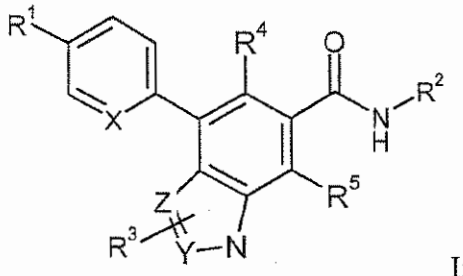
transmission in the lung. More recently, others have implicated $P2X_2$ and $P2X_3$ receptors in pO_2 detection in pulmonary NEBs (Rong et al., *J Neurosci* (2003) **23(36)**:11315-21) and cough.

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 invention satisfies these needs as well as others.

The invention provides compounds of the formula I:



I;

or pharmaceutically acceptable salts thereof,

wherein:

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

R^2 is: C_{3-6}cycloalkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; or heteroaryl-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_{3-6}cycloalkyl; C_{3-6}cycloalkyl- C_{1-6}alkyl; phenyl optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or halo- C_{1-6}alkyl; or phenyl-C_{1-6}alkyl wherein the phenyl portion thereof is optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or halo- C_{1-6}alkyl;

R^4 and R^5 each independently is: hydrogen; or fluoro;

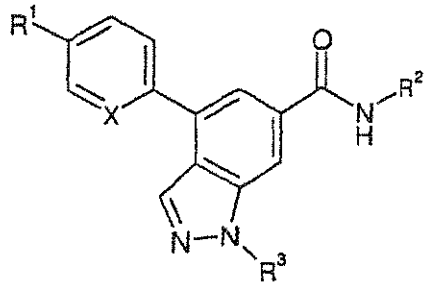
X is: N; or CR^a wherein R^a is C_{1-6}alkyl or halo;

Y is: N; or CR^b wherein R^b is hydrogen or C_{1-6}alkyl; and

Z is: N; or CR^c; wherein R^c is hydrogen or C_{1-6}alkyl.

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

In a first aspect, there is provided a compound of formula III:



III;

or a pharmaceutically acceptable salt thereof,

wherein:

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

R^2 is: C_{3-6}cycloalkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; or heteroaryl-C_{1-6}alkyl selected from the group consisting of pyrazinyl-methyl and pyridazinyl-methyl; wherein the pyrazinyl and pyridazinyl portions thereof may be optionally substituted once with methyl;

R^3 is: C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; halo-C_{1-6}alkyl; phenyl optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or halo- C_{1-6}alkyl; or phenyl-C_{1-6}alkyl wherein the phenyl portion thereof is optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or halo- C_{1-6}alkyl;

X is: N.

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

In 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.

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

In 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.