereof

wherein,

R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4)alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

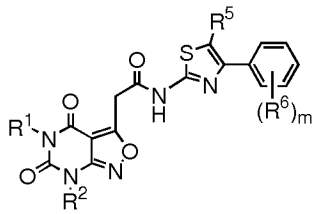
A representative TRPA1 antagonist useful in the context of the invention is Compound 91:



Compound 91

The Compound 91 may be prepared, for example, by following the process provided for the preparation of similar compounds in PCT publication No. WO2007073505.

In another aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2011114184. Accordingly, a TRPA1 antagonist useful in the context of the invention has the formula (IX):



(IX)

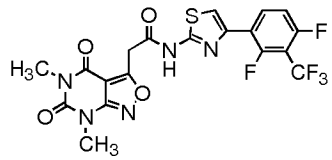
or a pharmaceutically-acceptable salt thereof

wherein at each occurrence, R^1 and R^2 are independently selected from hydrogen or substituted or unsubstituted alkyl;

at each occurrence, R^5 is selected from hydrogen, halogen or substituted or unsubstituted alkyl;

at each occurrence, R^6 is selected from hydrogen, cyano, nitro, halogen, hydroxyl, substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, haloalkyl, haloalkoxy, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

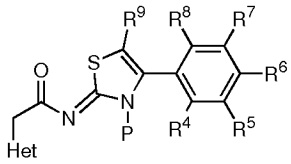
A representative TRPA1 antagonist useful in the methods of the invention is mentioned below:



Compound 92

The preparation of above said compounds is described in WO2011114184.

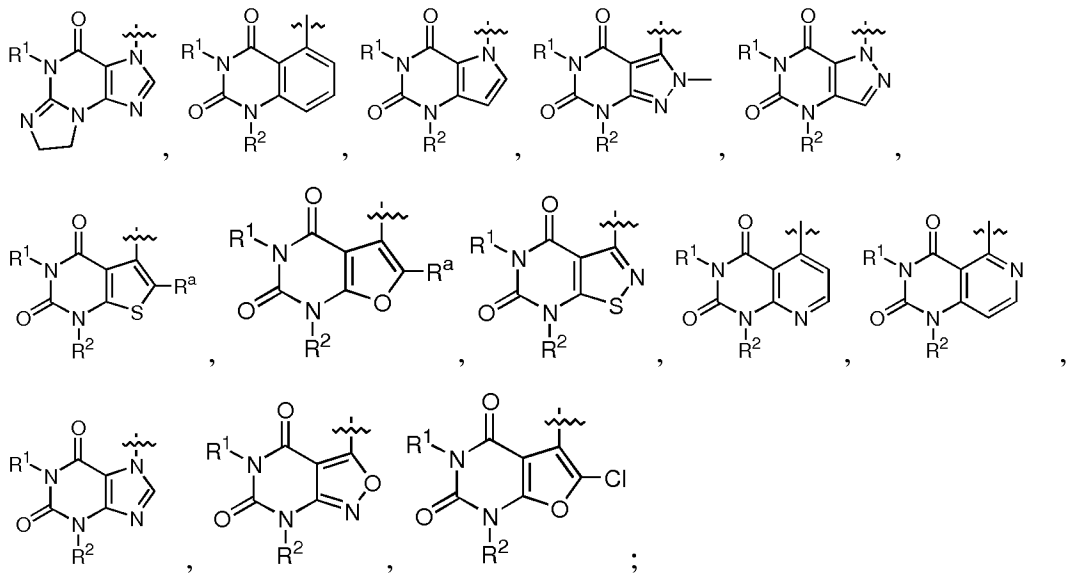
In another aspect, TRPA1 antagonist useful in the context of the invention has the formula (X):



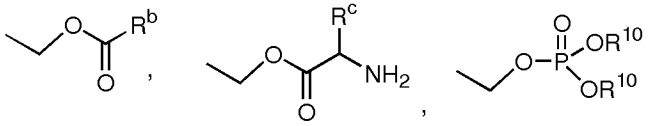
(X)

wherein,

'Het' is selected from groups consisting of



P is selected from



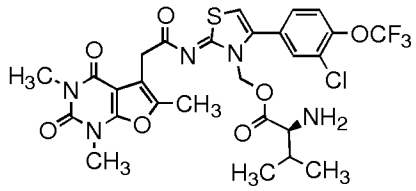
R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4)alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl;

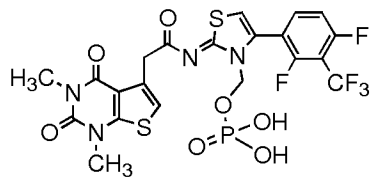
R^b and R^c independently selected from hydrogen, substituted or unsubstituted alkyl arylalkyl, amino acid and heterocyclic ring;

R^{10} is selected from hydrogen, alkyl, arylalkyl and pharmaceutically acceptable cation.

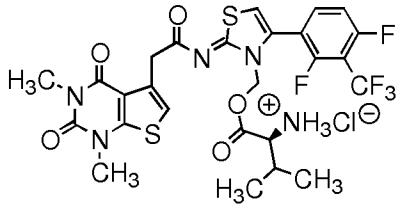
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



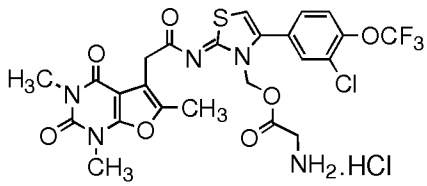
Compound 95



Compound 96

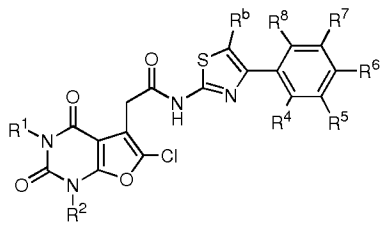


Compound 97



Compound 98

In another aspect, TRPA1 antagonists useful in the context of the invention are selected from those compounds generically or specifically disclosed in WO2011114184. Accordingly, TRPA1 antagonist useful in the context of the invention has the formula (XI):



(XI)

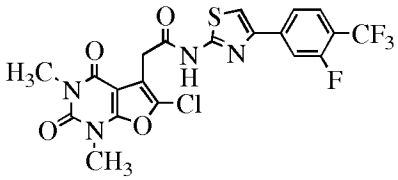
or a pharmaceutically acceptable salt thereof,

wherein,

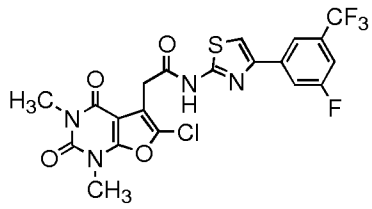
R^1, and R^2 are independently hydrogen or (C_1-C_4)alkyl; and

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from halogen haloalkyl, dialkylamino, and haloalkoxy.

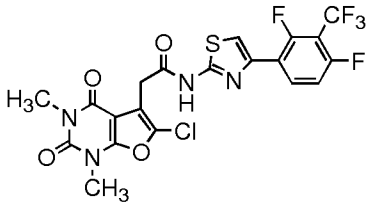
Few representative TRPA1 antagonists useful in the context of the invention are mentioned below:



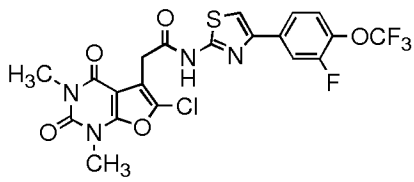
Compound 99



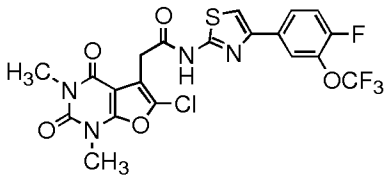
Compound 100



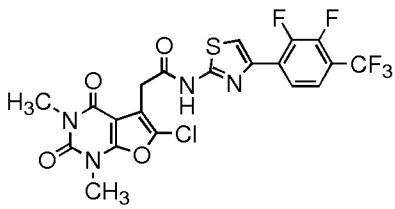
Compound 101



Compound 102



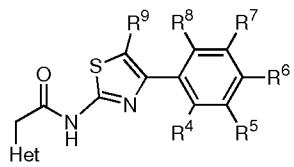
Compound 103



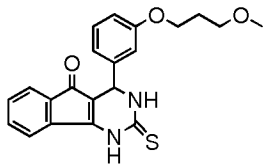
Compound 104

The preparation of above said compounds is described in WO2011114184.

In an aspect, TRPA1 antagonists useful in the context of the invention, is selected from one of the following formulae: (XII) or (D)

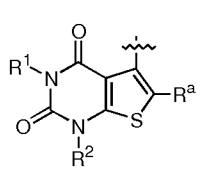
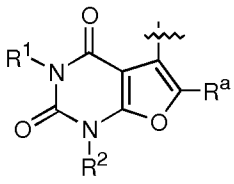
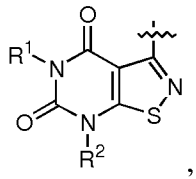
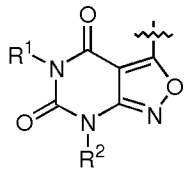


(XII)



(D)

or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of

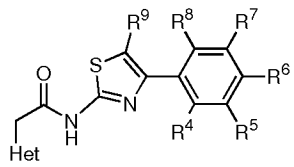

,

,

,

;

R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4)alkyl;

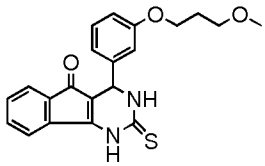
R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

Few representative TRPA1 antagonists of the formula (XII) useful in the context of the invention are compound 52, compound 73 and compound 84 as described above.

In another embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar having structure of formulae: (XII) or (D)

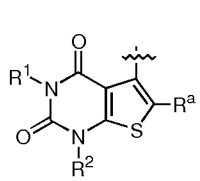


(XII)

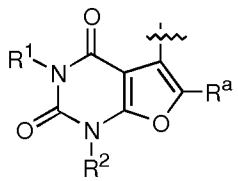


(D)

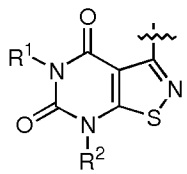
or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of



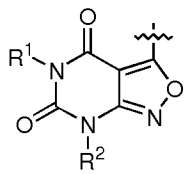
,



,



,



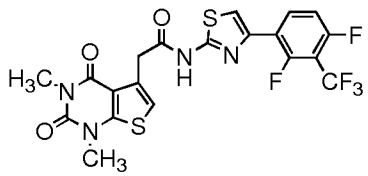
;

R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl

and a leukotriene receptor antagonist.

In another embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

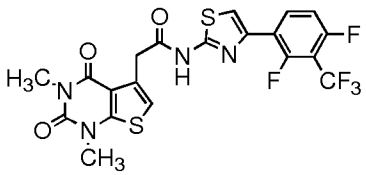
and a leukotriene receptor antagonist.

The leukotriene receptor antagonist, as contemplated herein, includes montelukast, zafirlukast, pranlukast, tipelukast, masilukast, iralukast, cinalukast, tomelukast, verlukast, pobilukast, sulukast, SKF-106203, L-648051, DS-4574, CGP-57698, YM-158, AS-35, KP-496, MEN-91507, KP-496, MK-571 and CR-3465 or salt may be present in the form of their isomers, polymorphs, and solvates, including hydrates, all of which are included in the scope of the invention. Preferably, the leukotriene receptor antagonist includes montelukast, zafirlukast or its salt.

In another embodiment, there is provided a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist in a weight ratio ranging from about 1:0.005 to about 1:10, and preferably from about 1:0.05 to about 1:5 respectively.

In the pharmaceutical composition as described herein, the active ingredient may be in the form of a single dosage form (i.e., fixed-dose formulation in which both the active ingredients are present together) or they may be divided doses, formulated separately, each in its individual dosage forms but as part of the same therapeutic treatment, program or regimen, either once daily or two/three/four times a day.

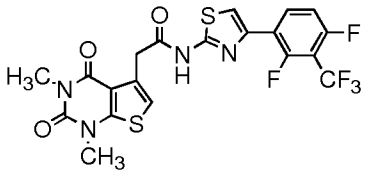
In an embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

and a leukotriene receptor antagonist, wherein the composition is a fixed dose combination.

In an aspect, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

and montelukast sodium, wherein the composition is a fixed dose combination.

Alternately, the invention relates to a pharmaceutical composition wherein the composition is in the form of kit comprising separate formulations of a TRPA1 antagonist and a leukotriene receptor antagonist. The separate formulations are to be administered by same or different routes, either separately, simultaneously, or sequentially, where the sequential administration is close in time or remote in time. For sequential administration, the period of time may be in the range from 10 min to 12 hours.

As contemplated herein, the active ingredients may be administered together in a single dosage form or they may be administered in different dosage forms. They may be administered at the same time or they may be administered either close in time or remotely, such as, where one drug is administered in the morning and the second drug is administered in the evening. The combination may be used prophylactically or after the onset of symptoms has occurred.

The pharmaceutical composition of the present invention may be administered orally, nasally, intra-tracheally, parenterally, transdermally, transmucosal, inhalation or by any other route that a physician or a health-care

provider may determine to be appropriate. Preferably, the route of administration is oral or by inhalation.

The pharmaceutical compositions of the invention include those for oral, parenteral, inhalation, transdermal, transmucosal and nasal administration, among others. Preferably, pharmaceutical composition of present invention is for oral or inhalation administration.

The pharmaceutical compositions for oral administration may be in conventional forms, for example, tablets, capsules, granules (synonymously, "beads" or "particles" or "pellets"), suspensions, emulsions, powders, dry syrups, and the like. The capsules may contain granule/pellet/particle/mini-tablets/mini-capsules containing the active ingredients. The amount of the active agent that may be incorporated in the pharmaceutical composition may range from about 1% w/w to about 98% w/w, or from about 5% w/w to about 90% w/w.

The pharmaceutical compositions for parenteral administration include but are not limited to solutions/suspension/emulsion for intravenous, subcutaneous or intramuscular injection/infusion, and implants.

The pharmaceutical compositions for transdermal or transmucosal administration include but are not limited to patches, gels, creams, ointments and the like.

The pharmaceutical composition in the above embodiments may optionally comprise one or more pharmaceutically acceptable excipients.

As set forth above, the pharmaceutical composition includes at least one pharmaceutically acceptable excipient, which includes but is not limited to one or more of the following; diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents/viscosifying agents, surfactants, solvents and the like.

The therapeutically effective amount of a TRPA1 antagonist to be administered per day ranges from about 10µg/kg to about 20mg/kg, and preferably from about 50µg/kg to about 15mg/kg.

The therapeutically effective amount of montelukast or its salt to be administered per day ranges from about 0.1 mg to about 50 mg and more

preferably from about 1 mg to about 30 mg. Preferably, the discrete dosage strengths of montelukast or its salt to be administered per day are 2mg, 4mg, 5mg and 10mg.

The optimal dose of the active ingredient or the combination of the active ingredients can vary as a function of the severity of disease, route of administration, composition type, the patient body weight, the age and the general state of mind of the patient, and the response to behavior to the active ingredient or the combination of the active ingredients.

The process for making the pharmaceutical composition may for example include, (1) granulating either or both the active ingredients, combined or separately, along with pharmaceutically acceptable carriers so as to obtain granulate, and (2) converting the granulate into suitable dosage forms for oral administration. The typical processes involved in the preparation of the pharmaceutical combinations include various unit operations such as mixing, sifting, solubilizing, dispersing, granulating, lubricating, compressing, coating, and the like. These processes, as contemplated by a person skilled in the formulation art, have been incorporated herein for preparing the pharmaceutical composition of the present invention.

Methods of treatment

Asthma and COPD are major chronic diseases related to airway obstruction. The Global Initiative for Chronic Obstructive Lung Disease provides guidelines for the distinction between asthma and COPD. Asthma is believed to be a chronic inflammatory disease wherein the airflow limitation is more or less reversible while it is more or less irreversible in case of COPD. Asthma among other things is believed to be triggered by inhalation of sensitizing agents (like allergens) unlike noxious agents (like particles and certain gases) in case of COPD. Though both are believed to have an inflammatory component, the inflammation in asthma is believed to be mostly eosinophilic and CD-4 driven, while it is believed to be mostly neutrophilic and CD-8 driven in COPD.

Rhinitis as described herein is characterized by irritation and inflammation of some internal areas of nose. It is caused by chronic or acute inflammation of the mucous membrane of the nose due to viruses, bacteria or irritants. The inflammation results in the generating of excessive amounts of mucous causing nasal congestion. Rhinitis is categorized into three types: infective, non-allergic (vasomotor) and allergic rhinitis. Allergic rhinitis is caused by allergens such as dust or pollen which, when inhaled by the sensitized individuals, trigger antibody production. The antibodies bind to mast cells (containing histamine), which upon stimulation cause itching (urticaria), swelling and mucous production. Thus, it leads to inflammation of the mucous membranes of the nose, eyes, eustachian tubes, middle ear, sinuses, and pharynx. The nose invariably is involved, and the other organs are also affected in certain individuals. Inflammation of the mucous membranes is characterized by a complex interaction of inflammatory mediators but ultimately is triggered by an immunoglobulin E (IgE)–mediated response to an extrinsic protein.

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV_1), peak expiratory flow rate and severity (e.g., acute, intermittent, mild persistent, moderate persistent, and severe persistent**).** Asthma may also be classified as allergic (extrinsic) or non-allergic (intrinsic), based on whether symptoms are precipitated by allergens or not. Asthma can also be categorized according to following types viz., nocturnal asthma, bronchial asthma, exercise induced asthma, occupational asthma, seasonal asthma, silent asthma, and cough variant asthma.

It is believed that reduction of eosinophil count and increase in FEV1 are important components of the treatment of respiratory disorders such as asthma. Ulrik CS, 1995 (Peripheral eosinophil counts as a marker of disease activity in intrinsic and extrinsic asthma; Clinical and Experimental Allergy; 1995, Volume 25, pages 820-827) discloses the relationship between eosinophil count and severity of asthmatic symptoms. It describes that in childhood and adulthood subjects, there exists an inverse correlation between number of eosinophils and FEV1% ($r = -0.75$, $P < 0.001$, and $r = -0.80$, $P < 0.001$, respectively).

COPD, also known as chronic obstructive lung disease (COLD), chronic obstructive airway disease (COAD), or chronic obstructive respiratory disease (CORD), is believed to be the co-occurrence of chronic bronchitis (characterized by a long-term cough with mucus) and emphysema (characterized by destruction of the lungs over time), a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs, causing shortness of breath. An acute exacerbation of COPD is a sudden worsening of COPD symptoms (shortness of breath, quantity and color of phlegm) that typically lasts for several days and is believed to be triggered by an infection with bacteria or viruses or by environmental pollutants. Based on the FEV_1 values, COPD can be classified as mild, moderate, severe and very severe.

Various classes of drugs are currently being used for the treatment and/or prophylaxis of respiratory disorders like asthma and COPD. Some of the classes of such drugs are leukotriene receptor antagonists, antihistamines, beta-2 agonists, anticholinergic agents and corticosteroids.

Leukotrienes are a class of inflammatory mediators derived from arachidonic acid that are believed to act at the leukotriene receptors and bring about inflammatory and bronchoconstrictive events in the airway. The major leukotrienes are the cysteinyl leukotrienes (Cys-LTs) - LTC4, LTD4 and LTE4. Of these, LTE4 and LTD4 are believed to be the more potent mediators of airway inflammation. The receptors for these mediators have been identified as Cys-LT receptor Type-1 (Cys-LT1) and Cys-LT receptor Type-2 (Cys-LT2). The Cys-LT receptors are also believed to induce airway eosinophilia in patients with asthma. Antagonists to these receptors are thus believed to alleviate the airway inflammation and bronchoconstriction brought about by the activation of the receptors by the leukotrienes. The Cys-LT receptor antagonists that are currently available commercially are montelukast and zafirlukast, both of which are antagonists to the Cys-LT1 receptor. These antagonists find use in indications like early and late response to allergen and exercise-induced asthma.

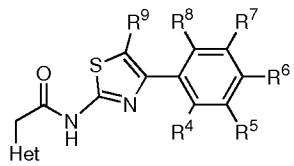
Thus, it is believed that though the therapeutic outcomes of these two classes of drugs, the TRPA1 antagonists and the leukotriene receptor antagonists

are similar to some extent, the mechanism of actions may vary to a good extent and thus the therapeutic effect of their combination in the treatment of respiratory disorders is highly unpredictable. Particularly, the therapeutic effect of the combination of a TRPA1 antagonist and a leukotriene receptor antagonist is highly unpredictable.

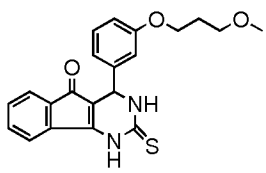
The inventors of the present invention have surprisingly found that a pharmaceutical composition comprising a TRPA1 antagonist and a leukotriene receptor antagonists are more effective in the treatment of respiratory disorders, and provide better therapeutic value when compared to both the actives alone (when administered individually) for the treatment of respiratory disorders.

In an embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, the method comprising administering the subject a pharmaceutical composition of the present invention.

In an embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist. In an aspect of this embodiment, the TRPA1 antagonist has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar having structure of formulae: (XII) or (D)

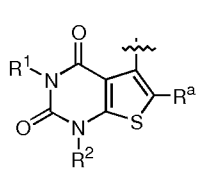
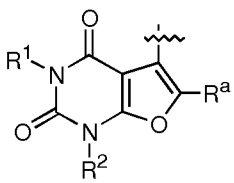
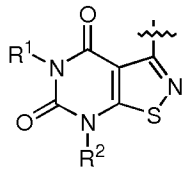
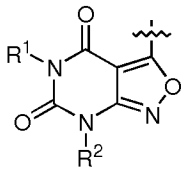


(XII)



(D)

or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of


,

,

,

;

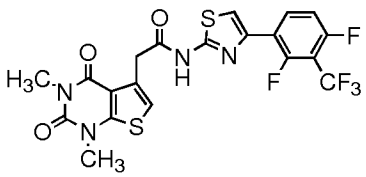
R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

In a further embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, said method comprising administering the subject a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and montelukast or its salt.

In a further embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human a TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist for the treatment of respiratory disorders in a subject.

In an embodiment, the present invention relates to a method of treating a respiratory disorder by reducing eosinophils count and/or increasing FEV1 value in a subject, method comprising administering to the subject the pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:

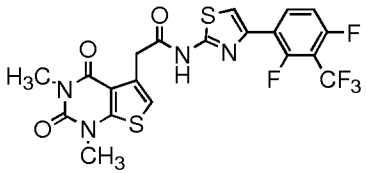


(Compound 52).

and a leukotriene receptor antagonist.

In an embodiment, the present invention relates to a method of reducing eosinophils count and/or increasing FEV1 value in a subject, method comprising administering to the subject the pharmaceutical composition comprising

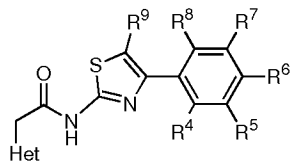
synergistically effective amount of a TRPA1 antagonist having structure of formula:



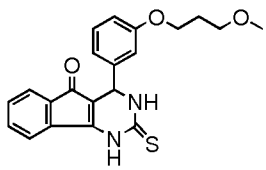
(Compound 52),

and a leukotriene receptor antagonist, thereby reducing said eosinophil count and/or increasing FEV1 value in said subject.

In a further embodiment, the present invention relates to use of synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist in the preparation of a pharmaceutical composition of the present invention for the treatment of a respiratory disorder in a subject. In an aspect of this embodiment, the TRPA1 antagonist has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar having structure of formulae: (XII) or (D)

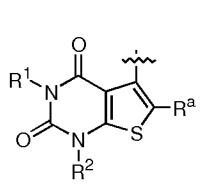
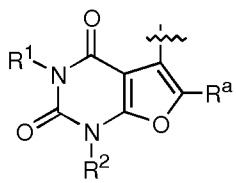
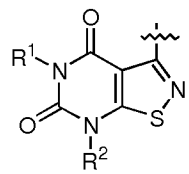
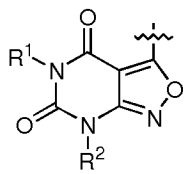


(XII)



(D)

or a pharmaceutically-acceptable salt thereof, wherein, 'Het' is selected from the group consisting of


,

,

,

;

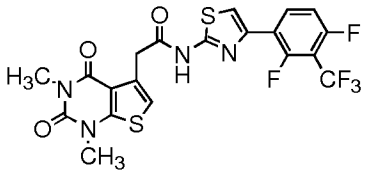
R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy,

cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl.

In a further embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist for the treatment of respiratory disorders in a subject.

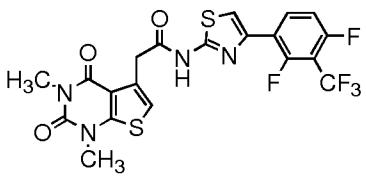
In an embodiment, the present invention relates to a method of reducing eosinophils count and/or increasing FEV1 value in a subject having a respiratory disorder, said method comprising administering to the subject the pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and a leukotriene receptor antagonist, thereby reducing said eosinophil count and/or increasing FEV1 value in said subject.

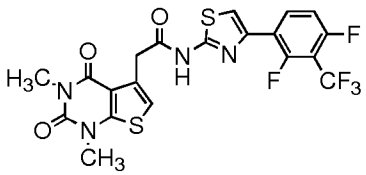
In another embodiment, the present invention relates to a pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52).

and montelukast sodium present in a weight ratio from about 1:0.005 to about 1:5, wherein the composition is a fixed dose combination.

In a further embodiment, the present invention relates to use of synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and montelukast sodium present in a weight ratio from about 1:0.005 to about 1:5 in the preparation of a pharmaceutical composition for the treatment of a respiratory disorder in a subject, wherein the composition is a fixed dose combination.

Various animal models have been used for the evaluation of the therapeutic efficacy of drug candidates for respiratory disorders like asthma and COPD. For example, commonly used strategy for evaluation of drug candidates in asthma is the allergen sensitization and challenge method. The commonly used such model is the ovalbumin (OVA) sensitization and challenge in laboratory animals. Another model that can be used is the methacholine challenge test by using invasive whole body plethysmograph.

A commonly used model for evaluation of drug candidates in COPD involves the chronic exposure of the animal to SO_2 or tobacco/cigarette smoke. The model is believed to generate sloughing of epithelial cells, increase in the mucus secretions, increase in the polymorphonuclear cells and pulmonary resistance, and increase in the airway hyper-responsiveness (in rats).

Another model that can be used for evaluation of drug candidates in COPD involves the exposure of animals (e.g., rats) to lipopolysaccharide (LPS). The exposure to LPS is believed to result in the influx of neutrophils in the lungs, a condition that is believed to be one of the characteristics of COPD.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples

should not be read as limiting the scope of the invention.

EXAMPLES

EXAMPLE 1: Determination of IC_{50} of TRPA1 antagonists

The human IC_{50} values were measured by the following method: the inhibition of TRPA1 receptor activation is measured as inhibition of allylisothiocyanate (AITC) induced cellular uptake of radioactive calcium. Test compound solution is prepared in a suitable solvent. Human TRPA1 expressing CHO cells are grown in suitable medium. Cells are treated with test compounds followed by addition of AITC. Cells are washed, lysed and the radioactivity in the lysate is measured in Packard Top count after addition of liquid scintillant. The concentration response curves for compounds are plotted as a % of maximal response obtained in the absence of test antagonist, and the IC_{50} values are calculated from such concentration response curve by nonlinear regression analysis using GraphPad PRISM software.

Table 1: TRPA1 antagonists having a human IC_{50} for inhibiting human TRPA1 receptor activity of less than 1micromolar.

Compound No	**hTRPA1 IC_{50} values**	**Compound No**	**hTRPA1 IC_{50} values**
1	920.9 nM	52	2.49 nM
2	381.8 nM	53	18.20 nM
3	73.35 nM	54	17.74 nM
4	98.32 nM	55	2.15 nM
5	66.28 nM	56	3.38 nM
6	97.42 nM	57	1.45 nM
7	47.37 nM	58	11.88 nM
8	55.02 nM	59	2.21 nM
9	102.5 nM	60	3.54 nM
10	46.74 nM	61	2.93 nM
11	46.27 nM	62	1.68 nM

Compound No	hTRPA1 IC_{50} values	Compound No	hTRPA1 IC_{50} values
12	51.68 nM	63	9.04 nM
13	48.21 nM	64	4.52 nM
14	60.42 nM	65	6.65 nM
15	53.57 nM	66	3.63 nM
16	58.94 nM	67	13.59 nM
17	56.02 nM	68	4.84 nM
18	13.38 nM	69	7.10 nM
19	26.13 nM	70	12.57 nM
20	20.09 nM	71	3.18 nM
21	48.18 nM	72	4.16 nM
22	79.77 nM	73	8.54 nM
23	43.93 nM	74	5.29 nM
24	138.1 nM	75	3.34 nM
25	58.55 nM	76	4.02 nM
26	47.91 nM	77	5.60 nM
27	65.45 nM	78	10.57 nM
28	6.49 nM	79	5.29 nM
29	11.38 nM	80	6.28 nM
30	34.03 nM	81	6.74 nM
31	17.3 nM	82	8.04 nM
32	5.96 nM	83	4.40 nM
33	5.37 nM	84	5.35 nM
34	38.46 nM	85	8.92 nM
35	18.05 nM	86	6.91 nM
36	49.92 nM	87	19.32 nM
37	12.26 nM	88	11.45 nM
38	15.92 nM	89	98.44 nM
39	26.56 nM	90	5.61 nM
40	22.82 nM	91	451.4 nM

Compound No	hTRPA1 IC_{50} values	Compound No	hTRPA1 IC_{50} values
41	11.04 nM	92	17.08 nM
42	11.38 nM	95	88.50 nM
43	18.37 nM	96	559.3 nM
44	8.36 nM	97	21.91 nM
45	26.39 nM	98	54.29 nM
46	41.31 nM	99	5.06 nM
47	33.61 nM	100	5.15 nM
48	18.12 nM	101	10.10 nM
49	3.98 nM	102	7.67 nM
50	16.73 nM	103	27.41 nM
51	4.84 nM	104	7.58 nM

EXAMPLE 2: Effect of Compound 52 and montelukast on ovalbumin induced eosinophilia in ovalbumin sensitized female Balb/C mice.

Female BALB/c mice were sensitized on day 0 and 7 with 50 µg ovalbumin and 4 mg alum given i.p. Mice were challenged with 3% aerosolized ovalbumin from Day 11-13 following sensitization. Sensitized mice were randomly assigned to different treatment groups. Test compounds were triturated with 2 drops of Tween-80 and volume was made up with 0.5% methyl cellulose (MC) solution for oral administration. Animals were administered Compound 52 orally 24 hrs before 1st ovalbumin challenge and 2 hrs before ovalbumin challenge from Day-11 to 13. Animals were assigned to one of the following 6 groups during each experiment as per Table 2.

Table 2

Group	Treatment
A	Saline Control
B	Vehicle (p.o.) treated /Ovalbumin sensitized/Ovalbumin challenged (Vehicle)
C	Compound 52 treated/Ovalbumin sensitized/

	Ovalbumin challenged (Ova + Compound 52)
D	Montelukast treated/Ovalbumin sensitized/Ovalbumin challenged (Ova + montelukast)
E	(Compound 52+ Montelukast) treated/ Ovalbumin sensitized/ Ovalbumin challenged (Combination)

Broncho Alveolar Lavage (BAL) was performed at 24 hours after challenge with ovalbumin. Animals were anesthetized with an overdose of urethane, trachea was exposed and BAL was performed 4 times using 0.3 mL PBS. All aspirates of BAL were pooled and total number of cells determined using a hemocytometer. The BAL was centrifuged, and the cell pellet was used for preparation of smears. Slides were stained with Giemsa stain and a differential cell count of 500 cells based on standard morphology was performed manually.

The total leukocyte count and the total eosinophil count were taken into account. It was surprisingly found that the combination of Compound 52 and montelukast (Group E) produced significantly superior inhibition of leukocytes and eosinophils as compared to the individual activity of both treatments (Group C and Group D). The results are given in Table 3 and Figure 1.

Table 3

Group (N)	**Dose**	**Total leukocytes**	**Total Eosinophils**	**% inhibition**	
				Leukocytes	**Eosinophils**
A (12)	-	1.90±0.2	0.0±0.0	-	-
B (12)	-	11.55±0.8	5.31±0.6	-	-
C (6)	1 mg/kg p.o.	10.46±1.0	4.33±1.1	11.3±10.4	18.6 ± 8.6
D (6)	5 mg/kg p.o.	11.88±1.0	4.23±1.5	-3.5± 10.1	20.4 ± 11.3
E (6)	1 mg/kg + 5 mg/kg p.o.	6.57±0.8	1.36±0.5	51.4 ± 8.6	74.4 ± 3.7

EXAMPLE 3: Animal study for the effect of combination of TRPA1 antagonist and montelukast in rhinitis model.

Animals are sensitized with ovalbumin and aluminum hydroxide. Control animals receive aluminium hydroxide in 0.9% saline. Animals are challenged with Ovalbumin intranasally on 4th week. The number of sneezes is counted following Ovalbumin challenge. Compound 52 is administered orally at a dose ranging from 0.01 to 30 mg/kg, and montelukast is administered orally at a dose ranging from 0.01 to 30 mg/kg.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and application of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments of the present invention as described.

All publications, patents, and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated herein by reference.

We claim:

1. A pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar, and a leukotriene receptor antagonist.

2. The pharmaceutical composition according to claim 1, wherein the TRPA1 antagonist has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 500 nanomolar.

3. The pharmaceutical composition according to claim 2, wherein the TRPA1 antagonist has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 250 nanomolar.

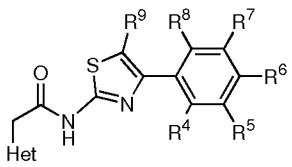
4. The pharmaceutical composition according to claim 1, wherein the TRPA1 antagonist and the leukotriene receptor antagonist are present in a weight ratio from about 1:0.005 to about 1:10.

5. A method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 1-4.

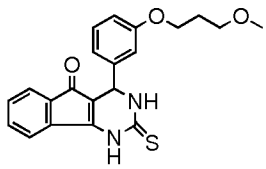
6. Use of synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar and a leukotriene receptor antagonist in the preparation of the pharmaceutical composition according to any one of claims 1-4 for the treatment of a respiratory disorder in a subject.

7. The pharmaceutical composition according to claims 1-4, for the treatment of respiratory disorder in a subject.

8. A pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist that has an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar having structure of formulae: (XII) or (D)



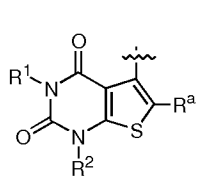
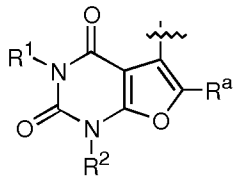
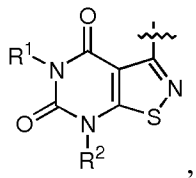
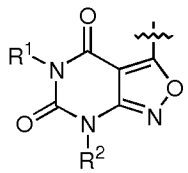
(XII)



(D)

or a pharmaceutically-acceptable salt thereof, wherein,

'Het' is selected from the group consisting of


,

,

,

;

R^1, R^2 and R^a, which may be the same or different, are each independently hydrogen or (C_1-C_4) alkyl;

R^4, R^5, R^6, R^7, R^8 and R^9, which may be same or different, are each independently selected from the group comprising of hydrogen, halogen, cyano, hydroxyl, nitro, amino, substituted or unsubstituted alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkylalkoxy, aryl, arylalkyl, biaryl, heteroaryl, heteroarylalkyl, heterocyclic ring and heterocyclylalkyl,

and a leukotriene receptor antagonist.

9. The pharmaceutical composition according to any one of claims 1-4 or 8, wherein the leukotriene receptor antagonist comprises montelukast, zafirlukast, pranlukast, tipelukast, masilukast, iralukast, cinalukast, tomelukast, verlukast, pobilukast, sulukast, SKF-106203, L-648051, DS-4574, CGP-57698, YM-158, AS-35, KP-496, MEN-91507, KP-496, MK-571, CR-3465 or salts thereof.

10. The pharmaceutical composition according to claim 9, wherein the leukotriene receptor antagonist is montelukast or its salt.

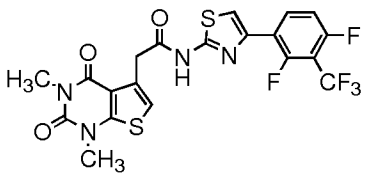
11. The pharmaceutical composition according to any one of claims 8-10, wherein the TRPA1 antagonist and the leukotriene receptor antagonist are present in a weight ratio from about 1:0.05 to about 1:5.

12. A method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 8-11.

13. Use of synergistically effective amount of a TRPA1 antagonist having an IC_{50} for inhibiting human TRPA1 receptor activity of less than 1 micromolar, and the leukotriene receptor in the preparation of the pharmaceutical composition according to claims 8-11 for oral administration for the treatment of a respiratory disorder in a subject.

14. The pharmaceutical composition according to any one of claims 8-11, for the treatment of respiratory disorder in a subject.

15. A pharmaceutical composition comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and a leukotriene receptor antagonist.

16. The pharmaceutical composition according to claim 15, wherein the leukotriene receptor antagonist is montelukast, zafirlukast, pranlukast, tipelukast, masilukast, iralukast, cinalukast, tomelukast, verlukast,

pobilukast, sulukast, SKF-106203, L-648051, DS-4574, CGP-57698, YM-158, AS-35, KP-496, MEN-91507, KP-496, MK-571, CR-3465 or salts thereof.

17. The pharmaceutical composition according to claim 16, wherein the leukotriene receptor antagonist is montelukast or its salt.

18. The pharmaceutical composition according to claim 15, wherein the TRPA1 antagonist and the leukotriene receptor antagonist are present in a weight ratio from about 1:0.05 to about 1:5.

19. The pharmaceutical composition according to any one of claims 15-18, wherein the composition is administered orally.

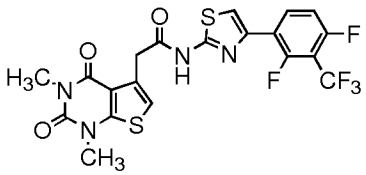
20. The pharmaceutical composition according to any one of claims 15-19, wherein the composition is a fixed dose combination.

21. A method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 15-20.

22. A method of treating a respiratory disorder by reducing eosinophils count and/or increasing FEV1 value in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 15-20.

23. A method of reducing eosinophils count and/or increasing FEV1 value in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 15-20, thereby reducing said eosinophil count and/or increasing FEV1 value in said subject.

24. Use of synergistically effective amount of a TRPA1 antagonist having structure of formula:

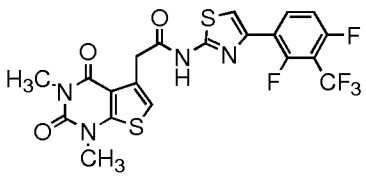


(Compound 52),

and a leukotriene receptor antagonist in the preparation of a pharmaceutical composition according to any one of claims 15-20 for the treatment of a respiratory disorder in a subject.

25. The pharmaceutical composition according to any one of claims 15-20, for the treatment of respiratory disorder in a subject.

26. A pharmaceutical composition for oral administration comprising synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and montelukast sodium, wherein the composition is a fixed dose combination.

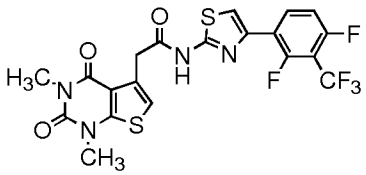
27. The pharmaceutical composition according to claim 26, wherein the TRPA1 antagonist and montelukast sodium are present in a weight ratio from about 1:0.05 to about 1:5.

28. A method of treating a respiratory disorder by reducing eosinophils count and/or increasing FEV1 value in a subject, said method comprising

administering to the subject the pharmaceutical composition according to any one of claims 26-27.

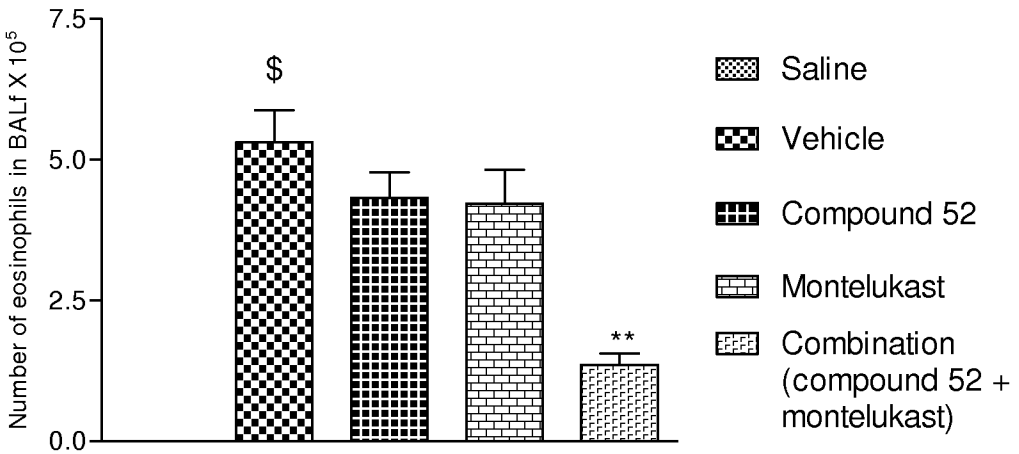
29. The method according to claim 28, wherein the respiratory disorder is asthma.

30. Use of synergistically effective amount of a TRPA1 antagonist having structure of formula:



(Compound 52),

and montelukast sodium in the preparation of the pharmaceutical composition according to any one of claims 26-27 for the treatment of a respiratory disorder in a subject.



$ P< 0.001 Significant, Vehicle compared to Saline
** P< 0.001 Significant compared to Vehicle treated group

Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053049

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/404 A61K31/407 A61K31/41 A61K31/429 A61K31/47
A61K31/4985 A61P11/00
ADD.
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)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/002933 A1 (HYDRA BIOSCIENCES INC [US]; NG HOWARD [US]; WEIGELE MANFRED [US]; MORA) 31 December 2008 (2008-12-31) cited in the application page 33, line 22 - line 23	1-30
Y	US 2002/151562 A1 (SELIGMAN MORTON J [US]) 17 October 2002 (2002-10-17) paragraph [0008]	1-30
Y	WO 2009/137087 A2 (UNIV YALE [US]; JORDT SVEN-ERIC [US]; BESSAC BRET [US]; SIVULA MICHAEL) 12 November 2009 (2009-11-12) claims 1-29	1-30

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

☒ See patent family annex.

* 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
26 September 2012	04/10/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Albayrak, Timur

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/053049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009002933 A1	31-12-2008	AU 2008268463 A1	31-12-2008
		CA 2691468 A1	31-12-2008
		CN 101801362 A	11-08-2010
		EP 2170309 A1	07-04-2010
		JP 2010530901 A	16-09-2010
		US 2009143377 A1	04-06-2009
		WO 2009002933 A1	31-12-2008
US 2002151562 A1	17-10-2002	NONE	
WO 2009137087 A2	12-11-2009	US 2011144137 A1	16-06-2011
		WO 2009137087 A2	12-11-2009