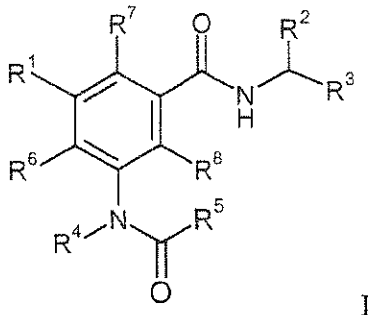
transmission in the lung. More recently, others have implicated $P2X_2$ and $P2X_3$ receptors in pO_2 detection in pulmonary NEBs (Rong et al., *J Neurosci* (2003) **23(36)**:11315-21) and cough.

There is accordingly a need for compounds that act as modulators of P2X receptors, including antagonists of $P2X_3$ and $P2X_{2/3}$ receptors, as well as a need for methods of treating diseases, conditions and disorders mediated by $P2X_3$ and/or $P2X_{2/3}$ receptors. The present disclosure~~invention~~ satisfies these needs as well as others.

The disclosure~~invention~~ provides compounds of the formula I:



I

wherein:

R^1 is: optionally substituted phenyl; optionally substituted thienyl; optionally substituted pyrimidinyl; optionally substituted pyridazinyl; or optionally substituted pyridinyl;

R^2 is: hydrogen; or C_{1-6}alkyl; ;

R^3 is: C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{3-7}cycloalkyl; heteroaryl; heterocyclyl; heterocyclyl-C_{1-6}alkyl; or C_{3-7}cycloalkyl-C_{1-6}alkyl;

or R^2 and R^3 together form a C_{3-7}cycloalkyl;

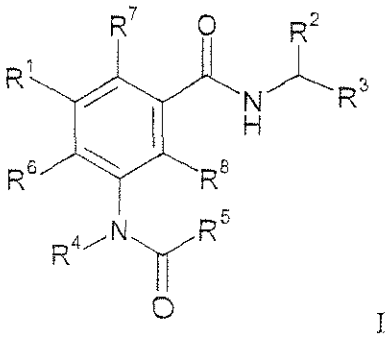
R^4 is: hydrogen; C_{1-6}alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl-C_{1-6}alkyl; or pyrimidinyl;

R^5 is: C_{1-6}alkyl; C_{1-6}alkoxy; C_{3-7}cycloalkyl; C_{1-6}alkoxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; amino; oxetanyl optionally substituted once or twice with C_{1-6}alkyl; phenyl optionally substituted once or twice with a group or groups independently selected from C_{1-6}alkyl, halo, halo-C_{1-6}alkyl and C_{1-6}alkoxy; thienyl optionally substituted once or twice with a group or groups independently selected from C_{1-6}alkyl and C_{1-6}alkoxy; furanyl optionally substituted once or twice with C_{1-6}alkyl; thiazolyl optionally substituted once or twice with C_{1-6}alkyl; oxazolyl optionally substituted once or twice with C_{1-6}alkyl; isoxazolyl optionally substituted once or twice with a group or groups independently selected from C_{1-6}alkyl and phenyl; pyrazolyl optionally substituted once or twice with C_{1-6}alkyl; thiadiazolyl optionally substituted once with C_{1-6}alkyl; tetrahydropyranyl; morpholinyl;

piperidinyl optionally substituted with C_{1-6}alkyl or acetyl; pyrazinyl; or pyridinyl optionally substituted once or twice with C_{1-6}alkyl; and

R^6 , R^7 and R^8 each independently is: hydrogen; or halo.

According to a first aspect, there is provided a compound of formula I



I

wherein:

R^1 is: phenyl substituted at the 4-position with methyl or halo and optionally substituted at the 2-position with halo;

R^2 is: hydrogen; or C_{1-6}alkyl;

R^3 is: hydroxy-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; heteroaryl selected from pyridinyl, pyrimidinyl, or pyrazinyl, each of which optionally substituted once or twice with methyl; or heterocycyl-C_{1-6}alkyl selected from morpholinomethyl, piperidinyl-methyl, piperazinyl-methyl, thiomorpholinylmethyl, pyrrolidinylmethyl, or azetidinylmethyl, the heterocyclyl portion of each of which optionally substituted once or twice with a group or groups independently selected from methyl, methoxy, halo, methanesulfonyl, oxo or acetyl;

or R^2 and R^3 together form a C_{3-7}cycloalkyl;

R^4 is: hydrogen; C_{1-6}alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl-C_{1-6}alkyl; or pyrimidinyl;

R^5 is: C_{1-6}alkyl; C_{1-6}alkoxy; C_{3-7}cycloalkyl; C_{1-6}alkoxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; amino; oxetanyl optionally substituted once or twice with C_{1-6}alkyl; phenyl optionally substituted once or twice with a group or groups independently selected from C_{1-6}alkyl, halo, halo-C_{1-6}alkyl and C_{1-6}alkoxy; thienyl optionally substituted once or twice with a group or groups independently selected from C_{1-6}alkyl and C_{1-6}alkoxy; furanyl optionally substituted once or twice with C_{1-6}alkyl; thiazolyl optionally substituted once or twice with C_{1-6}alkyl; oxazolyl optionally substituted once or twice with C_{1-6}alkyl; isoxazolyl optionally substituted once or twice with a group or groups independently selected from C_{1-6}alkyl and phenyl; pyrazolyl optionally substituted once or twice with C_{1-6}alkyl; thiadiazolyl optionally substituted once with C_{1-6}alkyl; tetrahydropyranyl; morpholinyl; piperidinyl optionally substituted with C_{1-6}alkyl or acetyl; pyrazinyl; or pyridinyl optionally substituted once or twice with C_{1-6}alkyl; and

R^6 , R^7 and R^8 are: hydrogen;.

The disclosure~~invention~~ also provides and pharmaceutical compositions comprising the compounds, methods of using the compounds, and methods of preparing the compounds.

According to a second aspect, there is provided a compound as defined above for use as therapeutically active substance.

According to a third aspect, there is provided a compound as defined above for use in the treatment of a urinary tract disease selected from reduced bladder capacity, frequenct micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benign prostatic hypertrophy, prostatitis, detrusor hyperreflexia, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity; or for use in the treatment of a pain condition selected from inflammatory pain, surgical pain, visceral pain, dental pain, premenstrual pain, central pain, pain due to burns, migraine or cluster headaches, nerve injury, neuritis, neuralgias, poisoning, ischemic injury, interstitial cystitis, cancer pain, viral, parasitic or bacterial infection, post-traumatic injury, or pain associated with irritable bowel syndrome.

According to a fourth aspect, there is provided a pharmaceutical composition comprising (a) a pharmaceutically acceptable carrier; and (b) a compound as defined above.

According to a fifth aspect, there is provided the use of a compound as defined above for the preparation of a medicament for the treatment of a urinary tract disease selected from reduced bladder capacity, frequenct micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benign prostatic hypertrophy, prostatitis, detrusor hyperreflexia, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity; or for the treatment of a pain condition selected from inflammatory pain, surgical pain, visceral pain, dental pain, premenstrual pain, central pain, pain due to burns, migraine or cluster headaches, nerve injury, neuritis, neuralgias, poisoning, ischemic injury, interstitial cystitis, cancer pain, viral, parasitic or bacterial infection, post-traumatic injury, or pain associated with irritable bowel syndrome.

Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

"Agonist" refers to a compound that enhances the activity of another compound or receptor site.

"Alkyl" means the monovalent linear or branched saturated hydrocarbon moiety, consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms. "Lower alkyl" refers to an alkyl group of one to six carbon atoms, i.e. C_1-C_6alkyl. Examples of alkyl groups or lower alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like.

"Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, *e.g.*, ethenyl, propenyl, and the like.

"Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one triple bond, *e.g.*, ethynyl, propynyl, and the like.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methylpropylene, butylene, pentylene, and the like.

"Alkoxy" and "alkyloxy", which may be used interchangeably, mean a moiety of the formula –OR, wherein R is an alkyl moiety as defined herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.