Abstract:

An improved pharmaceutical and veterinarily acceptable salt of 2,3-dichloro-JV-cyclopentyl-iV-[(3S)-pyrrolidin-3-yl]benzamide and compositions thereof, is described.

Title: PHARMACEUTICALLY & VETERINARILY SUITABLE SALT
Pharmaceutically & Veterinarily Suitable Salt

The present invention relates to an improved pharmaceutical and veterinarily acceptable salt of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide and compositions thereof.

The compound 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide exhibits activity as a serotonin and noradrenaline re-uptake inhibitor and therefore has utility in a variety of therapeutic areas. For example, this compound is of use in the treatment of disorders in which the regulation of monoamine transporter function is implicated, more particularly disorders in which inhibition of re-uptake of serotonin or noradrenaline is implicated. Furthermore, this compound is of use in disorders in which inhibition of both serotonin and noradrenaline is implicated, such as urinary incontinence. Additionally, this compound is of use in disorders in which it may be desired to inhibit preferentially the reuptake of one of noradrenaline or serotonin compared with the other, such as pain, fibromyalgia, ADHD and depression.

International Patent Application Publication Number WO2004/110995 discloses monoamine re-uptake inhibitors including 2,3-dichloro-N-cyclopentyl-N-pyrrolidin-3-yl-benzamide. It has now unexpectedly been found that the hemi-citrate salt of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide has a number of advantages making it suitable for the preparation of pharmaceutically and veterinarily acceptable formulations. As such, this particular salt form has been found to have a unique combination of good formulation properties which make it particularly suitable for the preparation of pharmaceutically and veterinarily acceptable formulations. A number of these properties are discussed in relation to the data in Tables 1, 2A and 2B hereinafter.

According to the present invention there is provided the hemi-citrate salt of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide. In a preferred embodiment the 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide hemi-citrate is characterized by a powdered X-ray diffraction pattern (PXRD) pattern which shows main 2\(\theta\) peaks at 12.9, 15.0, 15.2, 18.4 and 20.0 degrees (+/- 0.1\(^\circ\) 2\(\theta\)) by using CuK\(\alpha\) X-ray radiation (wavelength = 1.540562 \(\AA\)). This embodiment is further characterized by its differential scanning calorimetry (DSC) trace which shows a peak endotherm at 213\(^\circ\)C at a scan rate of 20\(^\circ\)C/min.

In a further aspect of the invention, there is provided a pharmaceutically or veterinarily acceptable composition of the hemi-citrate salt of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide together with a pharmaceutically or veterinarily acceptable diluent or carrier.

In particular the invention provides a tablet formulation comprising the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide in admixture with excipients. A preferred formulation includes the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide, a compression aid such as microcrystalline cellulose, an additive to provide sheen to the tablet such as
anhydrous dibasic calcium phosphate, a disintegrant such as sodium starch glycollate and a lubricant such as magnesium stearate. In addition, the invention provides a capsule formulation comprising the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide in admixture with excipients. A preferred formulation includes the hemi-citrate salt, an inert diluent, a disintegrant and a lubricant as described above. The invention further provides the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide in sterile aqueous solution for parenteral administration. Preferably such solution contains from 10 to 40% by volume of propylene glycol and preferably also sufficient sodium chloride to avoid haemolysis, e.g. about 1% w/v.

The hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide is useful because it has pharmacological activity in mammals, including humans. Thus, it is useful in the treatment or prevention of disorders in which the regulation of monoamine transporter function is implicated, more particularly disorders in which inhibition of re-uptake of serotonin or noradrenaline is implicated, and especially those in which inhibition of serotonin and noradrenaline re-uptake is implicated.

Accordingly the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide is useful in the treatment of urinary incontinence, such as genuine stress incontinence (GSI), stress urinary incontinence (SUI) or urinary incontinence in the elderly; overactive bladder (OAB), including idiopathic detrusor instability, detrusor overactivity secondary to neurological diseases (e.g. Parkinson's disease, multiple sclerosis, spinal cord injury and stroke) and detrusor overactivity secondary to bladder outflow obstruction (e.g. benign prostatic hyperplasia (BPH), urethral stricture or stenosis); nocturnal enuresis; urinary incontinence due to a combination of the above conditions (e.g. stress incontinence associated with overactive bladder); and lower urinary tract symptoms, such as frequency and urgency. The term OAB is intended to encompass both OAB wet and OAB dry.

In view of the aforementioned pharmacological activity, the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide is also useful in the treatment of depression, such as major depression, recurrent depression, single episode depression, subsyndromal symptomatic depression, depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, paediatric depression, child abuse induced depression, depression in infertile women, post partum depression, premenstrual dysphoria and grumpy old man syndrome.

In view of the aforementioned pharmacological activity, the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide is also useful in the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease) and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; mild cognitive impairment associated with ageing, particularly age associated memory
impairment (AAMI), amnestic disorder and age-related cognitive decline (ARCD); psychotic disorders, such as schizophrenia and mania; anxiety disorders, such as generalised anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), panic disorder, obsessive compulsive disorder, post traumatic stress disorder, mixed anxiety and depression; personality disorders such as avoidant personality disorder and attention deficit hyperactivity disorder (ADHD); sexual dysfunction, such as premature ejaculation, male erectile dysfunction (MED) and female sexual dysfunction (FSD) (e.g. female sexual arousal disorder (FSAD)); premenstrual syndrome; seasonal affective disorder (SAD); eating disorders, such as anorexia nervosa and bulimia nervosa; obesity; appetite suppression; chemical dependencies resulting from addiction to drugs or substances of abuse, such as addictions to nicotine, alcohol, cocaine, heroin, phenobarbital and benzodiazepines; withdrawal syndromes, such as those that may arise from the aforementioned chemical dependencies; cephalic pain, such as migraine, cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headache associated with chemical dependencies or withdrawal syndromes resulting from chemical dependencies, and tension headache; pain; Parkinson's diseases, such as dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias); endocrine disorders, such as hyperprolactinaemia; vasospasm, such as in the cerebral vasculature; cerebellar ataxia; Tourette's syndrome; trichotillomania; kleptomania; emotional lability; pathological crying; sleeping disorder (cataplexy); and shock.

From the above conditions, ADHD is of particular interest. The diagnosis of ADHD is based on clinical evaluation (M. Dulcan, et al. J Am Acad Child Adolesc Psychiatry, Oct. 1997, 36(10 Suppl), 85S-121S; National Institutes of Health, 1998). "The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparative level of development" (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), American Psychiatric Association, Washington, D.C., 1994). In order to be diagnosed with ADHD, patients must demonstrate symptoms of ADHD that cause impairment before the age of seven years, and symptoms must have been ongoing for longer than six months in at least two settings (e.g., school [or work] and home). (See DSM-IV).

In view of the aforementioned pharmacological activity, the hemi-citrate salt of 2,3-dichloro- \( N \)-cyclopentyl-\( N \)-[(3S)-pyrrolidin-3-yl]benzamide is also useful in the treatment of a number of other conditions or disorders, including hypotension; gastrointestinal tract disorders (involving changes in motility and secretion) such as irritable bowel syndrome (IBS), ileus (e.g. post-operative ileus and ileus during sepsis), gastroparesis (e.g. diabetic gastroparesis), peptic ulcer, gastroesophageal reflux disease (GORD, or its synonym GERD), flatulence and other functional bowel disorders, such as dyspepsia (e.g. non-ulcerative dyspepsia (NUD)) and non-cardiac chest pain (NCCP); and fibromyalgia syndrome.

In view of the aforementioned pharmacological activity, the hemi-citrate salt of 2,3-dichloro- \( N \)-cyclopentyl-\( N \)-[(3S)-pyrrolidin-3-yl]benzamide is also useful in the treatment of pain.
Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli via peripheral transducing mechanisms (see Millan, 1999, Prog. Neurobiol., 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually in twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, via disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a heightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, Science, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia - Meyer et al., 1994, Textbook of Pain, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.
Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, Lancet, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd, 1999, Pain Supp., 6, S141-S147; Woolf and Mannion, 1999, Lancet, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Qrennan & Jayson, 1994, Textbook of Pain, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age,
and this is expected to increase to 40 million as the age of the population increases, making this a public
McCarthy et al., 1994, Textbook of Pain, 387-395). Most patients with osteoarthritis seek medical
attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical
function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a
rheumatic disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent
episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine,
peripheral joints and other body organs.

Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel
disease (IBD). Visceral pain is pain associated with the viscera, which encompass the organs of the
abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain
associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain.
Commonly encountered gastrointestinal (GI) disorders that cause pain include functional bowel disorder
(FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states
that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux,
dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in
respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain.
Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and
pelvic pain.

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more
than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

Other types of pain include:

- pain resulting from musculoskeletal disorders, including myalgia, fibromyalgia, spondylitis, seronegative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenosis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardial infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, sclerodema and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster
  headache, tension-type headache mixed headache and headache associated with vascular
  disorders; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular
  myofascial pain.

Disorders of particular interest include urinary incontinence, such as mixed incontinence, GSI and SUI;
pain; fibromyalgia; ADHD and depression.
The invention further provides the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide for use in treating urinary incontinence, pain, fibromyalgia, ADHD, and depression in humans. More particularly the invention further provides the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide for use in the treatment of urinary incontinence, such as genuine stress incontinence (GSI), stress urinary incontinence (SUI) or urinary incontinence in the elderly; overactive bladder (OAB), including idiopathic detrusor instability, detrusor overactivity secondary to neurological diseases (e.g. Parkinson's disease, multiple sclerosis, spinal cord injury and stroke) and detrusor overactivity secondary to bladder outflow obstruction (e.g. benign prostatic hyperplasia (BPH), urethral stricture or stenosis); nocturnal enuresis; urinary incontinence due to a combination of the above conditions (e.g. stress incontinence associated with overactive bladder); and lower urinary tract symptoms, such as frequency and urgency. The term OAB is intended to encompass both OAB wet and OAB dry. The invention further provides the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide for use in treating urinary incontinence in animals, particularly dogs.

The invention also provides a process for preparing the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide by reacting 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-t(3S)-pyrrolidin-3-yl]benzamide with citric acid in an inert solvent and recovering the hemi-citrate salt. The preferred inert solvent is isopropyl alcohol (IPA).

The present invention also includes all suitable isotopic variations of the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide. An isotopic variation of the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide is defined as one in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide include isotopes of hydrogen, carbon, nitrogen and oxygen such as \(^2\text{H}\), \(^3\text{H}\), \(^{13}\text{C}\), \(^{14}\text{C}\), \(^{15}\text{N}\), \(^{17}\text{O}\) and \(^{18}\text{O}\) respectively. Certain isotopic variations of the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide, for example, those in which a radioactive isotope such as \(^{3}\text{H}\) or \(^{14}\text{C}\) is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e. \(^{3}\text{H}\), and carbon-14, i.e. \(^{14}\text{C}\), isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. \(^{2}\text{H}\), may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the hemi-citrate salt of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide can generally be prepared by conventional procedures such as those described in the following examples and preparations using appropriate isotopic variations of suitable reagents.

Although 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide is effective in its free base form, in practice, for formulation purposes, it is best administered in the form of a salt of a pharmaceutically and/or veterinarily acceptable acid. Several different potentially pharmaceutically acceptable salt forms of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide have been identified. In particular, acid addition
salts containing pharmaceutically and/or veterinarianly acceptable anions such as the hydrochloride, hydrobromide, hemi-ethane-1,2-disulfonate (hemi-edisylate), ethane-1,2-disulfonate (edisylate), fumarate, D-tartrate, L-tartrate, acetate and hemi-sulfate salts have been found suitable.

In order for a pharmaceutically and/or veterinarianly acceptable salt of 2,3-dichloro-\(\Lambda\) -cyclopentyl-\(\Lambda\) -[(3S)-pyrrolidin-3-yl]benzamide to be easily formulated, it must satisfy the following four physicochemical criteria: (1) good solubility; (2) suitable stability; (3) non-hygroscopicity; (4) good processability for pharmaceutical or veterinary formulation. It has been found that whilst many of the salts outlined above satisfy some of these criteria, none other than the preferred hemi-citrate have been observed to satisfy them all as well as providing both the chemical and physical stability required. Thus it has been found that the hemi-citrate salt of 2,3-dichloro-\(\Lambda\) -cyclopentyl-\(\Lambda\) -[(3S)-pyrrolidin-3-yl]benzamide has a number of advantages which make it particularly suitable for the preparation of pharmaceutical formulations of 2,3-dichloro-\(\Lambda\) -cyclopentyl-\(\Lambda\) -[(3S)-pyrrolidin-3-yl]benzamide. Salts over which the compound of the invention has been found to have formulation advantages include: the hydrochloride, hydrobromide, hemi-edisylate, edisylate, fumarate, L-tartrate, D-tartrate, acetate and hemi-sulfate. The hemi-edisylate may be prepared in accordance with the method disclosed at Example 1 in International Patent Application PCT/IB05/03643 (which published as WO 2006/056884 on 1st June 2006). Additional salts of 2,3-dichloro-\(\Lambda\) -cyclopentyl-\(\Lambda\) -[(3S)-pyrrolidin-3-yl]benzamide can be prepared in accordance with such methods as are known in the art for the manufacture of acid addition salts, or in accordance with the methods detailed hereinafter (at Examples 3 to 11). For example, alternative salts of 2,3-dichloro-\(\Lambda\) -cyclopentyl-\(\Lambda\) -[(3S)-pyrrolidin-3-yl]benzamide may be readily prepared by mixing together solutions of the compound and the, desired acid or base, as appropriate. Such alternative salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Table 1 illustrates a selection of the advantageous combination of formulation properties of the salt form according to the present invention [Example 2], including non-hygroscopicity and non-solvated.:

<table>
<thead>
<tr>
<th>Property</th>
<th>Hemi-Citrate</th>
</tr>
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<tbody>
<tr>
<td>Crystallinity(^1)</td>
<td>Crystalline</td>
</tr>
<tr>
<td>Thermal Events(^2)</td>
<td>206°C (Sample A (Ex2A) - Fig 4)</td>
</tr>
<tr>
<td></td>
<td>213°C (Sample B (Ex2) - Fig 5)</td>
</tr>
<tr>
<td>Solvates / Hydrates(^3)</td>
<td>Non-solvated</td>
</tr>
<tr>
<td>Hygroscopicity(^4)</td>
<td>Non-hygroscopic</td>
</tr>
</tbody>
</table>

\(^1\) Crystallinity measured by PXRD as detailed hereinafter.

\(^2\) Melting point measured by DSC according to the procedure discussed hereinafter in relation to Figures 4 and 5.
3 Solvation / Hydration assessed by Thermogravimetric Analysis (TGA) using a TA Instruments Hi-Res TGA 2950 instrument measuring the weight loss of a 6.3mg sample in an open platinum pan. The sample was heated at 20 °C/min from ambient to 300°C utilizing a nitrogen furnace purge gas.

4 Hygroscopicity assessed using a Surface Measurement Systems Ltd, dynamic vapour sorption equipment, model DVS-1. The analysis was conducted at 30°C with a nitrogen gas flow of 200cc/min. Water sorption and desorption were determined in the range 0 to 90% relative humidity (RH) using 15%RH intervals. Exposure was for a minimum of 2 hours at each humidity or until the rate of weight change was less than 0.0003%/minute (averaged over 10 minutes). Sample weight was 12.6mg. The sample was weighed using a CAHN D-200, seven place digital recording balance, which is an integral part of the equipment.

Tables 2A and 2B illustrates the results of laboratory scale studies of a selection of the formulation properties of the salt form according to the present invention [Example 2A] in comparison to other salt forms.
<table>
<thead>
<tr>
<th>Table 2A</th>
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<tbody>
<tr>
<td><strong>Salt</strong></td>
</tr>
<tr>
<td>Crystallinity</td>
</tr>
<tr>
<td><strong>Thermal Events</strong></td>
</tr>
<tr>
<td><strong>Solvates/Hydrates</strong></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 2B</th>
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<tbody>
<tr>
<td><strong>Salt</strong></td>
</tr>
<tr>
<td>Crystallinity</td>
</tr>
<tr>
<td><strong>Thermal Events</strong></td>
</tr>
<tr>
<td><strong>Solvates/Hydrates</strong></td>
</tr>
</tbody>
</table>

NS Non Solvated
S Solvated
*weight loss indicative of loss of solvation
The crystallinity, thermal events and solvation/hydration were measured in accordance with the methodologies indicated hereinbefore (at Table 1).

Tables 2A and 2B illustrate that, of all the salts tested, only the hemi-citrate salt of 2,3-dichloro-Λ-cyclopentyl-Λ-([3S]-pyrrolidin-3-yl)benzamide exhibits the advantageous combination of attributes: desired crystallinity; a single, sharp endotherm; and being non-solvated. The thermal results are positive as higher melting points are desirable for ease of processing.

The compound of the invention may be administered alone or as part of a combination therapy. If a combination of therapeutic agents is administered, then the active ingredients may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

Examples of suitable agents for adjunctive therapy include:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolfmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobartital, butabarbital, butalbita, mephobarbital, metharbital, methohexitol, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H₁ antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzintofet including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (-)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone;
an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, phenotolamine, terazaslaw, prazaslaw or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;

an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;

tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-([(2R,3S)-2-{[(1R)-1-[3,5-bis(trifluoromethyl)benzyl]ethoxy-3-(4-fluorophenyl)-4-morpholino]-methyl}-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, laneptant, dapitant or 3-[2-methoxy-5-(trifluoromethyl)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;

a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;

a coal-tar analgesic, in particular paracetamol;

a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;

a vanilloid receptor agonist (e.g. resiniferatoxin) or antagonist (e.g. capsazepine);

a beta-adrenergic such as propranolol;

a local anaesthetic such as mexiletine;

a corticosteroid such as dexamethasone;

a 5-HT receptor agonist or antagonist, particularly a 5-HT1B/ID agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;

a 5-HT2A receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);

a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

Tramadol®;

a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenoxy)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-.
ethoxy-S-C^ethylpiperazin-i-ylsulphonyOpyridin-S-y^-S-ethyl^-^-methoxyethyl^.
4-dihydro-yH-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-y]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-[(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-y]-N-[2-(1-methylpyrrolidin-2-y)ethyl]-4-propoxybenzenesulfonamide;

- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminoethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-6-oxo-2-oxo-2H-pyrimidin-7-one, 4[(1R,5R,6S)-6-((aminomethyl)bicyclo[3.2.0]hept-6-yl)-N-[(3S,4S)-3-aminomethyl-3,4-dimethyl-cyclopentyl]-acetic acid, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-y)ethyl]-4-propoxybenzenesulfonamide;
- a cannabinoid;
- a serotonin reuptake inhibitor such as sertraline, fluoxetine,
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline,
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine,
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptanoic acid, 2-[[1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-3-pyridinecarbonitrile, 2-[[1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[1R,3S)-3-amino-4-hydroxy-1-(S-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[[2-(3-chlorobenzyl)amino]ethyl]phenyl]thiophene-2-carboxamide, or guanidinoethyldisulfide;
- an acetylcholinesterase inhibitor such as donepezil;
• a prostaglandin E$_2$ subtype 4 (EP4) antagonist such as N-[(2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[1S]-1-[[5-chloro-2-(3-fluorophenoxy)pyridin-3-y1]carbonylamino]ethyl]benzoic acid;

• a leukotriene B$_4$ antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]valeric acid (ONO-4057) or DPC-11870;

• a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-y1])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);

• a sodium channel blocker, such as lidocaine;

• a 5-HT3 antagonist, such as ondansetron, granisetron, tropisetron, azasetron, dolasetron or alosetron;

• an oestrogen agonist or selective oestrogen receptor modulator (e.g. HRT therapies or lasofoxifene);

• an alpha-adrenergic receptor agonist, such as phenylpropanolamine or R-450;

• a dopamine receptor agonist (e.g. apomorphine, teachings on the use of which as a pharmaceutical may be found in US-A-5945117), including a dopamine D2 receptor agonist (e.g. premiprixal, Pharmacia Upjohn compound number PNU95666; or ropinirole);

• a PGE1 agonist (e.g. alprostadil);

and the pharmaceutically acceptable salts and solvates thereof.

The invention thus provides, in a further aspect, a combination comprising the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide together with a further therapeutic agent.

For human use the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide can be administered alone, but in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide, can be administered orally, buccally or sublingually in the form of tablets, capsules (including soft gel capsules), ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delay-, modified-, sustained-, dual-, controlled-release or pulsatile delivery applications. The the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide may also be administered via intracavemosal injection. The the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide may also be administered via fast dispersing or fast dissolving dosage forms.
Such tablets may contain excipients such as micro-crystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine, and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention, and their pharmaceutically acceptable salts, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Modified release and pulsatile release dosage forms may contain excipients such as those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacryl acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients. Release rate modifying excipients may be present both within the dosage form i.e. within the matrix, and/or on the dosage form, i.e. upon the surface or coating.

Fast dispersing or dissolving dosage formulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diasorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol, xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared.

The hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneal, intrathecal, intraventricularly, intraurethrally, intraretrially, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such parenteral administration they are best used in the
form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide will usually be from 10 to 500 mg (in single or divided doses).

Thus, for example, tablets or capsules of the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide thereof may contain from 5 mg to 250 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will also appreciate that, in the treatment of certain conditions (including PE), the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide may be taken as a single dose on an “as required” basis (i.e. as needed or desired).

Example Tablet Formulation

In general a tablet formulation could typically contain between about 0.01 mg and 500 mg of the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide whilst tablet fill weights may range from 50 mg to 1000 mg. An example formulation for a 10 mg tablet is illustrated:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemi-Citrate Salt of Example 2</td>
<td>10.000*</td>
</tr>
<tr>
<td>Lactose</td>
<td>64.125</td>
</tr>
<tr>
<td>Starch</td>
<td>21.375</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>3.000</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.500</td>
</tr>
</tbody>
</table>

* This quantity is typically adjusted in accordance with drug activity and is based on the weight of the free base.

The hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide can also be administered intranasally or by inhalation and may be conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebulizer with the
use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra- fluoro-ethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-
heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a
pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered
amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of
the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may
additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from
gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of
the invention and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or “puff” contains
from 1 to 50 mg of of the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-{(3S)-pyrrolidin-3-yl}benzamide
for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg
which may be administered in a single dose or, more usually, in divided doses throughout the day.

The hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-{(3S)-pyrrolidin-3-yl}benzamide may also be
formulated for delivery via an atomiser. Formulations for atomiser devices may contain the following
ingredients as solubilisers, emulsifiers or suspending agents: water, ethanol, glycerol, propylene glycol,
low molecular weight polyethylene glycols, sodium chloride, fluorocarbons, polyethylene glycol ethers,
sorbitan trioleate, oleic acid.

Alternatively, the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-{(3S)-pyrrolidin-3-yl}benzamide can be
administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel,
hydrogel, lotion, solution, cream, ointment or dusting powder. The hemi-citrate salt of 2,3-dichloro-N-
cyclopentyl-N-{(3S)-pyrrolidin-3-yl}benzamide may also be dermally or transdermally administered, for
example, by the use of a skin patch. The compound may also be administered by the ocular, pulmonary
or rectal routes.

For ophthalmic use, the compound can be formulated as micronized suspensions in isotonic, pH
adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in
combination with a preservative such as a benzylalkonium chloride. Alternatively, the compound may be
formulated in an ointment such as petrolatum.

For application topically to the skin, the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-{(3S)-pyrrolidin-3-
yl}benzamide can be formulated as a suitable ointment containing the active compound suspended or
dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white
petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.
Alternatively, the compound can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters, wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/1 1172, WO-A-94/02518 and WO-A-98/55148.

For oral or parenteral administration to human patients the daily dosage levels of compound, will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 5 mg/kg. Thus tablets will contain 1mg to 0.4g of compound for administration singly or two or more at a time, as appropriate. The physician will in any event determine the actual dosage which will be most suitable for any particular patient and it will vary with the age, weight and response of the particular patient. The above dosages are, of course only exemplary of the average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention.

Oral administration is preferred.

For veterinary use, the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

Thus according to a further aspect, the invention provides a pharmaceutical formulation containing of the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide and a pharmaceutically acceptable adjuvant, diluent or carrier.

The combinations referred to above may also conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable adjuvant, diluent or carrier comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.
When the hemi-citrate salt of 2,3-dichloro-N-cyclopentyl-N-[(3S)-pyrrolidin-3-yl]benzamide is used in combination with a second therapeutic the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The following figures are illustrative of the invention:

**Figure 1**: Calculated Powder X-ray Diffraction Pattern of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide hemi-citrate.

**Figure 2**: Measured Powder X-ray Diffraction Pattern of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide hemi-citrate, Sample A [Example 2A] (using a Bruker-AXS ltd D5000 powder X-ray diffractometer)

**Figure 3**: Measured Powder X-ray Diffraction Pattern of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide hemi-citrate, Sample B [Example 2] (using a Bruker-AXS ltd D4 powder X-ray diffractometer)

**Figure 4**: DSC Thermogram of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide hemi-citrate, Sample A [Example 2A] (using a TA Instruments Q1000 differential scanning calorimeter)

**Figure 5**: DSC Thermogram of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide hemi-citrate, Sample B [Example 2] (using a Perkin Elmer diamond differentials upsfiitfδalòrìmeter)

**Preparations and Examples:**

2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide may be prepared by the methods disclosed in International Patent Application Publication Number WO2004/110995 and International Patent Application Number PCT/IB05/003643 (which published as WO 2006/056884 on 1st June 2006), or as described below:

All temperatures are in °C. Flash column chromatography was carried out using Merck silica gel 60 (9385). Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg vacuum. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). Melting points were determined using a Gallenkamp MPD350 apparatus and are uncorrected. NMR was carried out using a Varian-Unity Inova 300MHz and 400MHz Nmr spectrometers or a Varian Mercury 400MHz nmr spectrometer. Mass spectroscopy was carried out using a Finnigan Navigator single quadrupole electrospray mass spectrometer or a Finnigan aQa APCI mass spectrometer.
Preparation 1: Preparation of ferf-butyl (3S)-3-aminopyrrolidine-1-carboxylate

Over a period of 1 hour 2N HCl (aq) (21.81L, 43.62mole) was added to a solution of (3S)-3-aminopyrrolidine \(^1\) (3.76kg, 43.62 mole) in methanol (18.8L) at 0°C. The reaction was stirred for 15 minutes upon which a solution of BoC\(_2\)O (9.52kg, 43.62mole) in methanol (3.8L) was added keeping the reaction mixture at or below 5°C. The reaction mixture was allowed to warm to room temperature over 2 hours upon which the methanol was removed by distillation under vacuum. The resulting aqueous solution pH was adjusted to below 6 with 2N HCl (aq) and then washed with TBME (7.52L) and the organic phase separated and discarded. The aqueous phase was cooled to 5°C and basified with aqueous potassium carbonate (6.63kg, 48 mole in water 7.52L) and the product extracted with dichloromethane (DCM) (3 x 18.8L). The combined DCM layers were washed with water (7.52L) and the solvent distilled and replaced under vacuum with iso-propyl alcohol (IPA) (31.3L) to give an IPA solution of the title compound in approximately 15L IPA (5.81kg product, 31.2 mole, 71%)

\(^1\)H NMR (MeOD, 400MHz)\(\delta\): 1.45 (br s, 9H), 1.69 (m, 1H), 2.05 (m, 1H), 3.03 (m, 1H), 3.33 (m, 1H), 3.49 (m, 3H)

\(^1\) available from TCI Japan via Fluorochem

Preparation 2: ferf-butyl (3S)-3-(cyclopentylamino)pyrrolidine-1-carboxylate

As detailed in Preparation 1 of WO 2006/056884, cyclopentanone (12.7ml, 143mmol) was added to tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate (26.6g, 143mmol) in a mixture of methanoktoluene 3:1 (600mL:200mL), and the reaction mixture was stirred at room temperature for 1.5 hours, under nitrogen. The reaction mixture was then evaporated to 50ml, azeotroped three times with methanoktoluene 3:1 (600ml:200ml) and concentrated in vacuo. The resulting residue was then taken up in methanol (250ml), cooled down to 0°C and sodium borohydride (7.5g, 200.2mmol) was added portionwise. After completion of the reaction, water (50ml) was added and the solvent was evaporated. The residue was diluted with more water (150ml) and extracted three times with dichloromethane (250ml). The organic phases were combined, dried over magnesium sulfate, and concentrated in vacuo to provide the title compound as a gum, 36.1g (99.4%).

\(^1\)HNR(CDC\(_3\), 400MHz)\(\delta\): 1.18(brs, 1H), 1.28(m, 2H), 1.44(s, 9H), 1.52(m, 2H), 1.67(m, 3H), 1.83(m, 3H), 2.05(m, 1H), 2.9β(m, 1H), 3.08(m, 1H), 3.30(m, 2H), 3.45(m, 1H), 3.58(m, 1H); MS APCI\(^+\) m/z 255 [MH]\(^+\)
Preparation 2A: Alternative preparation of tert-butyl (3S)-3-(cyclopentylamino)pyrrolidine-1-carboxylate

A solution of tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate in IPA (approx. 5.81 kg, 31.2 mole in a total of ~15L IPA) was diluted with isopropyl alcohol (IPA) (17.1 L). Cyclopentanone (2.62 kg, 31.2 mole) was added over a period of 30 minutes such that the temperature did not rise above 30 °C and the residue of addition washed with IPA (3L). This imine reaction mixture was stirred at room temperature for a minimum of 5 hours. A slurry of NaBH₄ (1.3 kg, 34.3 mole) in tert-butyl methyl ether (TBME) (11.62 L) and IPA (3L) was cooled to 5 °C and methanol (5.2 L) added at such a rate to keep the reaction temperature below 10 °C. The imine solution in IPA was then added to the sodium borohydride mixture at such a rate that the reaction temperature was kept below 5 °C, and the line washed with IPA (3L). The reaction mixture was then warmed to room temperature and stirred for at least 8 hours. The reaction was carefully quenched with water (11.6 L) and then diluted with TBME (11.6 L), upon which the phases were separated. The organic phase was washed with water (11.6 L) and the combined aqueous washes were back extracted with TBME (11.6 L). The combined TBME layers were then evaporated in vacuo to an oil which was dissolved in ethyl acetate and evaporated once again to give the title compound as an oil (7.75 kg equivalent to 7.61 kg A product, 29.9 mole, 96%)

Preparation 3: tert-butyl (3S)-3-(cyclopentylamino)pyrrolidine-1-carboxylate toluensulfonate

A solution of tert-butyl (3S)-3-(cyclopentylamino)pyrrolidine-1-carboxylate (7.61 kg A, 29.9 mole) in ethyl acetate (38 L) was cooled to 0 °C upon which a solution of toluenesulfonic acid (5.69 kg, 29.9 mole) in ethyl acetate (85.4 L) was added. The resultant slurry was stirred at 0 °C for 1 hour, allowed to warm to room temperature and stirred overnight. The slurry was filtered and washed with ethyl acetate (7.6 L) and dried in vacuo at 55°C overnight to yield the title compound as a white solid (10.48 kg, 24.6 mole, 82%)

1H NMR (MeOD, 300 MHz): 1.49 (s, 9H), 1.68 - 1.83 (br m, 6H), 2.18 (br m, 3H), 2.38 (br s, 4H), 3.44 - 3.63 (br m, 4H), 3.77 (m, 1H), 3.92 (m, 1H), 7.24 (d, J = 7.9 Hz, 2H), 7.72 (d, J = 7.9 Hz, 2H).

Preparation 4: tert-Butyl (3S)-3-(cyclopentyl[2,3-dichlorobenzoyl]aminolpyrrolidine-1-carboxylate

As detailed in Preparation 2 of WO 2006/056884, triethylamine (24 ml, 170 mmol) was added to a solution of the amine of preparation 2 (36.1 g, 142 mmol) in dichloromethane (350 ml), under nitrogen. The reaction
mixture was cooled to 0°C and 2,3-dichloro-benzoyl chloride (29.8g, 142mmol), in dichloromethane, was added dropwise, keeping the temperature below 5°C. The reaction mixture was then stirred for 6 hours, after which time water (200ml) was added and the organic phase was separated. The aqueous layer was then extracted with dichloromethane (250ml). The combined organic phases were washed with 2M aqueous sodium hydroxide and 10% citric acid solution, dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate:cyclohexane (1:6 to 1:4 to 1:2 to 1:1 by volume) to yield the title product, 50g (82.4%).

$^1$H NMR (CDCl₃, 400 MHz, rotamers) δ: 1.43-1.47 (d, 9H), 1.56-1.66 (m, 5H), 1.79 (m, 0.5H), 1.98 (m, 3H), 2.37 (m, 1H), 2.92 (m, 0.5H), 3.15 (m, 0.5H), 3.40 (m, 1H), 3.58 (m, 1.5H), 3.74 (m, 2H), 3.97 (m, 1H), 7.10 (m, 1H), 7.24 (m, 1H), 7.46 (d, 1H); MS APCI$^+$ m/z 427 [MH]+ and m/z 327 [MH-BoC]$^+$

**Preparation 4A: Alternative preparation of tert-Butyl (3S)-3-cyclopentyl(2,3-dichlorobenzoyl)amino7pyrrolidine-1-carboxylate**

Sodium hydroxide solution ([2M aq., 31.4L, 62.8mole]) was added to a stirred slurry of the compound of Preparation 3 tert-butyl (3S)-3-(cyclopentylamino)pyrrolidine-1-carboxylate toluensulfonate (10.48kg, 24.6mole) in toluene (34.54L). The biphasic mixture was cooled to 0°C and a solution of 2,3-dichlorobenzoyl chloride (5.66kg, 27.0mole) in toluene (5.4L) and toluene vessel rinse (3L) were added at such a rate that the reaction temperature to not rise above 15°C. The resultant mixture was allowed to warm to room temperature at stirred for a minimum of 5 hours upon which the phases were separated. The organic phase was washed with hydrochloric acid ([1M]), 31.4L, 31.4mole) and water (31.4L) and then azeotropically dried by the addition and distillation of a further portion of toluene (20L) at reduced pressure. The title product was held as a toluene solution (38.25kg of solution containing 10.4kg A product, 24.3mole, 99%).

**Example 1: 2,3-dichloro-N-cyclopentyl-1H(3S)-PyrroKdin-3-ylbenzamide**

As detailed in Example 1 of WO 2006/056884, (free-base of titled product) the tert-butoxycarbonyl (Boc) protected product of preparation 4 (46g, 107mmol) was dissolved in dichloromethane (85ml), under nitrogen, and the reaction mixture was treated with trifluoroacetic acid (85ml, 1mol), which was added dropwise at 0°C. The reaction mixture was then stirred at room temperature for 4 hours, after which time it was evaporated under reduced pressure, azeotroped twice with toluene and concentrated in vacuo. The resulting residue was taken up in dichloromethane (400ml) and washed with 1M aqueous sodium
hydroxide (200ml). The organic phase was separated, dried over magnesium sulfate and concentrated *in vacuo*. The residue was azeotroped with ethyl acetate (10x) and then dried under vacuum to yield the free base of the title product as a gum, 34g (97%).

**Example 1A: Alternative preparation of 2,3-dichloro-\(N\)-cyclopentyl-(3S)-pyrrolidin-3-ylbenzamide.**

Toluene (4.4L) was added to the previously described solution of tert-butyl (3S)-3-[cyclopentyl(2,3-dichlorobenzoyl)amino]pyrrolidine-1-carboxylate (of Preparation 4A) in toluene and the solution was cooled to 0°C. Trifluoroacetic acid (TFA) (13.85 kg, 121.5mole, 5 equiv.) was added at such a rate as to maintain the temperature below 15°C, and the line rinsed in with toluene (5L). The reaction mixture was heated to 45°C for 3 hours. Upon reaction completion the TFA was removed by two reduced pressure distillation and replacements with toluene (2 x 20L) and 2 x 20L distillate was collected and discarded. The toluene solution was cooled to room temperature and basified with aqueous sodium hydroxide ([2M], 36.4L, 36.4mole) until the aqueous phase was above pH 10. The phases were separated and the product extracted back in aqueous hydrochloric acid ([1M], 31.2L, 31.2mole). The organic phase was further extracted with water (10.4L) and combined with the hydrochloric acid extract. The combined acidic aqueous phase was washed with toluene (10.4L) and then basified to greater than pH 9 with aqueous sodium hydroxide ([5M], 10.4L, 52mole). The aqueous phase was extracted with TBME (2 x 31.2L) and the combined organic phase washed with water (20.8L). The TBME was distilled and replaced to IPA under reduced pressure (2 x 20L) to give the title compound as an IPA solution (26.2kg of solution, 6.95kgÅ of product, 21.2mole, 87%).

\(^1\)H NMR (MeOD, 300MHz) \(\delta\): 1.37 - 1.98 (br m, 8H), 2.07 - 2.42 (br m, 2H), 2.84 - 3.03 (br m, 2H), 3.36 (m, 2H), 3.77 (m, 1H), 3.96 (m, 1H), 7.27 (m, 1H), 7.41 (br t, J= 7.9Hz, 1H), 7.62 (br d, J=8.0Hz, 1H),

**Example 2: Preparation of 2,3-dichloro-\(N\)-cyclopentyl-(3S)pyrrolidin-3-v benzamide hemicitrate.**

\[
\text{Cl} \quad \text{Cl} \\
\text{N} \quad \text{N} \\
\text{CO} \quad \text{CO} \\
\text{H} \quad \text{H} \\
\text{HO} \quad \text{HO} \\
\text{C} \quad \text{C} \\
\text{O} \\
0.5 \quad 0.5
\]

A solution of citric acid (2.04kg, 0.5 equivalents) in water (2L) was added to a solution of 2,3-dichloro-\(N\)-cyclopentyl-(3S)-pyrrolidin-3-yl)benzamide free base (6.95kg, 1 equivalent) in isopropyl alcohol (35L) at such a rate that the internal temperature did not rise above 25°C. The resultant slurry was stirred at 25°C for 2 hours after which it was filtered. The filter cake was pulled dry and washed with isopropyl alcohol (20.8L) and again pulled as dry as possible. The damp product was dried *in vacuo* at 50°C.
overnight to yield (S)-2,3-dichloro-\(N\)-cyclopentyl-\(N\)-pyrrolidin-3-ylbenzamide hemi-citrate as a white solid (7.7 kg, 86%).

\(\text{H NMR (MeOD, 300MHz) } \delta:\) 1.37 - 2.04 (br m, 8H), 2.49 (m, 2H), 2.69 (d, \(J = 15.2\text{Hz}, 1\text{H})\), 2.78 (d, \(J = 15.2\text{Hz}, 1\text{H})\), 3.27 (m, 1H), 3.56 (m, 1H), 3.75 (br m, 3H), 4.29 (m, 1H), 7.33 (m, 1H), 7.43 (brt, \(J = 7.9\text{Hz}, 1\text{H})\), 7.64 (br d, \(J = 7.9\text{Hz}, 1\text{H})\).

**Example 2A: Preparation of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[H(3S)]-pyrrolidin-3-yl]benzamide hemi-citrate**

A solution of citric acid (30 mg, 0.16 mmol, 0.5 equivalents) in methanol (2 mL) was added to a solution of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from methanol (2 mL)-di-isopropyl ether (10 mL). The solid was washed with di-isopropyl ether (2 mL) and dried in vacuo to yield (S\(^4\)-S-dichloro-W-cyclopentyl-N-pyrrolidin-S-ylbenzamide hemi-citrate as a white solid.

\(\text{H NMR (400 MHz, MeOH-} \text{O}^6\text{)} \delta:\) 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, m), 2.72 (2H, dd), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).

**Example 3: Preparation of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-f(3S)-pyrrolidin-3-yl]benzamide hydrochloride**

A solution of aqueous hydrochloric acid (0.32 mL, 1.0 M, 0.32 mmol, 1.0 equivalents) was added to a solution of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from methanol (2 mL)-di-isopropyl ether (10 mL). The solid was washed with di-isopropyl ether (2 mL) and dried in vacuo to yield (S)-2,3-dichloro-\(N\)-cyclopentyl-\(N\)-pyrrolidin-3-ylbenzamide hydrochloride as colourless crystals.
Example 4: Preparation of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-r(3S)-Pyrrolidin-3-ylbenzamide hydrobromide

\[
\text{HBr}
\]

A solution of aqueous hydrobromic acid (0.32 ml, 1.0 M, 0.32 mmol, 1.0 equivalents) was added to a solution of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 ml). The solvents were evaporated in vacuo and the residue was crystallised from methanol (2 ml)-di-isopropyl ether (10 ml). The solid was washed with di-isopropyl ether (2 mL) and dried in vacuo to yield (S)-2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-pyrrolidin-3-ylbenzamide hydrobromide as colourless crystals.

\(\text{H NMR (400 MHz, MeOH-CD}_3\text{)}\) \(\delta\): 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, m), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).

Example 5: Preparation of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-r(3S)-pyrrolidin-3-ylbenzamide hemi-edisylate

\[
\text{HO}_3\text{SCCH}_2\text{CH}_2\text{SO}_3\text{H}
\]

A solution of 1,2-ethanedisulfonic acid (30 mg, 0.16 mmol, 0.5 equivalents) in methanol (2 mL) was added to a solution of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from ethyl acetate (5 mL). The solid was dried in vacuo to yield (S)-2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-pyrrolidin-3-ylbenzamide hemi-edisylate as a white solid.

\(\text{H NMR (400 MHz, MeOH-CD}_3\text{)}\) \(\delta\): 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, m), 3.22 (2H, s), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).
Example 6: Preparation of 2,3-dichloro-Λ-cyclopentyl-Λ-r(3S)-pyrrolidin-3-yllbenzatnide edisylate

A solution of 1,2-ethanedisulfonic acid (61 mg, 0.32 mmol, 1.0 equivalents) in methanol (2 mL) was added to a solution of 2,3-dichloro-Λ-cyclopentyl-Λ-[3S]-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from ethyl acetate (5 mL). The solid was dried in vacuo to yield (S)-2,3-dichloro-Λ-cyclopentyl-Λ-pyrrolidin-3-ylbenzamide edisylate as a white solid.

^1H NMR (400 MHz, MeOH-Cl) δ: 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, d), 3.22 (4H, s), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).

Example 7: Preparation of 2,3-dichloro-Λ-cyclopentyl-Λ(3S)-pyrrolidin-3-yl benzamide fumarate

A solution of fumaric acid (37 mg, 0.32 mmol, 1.0 equivalents) in methanol (2 mL) was added to a solution of 2,3-dichloro-Λ-cyclopentyl-Λ-[3S]-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from ethyl acetate (5 mL). The solid was dried in vacuo to yield (S)-2,3-dichloro-Λ-cyclopentyl-Λ-pyrrolidin-3-ylbenzamide fumarate as a white solid.

^1H NMR (400 MHz, MeOH-Cl) δ: 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 6.70 (2H, s), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, d), 3.22 (4H, s), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).

Example 8: Preparation of 2,3-dichloro-Λ-cyclopentyl-Λ(3S)-pyrrolidin-3-yl benzamide L-tartrate
A solution of L-(+)-tartaric acid (48 mg, 0.32 mmol, 1.0 equivalents) in methanol (2 mL) was added to a solution of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from ethyl acetate (5 mL). The solid was dried in vacuo to yield \((S)-2,3\text{-dichloro-}\Lambda\text{-cyclopentyl-}\Lambda\text{-pyrrolidin-3-yl}benzamide L-tartrate as a white solid.

1H NMR (400 MHz, MeOH-d\(_4\)) \(\delta\): 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.40 (2H, s), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, m), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).

**Example 9:** Preparation of 2,3-dichloro-\(\Lambda\)\text{-cyclopentyl-\(\Lambda\)H(3S)-pyrrolidin-3-\(\pi\)benzamide D-tartrate

\[
\text{Cl} \quad \text{Cl} \quad \text{N} \quad \text{O} \quad \text{D}(-)\text{-HO}_2\text{CCH(OH)CH(OH)CO}_2\text{H}
\]

A solution of D-(−)-tartaric acid (48 mg, 0.32 mmol, 1.0 equivalents) in methanol (2 mL) was added to a solution of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from ethyl acetate (5 mL). The solid was dried in vacuo to yield \((S)-2,3\text{-dichloro-}\Lambda\text{-cyclopentyl-}\Lambda\text{-pyrrolidin-3-yl}benzamide D-tartrate as a white solid.

1H NMR (400 MHz, MeOH-d\(_4\)) \(\delta\): 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.40 (2H, s), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, m), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).

**Example 10:** Preparation of 2,3-dichloro-\(\Lambda\)\text{-cyclopentyl-\(J\)\text{-f(3S)-pyrrolidin-3-\(\pi\)benzarnide hemi-sulfate

\[
\text{Cl} \quad \text{Cl} \quad \text{N} \quad \text{O} \quad \text{H}_2\text{SO}_4\text{]}_{0.5}
\]

A solution of aqueous sulfuric acid (0.16 mL, 1.0 M, 0.16 mmol, 0.5 equivalents) was added to a solution of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from ethyl acetate (5 mL). The solid was dried in vacuo to yield \((S)-2,3\text{-dichloro-}\Lambda\text{-cyclopentyl-}\Lambda\text{-pyrrolidin-3-yl}benzamide hemi-sulfate as a crystalline white solid.

1H NMR (400 MHz, MeOH-d\(_4\)) \(\delta\): 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, m), 2.60-2.42 (2H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).
Example 11: Preparation of 2,3-dichloro-\(N\)-cyclopentyl-\(\Lambda^f\)-(3S)-pyrrolidin-3-ylbenzamide acetate

A solution of aqueous acetic acid (0.32 mL, 1.0 M, 0.32 mmol, 1.0 equivalents) was added to a solution of 2,3-dichloro-\(N\)-cyclopentyl-\(N\)-[(3S)-pyrrolidin-3-yl]benzamide free base (105 mg, 0.32 mmol) in methanol (2.5 mL). The solvents were evaporated in vacuo and the residue was crystallised from ethyl acetate (5 mL). The solid was dried in vacuo to yield (S)-2,3-dichloro-\(N\)-cyclopentyl-\(N\)-pyrrolidin-3-ylbenzamide acetate as a crystalline white solid.

\(^1\)H NMR (400 MHz, MeOH-\(d_6\)) \(\delta\): 7.65 (1H, d), 7.43 (1H, dd), 7.30 (1H, dd), 4.34 (1H, m), 3.85-3.68 (3H, m), 3.52 (1H, m), 3.26 (1H, m), 2.60-2.42 (2H, m), 1.96 (3H, m), 1.95 (1H, m), 1.92-1.65 (3H, m), 1.65-1.40 (4H, m).

Characterisation of 2,3-dichloro-\(\nu\)-cyclopentyl-\(\Lambda\)(3S)-pyrrolidin-3-\(\pi\)benzamide hemi-citrate by PXRD and DSC Analysis.

(a) PXRD Analysis

(i) Calculated

The simulated powder X-ray diffraction pattern (Figure 1) was calculated from the single crystal structure of 2,3-dichloro-\(\Lambda\)-cyclopentyl-\(\Lambda\)-[(3S)-pyrrolidin-3-yl]benzamide determined at room temperature using the "Reflex Powder Diffraction" module of Accelrys Materials Studio™ [version 3]. Pertinent calculation parameters were in each case:

Wavelength = 1.540562 Å (Cu Ka₁)

Polarisation Factor = 0.5

Pseudo-Voigt Profile (U = 0.01, V = -0.001, W = 0.002)

The resultant powder X-ray diffraction peaks having a relative intensity of greater than 20% and their 2\(\Theta\) values are shown in Table 3.
Table 3
Calculated PXRP Peak Data for 2,3-dichloro-Λ-f-cyclopentyl-Λ-H(3S)-pyrroloidin-3-ν benzamide, hemi-citrate

<table>
<thead>
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<th>2θ / °</th>
<th>Relative Intensity / %</th>
<th>2θ / °</th>
<th>Relative Intensity / %</th>
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<tr>
<td>18.4</td>
<td>41.3</td>
<td>27.3</td>
<td>25.4</td>
</tr>
</tbody>
</table>

As will be appreciated by the skilled crystallographer, the relative intensities of the various peaks within the given tables may vary due to a number of factors such as, for example, orientation effects of crystals in the X-ray beam, or the purity of the material being analysed, or the degree of crystallinity of the sample. The peak positions may also shift for variations in sample height, but the peak positions will remain substantially as defined in the given tables.

The skilled crystallographer will also appreciate that measurements using a different wavelength will result in different shifts according to the Bragg equation \( n\lambda = 2d \sin \theta \).

Such further PXRD patterns generated by use of alternative wavelengths are considered to be alternative representations of the PXRD patterns of the crystalline materials of the present invention and as such are within the scope of the present invention.

(ii) Measured

The powder X-ray diffraction pattern (Figure 2) of 2,3-dichloro-\( N \)-cyclopentyl-\( N \)-[(3S)-pyrroloidin-3-yl] benzamide hemi-citrate [Sample A] was obtained using a Bruker D5000 diffractometer (\( \lambda = 1.54178\)A), calibrated using a powdered \( \alpha \)-quartz (ICDD 46-1045) standard. The data was collected at room temperature over the 2\( \Theta \) angular range 2-40\( ^\circ \) with a 0.02\( ^\circ \) step size. Data was collected at each step for 3.5 seconds. Resultant powder X-ray diffraction peaks having a relative intensity of greater than 20% and their 2\( \Theta \) values +/- 0.1\( ^\circ \) are shown in Table 4. Peak positions were further calibrated by alignment with the calculated powder X-ray diffraction pattern shown in Figure 1.
Table 4

Measured PXRD Peak Data for 2,3-dichloro-/V-cyclopentyl-/V-[W3S]-pyrrolidi π-3-v π benzamide hemi-citrate [Sample A]

<table>
<thead>
<tr>
<th>2θ / °</th>
<th>Relative Intensity / %</th>
<th>2θ / °</th>
<th>Relative Intensity / %</th>
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<td>21.7</td>
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Alternatively, the powder X-ray diffraction pattern (Figure 3) of 2,3-dichloro-N-cyclopentyl-N-[W3S]-pyrrolidin-3-yl benzamide hemi-citrate [Sample B] was obtained using a Bruker-AXS Ltd. D4 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slit, and a PSD Vantec-1 detector. The sample was prepared for analysis by mounting on a low background cavity silicon wafer specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha1 X-rays (wavelength = 1.5406 Ångstroms) with the X-ray tube operated at 40kV/35mA. The analyses were performed with the goniometer running in continuous mode set for a 0.2 second count per 0.018° step over a two theta range of 2° to 55°. Resultant powder X-ray diffraction peaks having a relative intensity of greater than 25% and their 2θ values +/- 0.1° are shown in Table 5. Peak positions were calibrated by alignment with the calculated powder X-ray diffraction pattern shown in Figure 1.
Table 5

Measured PXRD Peak Data for 2,3-dichloro-N^1-cyclopentyl-V-[(3S)-pyrrolidin-3-yl] benzamide hemi-citrate [Sample B]

<table>
<thead>
<tr>
<th>2θ / °</th>
<th>Relative Intensity / %</th>
<th>2θ / °</th>
<th>Relative Intensity / %</th>
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</table>

(b) DSC Analysis

The DSC thermogram (Figure 4) was generated from a 2.382mg sample of 2,3-dichloro-N^1-cyclopentyl-N^1-[3S]-pyrrolidin-3-yl] benzamide hemi-citrate [Sample A] in an aluminium pan with lid using a TA Instruments Q1000 differential scanning calorimeter. The sample was heated from 30-300°C at a rate of 20°C/min. in a nitrogen furnace atmosphere purged at 50 cm³/min. A sharp melt endotherm peak was seen at 206°, followed by multiple degradation events.

Alternatively The DSC thermogram (Figure 5) was generated from a 3.008mg sample of 2,3-dichloro-V-cyclopentyl-N-[3S]-pyrrolidin-3-yl] benzamide hemi-citrate [Sample B] in an aluminium vented pan using a Perkin Elmer Diamond differential scanning calorimeter. The sample was heated from ambient-300°C at a rate of 20°C/min. in a nitrogen furnace atmosphere purged at 40 cm³/min. A melt endotherm peak was seen at 213°, followed by multiple degradation events. The increase in DSC peak temperature from 206°C (Figure 4) to 213°C (Figure 5) has been attributed to a likely increase in the purity of Sample B (Fig 5), versus Sample A (Fig 4) tested and is not considered to be indicative of a form change.
Biological activity

The biological activity of the pharmacologically active moiety 2,3-dichloro-Λ'-cyclopentyl-Λ'-(3S)-pyrrolidin-3-yl]benzamide was described in International Patent Application’ PCT/IB05/003643 (which published as WO 2006/056884 on 1st June 2006). Example 1 therein exhibited an NRI Ki of 15 nM and an SRI Ki of 5nM. The NRI Ki and the SRI Ki of the compounds of the Examples therein were determined as follows.

The compounds were tested for biological activity by their ability to inhibit binding of selective radioligands at the human serotonin and noradrenaline transporters (SERT and NET, respectively), using scintillation proximity assay (SPA) technology. The SPA binding was performed using cellular membrane preparations prepared from cell lines expressing human cDNA encoding either SERT or NET (hSERT, hNET), using the radioligands \(^{3}H\)-citalopram and \(^{3}H\)-nisoxetine.

i) Cell culture methodology

Human embryonic kidney cells (HEK-293) expressing each transporter were maintained as a continuous culture, using standard cell culture techniques, in 50 mL of growth medium (see Media and Buffers for composition) in 225 cm\(^2\) flasks, at 37 °C in a humidified atmosphere with 5 % CO\(_2\) present. Cells were passaged from a 90 % confluent monolayer at a ratio of 1:3 - 1:4.

For cell harvesting, the growth medium was removed from the monolayer and the cells were incubated with cell dissociation solution (Sigma) until showing signs of dissociation. The cells were subsequently knocked from the base of the flask and pelleted by centrifugation for storage (frozen at -80 °C) prior to further use.

Cellular membrane preparation

Cell pellets were thawed on ice and resuspended in 3 mL of membrane preparation buffer (see Media and Buffers for composition) per 1 mL of packed cell volume, using a vortex mixer to disperse the cell pellet.

After incubation on ice for 10 minutes, the suspension was homogenised for four individual 10 second intervals using a hand-held homogeniser. The homogenate was then centrifuged at 1075 x g for 20 minutes at 4 °C.

The supernatants were then collected and retained. Initial cell & nuclei pellets (P1) were subsequently rehomogenised and centrifuged using the conditions cited above, and the supernatants collected and pooled with those retained from the first spin.

The pooled supernatants were centrifuged at 35000 x g for 30 minutes at 4 °C, and the supernatants discarded. The pellets (P2) were then resuspended in 1 mL of membrane preparation buffer per 1 mL of
the original packed cell volume. Protein concentrations were then measured and the membrane suspension was finally frozen in aliquots of set volume and stored at -80 °C prior to use in assays.

iii) Assay methodology

A. Determination of Optimal Assay Conditions for Individual Membrane Batches

The specific SPA bead type differed for each transporter, wheat germ agglutinin-coated yttrium silicate (YSi WGA) SPA beads were used for hSERT and WGA-coated polyvinyltoluene (PVT WGA) SPA beads for hNET assays. For each batch of membrane used, optimal concentrations of bead and membrane were determined.

Tritiated radioligands specific to each transporter (³H-citalopram for rtSERT and ³H-nisoxetine for hNET) were used. The assay free radioligand concentration was expressed as a percentage of the total free radioligand concentration to give an estimate of the radioligand depletion. The radioligand depletion in assays for both transporters was less than 30% to ensure that there was sufficient radioligand available for binding. The ligand depletion value was also used for selecting the optimal assay conditions when using new batches of membranes.

The affinity of the specific radioligand for the respective transporter was determined for each membrane batch at the selected protein and bead concentrations. This was achieved by the determination of the $K_i$, the concentration of free radioligand at which 50% of the transporter binding sites were occupied.

The mean $K_i$ for a radioligand at a batch of membranes was determined from data from a minimum of three separate assays. The mean $K_i$ was subsequently used for all assays using the membrane batch profiled to enable determination of $K_i$ values of compounds studied using the method determined by Cheng and Prussoff (Cheng YC and Prussof WH. Relationship between the inhibition constant ($K_i$) and the concentration of inhibitor which causes 50% inhibition of an enzymatic reaction. Biochem Pharmacol 1973; 22:2099-3108.)

B. Assay protocol

Bead/membrane complex preparation

The required amount of membrane was thawed on ice and added to a predetermined volume of bead suspension in assay buffer. The beads were then pre-coupled by incubating the predetermined protein quantity per mg of bead on a shaker at a temperature of 4 °C for 2 hours.

Subsequently, the bead/membrane complex was spun down at 865 x g for 5 minutes. The resulting pellet was resuspended in assay buffer and this spin/wash step then repeated. The final pellet was then resuspended in assay buffer at the specific concentration required for the final assay.
**Ligand preparation**

An aliquot of [³H]-radioligand stock was diluted in assay buffer to give a pre-determined final assay concentration less than the equilibrium dissociation constant (Kᵦ) value.

**Compound plate preparation**

All test compounds were prepared at a concentration of 4 mM in 100 % dimethyl sulphoxide (DMSO) from dry samples. Compounds were diluted in 0.75 % DMSO in ddH₂O to give appropriate test concentrations in a 384 well plate to give a final volume of 20 µL. The same volume of assay buffer was added to specific wells of the plate to enable subsequent measurement of total radioligand binding. Furthermore, 20 µL a high concentration of compound specific to each transporter assay was subsequently added to predetermined wells to determine non-specific binding (NSB). Fluoxetine (10µM final assay concentration) was used for hSERT and desipramine (40µM final assay concentration) for hNET.

For each individual transporter assay, 20 µL of the prepared specific radioligand was added to each well of the final assay plates (containing compound solutions). Subsequently, 20 µL of the corresponding bead/membrane complex was added to each well of the final assay plate, ensuring that the suspension was mixed well. The plates were then sealed and incubated, with shaking, for 1 hour at room temperature. The plates were subsequently incubated for an additional 6 hours, with dark adaptation, prior to reading.

C. **Data analysis**

The assay window (specific binding) per plate was calculated by subtracting the mean NSB readings (in counts per minute, or cpm) from the mean of total binding readings. Subsequently the cpm read per well (with mean NSB subtracted) were expressed as a percentage of the plate window to determine the amount of radioligand bound to the transporter.

These values were plotted against the concentration of the compound tested and a sigmoidal inhibitory concentration effect curve was fitted to the data using a four-parameter logisitic equation and free-fitting parameters to give an IC₅₀ value (the concentration of compound required to inhibit 50% of the specific binding at the neurotransmitter transporter).

The inhibitory dissociation constant (Kᵢ) value was then calculated from the IC₅₀ value using the Cheng-Prusoff equation

Following determination of individual Kᵢ values for compounds tested, an overall geometric mean was calculated together with 95% confidence intervals and n values, where n is the total number of individual Kᵢ values.
iv) Media and Buffers

**hSERT Cell Growth Medium**
DMEM, 10 % (w/v) dialysed FCS
2 mM L-glutamine (diluted from 200 mM stock)
25 mM HEPES *(diluted from 1 M stock)*
250 µg/mL genetecin

**hNET Cell Growth Medium**
DMEM, 10 % (w/v) FCS
2 mM L-glutamine (diluted from 200 mM stock)
25 mM HEPES (diluted from 1 M stock)
250 µg/mL genetecin

**Membrane Preparation Buffer**
20 mM HEPES (diluted from 1M stock with ddH₂O), pH 7.4 at room temperature, stored at 4 °C. Prior to use, one complete protease inhibitor tablet was dissolved per 50 mL of buffer.

**Assay Buffer (1.5 x final assay concentration)**
30 mM HEPES (diluted from 1 M stock with ddH₂O) and 180 mM NaCl (diluted from 5 M stock with ddH₂O), pH 7.4 at room temperature, stored at 4 °C.
CLAIMS

1. 2,3-dichloro-N-cyclopentyl-N-[3S]-pyrrolidin-3-yl]benzamide hemi-citrate.
2. A compound according to claim 1 characterised by a Powder X-Ray Diffraction pattern (PXRD) pattern which shows major peaks at 12.9, 15.0, 15.2, 18.4 and 20.0 degrees 2Θ±0.1° when measured using Cu Ka radiation (wavelength=1.5406 Å).
3. A pharmaceutical or veterinary composition comprising a compound according to claim 1 or 2 together with a pharmaceutically or veterinarily acceptable diluent or carrier and further optional excipients.
4. A composition according to claim 3 which is in the form of a tablet.
5. A composition according to claim 4 wherein the further optional excipients are selected from a compression aid, an additive to provide sheen to the tablet, a disintegrant and a lubricant.
6. A composition according to claim 3 which is in the form of a capsule.
7. A composition according to claim 6 wherein the further optional excipients are selected from an inert diluent, a dried disintegrant and a lubricant.
8. A sterile aqueous solution comprising a compound according to claim 1 or 2 suitable for use for parenteral administration.
9. A compound according to claim 1 or 2 for use in treating urinary incontinence, pain, fibromyalgia, ADHD, or depression in a human.
10. A compound according to claim 9 for use in treating urinary incontinence in a human.
11. A compound according to claim 1 or 2 for use in treating urinary incontinence in an animal.
12. A compound according to claim 10 or 11 wherein the urinary incontinence is genuine stress incontinence (GSI), stress urinary incontinence (SUI), or urinary incontinence in the elderly human or animal.
13. Use of a compound according to claim 1 or 2, in the manufacture of a medicament for the treatment of urinary incontinence, pain, fibromyalgia, ADHD, or depression in a human.
14. Use according to claim 13 for the treatment of urinary incontinence in a human.
15. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for the treatment of urinary incontinence in an animal.
16. Use according to claim 14 or 15 wherein the urinary incontinence is genuine stress incontinence (GSI), stress urinary incontinence (SUI), or urinary incontinence in the elderly human or animal.
17. A method of treatment of urinary incontinence, pain, fibromyalgia, ADHD, or depression which comprises administering a therapeutically effective amount of a compound according to claim 1 or 2 to a human patient in need of such treatment.
19. A method of treatment of urinary incontinence which comprises administering a compound according to claim 1 or 2 to an animal patient in need of such treatment.
20. A method according to claim 18 or 19 wherein the urinary incontinence is genuine stress incontinence (GSI), stress urinary incontinence (SUI), or urinary incontinence in the elderly human or animal.