Title: TREATMENT OF INCONTINENCE

Abstract: The present invention relates to the use of modulators of synaptic vesicle protein 2A (SV2A), such as levetiracetam or UCB-34714, for the treatment of conditions of lower urinary tract dysfunction, including urinary incontinence and overactive bladder. The present invention also relates to the use of modulators of SV2A for the treatment of faecal incontinence. The present invention also relates to a method of treatment of conditions of lower urinary tract dysfunction, using a modulator of SV2A. The present invention also relates to assays to screen for compounds useful in the treatment of conditions of lower urinary tract dysfunction.
Treatment of Incontinence

The present invention relates to the use of modulators of synaptic vesicle protein 2A (SV2A) for the treatment of conditions of lower urinary tract dysfunction, including urinary incontinence and overactive bladder.

The present invention also relates to a method of treatment of conditions of lower urinary tract dysfunction, using a modulator of SV2A.

The present invention also relates to assays to screen for compounds useful in the treatment of conditions of lower urinary tract dysfunction.

Many otherwise healthy, active individuals suffer from conditions which result in disturbances in normal urinary function including increased urinary frequency, urgency and potentially associated incontinence. Such conditions including incontinence significantly impact on social and work related aspects of an individual's life. Failure to control the elimination or storage of urine causes psychological stress, complicates medical illnesses and management, and has major economic consequences. Patients often describe the impact of both lower urinary tract dysfunction such as urinary incontinence or urgency and frequency in terms of shame, embarrassment and a major disruption to every day life; many report that it causes them to isolate themselves from friends and family. Incontinence frequently results in an early decision to institutionalize elderly relatives because families have difficulty coping with incontinence at home. Not surprisingly, there is an increase in symptoms of depression and anxiety in patients with incontinence as well as degradation in quality of life that has been documented by standardized assessment instruments. The direct health care costs for urinary incontinence were estimated to be $16.3 billion in 1995.

Faecal incontinence (also called bowel incontinence or anal incontinence) affects people of all ages. It may be defined as the involuntary loss of solid or liquid stool sufficient to result in impaired quality of life for the individual.

Urinary incontinence is the complaint of any involuntary leakage of urine. Many forms of urinary incontinence are known, including urge urinary incontinence, stress urinary incontinence (SUI), overactive bladder associated with incontinence, mixed urinary incontinence (MUI), overflow urinary incontinence, nocturnal enuresis, and others.
The medical need is high for effective pharmacological treatments of conditions of lower urinary tract dysfunction and in particular urinary incontinence. This high medical need is a result of a lack of efficacious pharmacological therapy coupled with high patient numbers.

Pharmacological therapy may target the bladder directly, as is the case with muscarinic receptor antagonists used to treat overactive bladder (OAB), alternatively the pharmacological therapy may target neuronal pathways controlling micturition, for example when SNRI's are used to treat SUI.

A seminal finding of the present invention is the ability to treat conditions of lower urinary tract dysfunction with a modulator for SV2A.

Therefore the invention relates to SV2A modulators for use in the treatment of conditions of lower urinary tract dysfunction. The invention also relates to the use of SV2A modulators for the manufacture of a medicament for the treatment of conditions of lower urinary tract dysfunction. The invention also relates to a method of treatment of conditions of lower urinary tract dysfunction, with an SV2A modulator. One aspect of the invention is therefore a method of treating lower urinary tract dysfunction, comprising the administration to a patient in need of such treatment of an effective amount of an SV2A modulator.

The term "conditions of lower urinary tract dysfunction" includes frequency, nocturia, urgency, lower urinary tract symptoms associated with benign prostatic hypertrophy, urinary incontinence (i.e. any condition in which there is an involuntary leakage of urine), including urge urinary incontinence and mixed urinary incontinence, overactive bladder with or without associated urinary incontinence or urgency, enuresis, nocturnal enuresis, continuous urinary incontinence, and situational urinary incontinence such as incontinence during sexual intercourse; these conditions can occur alone or in combination.

The term “treating conditions of lower urinary tract dysfunction” includes the palliative, curative and prophylactic treatment of conditions of lower urinary tract dysfunction, complications arising from lower urinary tract dysfunction and other associated conditions, including benign prostatic hyperplasia (BPH), spinal cord injury, and others.

A more preferred aspect of the invention is the use of SV2A modulators for the treatment of urinary incontinence.

Another more preferred aspect of the invention is the use of SV2A modulators for the treatment of overactive bladder.

Another more preferred aspect of the invention is the use of SV2A modulators for the treatment of urgency and/or frequency.

Another more preferred aspect of the invention is the use of SV2A modulators for the treatment of lower urinary tract symptoms associated with benign prostatic hypertrophy.

The SV2A modulator preferably will have an IC₅₀ in a ligand binding assay of less than 10μM, preferably less than 1μM, more preferably less than 100nM, more preferably an IC₅₀ of less than 10nM, even more preferably an IC₅₀ of less than 1nM. The IC₅₀ may be measured in a ligand binding assay, e.g. as described in Example 2.

Preferably the SV2A modulator will be at least 10 fold selective over SV2C, more preferably at least 100 fold selective over SV2C. Preferably the SV2A modulator will be at least 10 fold selective over SV2B, more preferably at least 100 fold selective over SV2B. More preferably, the SV2A modulator will be at least 10 fold selective over SV2C and at least 10 fold selective over SV2B, most preferably at least 100 fold selective over SV2C and at least 100 fold selective over SV2B.

Suitable SV2A modulators include Levetiracetam ((S)-α-ethyl-oxo-pyrrolidine acetamide), and compounds that displace Levetiracetam from its binding site on SV2A such as ethosuximide, pentobarbital, pentylenetetrazole, bemegride, piracetam, and aniracetam.
One aspect of the invention is the use of a compound of formula (I), as disclosed in WO 01/62726:

\[
\begin{align*}
R^3 & \quad R^{3a} \quad R^{4a} \\
R^3 & \quad R^4 \\
R^2 & \quad R^{2a} \\
R^1 & \quad X
\end{align*}
\]

(1)

wherein

- \(X\) is \(-\text{CA}^1\text{NR}^5\text{R}^6\) or \(-\text{CA}^1\text{OR}^7\) or \(-\text{CA}^1\text{R}^8\) or \(\text{CN}\);
- \(A^1\) and \(A^2\) are independently oxygen, sulfur or \(\text{NR}^8\);
- \(R^1\) is hydrogen, \(\text{C}_{1-20}\) alkyl, aryl or \(\text{CH}_2\text{-R}^{1a}\) wherein \(R^{1a}\) is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;
- \(R^2, R^3\) and \(R^4\) are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, \(\text{C}_{1-20}\) alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative;
- \(R^{2a}, R^{3a}\) and \(R^{4a}\) are the same or different and each is independently hydrogen, halogen, \(\text{C}_{1-20}\) alkyl, alkenyl, alkynyl or aryl;
- \(R^5, R^6, R^7\) and \(R^9\) are the same or different and each is independently hydrogen, hydroxy, \(\text{C}_{1-20}\) alkyl, aryl, heterocycle or an oxy derivative; and
- \(R^8\) is hydrogen, hydroxy, thiol, halogen, \(\text{C}_{1-20}\) alkyl, aryl, heterocycle or a thio derivative;
- with the provisos that at least one of \(R^2, R^3, R^4, R^{2a}, R^{3a}\) and \(R^{4a}\) is other than hydrogen;
- and that when the compound is a mixture of all possible isomers, \(X\) is \(-\text{CONR}^5\text{R}^6\), \(A^2\) is oxygen and \(R^1\) is hydrogen, methyl, ethyl or propyl then substitution on the pyrrolidine ring is other than mono-, di- or tri-methyl or mono-ethyl; and that when \(R^1, R^2, R^4, R^{2a}, R^{3a}\) and \(R^{4a}\) are each hydrogen, \(A^2\) is oxygen and \(X\) is \(-\text{CONR}^5\text{R}^6\) then \(R^3\) is different from carboxy, ester, amido, substituted oxo-pyrrolidine, hydroxy, oxy derivative, amino, amino derivatives, methyl, naphthyl, phenyl optionally substituted by oxy derivatives or in the para position by a halogen atom.

In the definitions set forth below for this aspect of the invention, unless otherwise stated,

- \(R^{11}\) and \(R^{12}\) are the same or different and each is independently amido, alkyl, alkenyl, alkynyl, acyl, ester, ether, aryl, aralkyl, heterocycle or an oxy derivative, thio derivative, acyl derivative, amino derivative, sulfonyle derivative, or sulfinyl derivative, each optionally
substituted with any suitable group, including but not limited to, one or more moieties selected from lower alkyl or other groups as described below as substituents for alkyl.

The term "oxy derivative", as used herein, is defined as including –O-R\textsuperscript{11} groups, wherein \( R^{11} \) is as defined above except for "oxy derivative". Non-limiting examples are alkoxy, alkenyloxy, alkynyloxy, acyloxy, oxyester, oxyamido, alkylsulfonxyloxy, alkylsulfinloxy, arylsulfonxyloxy, arylsulfinloxy, aryloxy, aralkoxy or heterocycloxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzylloxy, 2-naphthyloxy, 2-pyridyloxy, methylenedioxy, carbonate.

The term "thio derivative" as used herein, is defined as including –S-R\textsuperscript{11} groups, wherein \( R^{11} \) is as defined above except for "thio derivative". Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arythio.

The term "amino derivative" as used herein, is defined as including –NHR\textsuperscript{11} or –NR\textsuperscript{11}R\textsuperscript{12} groups, wherein \( R^{11} \) and \( R^{12} \) are as defined above. Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl- and arylamino or mixed amino.

The term "acyl derivative" as used herein, represents a radical derived from carboxylic acid and thus is defined as including groups of the formula \( R^{11}\text{-CO-} \), wherein \( R^{11} \) is as defined above and may also be hydrogen. Non-limiting examples are formyl, acetyl, propionyl, isobutryl, valeryl, lauroyl, heptanediol, cyclohexanecarboxyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxalyl, ethoxalyl, cysteinyloxy, oxamoyl.

The term "sulfonyl derivative" as used herein, is as defined above except for "sulfonyl derivative". Non-limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

The term "sulfinyl derivative" as used herein, is defined as including a group of the formula –SO-R\textsuperscript{11}, wherein \( R^{11} \) is as defined above except for "sulfinyl derivative". Non-limiting examples are alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl and arylsulfinyl.

The term "alkyl" as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and 3-6 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise
specified, "lower alkyl"). Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, thiocyanato, acyl, acyloxy, sulfonyl derivative, sulfanyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, oxyester, oxyamido, heterocycle, vinyl, C1-5-alkoxy, C6-10-aryloxy and C6-10-aryl.

Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, iso- or ter-butyl, and 2,2,2-trimethylethyl, each optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro and cyano, such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

The term "alkenyl" as used herein, is defined as including both branched and unbranched, unsaturated hydrocarbon radicals having at least one double bond such as ethenyl (=vinyl), 1-methyl-1-ethenyl, 2,2-dimethyl-1-ethenyl, 1-propenyl, 2-propenyl (=allyl), 1-butene, 2-butene, 3-butene, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 1-hexenyl, 2-hexenyl, and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle such as mono and di-halo vinyl where halo is fluoro, chloro or bromo.

The term "alkynyl" as used herein, is defined as including a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl (=propargyl), and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle, such as haloethynyl.

When present as bridging groups, alkyl, alkenyl and alkynyl represent straight- or branched chains, C1-12, preferably C1-4-alkylene or C2-C12-, preferably C2-4-alkenylene or -alkynylene moieties respectively.

Groups where branched derivatives are conventionally qualified by prefixes such as "n", "sec", "iso" and the like (e.g. "n-propyl", "sec-butyl") are in the n-form unless otherwise stated.
The term "aryl" as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, acyl, acyloxy, sulfonyl, sulfanyl, alkylamino, carboxy, ester, ether, amido, azido, sulfonic acid, sulfonamide, alkylsulfonyl, alkylsulfanyl, alkylthio, oxoester, oxamido, aryl, C1-6-alkoxy, C6-10-aryloxy-, C1-6-alkyl, C1-6-haloalkyl. Aryl radicals are preferably monocyclic containing 6-10 carbon atoms. Preferred aryl groups are phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl and phenyl.

The term "halogen" as used herein, includes an atom of Cl, Br, F, I.

The term "ester" as used herein is defined as including a group of formula –COO-R11 wherein R11 is as defined above except oxy derivative, thio derivative or amino derivative.

The term "ether" is defined as including a group selected from C1-50- straight or branched alkyl, or C2-50- straight or branched alkenyl or alkynyl groups or a combination of the same, interrupted by one or more oxygen atoms.

The term "amido" is defined as including a group of formula –CONH2 or –CONHR11 or –CONR11R12 wherein R11 and R12 are as defined above.

The term "heterocycle", as used herein is defined as including an aromatic or non-aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S, and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Non-limiting examples of aromatic heterocycles are pyridyl, furyl, pyrrolyl, thienny, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiadiazolyl, 1,2,4-thiadiazolyl, thieno(2,3-b)furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isoaxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, phenantridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, isochromanyl, indoliny, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl,
triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl optionally substituted by alkyl or as described above for the alkyl groups. Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, sugar moieties (i.e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) or the same which can optionally be substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl, or other groups as described above for the alkyl groups. The term “heterocycle” also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptanyl, 7-oxabicyclo(2.2.1)heptanyl, 8-azabicyclo(3.2.1)octanyl.

In the above definitions it is to be understood that when a substituent such as R², R³, R⁴, R⁵a, R⁵b, R⁴a, R⁴b, R⁵, R⁶, R⁷, R⁸ is attached to the rest of the molecule via a heteroatom or a carbonyl, a straight- or branched-chain, C1-12-, preferably C1-4 alkylene or C2-12, preferably C2-4-alkenylene or -alkynylene bridge may optionally be interposed between the heteroatom or the carbonyl and the point of attachment to the rest of the molecule.

Preferred examples of X are –COOR⁷ or –CONR⁵⁶, wherein R⁵, R⁶ and R⁷ are preferably hydrogen, C1-4-alkyl, phenyl or alklyphenyl.

Preferably X is carboxy or –CONR⁵⁶, wherein R⁵ and R⁶ are preferably hydrogen, C1-4-alkyl, phenyl or alklyphenyl, especially –CONH₂.

Preferably A¹ and A² are each oxygen.

Preferably R¹ is hydrogen, alkyl, especially C1-12-alkyl, particularly lower alkyl or aryl especially phenyl.

Examples of preferred R¹ groups are methyl, ethyl, propyl, isopropyl, butyl, iso- or tert-butyl, 2,2,2-trimethyl ethyl each optionally attached via a methylene bridge or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.
R<sup>1</sup> as ethyl is especially preferred.

Preferably R<sup>2</sup> and R<sup>2a</sup> are independently hydrogen, halogen or alkyl, especially lower alkyl.

Examples of preferred R<sup>2</sup> and R<sup>2a</sup> groups are independently hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso- or ter-butyl, 2,2,2-trimethylthethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

Especially at least one and most preferably both of R<sup>2</sup> and R<sup>2a</sup> are hydrogen.

Preferably R<sup>3a</sup>, R<sup>4</sup> and R<sup>4a</sup> are independently hydrogen, alkyl, especially methyl or ethyl or aryl especially phenyl or aralkyl, especially benzyl.

Examples of preferred R<sup>3a</sup>, R<sup>4</sup> and R<sup>4a</sup> groups are independently hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylthethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

Especially at least one and most preferably both of R<sup>4</sup> and R<sup>4a</sup> are hydrogen.

R<sup>3a</sup> is particularly hydrogen or alkyl, especially lower alkyl and is most preferably hydrogen.

Preferably R<sup>3</sup> is hydrogen, C1-12-alkyl, especially C1-6 alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato or alkoxy and attached to the ring either directly or via a thio, sulfanyl, sulfonyl, carbonyl or oxycarbonyl group and optionally, a C1-4-alkylene bridge, particularly methylene; C2-6-alkenyl or –alkynyl, especially C2-3-alkenyl or –alkynyl each optionally substituted by one or more halogens; azido; cyano; amido; carboxy; triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzoxoloxyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl or piperazinyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl and phenyl and attached to the ring either directly or via a carbonyl group or a C1-4-alkylene bridge, particularly methylene; naphthyl; or phenyl, phenylalkyl or phenylalkynyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6-haloalkyl, C1-6-alkoxy, C1-6-
alkylthio, amino, azido, phenyl and nitro and each attached to the ring either directly or via an oxy, sulfonyl, sulfonyloxy, carbonyl or carbonyloxy group and optionally additionally a C1-4-alkylene bridge, particularly methylene.

5 Also, preferably, R³ is C1-6-alkyl optionally substituted by one or more substituents selected from halogen, thiocyanato, azido, alkoxy, alkylthio, phenylsulfonyl, nitrooxy, C2-3-alkenyl or -alkynyl each optionally substituted by one or more halogens or by acetyl; tetrazolyl, pyridyl, furyl, pyrrolyl, thiazolyl or thieryl; or phenyl or phenylalkyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6-haloalkyl, C1-6-alkoxy, amino, azido, phenyl and nitro and each attached to the ring either directly or via a sulfonyloxy and optionally additionally a C1-4-alkylene bridge, particularly methylene.

10 Other examples of preferred R³ groups are hydrogen, halogen, or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethyl ethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

R³ is especially C1-4-alkyl optionally substituted by one or more substituents selected from halogen, thiocyanato or azido; C2-5-alkenyl or -alkynyl, each optionally substituted by one or more halogens; thienyl; or phenyl optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6-haloalkyl or azido.

20 Further examples of preferred R³ groups are C1-6-alkyl and C2-6-haloalkenyl.

25 Preferably R⁵ and R⁶ are independently hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethyl ethyl, especially hydrogen or methyl.

Especially at least one and most preferably both of R⁵ and R⁶ are hydrogen.

30 Preferably, R⁷ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethyl ethyl, methoxy, ethoxy, phenyl, benzyl or the same substituted by at least one halogen atom such as trifluoromethyl, chlorophenyl.

35 Preferably, R⁷ is hydrogen, methyl or ethyl, especially hydrogen.
Preferably R\(^8\) is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-
trimethylethyl, phenyl, benzyl or the same substituted by at least one halogen atom such as
trifluoromethyl, chlorobenzyl.

Preferably R\(^8\) is hydrogen or methyl.

Combinations of one or more of these preferred compound groups are especially preferred.

Particularly preferred compounds include:
(2S)-2-[4-(bromomethyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(4R)-4-(iodomethyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-phenyl-1-pyrrolidinyl]butanamide;
(2S)-2-[(iodomethyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(1S)-1-(aminocarbonyl)propyl]-5-oxo-3-pyrrolidinyl]methyl-4-methylbenzenesulfonate;
(2S)-2-[(4R)-4-(azidomethyl)-2-oxopyrrolidinyl]butanamide;
2-[4-(2,2-dibromovinyl)-2-oxo-1-pyrrolidinyl]butanamide;
1-[(1S)-1-(aminocarbonyl)propyl]-5-oxo-3-pyrrolidinyl]methyl nitrate;
(2S)-2-[2-oxo-4-(1H-tetraazol-1-ylmethyl)-1-pyrrolidinyl]butanamide;
2-(2-oxo-4-vinyl-1-pyrrolidinyl)butanamide;
2-[2-oxo-4-[(phenylsulfonyl)methyl]-1-pyrrolidinyl]butanamide;
(2S)-2-[(4R)-4-(2,2-dibromovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[(4S)-4-(2,2-dibromovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[4-(isothiocyanatomethyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[2-oxo-4-(1,3-thiazol-2-yl)-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(2-thienyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(2-methoxyphenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(3-methoxyphenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(4S)-2-oxo-4-vinylpyrrolidinyl]butanamide;
2-[4-(2-bromophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(3-pyridinyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[(1,1'-biphenyl]-4-yl-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-[[methylsulfanyl]methyl]-2-oxo-1-pyrrolidinyl]butanamide;
2-(4-(iodomethyl)-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-[(4R)-4-(iodomethyl)-2-oxo-1-pyrrolidinyl]pentanamide;
(2S)-2-[(4R)-4-(iodomethyl)-2-oxopyrrolidinyl]propanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)propanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)butanamide;
2-(2-oxo-4-pentyl-1-pyrrolidinyl)butanamide;
(2S)-2-[(4R)-4-(iodomethyl)-2-oxopyrrolidinyl]-N-methylbutanamide;
(2S)-2-(4-neopentyl-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-(4-ethyl-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-(2,2-difluorovinyl)-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-(2,2-difluoroethyl)-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide;
(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide;
2-(4-[(2)2-fluoroethyl]-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-(2-methyl-1-propenyl)-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-butyl-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-(cyclopropylmethyl)-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-isobutyl-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-(4-chlorophenyl)-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-(3-chlorophenyl)-2-oxo-1-pyrrolidinyl)butanamide;
2-(2-oxo-4-[2-(trifluoromethyl)phenyl]-1-pyrrolidinyl)butanamide;
2-(4-(2-fluorophenyl)-2-oxo-1-pyrrolidinyl)butanamide;
2-(4-(3-methylphenyl)-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-[2-oxo-4-(2-phenylethyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(3-bromophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-{4-[3,5-bis(trifluoromethyl)phenyl]-2-oxo-1-pyrrolidinyl]butanamide;
2-(4-(3,4-dichlorophenyl)-2-oxo-1-pyrrolidinyl)butanamide;
2-[4-(2,4-dichlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(2-furyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[2-oxo-4-(3-phenylpropyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(3,5-dibromophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[2-oxo-4-propyl-1-pyrrolidinyl]butanamide;
2-[4-(3-chlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-(4-ethynyl-2-oxo-1-pyrrolidinyl)butanamide;
2-[4-(2-fluorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(cyclopropylmethyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(3,3,3-trifluoropropyl)-1-pyrrolidinyl]butanamide;
2-[4-(3-methylphenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(cyclopropylmethyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(4R)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(1H-pyrrol-1-yl)-1-pyrrolidinyl]butanamide;
(2S)-2-(4-allyl-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-[4-(2-iodopropyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-(4-allyl-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-[2-oxo-4-(2-oxopropyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(2-bromo-1H-pyrrol-1-yl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-(4-methyl-2-oxo-4-propyl-1-pyrrolidinyl)butanamide;
(2R)-2-[4-(2,2-dichlorovinyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(bromoethyl)yl]-2-oxo-1-pyrrolidinyl]butanamide;
2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[4-(bromoethyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)pentanamide;
3-cyclopropyl-2-(2-oxo-4-propyl-1-pyrrolidinyl)propanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)-3-(1,3-thiazol-4-yl)propanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)-4-pentanamide;
(2S)-2-[(4R)-2-oxo-4-vinylpyrrolidinyl]butanamide;
including all isomeric forms and mixtures thereof or a pharmaceutically acceptable salt thereof.

 Particularly preferred are:

(2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide;
(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide (also referred to as UCB-34714 herein).

Methods for the preparation of these compounds are described in WO 01/62726.

Another aspect of the invention is the use of SV2A modulators disclosed in WO 2004/087658. These are compounds of formula (II)
wherein

R\(^1\) is hydrogen,

R\(^2\) is hydrogen or C1-20-alkyl,

R\(^3\) is hydrogen, C1-20-alkyl, C4-8-cycloalkyl, C5-8-cycloalkenyl, aryl, aromatic or non-aromatic heterocycle, C1-20-alkoxy, or a group of formula -W-R\(^8\),

R\(^{3a}\) is hydrogen, C1-20-alkyl or a group of formula:

\[ \text{structure image} \]

or NR\(^3\)R\(^{3a}\) is a group of formula

\[ \text{structure image} \]

R\(^4\) is hydrogen,

R\(^6\) is hydrogen; nitro; halogen; azido; cyano; -S-C1-4-alkyl; -SO-C1-4-alkyl; -SO\(_2\)-C1-4-alkyl; -SONH\(_2\); C1-20-alkyl unsubstituted or substituted by halogen; or C1-20 alkoxy unsubstituted or substituted by halogen,

R\(^7\) is hydrogen, C1-20-alkyl or halogen,

W is C1-12-alkylene, -NH- or -NHC(=O)-,

X is O, S or NH,

Y is O, S, -CR\(^1\)R\(^{12}\), -NR\(^{14}\) or -C(=O)-,

R\(^8\) is aryl or heterocycle,

R\(^9\), R\(^{10}\), R\(^{10a}\) and R\(^{11}\) are independently selected from hydrogen, C1-4-alkyl, halogen, hydroxy or methoxycarbonyl,

or R\(^{10}\) and R\(^{10a}\) together form a C3-6-alkylene,
R^{12} is hydrogen, C1-4-alkyl, halogen or hydroxy,
R^{13} is hydrogen,
or CR^{12}R^{13} is dioxyalkyl,
R^{14} is aryl, heterocycle or a group of formula -V-R^{15},
V is C1-12-alkylene,
R^{15} is aryl or heterocycle,
m is 1 to 4,
n is 0 or 1,
and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen, R^3 is H
or 2,6-diisopropylphenyl, and R^{3a} is H.

The term "alkyl", as used for this aspect of the invention, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms and more preferably 1-4 carbon atoms for non-cyclic alkyl and 3-8 carbon atoms for cycloalkyl. Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from halogen, hydroxy, alkoxy, alkoxy carbonyl, ester or alkylamino. Preferred alkyl groups are methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, n-butyl, 2-fluoroethyl, 3-hydroxypropyl, 3-hydroxy-2,2-dimethylpropyl, 1-(hydroxymethyl)propyl, 3,3,3-trifluoro-2-hydroxypropyl, 3-ethoxypropyl, 2-ethoxy-2-oxoethyl and 3-(dimethylamino)propyl.

The term "cycloalkyl", as used for this aspect of the invention, refers to a monovalent group of 3 to 18 carbon atoms, preferably 4-8 carbon atoms, derived from a saturated cyclic or polycyclic hydrocarbon which may be substituted by any suitable group including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred cycloalkyl group is cycloheptyl.

The term "alkylene", as used for this aspect of the invention, represents a divalent alkyl group, having straight or branched moieties, containing 1-12 carbon atoms, preferably 1-6 carbon atoms, and being optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred alkyene groups are methylene, ethylene, hydroxyethylene, trimethylene or propylene.

The term "cycloalkenyl", as used for this aspect of the invention, is defined as a cyclic unsaturated hydrocarbon radical having at least one double bond, containing 4-20 carbon atoms, preferably 5-8 carbon atoms, and being optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as
described above for the alkyl groups. Preferred cycloalkenyl group is 6-(hydroxymethyl)cyclohex-3-en-1-yl.

The term “aryl”, as used for this aspect of the invention, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, nitro, C1-6-alkyl, C1-6-alkoxy, C1-6-alkylsulfonyl, trifluoromethylthio or pyridinylalkyl. Aryl radicals are preferably phenyl radicals. Preferred aryl groups are phenyl, 3-hydroxyphenyl, 3-fluorophenyl, 3-methylphenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-(2-pyridin-2-ylethyl)phenyl, 3,4-dimethylphenyl, 4-tert-butylphenyl, 4-methylsulfonylphenyl, 2-nitrophenyl, 2-chloro-6-fluorophenyl, 2-[(trifluoromethyl)thio]phenyl, 2-chlorophenyl or 4-bromophenyl.

The term “halogen”, as used for this aspect of the invention, includes an atom of Cl, Br, F, I.

The term “nitro”, as used for this aspect of the invention, represents a group of the formula –NO₂.

The term “hydroxy”, as used for this aspect of the invention, represents a group of the formula –OH.

The term “alkoxy”, as used for this aspect of the invention, represents a group of formula –OR wherein R is an alkyl group, as defined above.

The term “ester”, as used for this aspect of the invention, represents a group of formula –COOR wherein R is an alkyl group or an aryl group as defined above.

The term “alkoxycarbonyl”, as used for this aspect of the invention, represents a group of formula –COOR wherein R is an alkyl group as defined above.

The term “amino”, as used for this aspect of the invention, represents a group of formula –NH₂.

The term “alkylamino”, as used for this aspect of the invention, represents a group of formula –NHR or NR₉R' wherein R and R' are alkyl group as defined above.

The term “alkylsulfonyl”, as used for this aspect of the invention, is defined as representing a group of formula –SO₂R, wherein R is C1-4-alkyl.

The term “heterocycle”, as used for this aspect of the invention, is defined as including an aromatic or non-aromatic cycloalkyl or cycloalkenyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl.

Non-limiting examples of aromatic heterocycles are pyrazolyl, furyl, imidazolyl, triazolyl, oxazolyl, pyridinyl, pyrrolyl, thienyl, isothiazolyl, benzimidazolyl, tetrazolyl, isooxazolyl, oxazolyl, thiazolyl, 1,2,4-thiadiazolyl, oxadiazole, pyridazine, pyrimidinyl, pyrazinyl,
isoindolyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, quinazolinyl, quinolizinyl, naphthyridinyl, quinolyl, isoquinoxy, isobenzofuranyl, benzothienyl, indolyl, indolizinyl, purinyl, carbazolyl, thieno(2,3-b)furany, thianthrenyl, benzothiazolyl, benzoxazolyl, cinnolyl, quinoxalinyl, phenothiazinyl, isochromanyl and xanthenyl, optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl, formyl or ester. More preferred aromatic heterocycles are pyrazolyl, furyl, imidazolyl, triazolyl, oxazolyl and pyridinyl.

Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, thiazolidinyl, indolyl, tetrahydrobenzazocinyl, dihydroisochromenyl, tetrahydropyranyl, oxoocotahydroquinolyl, dioxolanyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxopyrrolidinyl, 8-thiabicyclo[3.2.1]octoanly, 1,4-dithiepanyl, tetrahydro-2H-thiopyranyl, azepanyl and azocanly, optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl, formyl or ester. More preferred non aromatic heterocycles are tetrahydrofuranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, thiazolidinyl, indolyl, tetrahydro-1-benzazocinyl-1(2H)-yl, 3,4-dihydro-1H-isoquomoxy-1-yl, tetrahydropyranly, oxoocotahydroquinolyl and dioxolanyl. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cycloalkyl ring, a cycloalkenyl ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptany, 7-oxabicyclo(2.2.1)heptany and 8-azabicyclo(3.2.1)octany.

The term "pyridinylalkyl", as used for this aspect of the invention, represents a group of formula –R<sup>n</sup>-pyridinyl in which R<sup>n</sup> is C1-4-alkylene.

The term "azido", as used for this aspect of the invention, represents a group of the formula –N<sub>3</sub>.

The term "cyano", as used for this aspect of the invention, represents a group of the formula –CN.

Generally, R<sup>2</sup> is hydrogen or C1-4-alkyl.

Preferably R<sup>2</sup> is hydrogen, methyl or ethyl. More preferably, R<sup>2</sup> is hydrogen or methyl.

Generally, R<sup>3</sup> is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxy carbonyl or alkylamino; C5-7-cycloalkyl; (hydroxymethyl)cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents...
selected from halogen, C1-4-alkyl, hydroxy, methoxy, nitro, methylsulfonyl, trifluoromethylthio or pyridinylalkyl; pyridinyl unsubstituted or substituted by methoxy; triazolyl; C1-4-alkoxy; or a group of formula –W–R⁸ wherein:
Generally, W is C1-4-alkylene unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl or alkoxy; -NH⁻; or –NHC(=O)⁻; and
R³ is phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-alkyl, hydroxy, methoxy, nitro, methylsulfonyl or trifluoromethylthio; furyl unsubstituted or substituted by methyl; pyrazolyl, pyridinyl, morpholinyl; tetrahydrobenzazocinyl, piperidinyl unsubstituted or substituted by methyl; dihydroisochromenyl or dihydroimidazolyl.
Preferably, R³ is hydrogen, n-butyl, cycloheptyl, 2-fluoroethyl, 3-hydroxypropyl, 3-hydroxy-2,2-dimethylpropyl, 1-(hydroxymethyl)propyl, 3,3,3-trifluoro-2-hydroxypropyl, 3-ethoxypropyl, 2-ethoxy-2-oxoethyl, 3-(dimethylamino)propyl, 6-(hydroxyethyl)cyclohex-3-en-1-yl, 3-hydroxyphenyl, 3-fluorophenyl, 3-(2-pyridin-2-yl)phenyl, 3,4-dimethylphenyl, 4-tert-butylphenyl, benzyl, 4-hydroxy-3-methoxybenzyl, 4-methylsulfonylbenzyl, 2-nitrobenzyl, 2-chloro-6-fluorobenzyl, 2-[(trifluoromethyl)thio]benzyl, 2-hydroxy-2-phenylethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-chlorophenyl)ethyl, 2-(4-methylphenyl)ethyl, (4-bromophenyl)amino, pyridin-3-yl, 6-methoxypyridin-3-yl, 4H-1,2,4-triazol-3-yl, pyridin-4-ylmethyl, (5-methyl-2-furyl)methyl, 3-(1H-pyrazol-1-yl)propyl, 2-morpholin-4-yIethyI, 2-((3,4,5,6-tetrahydro-1-benzazocin-1(2H)-yl)propyl, 2-(2-methylpiperidin-1-yl)ethyl, 3,4-dihydro-1H-isochromen-1-ylmethyl, methoxy, (4-pyridinylcarbonyl)amino or 4,5-dihydro-1H-imidazol-2-ylamino. More preferably, R³ is hydrogen.
Generally R³a is hydrogen, C1-4-alkyl or a group of formula

\[
\begin{array}{c}
\text{O} \\
\text{m}
\end{array}
\]

wherein m is 1 to 4.
Preferably, R³a is hydrogen, methyl or tetrahydrofuran-2-ylmethyl. More preferably, R³a is hydrogen.
In another embodiment, NR³R³a is piperidinyl unsubstituted or substituted by hydroxy; thiomorpholinyl, thiazolidinyl unsubstituted or substituted by C1-4-alkoxy carbonyl; 2,5-dihydro-1H-pyrrol-1-yl; 1,4-dioxo-8-azaspiro[4.5]dec-8-yl; 4-oxooctahydro-1(2H)-quinolinyl; or a group of formula

\[
\text{N} \quad \text{R}^{14}
\]
wherein R\textsuperscript{14} is pyridinyl, phenyl unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl; or a group of formula \(-V-R\textsuperscript{15}\) wherein V is unsubstituted C1-4-alkylene and R\textsuperscript{15} is phenyl or morpholinyl.

In a preferred embodiment, NR\textsuperscript{3}R\textsuperscript{3a} is 4-pyridin-2-ylpiperazin-1-yl, 4-(3-methylphenyl)piperazin-1-yl, 4-(4-hydroxyphenyl)piperazin-1-yl, 4-(2-phenylethyl)piperazin-1-yl, 4-(2-morpholin-4-ylethyl)piperazin-1-yl, 3-hydroxypiperidin-1-yl, thiomorpholin-4-yl, 4-methoxycarbonyl-1,3-thiazolidin-3-yl, 2,5-dihydro-1H-pyrrol-1-yl, 1,4-dioxo-8-azaspiro[4,5]deca-8-yl or 4-oxo-octahydro-1(2H)-quinolinyl.

Generally R\textsuperscript{5} is hydrogen, nitro, halogen, C1-4-alkyl, unsubstituted or substituted by halogen, or C1-4-alkoxy unsubstituted or substituted by halogen.

Preferably, R\textsuperscript{5} is hydrogen, methyl, ethyl, trifluoromethyl, trifluoromethoxy, n-propyl, isopropyl, nitro, or halogen. More preferably, R5 is halogen or trifluoromethyl.

Generally, R\textsuperscript{6} is hydrogen, C1-6-alkyl or halogen.

Preferably, R\textsuperscript{6} is hydrogen, methyl or Cl. More preferably, R\textsuperscript{6} is hydrogen.

Generally, R\textsuperscript{7} is hydrogen, methyl or halogen.

Preferably, R\textsuperscript{7} is hydrogen, methyl, Br, F or Cl. More preferably, R\textsuperscript{7} is hydrogen, Br or F.

Combinations of one or more of these preferred compound groups are especially preferred.

Preferred compounds are listed in WO 2004/087658 on page 10, line 17 to page 12, line 18.

More preferred compounds are 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5,7-dibromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; 2-(2-oxo-5-(trifluoromethyl)-2,3-dihydro-1H-indol-1-yl)acetaamide and 2-(5-chloro-7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetaamide. Most preferred are 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide and (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide.

The preparation of these compounds is described in WO 2004/087658.

Further SV2a modulators for use in the invention include those disclosed in WO 2004/085438.

These compounds are compounds of formula (III)
in which A is chosen among carbocyclic aromatic groups, heterocyclic aromatic groups and arylC\textsubscript{1-4}alkyl;

R\textsubscript{1} is chosen among

- hydrogen,

- arylC\textsubscript{1-7}alkyl, optionally substituted on the aryl moiety with one or more groups chosen among hydroxy, C\textsubscript{1-4} alkoxy, halogen, haloC\textsubscript{1-4}alkyl;

- heterocyclylC\textsubscript{1-7}alkyl, optionally substituted on the heterocycl moiety with one or more groups chosen among C\textsubscript{1-4}alkyl and hydroxy;

- C\textsubscript{1-7} alkyl, optionally interrupted by an oxygen or sulphur atom or optionally substituted at any position by one or more groups chosen among hydroxy, thio, amino, carboxyl, aminocarboxyl, guanidinyl.

R\textsubscript{2} is chosen among hydrogen, C\textsubscript{1-4} alkyl, arylC\textsubscript{1-4}alkyl and phenyl; or else R\textsubscript{1} and R\textsubscript{2}, taken together, form a saturated carbocyclic ring containing from 3 to 8 carbon atoms;

R\textsubscript{3} is chosen among hydrogen, C\textsubscript{1-4}alkyl, arylC\textsubscript{1-4}alkyl, CONH\textsubscript{2} and COOR\textsubscript{5} in which R\textsubscript{5} is chosen between hydrogen and C\textsubscript{1-4}alkyl;

R\textsubscript{4} is chosen among hydrogen, C\textsubscript{1-4}alkyl, aryl, arylC\textsubscript{1-4}alkyl and heterocycl;

and

n is 2, 3 or 4;

in the form of a racemic mixture or in the form of enantiomers, and pharmaceutically acceptable salts or solvates thereof.

In the framework of this aspect of the invention, the following definitions apply:

The term "carbocyclic aromatic group" means a single or fused aromatic rings with 6 to 12 ring members, optionally substituted.

The terms "heterocyclic aromatic group" and "heterocyclyl" mean single or fused aromatic rings, each ring having 5 to 12 members and comprising up to four heteroatoms, chosen among oxygen, sulphur and nitrogen, optionally substituted.

Whenever not otherwise specified, the term "aryl" means single or fused unsaturated rings, each ring having from 5 to 8 members, and preferably 5 or 6 members, optionally substituted; by the term arylC\textsubscript{1-4}alkyl" is indicated a group having an aryl group, as
defined above, and a C\textsubscript{1-4} alkyl moiety connecting the aryl group to the point of substitution.

All the aforesaid C\textsubscript{1-4} alkyl groups, including those being part of the arylC\textsubscript{1-4}alkyl group, may be indifferently linear or branched or cyclic (i.e. cyclopropyl, cyclopropylmethyl or methycyclopropyl). Preferred C1-C4 alkyl groups are methyl (Me), ethyl (Et), iso-propyl (i-Pr), iso-buty1 (i-Bu) and cyclopropylmethyl.

All the aforesaid C\textsubscript{1-7} alkyl groups, including those being part of C\textsubscript{1-7} alkyl-containing groups, can either be linear, branched or cyclic, and may include double or triple bonds. The term “C\textsubscript{1-7} alkyl groups interrupted by oxygen or sulphur” means, respectively, any ether and thioether groups containing from 1 to 7 carbon atoms.

By the term “heterocyclylC\textsubscript{1-7}alkyl” is indicated a group having an heterocyclyl group, as defined above, and a C\textsubscript{1-7} alkyl moiety connecting the aryl group to the point of substitution.

By the term “arylC\textsubscript{1-7}alkyl” is indicated a group having an aryl group, as defined above, and a C\textsubscript{1-7} alkyl moiety connecting the aryl group to the point of substitution. By “halogen” is meant an atom chosen among fluorine, chlorine, bromine or iodine; by “haloC\textsubscript{1-4}alkyl” is meant a C\textsubscript{1-4} alkyl group substituted at any position by one or more halogen atoms, e.g. trifluoromethyl.

Unless differently specified, “optionally substituted” groups are optionally substituted with 1 to 3 substituents, chosen preferably among Me, Et, i-Pr, OH, COOEt, COOH, CH\textsubscript{2}OH, SO\textsubscript{2}NH\textsubscript{2}, SO\textsubscript{2}Me, OMe, Cl, F, CN and CF\textsubscript{3}, and more preferably among Me, Et, i-Pr, OH, CN, Cl and CF\textsubscript{3}; the substituents may be in any position of the group to be substituted.

Preferred compounds for use according to this aspect of the invention are the compounds of formula (III), in which A is a optionally substituted phenyl, optionally substituted benzyl, or else a optionally substituted heterocyclic aromatic group with 5 or 6 members and comprising up to two hetero atoms chosen between oxygen, sulphur and nitrogen, R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{3} and R\textsubscript{4} are chosen among hydrogen, C\textsubscript{1-4} alkyl or benzyl, and n is equal to 2 or 3.

Preferably, A is phenyl, thienyl, pyridyl, pyrimidiny1 group, optionally substituted, benzyl or 4-methylbenzyl; R\textsubscript{1} is hydrogen, C\textsubscript{1-4} alkyl (for example methyl, isopropyl or isobutyl), benzyl, -CH\textsubscript{2}OH, -CH\textsubscript{2}CH\textsubscript{2}CONH\textsubscript{2}, -CH\textsubscript{2}COOH, indol(3-yl)methyl, R\textsubscript{2} is hydrogen, C\textsubscript{1-4} alkyl or benzyl, R\textsubscript{3} and R\textsubscript{4} are hydrogen or methyl, and n is 2.

More preferably, A is phenyl, optionally substituted, R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{3} and R\textsubscript{4} are hydrogen, and n is equal to 2.

When R\textsubscript{1} and R\textsubscript{2}, taken together, form a saturated carbocyclic ring containing from 3 to 8 carbon atoms, the resulting compound of formula (III) is a spirocyclic compound.
Preferred compounds of formula (III) are listed in WO 2004/085438 on page 5, line 12 to page 6, line 24. Particularly preferred compounds of this aspect of the invention are 1-m-Tolyl-tetrahydropyrrolo[1,2-a] imidazole-2,5-dione and 1-p-Tolyl-tetrahydropyrrolo[1,2-a] imidazole-2,5-dione.

A method for the preparation of the compounds of this aspect of the invention is described in WO 2004/085438.

WO 2004/080444 is directed to the use of Cav2.2 calcium channel modulators for the treatment of lower urinary tract disorders, including overactive bladder. While a potentially beneficial effect is only shown for \( \omega \)-conotoxin, the document includes a lengthy list of other, very different compounds presumed to be Cav2.2 calcium channel modulators. One of these other compounds mentioned is "Levetiracetam or a salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof". However, following the teachings of this document, the skilled person would look for good Cav2.2 calcium channel modulators. Levetiracetam is not a Cav2.2 calcium channel modulator, and therefore the skilled person would discount this part of the disclosure. However, another aspect of the present invention is the use of SV2A modulators for treating incontinence, preferably urinary incontinence, more preferably OAB, with the proviso that, when the treatment is for lower urinary tract disorders such as overactive bladder, benign prostatic hyperplasia or spastic bladder, then the SV2A modulator is not Levetiracetam. A further aspect of the present invention is the use of SV2A modulators for treating conditions of lower urinary tract dysfunction, with the proviso that, when the treatment is for lower urinary tract disorders such as overactive bladder, benign prostatic hyperplasia or spastic bladder, then the SV2A modulator is not Levetiracetam or a salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

A method of enhancing normal bladder storage function of a person comprising administering a SV2A modulator to a healthy person when desired is a further aspect of the invention.

Another aspect of the invention is the use of a SV2A modulator in the manufacture of a medicament for the treatment of faecal incontinence.

Yet a further aspect of the invention is a method of screening for compounds useful for treating conditions of lower urinary tract dysfunction, comprising screening compounds for binding activity on SV2A, preferably for binding activity at the Levetiracetam binding
site on SV2A, and selecting compounds with an IC\textsubscript{50} of less than 10\(\mu\)M, preferably less than 1\(\mu\)M, more preferably less than 100nM, even more preferably less than 10nM.

Another aspect of the invention is a process for providing a medicament for the treatment of conditions of lower urinary tract dysfunction, comprising the following steps:

(a) testing compounds in a ligand binding assay against SV2A, preferably for binding activity at the Levetiracetam binding site on SV2A;
(b) selecting a compound with an IC\textsubscript{50} of less than 10 \(\mu\)M;
(c) formulating a compound with the same structure as that selected in step (b), or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier or excipient; the process may also comprise the additional steps of:
(d) packaging the formulation of step (c); and
(e) making the package of step (d) available to a patient suffering from conditions of lower urinary tract dysfunction.

Preferably, the compound selected in step (b) will have an IC\textsubscript{50} of less than 1\(\mu\)M, more preferably less than 100nM, even more preferably it will have an IC\textsubscript{50} of less than 10nM.

Another aspect of the invention is a process for preparing a medicament for the treatment of conditions of lower urinary tract dysfunction, comprising the steps of (a) testing compounds in a ligand binding assay against SV2A, preferably for binding activity at the Levetiracetam binding site on SV2A; (b) identifying one or more compounds capable of modulating SV2A with an IC\textsubscript{50} of less than 10\(\mu\)M; and (c) preparing a quantity of those one or more identified compounds. Preferably, the compound(s) selected in step (b) will have an IC\textsubscript{50} of less than 1\(\mu\)M, more preferably less than 100 nM, even more preferably it/they will have an IC\textsubscript{50} of less than 10 nM.

Another aspect of the invention is a method of preparing a composition for treating incontinence, conditions of lower urinary tract dysfunction, which comprises:

(a) identifying a compound which specifically binds to SV2A by a method which comprises contacting cells expressing SV2A or membranes prepared from such cells with a radiolabelled SV2A ligand in the presence or absence of a test compound, measuring the radioactivity bound to the cells or membranes, comparing the radioactivity bound to the cells or membranes in the presence and absence of test compound, whereby a compound which causes a reduction in the radioactivity bound is a compound specifically binding to SV2A; and
(b) admixing said compound with a carrier.
The invention relates to the use of a modulator of SV2A for the treatment of conditions of lower urinary tract dysfunction, alone, or in combination with one or more other agents such as

- An anti-muscarinic compound such as tolterodine, hydroxytolterodine and other derivatives and analogues of tolterodine; darifenacin and analogues thereof; solifenacin and analogues thereof; oxybutynin and analogues thereof;
- An SNRI such as duloxetine and analogues thereof; reboxetine and analogues thereof;
- An SSRI such as paroxetine, citalopram, escitalopram, fluoxetine, fluvoxamine and sertraline, and analogues of each of these compounds;
- A 5HT2C agonist such as compounds shown in WO 2004/096196;
- A partial alpha1 adrenergic receptor agonist such as Ro115-1240, compounds in EP 887346, WO 03064387, WO 03/091236;
- An alpha2delta ligand such as gabapentin, pregabalin, compounds in WO 04/054559;
- A COX-2 Inhibitor such as Celecoxib, Bextra;
- A SERM such as lasofoxifene;
- A $K_{ATP}$ potassium channel opener, such as BL-1249.

The advantage of the present invention is that the SV2A modulators may be superior to other forms of treatment for conditions of lower urinary tract dysfunction found in the prior art. For example, they may be more efficacious, longer lasting, less prone to adverse effects, safer, etc.

Reference to a compound, an antagonist, an agonist, a modulator or an inhibitor shall at all times be understood to include all active forms of such agents, including the free form thereof (e.g. the free and/or base form) and also all pharmaceutically acceptable salts, polymorphs, hydrates, silicates, stereo-isomers (e.g. diastereoisomers and enantiomers) and so forth. Active metabolites of any of the compounds, in any form, are also included.

SV2A is a member of a small family of synaptic vesicle proteins, designated SV2A, SV2B, and SV2C. These proteins were first identified with a monoclonal antibody prepared against cholinergic vesicles from the electric organ of a marine ray (Buckley et al (1985) J. Cell Biol. 100, 861-867). Cloning of the individual family members labeled by the antibody resulted in the identification of the 3 different isoforms, SV2A (Bajjalieh,

A DNA and protein sequence of human SV2A is shown in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, of EP 1426768. Also, the sequences of the rat SV2A DNA and protein are shown in SEQ ID NO: 9 and SEQ ID NO: 10 in EP 1426768 respectively. The mouse sequences are also available (see Janz et al (1999) Neuron 24, 1003-1016).

As used herein, the term "amino acid sequence" is synonymous with the term "polypeptide" and/or the term "protein". In some instances, the term "amino acid sequence" is synonymous with the term "peptide". In some instances, the term "amino acid sequence" is synonymous with the term "protein".

In addition to the specific amino acid sequences mentioned herein, the present invention also encompasses the use of variants, homologues, fragments and derivatives thereof. The terms "variant", "homologue", "fragment", or "derivative" in relation to the amino acid sequence for the SV2A polypeptide include any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid from or to the sequence providing the resultant polypeptide has SV2A activity and/or retain a binding site for Levetiracetam.

In the present context, a homologous sequence is taken to include an amino acid sequence which may be at least 75, 85 or 90% identical to the amino acid sequence of the human SV2A sequence shown in SEQ ID NO: 2 in EP 1426768, preferably at least 95 or 98% identical. In particular, homology should typically be considered with respect to those regions of the sequence known to be essential for an activity. Although homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions), in the context of the present invention it is
preferred to express homology in terms of sequence identity. Such sequence homology/identity can be easily assessed by publicly or commercially available bioinformatics software, such as Blast2 (Altschul, S.F. et al (1997) Nucl. Acids Res. 25, 3389-3402), or programs included in the GCG software package (Devereux et al (1984) Nucl. Acids Res. 12, 387; Wisconsin Package Version 10, Genetics Computer Group (GCG, Madison, Wisconsin), such as Bestfit or Gap. In most cases, the default parameters offered by the software, e.g. Bestfit or Gap, for Gap Penalties etc. are suitable for this assessment.

“Potency” as used herein is a measure of how effective a compound is at producing the desired response and can be expressed in terms of the concentration which produces a particular level of the response attainable. Affinity as used herein is a measure of how well a compound binds to or becomes associated with a receptor, such as SV2A. The affinity of a compound can be determined in a binding assay as described in Example 2 herein, and affinity in this context will refer to the IC50 of the compound, i.e. to the concentration inhibiting 50% of the labelled compound from binding to the receptors, or to the Kd, which is the dissociation constant of the compound. The potency or efficacy of a compound can be determined in an animal model designed to test the effect of compounds on micturition or urine leakage as described in Example 1 herein. The potency/efficacy in this case could refer to the EC50 of the compound, i.e. the concentration which shows 50% of the maximal response to a modulator of SV2A or to the minimally effective dose.

“Selectivity” as used herein is a measure of the relative potency of a drug between SV2A and another receptor such as SV2B or SV2C for the same ligand. This can be determined in binding assays, e.g. as described in Example 2 herein. An assay to test for binding of a compound to SV2B and SV2C can also be found in Lynch et al (2004) Proc. Natl. Acad. Sci (USA) 101, 9861-9866.

For the avoidance of doubt, the term “compound” may refer to a chemical or biological agent, and includes, for example, antibodies, antibody fragments, other proteins, peptides, sugars, any organic or inorganic molecules. Compounds that may be used for screening include, but are not limited to, peptides such as, for example, soluble peptides, including but not limited to members of random peptide libraries; (see, e.g., Lam et al. (1991) Nature 354, 82-84; Houghten et al. (1991) Nature 354, 84-86), and combinatorial chemistry-derived molecular library made of D- and/or L- configuration amino acids, phosphopeptides (including, but not limited to, members of random or partially
degenerate, directed phosphopeptide libraries; see, e.g., Songyang et al. (1993) Cell 72, 767-778), antibodies (including, but not limited to, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, and Fab, F(ab')2 and Fab expression library fragments, and epitope-binding fragments thereof), and small organic or inorganic molecules.

The skilled person will be well aware how to obtain antibodies or antibody fragments that recognise SV2A and can then be screened by the methods of the invention for their potential to be suitable for use in the treatment of incontinence, preferably urinary incontinence. For the production of antibodies, various host animals may be immunized by injection with SV2A, a SV2A peptide (e.g. one corresponding to extracellular loops or the extracellular domain), truncated SV2A polypeptides (SV2A in which one or more domains, e.g. the transmembrane domain or cellular domain, has been deleted), functional equivalents of SV2A or mutants of SV2A. Such host animals may include but are not limited to rabbits, mice, hamsters and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and Corynebacterium parvum. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies (mAbs), which are homogeneous populations of antibodies to a particular antigen, may be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, ((1975) Nature 256, 495-497 and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor et al. (1983) Immunology Today 4, 72; Cole et al. (1983) Proc. Natl. Acad. Sci. USA 80, 2026-2030), and the EBV-hybridoma technique (Cole et al. (1985) Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated in vitro or in vivo. Production of high titers of mAbs in vivo makes this the presently preferred method of production.
In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al. (1984) Proc. Natl. Acad. Sci., 81, 6851-6855; Neuberger et al. (1984) Nature, 312, 604-608; Takeda et al. (1985) Nature, 314, 452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region.


Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments include but are not limited to: the F(ab')2 fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')2 fragments or by papain digestion of antibody molecules. Alternatively, Fab expression libraries may be constructed (Huse et al. (1989) Science, 246, 1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to SV2A may also be obtained by generating anti-idiotypic antibodies against a SV2A ligand such as Levetiracetam, using techniques well known to those skilled in the art (see, e.g. Greenspan & Bona (1993) FASEB J 7, 437-444; and Nissinoff (1991) J. Immunol. 147, 2429-2438).

The suitability of the SV2A modulator can be readily determined by evaluation of their potency and selectivity using methods such as those disclosed herein, followed by evaluation of their toxicity, pharmacokinetics (absorption, metabolism, distribution and elimination), etc in accordance with standard pharmaceutical practice. Suitable compounds are those that are potent and selective, have no significant toxic effect at the therapeutic dose, and preferably are bioavailable following oral administration.
Oral bioavailability refers to the proportion of an orally administered drug that reaches the systemic circulation. The factors that determine oral bioavailability of a drug are dissolution, membrane permeability and hepatic clearance. Typically, a screening cascade of firstly in vitro and then in vivo techniques is used to determine oral bioavailability.

Dissolution, the solubilisation of the drug by the aqueous contents of the gastro-intestinal tract (GIT), can be predicted from in vitro solubility experiments conducted at appropriate pH to mimic the GIT. Preferably the SV2A modulators have a minimum solubility of 50μg/ml. Solubility can be determined by standard procedures known in the art such as described in Lipinski CA et al.; Adv. Drug Deliv. Rev. 23(1-3), 3-25, 1997.

Membrane permeability refers to the passage of a compound through the cells of the GIT. Lipophilicity is a key property in predicting this and is determined by in vitro Log $D_{7.4}$ measurements using organic solvents and buffer. Preferably the SV2A modulators have a Log $D_{7.4}$ of -2 to +4, more preferably -1 to +3. The Log D can be determined by standard procedures known in the art such as described in Stopher, D and McClean, S; J. Pharm. Pharmacol. 42(2), 144, 1990.

Cell monolayer assays such as Caco2 add substantially to prediction of favourable membrane permeability in the presence of efflux transporters such as P-glycoprotein, so-called Caco2 flux. Preferably, the SV2A modulators have a Caco2 flux of greater than 2x10^{-6}cms^{-1}, more preferably greater than 5x10^{-6}cms^{-1}. The Caco2 flux value can be determined by standard procedures known in the art such as described in Artursson, P and Magnusson, C; J. Pharm. Sci, 79(7), 595-600, 1990.

Metabolic stability addresses the ability of the GIT to metabolise compounds during the absorption process or the liver to do so immediately post-absorption: the first pass effect. Assay systems such as microsomes, hepatocytes etc are predictive of metabolic lability. Preferably SV2A modulators show metabolic stability in the assay system that is commensurate with an hepatic extraction of less then 0.5. Examples of assay systems and data manipulation are described in Obach, RS; Curr. Opin. Drug Disc. Devel. 4(1), 36-44, 2001 and Shibata, Y et al.; Drug Met. Dispp. 28(12), 1518-1523, 2000.

Because of the interplay of the above processes, further support that a drug will be orally bioavailable in humans can be gained by in vivo experiments in animals. Absolute bioavailability is determined in these studies by administering the compound separately
or in mixtures by the oral route. For absolute determinations (% orally bioavailable) the intravenous route is also employed. Examples of the assessment of oral bioavailability in animals can be found in Ward, KW et al.; Drug Met. Disp. 29(1), 82-87, 2001; Berman, J et al.; J. Med. Chem. 40(6), 827-829, 1997 and Han KS and Lee, MG; Drug Met. Disp. 27(2), 221-226, 1999.

The compounds for use in the invention should be assessed for their biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, etc., in order to select the most appropriate dosage form and route of administration for treatment of the proposed indication.

For pharmaceutical use, the compounds may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of use in the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

Formulations for any route of administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds used in the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or
buccal, lingual, or sublingual administration by which the compound enters the bloodstream directly from the mouth.

Formulations suitable for oral administration include solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds used in the invention may also be used in fast-dissolving, fast-dissintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.
Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.


Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swelling thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula I, a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound used in the invention may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a
greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma et al (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds used in the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.
The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Compounds for use in the invention may be formulated as a suspension or as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(\(d\)l-lactic-coglycolic)acid (PGLA) microspheres.

The compounds used in the invention may also be administered topically, (intra)dermally, or transdermally to the skin or mucosa. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject\textsuperscript{TM}, Bioject\textsuperscript{TM}, etc.) injection.

The compounds used in the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.
The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) used in the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as β-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μl to 100μl. A typical formulation may comprise a compound used in the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations intended for inhaled/intranasal administration.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or “puff”. The overall daily dose will typically be administered in a single dose or, more usually, as divided doses throughout the day.
The compounds used in the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

The compounds used in the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, gels, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

The compounds used in the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.
Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.01 mg to 100 mg/kg body weight depending, of course, on the mode of administration. It should be understood that the specific doses can be adapted to particular cases depending on the individual requirements, at the physician's discretion. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

Oral administration of the compounds of the invention is a preferred route, being the most convenient. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, sublingually or buccally.
Examples

The examples below are carried out using standard techniques, which are well-known and routinely used by those skilled in the art; the examples illustrate but do not limit the invention.

Figure 1 shows the increase in bladder capacity after administration of SV2A modulator UCB-34714.

Example 1: The effect of SV2A modulator UCB-34714 on bladder capacity

Ovariectomised (OVX) mice were used in this study, as they have been found to produce more frequent voids of smaller volume than intact mice.

Four groups of 16 OVX mice were each dosed subcutaneously with either vehicle, 10mg/kg, 75mg/kg or 150mg/kg UCB-34714. Each mouse was then placed in a metaboles for 3hrs and their urine production, including void/void measured. There was no difference in response between all treated groups and so they could be combined. The results are shown in Fig. 1. The treated groups combined demonstrated a 35% increase in average void/void compared to vehicle treated animals. This was significant at the 5% level.

A blood sample of 0.075mls was taken after 3hrs in the metaboles after two dosing runs for PK analysis.

Example 2: Ligand binding assay for SV2A


Briefly, human SV2A cDNA can be obtained from a human fetal brain cDNA library as a PCR product, using primers designed around the start and stop codons. The PCR product can then be cloned using standard molecular biology techniques into a cloning vector of choice with suitable restriction sites for ease of later manipulation of the inserted DNA. It may be necessary to select a cloning vector with a strong transcription
stop site directly upstream of the cloning site. Typically, the inserted DNA will be sequenced to confirm that the desired sequence is present.

The coding region can then be excised from the cloning vector using appropriate restriction endonucleases, and can be inserted into a suitable mammalian expression vector such as a pDEST 12.2 Gateway expression vector.

A suitable host cell line, such as COS or CHO cells, can then be transfected with the expression vector, using standard techniques such as lipofection, e.g. using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. To generate a stable cell line continuously expressing SV2A, the transfection is followed by selection with an appropriate reagent and screening of resultant clones for high SV2A expressing cell lines.

Membranes can be prepared from cell lines expressing SV2A, or whole cells can be employed in ligand binding assays, using standard techniques known to the skilled person. Alternatively, brain membrane preparations can be used. These will be referred to as SV2A samples below.

3H-Levetiracetam or a radiolabelled compound that binds to SV2A such as UCB-34714 can be produced using standard technologies. In a binding experiment, specific binding is measured by incubating the SV2A samples with the radiolabelled ligand, in the absence and presence of excess unlabelled ligand. The incubation is carried out for 2 hours at 4°C, followed by rapid washing with ice-cold PBS. The samples are then subjected to scintillation counting. Specific binding is calculated by subtracting the radioactivity in the sample with excess cold ligand from the sample with radiolabelled ligand only.

To identify compounds useful for the treatment of incontinence, test compound(s) is/are added to SV2A samples, together with radiolabelled ligand as described above. Test compounds which reduce the amount of the radiolabelled ligand bound to the SV2A sample are candidate compounds for use in the treatment of incontinence.
Claims

1. Use of a SV2A modulator in the manufacture of a medicament for the treatment of conditions of lower urinary tract dysfunction.

2. The use according to claim 1, wherein the condition of lower urinary tract dysfunction is urinary incontinence.

3. The use according to claim 1, wherein the condition of lower urinary tract dysfunction is overactive bladder.

4. The use according to claim 1, wherein the condition of lower urinary tract dysfunction is urgency and/or frequency.

5. The use according to claim 1, wherein the condition of lower urinary tract dysfunction is lower urinary tract symptoms associated with benign prostatic hypertrophy.

6. The use according to any of claims 1 to 5, wherein the SV2A modulator is a compound of formula I,

\[
\begin{align*}
R^3 &- R^{3a} - R^{4a} & R^{4} \\
R^2 &- N & A^2 \\
R^{2a} &- R^1 & X \\
\end{align*}
\]

wherein

- \( X \) is \(-CA^1NR^5R^6\) or \(-CA^1OR^7\) or \(-CA^1-R^8\) or \(CN\);
- \( A^1 \) and \( A^2 \) are independently oxygen, sulfur or \(NR^9\);
- \( R^1 \) is hydrogen, \(C_{1-20}\) alkyl, aryl or \(CH_2-R^{1a}\) wherein \(R^{1a}\) is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;
- \( R^2, R^3 \) and \( R^4 \) are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, \(C_{1-20}\) alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative.
R²a, R³a and R⁴a are the same or different and each is independently hydrogen, halogen, C₁₋₂₀ alkyl, alkenyl, alkynyl or aryl;
R⁵, R⁶, R⁷ and R⁸ are the same or different and each is independently hydrogen, hydroxy, C₁₋₂₀ alkyl, aryl, heterocycle or an oxy derivative; and
R⁸ is hydrogen, hydroxy, thiol, halogen, C₁₋₂₀ alkyl, aryl, heterocycle or a thio derivative;
with the provisos that at least one of R², R³, R⁴, R²a, R³a and R⁴a is other than hydrogen; and that when the compound is a mixture of all possible isomers, X is – CONR⁵R⁶, A² is oxygen and R¹ is hydrogen, methyl, ethyl or propyl then substitution on the pyrrolidine ring is other than mono-, di- or tri-methyl or mono-ethyl; and that when R¹, R², R⁴, R²a, R³a and R⁴a are each hydrogen, A² is oxygen and X is – CONR⁵R⁶ then R³ is different from carboxy, ester, amido, substituted oxo-pyrrolidine, hydroxy, oxy derivative, amino, amino derivatives, methyl, naphthyl, phenyl optionally substituted by oxy derivatives or in the para position by a halogen atom.

7. The use of any of claims 1 to 6, wherein the IC₅₀ of the SV2A modulator is less than 10 µM.

8. The use of any of claims 1 to 7, wherein the SV2A modulator is selective for SV2A.

9. A method of screening for compounds useful for the treatment of conditions of lower urinary tract dysfunction, comprising screening compounds for binding activity on SV2A, and selecting compounds with an IC₅₀ of less than 10 µM.

10. Use of a SV2A modulator in the manufacture of a medicament for the treatment of faecal incontinence.
Figure 1

Effect of UCB 34714 on average Vol/vloid in OVX mice

![Graph showing the effect of UCB 34714 on average Vol/vloid in OVX mice. The x-axis represents Treatment Group with Vehicle and UCB (all Doses) categories, and the y-axis represents Geometric Mean Vol/vloid. The graph compares the two categories, showing a marked difference in the Vol/vloid values.]
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/4015 A61P13/00

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 practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim No.</th>
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<td>WO 2004/080444 A (DYNOGEN PHARMACEUTICALS, INC; FRASER, MATTHEW, OLIVER; THOR, KARL, BRU) 23 September 2004 (2004-09-23) cited in the application claims 1,33</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

**Date of the actual completion of the international search**

5 May 2006

**Date of mailing of the international search report**

24/05/2006

Name and mailing address of the ISA/Authorized officer

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Rodriguez-Palmero, M
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<td>MALAWSKA B ET AL: &quot;BRIVARACETAM UCB&quot; CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 6, no. 7, 2005, pages 740-746, XP009055914 ISSN: 1472-4472 the whole document</td>
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<td>WO 2004080444 A</td>
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