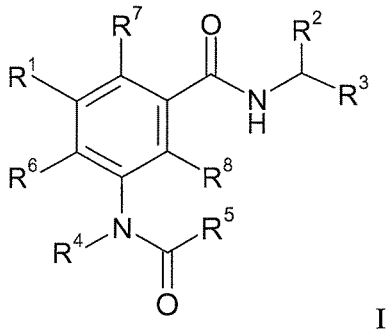
Claims

1. 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: ~~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 selected from pyridinyl, pyrimidinyl, or pyrazinyl, each of which optionally substituted once or twice with methyl; ~~heterocyclyl; 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 C_{3-7}cycloalkyl-C_{1-6}alkyl;~~

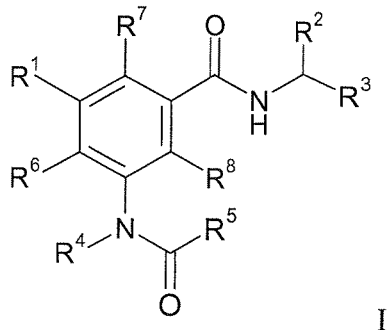
or R^2 and R^3 together form a C_{3-7}cycloalkyl;

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 are: hydrogen;.

2. The compound of claim 1 of the 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: ~~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;~~ or heteroaryl selected from pyridinyl, pyrimidinyl, or pyrazinyl, each of which optionally substituted once or twice with methyl; ~~heterocyclyl; or C_{3-7}cycloalkyl-C_{1-6}alkyl;~~ or R^2 and R^3 together form a C_{3-7}cycloalkyl;

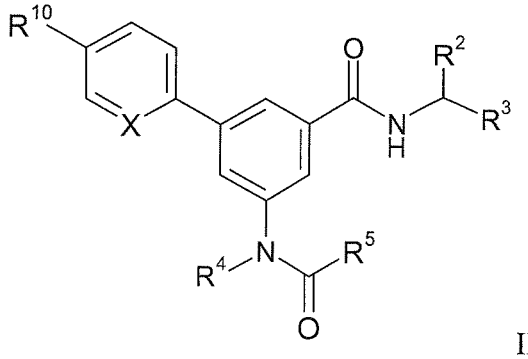
R^4 is: hydrogen; C_{1-6}alkyl; or pyrimidinyl;

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

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

3. The compound of claim 2, wherein R^1 is 4-methyl-phenyl.

4. The compound of claim 2, wherein said compound is of formula II:



II

wherein:

X is: -CR^a; wherein R^a is hydrogen, halo or methyl;

R^{10} is: methyl; or halo; and

R^2, R^3, R^4 and R^5 are as recited in claim 2.

5. The compound of claim 4, wherein R^2 is hydrogen; or wherein R^2 is methyl.

~~6. The compound of claim 4, wherein R^3 is: C_{1-6}alkyl; C_{1-6}alkyloxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; C_{1-6}alkylsulfanyl-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; amino-C_{1-6}alkyl; N-C_{1-6}alkyl-amino-C_{1-6}alkyl; N,N-di-C_{1-6}alkyl-amino-C_{1-6}alkyl; C_{3-7}cycloalkyl; optionally substituted phenyl; heteroaryl, or heterocyclyl-C_{1-6}alkyl.~~

~~7. The compound of claim 4, wherein R^3 is: C_{1-6}alkyloxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; heteroaryl, or heterocyclyl-C_{1-6}alkyl.~~

~~8~~6. The compound of claim 4, wherein R^3 is heteroaryl selected from pyridinyl, pyrimidinyl, or pyrazinyl, each of which may be optionally substituted once or twice with methyl.

~~9~~7. The compound of claim 4, wherein R^3 is hydroxymethyl, methoxymethyl, pyrazin-2-yl or 5-methyl-pyrazin-2-yl.

~~10~~8. The compound of claim 4, wherein R^4 is hydrogen, methyl, ethyl or pyrimidin-4-yl.

~~11~~9. The compound of claim 4, wherein R^5 is C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkyl-C_{1-6}alkyl.

~~12~~10. The compound of claim 2, wherein said compound is selected from:

4-Methyl-thiophene-2-carboxylic acid [5-(2-methoxy-1-methyl-ethylcarbamoyl)-4'-methyl-biphenyl-3-yl]-amide;

5-(Cyclohexanecarbonyl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide;

4'-Methyl-5-[methyl-(2-methyl-butyryl)-amino]-biphenyl-3-carboxylic acid ((S)-2-hydroxy-1-methyl-ethyl)-amide;

2'-Chloro-5-(isobutyryl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide;

2'-Chloro-5-(isobutyryl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid ((S)-2-hydroxy-1-methyl-ethyl)-amide;

2'-Chloro-5-(isobutyryl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid (pyrazin-2-ylmethyl)-amide;

4'-Chloro-5-(trimethyl-ureido)-biphenyl-3-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide;

2'-Fluoro-5-(isobutyryl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide;

2'-Fluoro-5-(isobutyryl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid ((S)-2-hydroxy-1-methyl-ethyl)-amide;

2'-Fluoro-5-(isobutyryl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid (pyrazin-2-ylmethyl)-amide;

1-Acetyl-piperidine-4-carboxylic acid methyl-[4'-methyl-5-(1-pyrazin-2-yl-ethylcarbamoyl)-biphenyl-3-yl]-amide;

5-(Isobutyryl-methyl-amino)-4'-methyl-biphenyl-3-carboxylic acid (pyrazin-2-ylmethyl)-amide;

2',4'-Dichloro-5-(isobutyryl-methyl-amino)-biphenyl-3-carboxylic acid ((R)-2-methoxy-1-methyl-ethyl)-amide;

2',4'-Dichloro-5-(isobutyryl-methyl-amino)-biphenyl-3-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide;

2',4'-Difluoro-5-(isobutyryl-methyl-amino)-biphenyl-3-carboxylic acid ((R)-2-methoxy-1-methyl-ethyl)-amide; and

2',4'-Difluoro-5-(isobutyryl-methyl-amino)-biphenyl-3-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide.

~~13~~11. A compound according to any one of claims 1 to ~~12~~10 for use as therapeutically active substance.

~~14~~12. A compound according to any one of claims 1 to ~~12~~10 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.

~~15~~13. A pharmaceutical composition comprising (a) a pharmaceutically acceptable carrier; and (b) a compound of claim 2.

~~16~~14. The use of a compound according to any one of claims 1 to ~~12~~ 10 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.