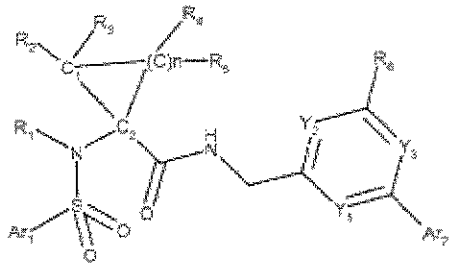
fibers of the urothelium, sub-urothelial space, muscle layers and around blood vessels (Du et al., Urology, 2008, 72, 450-455; Andrade et al., Biochem. Pharmacol., 2006, 72, 104-114; Gratzke et al., Eur. Urology, 2008, Apr 30 e-pub; Streng et al., Eur. Urology, 2008,53,391-400). TRPA1 expression is increased in bladder mucosa from patients with bladder outlet obstruction (Du et al., Urology, 2008, 72, 450-455). Activation of TRPA1 increases micturition frequency and reduces voiding volume (Streng et al., supra).

Activation of TRPA1 in the bladder by reactive metabolites of cyclophosphamide (e.g., acrolein) may be responsible for cystitis that sometimes accompanies the use of chemotherapeutic agents (Bautista et al., supra). TRPA1 is also expressed in colonic afferents, is upregulated following induction of experimental colitis, and TRPA1 antisense oligonucleotides suppresses colitis-induced hyperalgesia to colonic distension (Yang et al., Neurosci Lett, 2008, 440, 237-241). These data suggest a role for TRPA1 in the pathogenesis of visceral pain and dysfunction, such as bladder instability, urinary incontinence, cystitis and colitis.

Summary

In one aspect, there is provided a compound of formula (I)



(I)

wherein:

Ar_1 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or

ii) a 5- or 6-membered monocyclic aromatic heterocycle ring optionally substituted with one or two substituents R_a; where each R_a is independently halo, -C_{1-4}alkyl, -OC_{1-4}alkyl, -CN, -CF_3, -OCF_3, -NO_2, -$C(O)C_{1-4}$alkyl or - CO_2H;

Ar_2 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_b; where each R_b is independently halo, -C_{1-4}alkyl, -$C(O)NR_cR_d$, -OC_{1-4}alkyl, -OC_{0-4}alkylCF_3, -CN, -CF_3, -OCF_2H, -NO_2, -NR_cR_d, -$S(O)_{0-2}C_{1-4}$alkyl, -$C(O)C_{1-4}$alkyl, $S(O)(O)NH_2$, -$(CH_2)_{0-2}$-morpholinyl, piperidin-1-yl, piperazinyl, said piperazinyl being optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form -$O(CH_2)_{1-2}O$-;

ii) pyridyl substituted with 0, 1 or 2 substituents R_a; where each R_e is independently selected from halo, -C_{1-4}alkyl, -OC_{1-4}alkyl, -CF_3, -NR_cR_d or 4-morpholinyl; or

iii) a bicyclic 9-11-membered aromatic heterocycle, optionally substituted with 1 substituent R_f; where R_f is -C_{1-4}alkyl;

R_c and R_d are each independently selected from H or -C_{1-4}alkyl;

R_1 is H, C_{1-4}alkyl-O-C_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with halo;

R_2, R_3, R_4, and R_5 are each independently H, halo or -C_{1-4}alkyl;

n is 0 or 1 providing that when n is 1 the bond between C1 and C2 is single and when n is 0 the bond between C1 and C2 is double;

each Y_1, Y_2 and Y_3 is independently CH or N;

R_6 is

i) H, -C_{1-4}alkyl, -CF_3, -OR_z or -NR_hR_i;

where R_h is selected from:

a) H, -C_{0-4}alkylCF_3, -C_{1-4}alkyl-$N(CH_3)_2$, saturated C_{3-7}Cycloalkyl or -C_{1-4}alkyl-monocyclic heteroaryl ring;

b) -C_{1-5}alkyl optionally substituted with OH;

c) -C_{1-4}alkyl-heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with -C_{1-4}alkyl; or

d) -C_{0-4}alkyl-phenyl, said phenyl being optionally substituted with one or two R_j moieties; where each R_j is independently halo, -OC_{1-4}alkyl,

R_Z is -C_{1-4}alkyl, -C_{1-4}alkylCF_3 or -C_{1-4}alkyl- heterocycloalkyl;

ii) 1-pyrrolidinyl optionally substituted with a moiety selected from the group consisting of -NR_kR_i and -C_{1-4}alkyl, said -C_{1-4}alkyl optionally substituted with -OH;

iii) 1-piperidinyl optionally substituted with -C_{1-4}alkyl, -C(O)NH_2, -CO_2C_{1-4}alkyl or -C_{0-4}alkyl-phenyl;

iv) piperazinyl optionally substituted with -C_{1-5}alkyl, -OC_{1-4}alkyl, -C_{0-4}alkylpyridyl, -C_{0-4}alkyl-1-methyl-piperidin-4-yl, -C_{0-4}alkylNR_kR_i or -C_{0-4}alkyl-phenyl, said phenyl being optionally substituted with one or two R_T substituents; where each R_T substituent is selected from the group consisting of halo, -OCF_3, -C_{1-4}alkyl, -OC_{1-4}alkyl, -CO_2C_{1-4}alkyl, -C(O) C_{1-4}alkyl and -C_{0-4}alkylNR_kR_i, or two R_T substituents on adjacent carbon atoms taken together form -$O(CH_2)_{1-2}O$-;

v) phenyl optionally substituted with halo, -CF_3, -OCF_3;

vi) pyridyl;

vii) morpholin-yl;

R_k is H, -C_{1-4}alkyl or -$C(O)_{1-2}C_{1-4}$alkyl;

R_i is H or C_{1-4}alkyl;

N-oxides, enantiomers, racemic mixtures and pharmaceutically acceptable salts thereof.

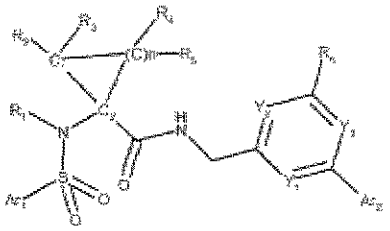
In another aspect, there is provided a pharmaceutical composition comprising one or more compounds described herein as an active ingredient.

In another aspect, there is provided a compound as described herein for use as a TRPA1 antagonist.

In another aspect, there is provided a compound as described herein for use in the treatment of pain and inflammatory diseases, including airways disorders such as asthma, chronic cough and COPD.

Description of the invention

The present invention relates to TRPA1 inhibitors of formula **(I)**



(I)

wherein:

Ar_1 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or

ii) a 5- or 6-membered monocyclic aromatic heterocycle ring optionally substituted with one or two substituents R_a; where each R_a is independently halo, $-C_1$.

v) phenyl optionally substituted with halo, $-CF_3$, $-OCF_3$;

vi) pyridyl;

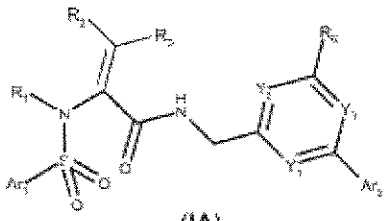
vii) morpholin-yl;

R_k is H, $-C_{1-4}$alkyl or $-C(O)_{1-2}C_{1-4}$alkyl;

R_i is H or C_{1-4}alkyl;

N-oxides, enantiomers, racemic mixtures and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 of formula (IA)



(IA)

wherein:

Ar_1 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or

ii) a 5-6-membered monocyclic aromatic heterocycle ring, optionally substituted with one or two substituents R_a; where each R_a is independently halo, $-C_{1-4}$alkyl, $-OC_{1-4}$alkyl, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)C_{1-4}$alkyl or - CO_2H;

Ar_2 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_b; where each R_b is independently halo, $-C_{1-4}$alkyl, $-C(O)NR_cR_d$, $-OC_{1-4}$alkyl, $-OC_{0-4}$alkylCF_3, -CN, $-CF_3$, $-OCF_2H$, $-NO_2$, $-NR_cR_d$, $-S(O)_{0-2}C_{1-4}$alkyl, $-C(O)C_{1-4}$alkyl, $S(O)(O)NH_2$, $-(CH_2)_{0-2}$-morpholinyl, piperidin-1-yl, piperazinyl, said piperazinyl being optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form $-O(CH_2)_{1-2}O$-;

ii) pyridyl substituted with 0, 1 or 2 substituents R_e; where each R_e is independently selected from halo, $-C_{1-4}$alkyl, $-OC_{1-4}$alkyl, $-CF_3$, $-NR_cR_d$ or 4-morpholinyl;

v) phenyl optionally substituted with halo, $-CF_3$, $-OCF_3$;

vi) pyridyl;

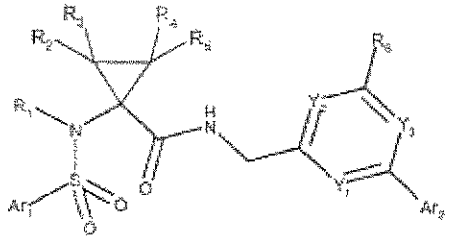
vii) morpholin-yl;

R_k is H, $-C_{1-4}$alkyl or $-C(O)_{1-2}C_{1-4}$alkyl;

R_i is H or C_{1-4}alkyl;

N-oxides, enantiomers, racemic mixtures and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 of formula (IB)



(IB)

wherein:

Ar_1 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or

ii) a 5- or 6-membered monocyclic aromatic heterocycle ring, optionally substituted with one or two substituents R_a; where each R_a is independently halo, $-C_{1-4}$alkyl, $-OC_{1-4}$alkyl, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)C_{1-4}$alkyl or - CO_2H;

Ar_2 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_b; where each R_b is independently halo, $-C_{1-4}$alkyl, $-C(O)NR_cR_d$, $-OC_{1-4}$alkyl, $-OC_{0-4}$alkylCF_3, -CN, $-CF_3$, $-OCF_2H$, $-NO_2$, $-NR_cR_d$, $-S(O)_{0-2}C_{1-4}$alkyl, $-C(O)C_{1-4}$alkyl, $S(O)(O)NH_2$, $-(CH_2)_{0-2}$-morpholinyl, piperidin-lyl, piperazinyl, said piperazinyl being optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form $-O(CH_2)_{1-2}O$-;

ii) pyridyl substituted with 0, 1 or 2 substituents R_e; where each R_e is

R_T substituents on adjacent carbon atoms taken together form -$O(CH_2)_{1-2}O$-;

v) phenyl optionally substituted with halo, CF_3;

vi) pyridyl;

vii) morpholin-yl;

R_k is H, -C_{1-4}alkyl or -$C(O)_{1-2}C_{1-4}$alkyl;

R_i is H or C_{1-4}alkyl;

N-oxides, enantiomers, racemic mixtures and pharmaceutically acceptable salts thereof.

4. A compound according to claims 1-3 wherein each Y_1, Y_2 are CH and Y_3 is N.

5. A compound according to claims 1-3 wherein each Y_1, Y_2 and Y_3 are CH.

6. A compound according to claim 4 or 5 wherein:

Ar_1 is:

i) phenyl substituted with one substituent R_a; where R_a is halo, or -C_{1-4}alkyl;

ii) a thienyl ring optionally substituted with one substituents R_a: where R_a is halo;

Ar_2 is:

i) phenyl substituted with 1 substituent R_b,; where R_b is -OC_{0-4}alkylCF_3;

R_i is H or C_{1-4} alkyl optionally substituted with halo;

R_2, R_3, R_4, and R_5 are each independently H, or-C_{1-4}alkyl;

R_6 is:

i) H;

ii) 1-pyrrolidinyl;

iii) phenyl optionally substituted with -CF_3 or -OCF_3;

iv) morpholin-yl.

7. A compound according to any of the preceeding claims, selected from:

2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;

2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-