PHARMACEUTICAL COMPOSITIONS COMPRISING 3 , 5-DIAMIN0-6- (2 , 3-DICHL0PHENYL) -L , 2 , 4-TRIAZINE OR R (-) -2 , 4-DIAMINO-5- (2 , 3-DICHLOROPHENYL) -6-FLUOROMETHYL PYRIMIDINE AND AN NK1

The present invention relates to pharmaceutical compositions comprising an NK1 receptor antagonist and a sodium channel blocker as a combined preparation for simultaneous or sequential administration. The invention further relates to the use of such compositions in the treatment of certain disorders, including epilepsy, mood disorders and pain.

Substance P is a short-chain polypeptide that functions as a neurotransmitter and a neuromodulator. It belongs to the tachykinin neuropeptide family. In the central nervous system Substance P has been associated with the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, respiratory rhythm, neurotoxicity, nausea/emesis and pain. The endogenous receptor for Substance P is the neurokinin 1 receptor (NK1 receptor). A large number of NK1 receptor antagonists are known, including aprepitant (Emend™), which is marketed for use in the prevention of acute and delayed chemotherapy-induced nausea and vomiting and in the prevention of post operative nausea and vomiting. Other potential uses of NK1 receptor antagonists include treatment of anxiety and depression, pain, inflammatory dieases, over-active bladder, sleep disorders, allergic disorders, CNS disorders, skin disorders, cough and gastrointestinal disorders.

Voltage-gated sodium channels are responsible for the initial phase of the action potential, which is a wave of electrical depolarisation usually initiated at the soma of the neuron and propagated along the nerve axon to the terminals. At the terminals, the action potential triggers the influx of calcium and the release of neurotransmitter. Some sodium channel blockers, such as lamotrigine and carbamazepine are used to treat epilepsy. In this case, partial inhibition of voltage-gated sodium channels reduces neuronal excitability and reduces seizure propagation. A key feature of these drugs is their use-dependent mechanism of action. The drugs are thought to stabilise an inactivated configuration of the channel that is adopted rapidly after the channel opens. This inactivated state provides a refractory period before the channel returns to its resting (closed) state ready to be reactivated. As a result, use-dependent sodium channel blockers retard the firing of neurons at high frequency, for example in response to painful stimuli, and will help to prevent repetitive firing during periods of prolonged neuronal depolarisation that might occur, for example, during a seizure. Action potentials triggered at low frequencies, for example in the heart, will not be significantly affected by these drugs, although the safety

margin differs in each case, since at high enough concentrations each of these drugs is capable of blocking the resting or open states of the channels.

Drugs that block voltage-gated sodium channels in a use-dependent manner are also used in the treatment of bipolar disorder, either to reduce symptoms of mania or depression, or as mood stabilisers to prevent the emergence of mood episodes. Clinical and preclinical evidence also suggests that use-dependent sodium channel blockers may help to reduce the symptoms of schizophrenia. It is hypothesised that efficacy in these psychiatric disorders may result in part from a reduction of excessive glutamate release. The reduction in glutamate release is thought to be a consequence of use-dependent sodium channel inhibition in key brain areas, such as the frontal cortex. However, interaction with voltage-gated calcium channels may also contribute to the efficacy of these drugs.

Lamotrigine is an effective anticonvulsant that is also indicated in the US for the prevention of mood episodes in patients with bipolar I disorder. However, the efficacy of the drug in an acute setting is limited by the need for a 4-6 week dose-titration to avoid rash. In addition, lamotrigine and other sodium channel blockers are limited in the range of doses that can be explored to achieve efficacy due to the appearance of CNS side-effects.

The aim of the present invention is to identify new pharmaceutical compositions that allow an improved clinical efficacy with respect to the individual components when administered alone.

A further aim of the present invention is to identify new pharmaceutical compositions that allow the use of a decreased dose of the active ingredient or ingredients, in order to achieve an improved tolerability profile, i.e. reduce side effects.

A solution provided by the present invention is a pharmaceutical composition comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, as a combined preparation for simultaneous or sequential administration.

Thus, in a first aspect the invention provides a pharmaceutical composition comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at

sub therapeutic dose, as a combined preparation for simultaneous or sequential administration.

Pharmaceutical compositions according to the present invention comprise an NK1 receptor antagonist and a Sodium Channel blocker, wherein at least one of them is at sub therapeutic dose, together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the composition are administered separately, they are generally each presented as a pharmaceutical composition. The references hereinafter to composition refer, unless otherwise stated, to compositions comprising either both the NK1 receptor antagonist and the Sodium Channel blocker or only one component thereof.

A subtherapeutic dose is intended to mean a dose of a drug below that required to produce significant clinical benefit for the patient when administered alone.

In one aspect, the invention provides a method of treating a human or animal subject suffering from epilepsy which comprises administering to said subject an effective amount of a pharmaceutical composition comprising an NK1 receptor antagonist and a Sodium Channel blocker, wherein at least one of them is at sub therapeutic dose.

In another aspect, the invention provides a method of treating a human or animal subject suffering from a mood disorder or pain, which comprises administering to said subject an effective amount of a pharmaceutical composition comprising an NK1 receptor antagonist and a Sodium Channel blocker, wherein at least one of them is at sub therapeutic dose.

In another aspect, the invention provides a pharmaceutical composition comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, for use in therapy.

In an additional aspect, the invention provides a pharmaceutical composition comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, for use in the treatment of epilepsy.

In another aspect, the invention provides a pharmaceutical composition comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, for use in the treatment of mood disorders or pain.

In another aspect, the invention provides the use of a pharmaceutical composition, comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, in the manufacture of a medicament for the treatment of epilepsy.

In one aspect, the invention provides the use of a pharmaceutical composition, comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, in the manufacture of a medicament for the treatment of mood disorders or pain.

In an additional aspect, the invention provides the use of a pharmaceutical composition, comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, for the treatment of epilepsy.

In one aspect, the invention provides the use of a pharmaceutical composition, comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, for the treatment of mood disorders or pain.

Within the context of the present invention, the term epilepsy is intented to include Seizure disorders and epilepsy syndromes. The various types of the Epilepsy and seizures mentioned hereinbelow are contemplated as part of the present invention: partial onset seizures (replacing temporal lobe epilepsy, neocortical epilepsy and Rasumssen's), generalized onset seizures, the seizures of the Lennox Gastaut syndrome (tonic, atonic, mycolonic, atypical absence and generalized tonic-clonic), absence seizure syndromes and juvenile myoclonic epilepsy.

Pharmaceutical compositions of the invention may also be useful in the treatment and/or prevention of disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, obsessive compulsive disorders (OCD), sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), ataxias, muscular rigidity (spasticity), and temporomandibular joint dysfunction.

Further diseases or conditions that may be treated by administration of the pharmaceutical compositions of the invention are selected from the list consisting of: psychotic disorders, mood disorders and pain.

Within the context of the present invention, the terms describing the Psychiatric indications used herein are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

Within the context of the present invention, the term “psychotic disorder” includes :

i) Schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

Within the context of the present invention, the term ”mood disorders” includes :

i) Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder

(including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90).
The term “mood disorders” also includes mood disorders in Epilepsy patients.

Within the context of the present invention, the term ”pain” includes : chronic inflammatory pain (e.g. pain associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis); musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with cluster and chronic daily headache; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; dysmenorrhea; neuralgia; fibromyalgia syndrome; complex regional pain syndrome (CRPS types I and II); neuropathic pain syndromes (including diabetic neuropathy; chemoterapeutically induced neuropathic pain; sciatica; non-specific lower back pain; multiple sclerosis pain;; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia); and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions.

In one embodiment, the “mood disorder” which may be treated by administration of the pharmaceutical compositions of the invention is a bipolar disorder.

It will be appreciated that references herein to “treatment” extend to prophylaxis, prevention of recurrence and suppression or amelioration of symptoms (whether mild, moderate or severe) as well as the treatment of established conditions.

The pharmaceutically acceptable salts of NK1 antagonist or Sodium Channel blocker compounds which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, isethionate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. For reviews on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977; P L Gould, International Journal of

Pharmaceutics, 33 (1986), 201-217; and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Pharmaceutical compositions comprising pharmaceutically acceptable solvates of NK1 antagonist or Sodium Channel blocker compounds are within the scope of the invention.

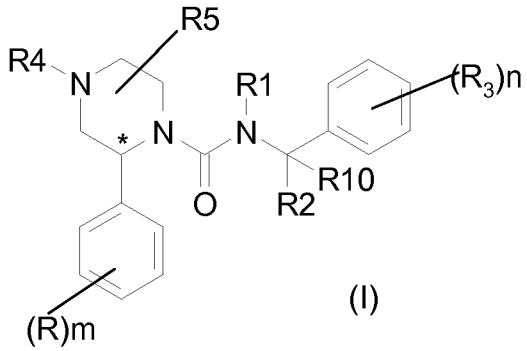
In one embodiment, the pharmaceutical composition of the invention as herein above defined comprises one of the NK1 receptor antagonists generically and specifically disclosed in the following patent specifications whose disclosures are here incorporated by reference:

US Patent Specification Nos. 4839465, 5338845, 5594022, 6169097, 6197772, 6222038, 6204265, 6329392, 6316445, 2001039286, 2001034343, 2001029297, 2002193402, 2002147212, 2002147207, 2002143003 and 2002022624; and in European Patent Specification Nos. 284942, 327009, 333174, 336230, 360390, 394989, 428434, 429366, 436334, 443132, 446706, 482539, 484719, 499313, 512901, 512902, 514273, 514275, 517589, 520555, 522808, 525360, 528495, 532456, 533280, 577394, 591040, 615751, 684257, 1176144, 1110958, 1176144, 1172106, 1103545, and 1256578; and in International Patent Publication Nos. 90/05525, 90/05729, 91/02745, 91/12266, 91/18016, 91/18899, 92/01688, 92/06079, 92/15585, 92/17449, 92/20676, 92/21677, 92/22569, 93/00331, 93/01159, 93/01160, 93/01165, 93/01169, 93/01170, 94/01402, 94/26735, 95/06645, 95/08549, 95/14017, 95/16679, 95/18124, 95/23798, 95/28389, 95/33744, 96/05181, 96/18643, 96/21661, 96/29326, 96/32386, 96/34857, 96/37489, 97/02824, 97/05110, 97/08166, 97/13514, 97/14671, 97/16440, 97/17362, 97/19074, 97/19084, 97/19942, 97/21702, 97/22597, 97/22604, 97/23455, 97/24324, 97/24350, 97/25322, 97/25988, 97/27185, 97/30989, 97/30990, 97/30991, 97/32865, 97/38692, 97/44035, 97/49393, 97/49710, 98/02158, 98/04561, 98/07694, 98/07722, 98/08826, 98/13369, 98/17276, 98/18761, 98/18785, 98/18788, 98/20010, 98/24438, 98/24439, 98/24440, 98/24441, 98/24442, 98/24442, 98/24443, 98/24444, 98/24445, 98/24446, 98/24447, 98/28297, 98/43639, 98/45262, 98/49170, 98/54187, 98/57954, 98/57972, 99/00388, 99/01444, 99/01451, 99/07677, 99/07681, 99/09987, 99/21823, 99/24423, 99/25364, 99/26924, 99/27938, 99/36424, 99/52903, 99/59583, 99/59972, 99/62893, 99/62900, 99/64000, 00/02859, 00/06544, 00/06571, 00/06572, 00/06578, 00/06580, 00/15621,

00/20003, 00/21512, 00/21564, 00/23061, 00/23062, 00/23066, 00/23072, 00/20389, 00/25745, 00/26214, 00/26215, 00/34243, 00/34274, 00/39114, 00/47562, 01/77069, 01/25233, 01/30348, 01/87866, 01/94346, 01/90083, 01/87838, 01/85732, 01/77100, 01/77089, 01/77069, 01/46176, 01/46167, 01/44200, 01/32625, 01/29027, 01/25219, 02/32865, 02/00631, 02/81461, 02/92604, 02/38575, 02/57250, 02/22574, 02/74771, 02/26710, 02/28853, 02/102372, 02/85458, 02/81457, 02/74771, 02/62784, 02/60898, 02/60875, 02/51848, 02/51807, 02/42280, 02/34699, 02/32867, 02/32866, 02/26724, 02/24673, 02/24629, 02/18346, 02/16344, 02/16343, 02/16324, 02/12168, 02/08232 and 02/06236; and in British Patent Specification Nos. 2216529, 2266529, 2268931, 2269170, 2269590, 2271774, 2292144, 2293168, 2293169 and 2302689; and in Japanese Patent Specification No 6040995.

In a further embodiment, the pharmaceutical composition of the invention as hereinabove defined comprises an NK1 receptor antagonist selected from the group consisting of aprepitant (Emend^{TM}), netupitant (R-1124), fosaprepitant (MK-0517), SSR-240600, cizolirtine, AV 608, TA-5538, E 6039 and nolpitantium besilate (SR 140333).

In a further embodiment, the pharmaceutical composition of the invention as hereinabove defined comprises an NK1 antagonist of formula (I)



(I)

wherein

R represents a halogen atom or a C_{1-4} alkyl group;
R1 represents hydrogen or a C_{1-4}alkyl group;
R2 represents hydrogen, a C_{1-4} alkyl, C_{2-6} alkenyl or a C_{3-7} cycloalkyl group; or R1 and R2 together with nitrogen and carbon atom to which they are attached respectively represent a 5-6 membered heterocyclic group;

R3 represents a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, a trifluoromethoxy or a halogen group;

R4 represents hydrogen, a $(CH_2)_qR7$ or a $(CH_2)_rCO(CH_2)_pR7$ group;

R5 represents hydrogen, a C_{1-4} alkyl or a COR6 group;

R6 represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R7 represents hydrogen, hydroxy or NR8R9 wherein R8 and R9 represent independently hydrogen or C_{1-4} alkyl optionally substituted by hydroxy, or by amino;

R10 represents hydrogen, a C_{1-4} alkyl group or

R10 together with R2 represents a a C_{3-7} cycloalkyl group;

m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that , when R1 and R2 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine,

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO01/25219, published 12 April 2001. The disclosure of this reference is incorporated herein in its entirety. Compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be prepared by any method described in WO01/25219.

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (I) from the group consisting of:

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

2-(4-Fluoro-phenyl)- piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide;

2-Phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl- amide;

2-(2,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;

2-(3,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;

2-(4-Fluoro-2-methyl-phenyl)-3-methyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(2-Methyl-4-Fluoro-phenyl)-6-Methyl- piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

4-(2-Amino-acetyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis -trifluoromethyl-benzyl)-methyl-amide ;

2-(S)-(4-Fluoro-2-methyl-phenyl)-4-(piperidine-4-carbonyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

4-(2-Amino-ethyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [(1-3,5-bis-trifluoromethyl-phenyl)-cyclopropyl]-methyl-amide;

[2-(3,5-Bis-trifluoromethyl-phenyl)-pyrrolidin-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;

[2-(3,5-Bis-trifluoromethyl-phenyl)-3,6-dihydro-*2H*-pyridyn-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;

2-(3,5-Bis-trifluoromethyl-phenyl)-piperidin-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;

2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-but-3-enyl]-methyl-amide;

2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propyl]-methyl-amide;

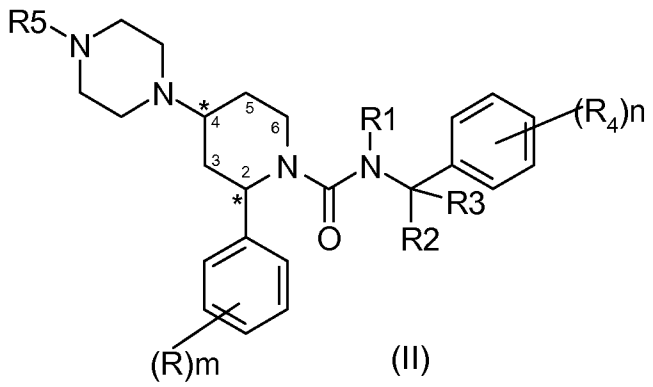
2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [(3,5-bis-trifluoromethyl-phenyl)-cyclopropyl-methyl]-methyl-amide;

and enantiomers or pharmaceutically acceptable salts or solvates thereof.

In another embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (I) which is : 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide; or a pharmaceutically acceptable salt or solvate thereof.

In a still further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (I) which is : 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In another embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (II)



(II)

wherein

R represents a halogen atom or a C_{1-4} alkyl group;

R_1 represents a C_{1-4} alkyl group;

R_2 represents hydrogen or a C_{1-4} alkyl group;

R_3 represents hydrogen or C_{1-4} alkyl group;

R_4 represents a trifluoromethyl group;

R_5 represents hydrogen, a C_{1-4} alkyl group or $C(O)R_6$;

R_6 represents C_{1-4} alkyl, C_{3-7} cycloalkyl, $NH(C_{1-4}$ alkyl) or $N(C_{1-4}alkyl)_2$;

m is zero or an integer from 1 to 3;

n is an integer from 1 to 3;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (II) and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO02/32867, published 25 April 2002. The disclosure of this reference is incorporated herein in its entirety. Compounds of formula (II) and

pharmaceutically acceptable salts and solvates thereof may be prepared by any method described in WO02/32867.

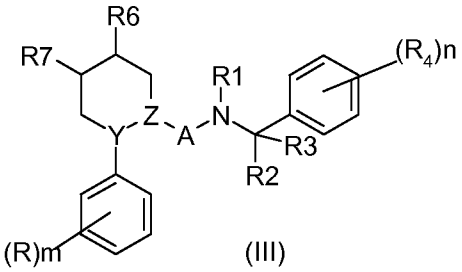
In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (II) selected from the group consisting of:
4-(R)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(R)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(R,S)-(4-methyl-piperazin-1-yl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-piperazin-1-yl-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(R,S)-(4-methyl-piperazin-1-yl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide ;
4-(S)-(4-Cyclopropanoyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide
4-(R)-(4-Cyclopropanoyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-[4-(2-Methyl-propanoyl)-piperazin-1-yl]-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(R)-[4-(2-Methyl-propanoyl)-piperazin-1-yl]-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-[1-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-piperazine-1-carboxylic acid, dimethylamide;
4-(S)-[1-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-1-carboxylic acid, methylamide;
4-(S)-[1-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-piperazine;
4-(S)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

4-(R)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
and pharmaceutically acceptable salts or solvates thereof.

In another embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (II) which is 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

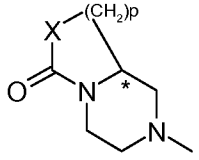
In a still further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (II) which is 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate.

In a still another embodiment, the pharmaceutical composition of the present invention as herein above defined comprises an NK1 antagonist of formula (III)



(III)

R represents halogen or C_{1-4} alkyl ;
R_1 represents C_{1-4} alkyl;
R_2 or R_3 independently represent hydrogen or C_{1-4} alkyl;
R_4 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;
R_5 represents hydrogen , C_{1-4} alkyl or C_{3-7} cycloalkyl;
R_6 is hydrogen and R_7 is a radical of formula (W):



(W)

or R_6 is a radical of formula (W) and R_7 is hydrogen;
X represents CH_2, NR_5 or O;

Y represents Nitrogen and Z is CH or Y represents CH and Z is Nitrogen;

A represents C(O) or S(O)q, provided that when Y is nitrogen and Z is CH, A is not S(O)q;

m is zero or an integer from 1 to 3;

n is an integer from 1 to 3;

p and q are independently an integer from 1 to 2;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (III) and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO 03/066635, published 14 August 2003. The disclosure of this reference is incorporated herein in its entirety. Compounds of formula (III) and pharmaceutically acceptable salts and solvates thereof may be prepared by any method described in WO 03/066635.

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (III) selected from the group consisting of:

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-(6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide;

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-(6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid[1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

1-(4-Fluoro-2-methyl-phenyl)-4-(6-oxo-hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-piperidine-2-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

and enantiomers, diastereoisomers pharmaceutically acceptable salts (e.g. hydrochloride, methanesulphonate or maleate) or solvates thereof.

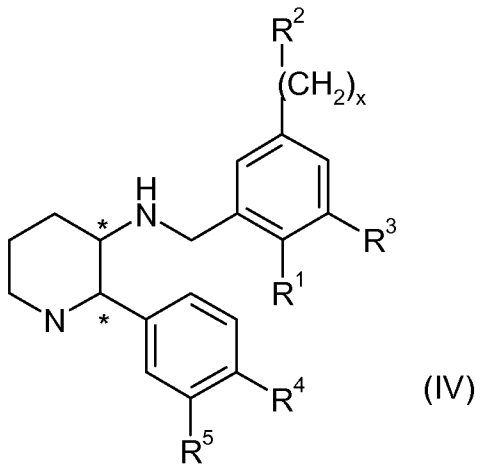
In a still further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (III) which is 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

or amorphous and crystalline forms thereof or pharmaceutically acceptable salts (e.g. hydrochloride or maleate) and solvates thereof.

In a still further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (III) which is 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

or amorphous and crystalline forms thereof or pharmaceutically acceptable salts (e.g. hydrochloride or maleate) and solvates thereof.

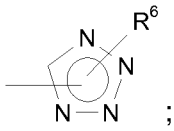
In a still another embodiment, the pharmaceutical composition of the present invention as herein above defined comprises an NK1 antagonist of formula (IV)



(IV)

wherein R^1 is a C_{1-4}alkoxy group;

R^2 is



;

R^3 is a hydrogen or halogen atom;

R^4 and R^5 may each independently represent a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy or trifluoromethyl group;

R^6 is a hydrogen atom, a C_{1-4}alkyl, $(CH_2)_m$cyclopropyl, $-S(O)_nC_{1-4}$alkyl, phenyl, NR^7R^8, $CH_2C(O)CF_3$ or trifluoromethyl group;

R^7 and R^8 may each independently represent a hydrogen atom, or a C_{1-4}alkyl or acyl group;

x represents zero or 1;

n represents zero, 1 or 2;

m represents zero or 1;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (IV) and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO95/08549, published 30 March 1995. The disclosure of this reference is incorporated herein in its entirety. Compounds of formula

(IV) and pharmaceutically acceptable salts and solvates thereof may be prepared by any method described in WO95/08549.

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (IV) selected from the group consisting of:

[2-Methoxy-5-(5-phenyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

[2-Methoxy-5-(5-methylimino-4,5-dihydro-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

N-(1-{4-Methoxy-3-[(2S-phenyl-piperidin-3S-ylamino)-methyl]-phenyl}-1H-tetrazol-5-yl)-acetamide;

[5-(5-Dimethylamino-tetrazol-1-yl)-2-methoxy-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

[5-(5-Diethylamino-tetrazol-1-yl)-2-methoxy-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

1,1,1-Trifluoro-3-(1-{4-methoxy-3-[(2S-phenyl-piperidin-3S-ylamino)-methyl]-phenyl}-1H-tetrazol-5-yl)-propan-2-one;

[5-(5-Methanesulfonyl-tetrazol-1-yl)-2-methoxy-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

[3-Chloro-2-methoxy-5-(5-methyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

[2S-(4-Fluoro-phenyl)-piperidin-3S-yl]-[2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-amine;

(2S,3S)-[2-(4-Fluorophenyl)-piperidin-3-yl]-(2-methoxy-5-tetrazol-1-yl-benzyl)-amine;

(5-(5-Amino-tetrazol-1-yl)-2-methoxy-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

(2-Ethoxy-5-tetrazol-1-yl-benzyl)-([2S,3S]-2-phenyl piperidin-3-yl) amine;

(2-Isopropoxy-5-tetrazol-1-ylbenzyl)-[(2S,3S]-2-phenyl piperidin-3-yl) amine;

and pharmaceutically acceptable salts and solvates thereof.

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (IV) selected from the group consisting of:

(2-Methoxy-5-tetrazol-1-yl-benzyl)-(2S-phenyl-piperidin-3S-yl)-amine; and

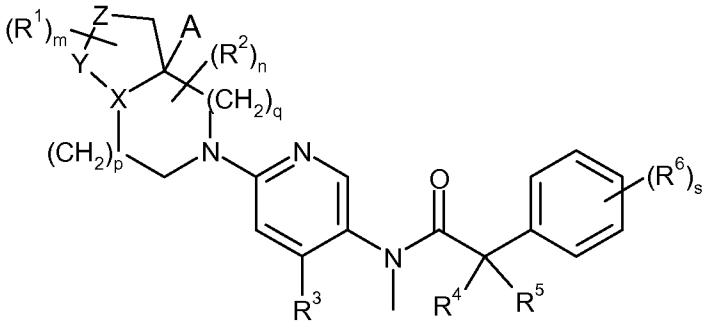
[2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

and pharmaceutically acceptable salts, including the dihydrochloride salts, and solvates thereof.

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist which is [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine;

or a pharmaceutically acceptable salt, including the dihydrochloride salts, or solvate thereof.

In a still another embodiment, the pharmaceutical composition of the present invention as herein above defined comprises an NK1 antagonist of formula (V):



(V)

wherein:

X represents a nitrogen atom;

Y represents $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ or $-C(=O)-$;

Z represents $-C(H_2)-$, $-S(O_2)-$, $-N(R^z)-$, or an oxygen or sulphur atom;

A represents hydrogen or $-CH_2OH$;

R^z represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-COR^7$ or $-SO_2R^7$;

R^1 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, =O, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, hydroxyl or $-CH_2OH$;

m represents an integer from 0 to 3;

R^2 represents halogen, =O, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), $-COOR^7$, $-CONR^7R^8$, C_{1-6} alkoxy, haloC_{1-6} alkyl, haloC_{1-6} alkoxy or C_{1-6}alkylOC_{1-6}alkyl;

n represents an integer from 0 to 3;

p and q independently represent an integer from 0 to 2;

R^3 represents an –aryl, -heteroaryl, -heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or –heterocyclyl-heterocyclyl group, all of which may be optionally substituted by one or more (e.g. 1, 2 or 3) halogen, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), C_{3-8} cycloalkyl, C_{1-6} alkoxy, hydroxyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, cyano, $-S-C_{1-6}$ alkyl, $-SO-C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, $-NR^7COC_{1-6}$ alkyl, $-NR^7SO_2-C_{1-6}$ alkyl, C_{1-6} alkyl-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ or $-SO_2NR^7R^8$ groups;

R^4 and R^5 independently represent C_{1-6} alkyl, or R^4 and R^5 together with the carbon atom to which they are attached may together form a C_{3-8} cycloalkyl group;
R^6 represents halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;
s represents an integer from 0 to 4;
R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;
or a pharmaceutically acceptable salt or solvate thereof.
Compounds of formula (V) and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO2007/028654, published 15 March 2007. The disclosure of this reference is incorporated herein in its entirety. Compounds of formula (V) and pharmaceutically acceptable salts and solvates thereof may be prepared by any method described in WO2007/028654.

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist of formula (V) selected from the group consisting of:
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,
N-[6-[(3*S*)-8-acetyl-3-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide,
and pharmaceutically acceptable salts and solvates thereof.

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises an NK1 antagonist which is 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or a pharmaceutically acceptable salt, including the hydrochloride salt, or solvate thereof.

In a further embodiment, the pharmaceutical composition of the invention as hereinabove defined comprises a Sodium Channel blocker selected from the group consisting of fosphenytoin (Cerebyx™, Prodilantin™, Pro-Epanutin™ or Cereneu™), oxcarbazepine (Trileptal™, Oxrate™ or Wockhardt™), phenytoin, carbamazepine (Carbatrol, Equetro ™), lidocaine (ALGRX-3268), Safinamide (NW-1015) and Ralfinamide (NW-1029).

In a further embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker selected from the group consisting of:
3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine ;
R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine;
(2R,5R)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,7-diazaspiro[4.4]nonan-6-one;
(2R,5R)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-6-one;
5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-prolinamide;
or a pharmaceutically acceptable salt or solvate thereof.

In a still further embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker selected from the group consisting of:
3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine ;
R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine;
or a pharmaceutically acceptable salt or solvate thereof.

In an additional further embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine or a pharmaceutically acceptable salt or solvate thereof.

Compound 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and pharmaceutically acceptable salts and solvates thereof are described in EP granted Patent EP0021121B and in US Patent US 4,602,017. The disclosure of this reference is incorporated herein in its entirety. Compound 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and pharmaceutically acceptable salts and solvates thereof may be prepared by any method described in EP0021121B and US 4,602,017.

In another embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker which is R(-)-2,4-diamino-5-(2,3-

dichlorophenyl)-6-fluoromethyl pyrimidine or a pharmaceutically acceptable salt, solvate or prodrug thereof.

Compound R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO 97/9317, published 13 March 1997. The disclosure of this reference is incorporated herein in its entirety. Compound R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and pharmaceutically acceptable salts and solvates thereof may be prepared by any method described in WO 97/9317.

In one embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker, which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, or R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and one of the NK1 receptor antagonists selected from the group consisting of: aprepitant (Emend™); netupitant (R-1124); fosaprepitant (MK-0517); SSR-240600; cizolirtine; AV 608; TA-5538; E 6039; nolpitantium besilate (SR 140333); 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof; 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof; such NK1 receptor antagonist being administered at sub therapeutic dose.

In one embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker at subtherapeutic dose, which is 3,5-

diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof or R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof and one of the NK1 receptor antagonists selected from the group consisting of: aprepitant (Emend™); netupitant (R-1124); fosaprepitant (MK-0517); SSR-240600; cizolirtine; AV 608; TA-5538; E 6039; nolpitantium besilate (SR 140333); 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof; 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker, which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, or R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and one of the NK1 receptor antagonists selected from the group consisting of: aprepitant (Emend™); netupitant (R-1124); fosaprepitant (MK-0517); SSR-240600; cizolirtine; AV 608; TA-5538; E 6039; nolpitantium besilate (SR 140333); 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof; 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-

piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof; such NK1 receptor antagonist and Sodium Channel blocker compounds being both administered at sub therapeutic dose.

In one embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker, which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, or R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and one of the NK1 receptor antagonists selected from the group consisting of: 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof; 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof; such NK1 receptor antagonist being administered at sub therapeutic dose.

In one embodiment, the pharmaceutical composition of the invention as herein above defined comprises a Sodium Channel blocker at sub therapeutic dose, which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, or R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and one of the NK1 receptor

antagonists selected from the group consisting of: 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof; 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, at sub therapeutic dose and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof, at sub therapeutic dose.

In an additional embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or

solvate thereof, and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at sub therapeutic dose.

In one embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In one embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In a further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-

benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In another embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, at sub therapeutic dose and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof, at sub therapeutic dose.

In another embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In another embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In another embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In a further embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically

acceptable salt or solvate thereof, and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In a further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, at sub therapeutic dose and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In a further embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In a further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine at sub therapeutic dose and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In another embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate at sub therapeutic dose.

In an additional embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine at subtherapeutic dose and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate.

In one embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate at subtherapeutic dose.

In one embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride.

In further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride at subtherapeutic dose.

In one embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-

(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In a further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine at subtherapeutic dose and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine dihydrochloride.

In another embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine dihydrochloride at subtherapeutic dose.

In another embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine at sub therapeutic dose and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate at sub therapeutic dose.

In another embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine at subtherapeutic dose and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate at subtherapeutic dose.

In another embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-

yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride at subtherapeutic dose.

In another embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine at subtherapeutic dose and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, at subtherapeutic dose.

In a further embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine at subtherapeutic dose and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine dihydrochloride.

In another embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine dihydrochloride at subtherapeutic dose.

In a further embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine at sub therapeutic dose and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment the pharmaceutical composition of the invention comprises 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or a pharmaceutically acceptable salt or solvate thereof, at sub therapeutic dose.

In a further embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine at subtherapeutic dose and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the pharmaceutical composition of the invention comprises R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof at subtherapeutic dose.

In one embodiment, a method of treating a human or animal subject suffering from epilepsy, mood disorders or pain, is provided, which comprises administering to said subject an effective amount of any one of the pharmaceutical compositions above described.

In another embodiment, any one of the pharmaceutical compositions above described is provided for use in therapy.

In a further embodiment, any one of the pharmaceutical compositions above described is provided for use in the treatment of epilepsy, mood disorders or pain.

In an additional embodiment, the use of any one of the pharmaceutical compositions above described is provided for the treatment of epilepsy, mood disorders or pain.

Furthermore in another aspect, a pharmaceutical composition is provided comprising a Sodium channel blocker and an NK1 receptor antagonist, wherein neither of the Sodium Channel blocker and NK1 receptor antagonist is administered at sub therapeutic dose, as

a combined preparation for simultaneous or sequential administration. Such a composition, within this specifications, is referred to as pharmaceutical composition (A).

In one embodiment, there is provided a pharmaceutical composition (A) comprising a Sodium channel blocker which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine or a pharmaceutically acceptable salt or solvate thereof, and an NK1 receptor antagonist.

In another aspect, there is provided a pharmaceutical composition (A) comprising a Sodium channel blocker which is which is R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine or a pharmaceutically acceptable salt or solvate thereof, and an NK1 receptor antagonist.

In one embodiment, there is provided a pharmaceutical composition (A) comprising a Sodium Channel blocker, which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, or R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and one of the NK1 receptor antagonists selected from the group consisting of: aprepitant (Emend™); netupitant (R-1124); fosaprepitant (MK-0517); SSR-240600; cizolirtine; AV 608; TA-5538; E 6039; nolpitantium besilate (SR 140333); 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof; 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, there is provided a pharmaceutical composition (A) comprising a Sodium Channel blocker, which is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, or R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and one of the NK1 receptor antagonists selected from the group consisting of: 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof; 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof; [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof; 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof, and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-

pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-

oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt or solvate thereof, and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt or solvate thereof, and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In one embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate.

In another embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-

((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride.

In a further embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine dihydrochloride.

In one embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-(*S*)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(*R*)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In another embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 4-(S)-(4-acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate.

In one embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride.

In one embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aR)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine dihydrochloride.

In another embodiment, a pharmaceutical composition (A) is provided comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a pharmaceutical composition (A) is provided comprising R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine and 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a method of treating a human or animal subject suffering from epilepsy, mood disorders or pain, is provided, which comprises administering to said subject an effective amount of any one of the pharmaceutical compositions (A) above described.

In another embodiment, any one of the pharmaceutical compositions (A) above described is provided for use in therapy.

In a further embodiment, any one of the pharmaceutical compositions (A) above described is provided for use in the treatment of epilepsy, mood disorders or pain.

In an additional embodiment, the use of any one of the pharmaceutical compositions (A) above described is provided for the treatment of epilepsy, mood disorders or pain.

The adjunctive therapy of the present invention is carried out by administering an NK1 receptor antagonist together with a Sodium Channel Blocker in any manner which provides effective levels of the compounds in the body at the same time. It will be appreciated that the compounds of the composition may be administered simultaneously, either in the same or separate dosage forms, or sequentially. It will also be understood that the compounds of the composition, whether presented simultaneously or

sequentially, may be administered individually, or in multiples, or in any combination thereof.

The amount of a pharmaceutical composition as hereinabove defined required to be effective as a treatment for epilepsy, psychotic disorders, mood disorders or pain may, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the subject mammal's body weight, age and general condition and the nature and severity of the condition to be treated.

Unless otherwise indicated, all weights of active ingredients are calculated in terms of the drug *per se*. The desired dose may preferably be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day.

A pharmaceutical composition as hereinabove defined for use in the treatement of mood disorders, psychotic disorders, epilepsy or pain may conveniently be presented as a pharmaceutical composition in a unitary dosage form. Thus pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, for example orally usable pharmaceutical compositions. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one- third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compound. The amounts of each drug to be contained in each dosage unit may depend on the identity of the drugs chosen for the therapy.

Pharmaceutical compositions as hereinabove defined for use in the treatment of mood disorders, psychotic disorders, epilepsy or pain include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature

of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Pharmaceutical compositions as hereinabove defined suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each comprising a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, sodium croscarmellose cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredients in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredients in a suitable liquid carrier. Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or polyethylene glycols.

Topical administration may also be by means of a transdermal iontophoretic device.

Pharmaceutical compositions suitable for vaginal administration may be presented as tablets, pessaries, tampons, creams, gels, pastes, foams or spray compositions comprising in addition to the active ingredients such carriers as are known in the art to be appropriate.

Pharmaceutical compositions suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Pharmaceutical compositions suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, preservatives and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

It should be understood that in addition to the ingredients particularly mentioned above the compositions of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The pharmaceutical compositions as hereinabove defined comprising the two active ingredients may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and [2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)-amine or pharmaceutically acceptable salts or solvates thereof, may be admixed

together with suitable excipients such as those described above for the formulation of each of the active ingredients separately. Tablets may be prepared, for example by direct compression of such a mixture or using other conventional methods. Bilayer tablets may be prepared according to conventional procedure. Thus, for example, by separately compressing the two blends in a suitable tabletting machine with two filling stations. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

Pharmaceutical compositions are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment.

It will be understood that the administration of the pharmaceutical composition as hereinabove defined by means of a single patient pack, or patient packs of each formulation,containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention there is provided a multiple, for example, double or triple, pack comprising an NK1 receptor antagonist and a Sodium Channel Blocker, and an information insert containing directions on the use of the compositions of the invention.

Experimental data

The following table lists the used abbreviations:

DMSO		dimethylsulfoxide
DCM	-	dichloromethane

DMAP	-	dimethylaminopyridine
DMF	-	dimethylformamide
TFA		Trifluoroacetic acid
LiHMDS	-	lithium bis(trimethylsilyl)amide
MeOH		Methanol
TEA	-	triethylamine
THF	-	tetrahydrofuran
MTBE	-	Methyl-t-butyl-ether
EtOAc, EA, AcOEt	-	Ethyl Acetate
CH		cyclohexane
Et_2O	-	Diethyl ether
EtOH		ethanol
DIPEA	-	Diisopropylethyl amine
BOC2O		di-t-butyl-dicarbonate

Intermediate 1

4-Fluoro-2-methyl-phenyl)-oxo-acetic acid methyl ester

1) To a suspension of magnesium turnings (617 mg) in anh. THF (6 mL), at r.t., under N2, a small crystal of I2 was added, followed by 10% of a solution of commercial 2-bromo-5-fluorotoluene (4.0g) in anh. THF (15 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The remaining bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min), the suspension was stirred at 70°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

2) A solution of LiBr (4.41 g) in anh. THF (50 mL) was added drop-wise to a suspension of CuBr (3.64g) in anh. THF (50 mL). The reaction mixture was stirred at r.t. for 1 hr (dark green solution with a small amount of white solid in suspension). The Grignard solution previously prepared was then added dropwise (an ice bath was used to maintain the temperature <25°C) followed by methyl oxalyl chloride (1.95 mL). The reaction mixture was stirred at r.t. for 2 hr. The THF was evaporated and the residue was taken up in

AcOEt. The organic layer was washed with sat.aq. NH4Cl (2x) and dried. The solids were filtered and the solvent evaporated to give a crude oil, which was purified by flash chromatography (CH/AcOEt 95:5) to obtain the title compound as a clear oil (2.44 g).
NMR (CDCl3): δ (ppm) 7.74 (m, 1H), 6.98-7.04 (m, 2H), 3.96 (s, 3H), 2.61 (s, 3H).

Intermediate 2

3-(4-Fluoro-2-methyl-phenyl)-5,6-dihydro-1H-pyrazin-2-one

To a solution of intermediate 1 (2.01g) and ethylenediamine (684 μL) in toluene (40 mL), at r.t., under N2, anh. Na2SO4 (2 g) was added. The reaction mixture was heated at reflux for 6 hr. It was then cooled down to r.t. and filtered. The solids were rinsed with DCM. The solvent was evaporated and the crude oil was purified by flash chromatography (AcOEt) affording the title compound as a white solid (1.29g).
NMR (CDCl3): δ (ppm) 7.33 (m, 1H), 6.95-6.90 (m, 2H), 6.56 (m, 1H), 3.97 (m, 2H), 3.58 (m, 2H), 2.31 (s, 3H).

Intermediate 2a

3-(4-Fluoro-2-methyl-phenyl)-piperazin-2-one

To a solution, at 25°C, of intermediate 2 (168g) in Methanol (2400mL) under nitrogen, Pd/C 10% (44g) was added. The reaction mixture was placed under a H_2 atmosphere and stirred at 25°C for about 16 hours (till no further hydrogen was consumed and the reaction was completed by TLC, EA/MeOH 9/1). The catalyst was filtered in nitrogen atmosphere and the solvent was removed to low volume (360mL) then Methanol (2040mL) and Ethyl Acetate (9600mL) were added and a silica pad (800g) was performed; the eluted solution was concentrated to obtain the title compound (168g).
^{1}H-NMR (DMSO) δ (ppm) 7.77 (bm, 1H); 7.24 (dd, 1H); 6.96 (dd, 1H); 6.92 (td, 1H); 4.43 (s, 1H); 3.30 (m, 1H); 3.14 (m, 1H); 2.92 (m, 1H); 2.82 (m, 2H); 2.33 (s, 3H).

Intermediate 3

(+)(S)-3-(4-Fluoro-2-methyl-phenyl)-piperazin - 2-one

Method A

To a suspension of intermediate 2 (35 g) in AcOEt (900 mL), L(+)-Mandelic Acid (27.3 g) was added. The suspension was stirred at r.t. for 1 hr then at 3-5°C for 2 hr, filtered and dried under vacuum at r.t to obtain crude L(+)-mandelate 3-(4-fluoro-2-methyl-phenyl)-piperazin-2-one (37 g), which was suspended in AcOEt (370 mL) and heated to reflux till complete solubilisation then cooled to room temperature and stirred for further 2 hours, filtered, washed with of AcOEt (150 mL) and dried under vacuum obtaining (+) L-

mandelate 3-(4-Fluoro-2-methyl-phenyl)-5,6 pyrazin-2-one (30.4 g) as white solid. This material (30.4g) was suspended in AcOEt (300 mL) and treated with NaOH (0.73M, 155 mL) saturated with NaCl. The organic phase was then washed with water (90 mL). The aqueous phase was counter-extracted 4 times with AcOEt (90 mL). The combined organic phase (1800 mL) was dried on 10 g of Na2SO4 and concentrated under vacuum obtaining the title compound (25.04 g) as white foam.

Method B

To a solution, heated at 45°C, of intermediate 2a (168 g) in Ethyl Acetate (2000mL) L(+)-Mandelic Acid (116g) and 3,5-dichloro-salicilaldehyde (10.8g) were added. The solution was stirred for 30min at 45°C then seeded with white crystals of L(+)mandelate-3-(4-Fluoro-2-methyl-phenyl)-piperazin - 2-one (0.4g). The obtained suspension was stirred under nitrogen atmosphere at 45°C for 16 hours then stirred for further 4 hour at 0°C, washed with cooled Ethyl Acetate (2x200ml) then dried under vacuum at room temperature for 2 hours to obtain L(+)mandelate-3-(4-Fluoro-2-methyl-phenyl)-piperazin - 2-one(126.22g) as a white/yellowish solid which was suspended in DCM (2760mL) then NaOH 0.8M in Brine (17.35g of NaOH in 530mL of Brine) was added. The organic phase was then washed with Brine (380mL) and the aqueous phase was counter extracted four times with DCM (4x1500mL). The combined organic phase was dried and concentrated to obtain the title compound (60.35g).

^{1}H-NMR (DMSO) δ (ppm) 7.77 (bm, 1H); 7.24 (dd, 1H); 6.96 (dd, 1H); 6.92 (td, 1H); 4.43 (s, 1H); 3.30 (m, 1H); 3.14 (m, 1H); 2.92 (m, 1H); 2.82 (m, 2H); 2.33 (s, 3H).

HPLC:Chiralcel OJ (4.6X250mm) from Daicel; Mobile Phase:n-Hexane/Ethanol 80:20 v/v;Flow:1 mL/min; Detector:UV @ 265nm (or 210 nm for higher signals); Dissolution phase:n-Hexane/Ethanol 80/20 v/v;

Sample Concentration 1 mg/ml; Injection:5 uL;Retention times: 2:8.4 min.

$[\alpha]_D$(solvent CHCl3, Source: Na; Cell volume [ml]: 1; Cell pathlength [dm]:1; Cell temperature [°C]:20; Wavelength [nm]: 589; Conc. sample [% p/v] :1.17)=+17.9.

Intermediate 4

(S)-3-(4-Fluoro-2-methyl-phenyl)-piperazine dihydrochloride

To a solution of intermediate 3 (60.35g) in dry THF (180ml), at 0-3°C, under N_2, BH_3·THF 1M/THF (1220mL) was added dropwise. The solution was refluxed for 4 hours then cooled to 0-3°C and methanol (240mL) was added. The reaction mixture was heated to room temperature then it was concentrated to dryness. The residue was redissolved in methanol (603.5mL), excess HCl 1N in Et_2O (1207mL) was added and the mixture was

refluxed for 2 hours then cooled at 3°C for 4 hours. The suspension was filtered to obtain a white solid that was washed with Et_2O (60.35mL) and dried to yield the title compound (72.02g)

^{1}H-NMR (DMSO) δ (ppm) 11.0-9.5 (b, 4H); 7.99-7.19 (dd-m, 3H); 4.96 (dd, 1H); 3.65-3.15 (m, 6H); 2.42 (s, 3H).

Intermediate 5

(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine

To a solution of 3,5-bis-trifluoromethylacetophenone (300g) in MeOH (1120mL), a solution of methylamine 8M in EtOH (372mL) was added dropwise during 15 min. at 25°C under N_2. The mixute was stirred for 24hrs at 25°C under N_2. Then, $NaBH_4$ was portionwise added over 30 min (27.9g) at 0°C. A second amount of $NaBH_4$ was added over 30 min (17.1g) and the mixture stirred for further 1.5hrs.

The mixture was concentrated by evaporating 600mL of solvent under vacuum then it was slowly poured into a mixture of AcOEt (1500mL)/NH_4Cl sat (750mL) and water (750mL). The water phase was back-extracted with AcOEt (1500mL). The combined organic phases were washed with Water/Brine (150mL/150mL) then evaporated to obtain 3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (305g) as a yellow oil

To a solution of 3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (245.6g) in EtOAc (2380mL), L(+) malic acid was added portionwise (118g). The suspension was stirred for 2hrs at 25°C then 3hrs at 0°C. The suspension was filtered and the cake was washed with EtOAc (240mL). The solid was dried under vacuum obtaining crude L(+)malate3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (135.3g) as a white solid which was suspended in Ethyl acetate (1760mL) then heated to reflux till complete dissolution and then cooled at 25°C. The suspension was filtered, washed with Ethyl acetate (135mL) then dried to obtain L(+)malate3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (128.5g). The solid was stirred in a mixture of NaOH 10%v/v (720mL) and Ethyl acetate (650mL). Organic phase was washed with water (720mL), then concentrated to yield the title compound (82.2g).

^{1}H-NMR (DMSO) δ (ppm) 7.99 (s, 2H); 7.85 (s, 1H); 3.78 (q, 1H); 2.34 (s, 1H); 2.09 (s, 3H); 1.23 (d, 3H).

Representative NK1 antagonist Example 1 (ENK1)

2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate

To a suspension of intermediate 4 (4.9Kg) in AcOEt (137.2L), triethylamine (5.63L) was added. The mixture was cooled to 0°C then a solution of diterbuthyl dicarbonate (3.134Kg) in AcOEt (24.5L) was added in 35 min, maintaining the temperature between 0 and 5°C. The suspension was stirred at 0°C for 15 min, at 20/25°C for 1 hr, then washed with water (3 x 39.2L), concentrated to 24.5L and then added to a solution of triphosgene (1.97Kg) in AcOEt (24.5L) cooled to 0°C. Triethylamine (3.28L) was then added in 40 min, maintaining the temperature between 0 and 8°C. The suspension was stirred for 1h and 45 min at 20/25°C and 30 min at 70Cand then the solution of intermediate 5 diluted with AcOEt (49L) and triethylamine (2.6L) was added in 30 min. The mixture was refluxed for 15 hrs.

The reaction mixture, cooled at 20/25°C was treated with aqueous solution of NaOH 10%v/v (36.75L). Organic phase was washed with HCl 4%v/v (46.55L) and NaCl 11,5%p/p (4 x 24.5L) then concentrated to 14.7L. and diluted with Ciclohexane (39.2L). The mixture was filtered through a silica pad (4.9Kg) that was washed twice with a mixture of CH/AcOEt 85/15 (2 x 49L). To the Eluted phases (14.7L) cooled at 20/25°C., methyl tertbutyl ether (49L) and methansulphonic acid (4.067L) were added. The mixture was washed with NaOH 10%v/v (31.85L) then with water (4 x 31.85L). Organic phase was concentrated to 9.8L, methyl tertbutyl ether (49L) was added and the solution filtered through a 5micron filter then concentrated to 9.8L. At 20/25°C MTBE (29.4L) and metansulphonic acid (1.098L) were added. The suspension was refluxed for 10 min, stirred at 20/25°C for 10hrs and 2 hrs at O°C.Then the precipitate was filtered, washed with methyl tertbutyl ether (4.9L) dried under vacuum at 20/25°C for 24 hrs to obtain the title compound (5.519Kg.) as white solid.

^{1}H-NMR (DMSO) δ (ppm) 8.99 (bm, 1H); 8.66 (bm, 1H); 8.00 (bs, 1H); 7.69 (bs, 2H); 7.27 (dd, 1H); 7.00 (dd, 1H); 6.83 (m, 1H); 5.32 (q, 1H); 4.47 (dd, 1H); 3.50-3.20 (m, 4H); 2.96 (m, 2H); 2.72 (s, 3H); 2.37 (s, 3H); 2.28 (s, 3H); 1.46 (d, 3H).

ES^+: m/z 492 $[MH - CH_3SO_3H]^+$

ES^-: m/z 586 $[M - H]^-$; 95 $[CH_3SO_3]^-$

Intermediate 6

1-(Benzyloxycarbonyl)-2-(4-fluoro-2-methyl-phenyl)-2,3-dihydro-4-pyridone

A small amount of iodine was added to a suspension of magnesium turnings (13.2 g) in dry THF (300 mL), at r.t., under a nitrogen atmosphere, then the mixture was vigorously refluxed for 20 minutes. To this suspension, a 15% of a solution of 2-bromo-5-fluoro-toluene (52.5 mL) in anhydrous THF (300 mL) was added. The suspension was heated

under vigorous reflux until the brown colour disappeared. The remaining part of the bromide solution was added drop-wise over 1 hour to the refluxing suspension which was then stirred for a further 1 hour. This solution of Grignard reagent was then added drop-wise to the pyridinium salt obtained from benzyl chloroformate (48.7 mL) and 4-methoxypyridine (25 mL) in dry THF (900 mL) at -23°C.

The obtained solution was stirred 1 hour at -20°C then it was warmed up to 20°C, a 10% hydrochloric acid solution (560 mL) was added and the aqueous layer was extracted with AcOEt (2 x 750 mL).

The combined organic extracts were washed with 5% sodium hydrogen carbonate solution (600 mL) and brine (600 mL) then partially concentrated *in vacuo.*

CH (400 mL) was added drop-wise over 1 hour at 20°C and the resulting mixture was stirred 30 minutes and then filtered to give the title compound as a white solid (66 g).

IR (nujol, cm^{-1}): 1726 and 1655 (C=O), 1608 (C=C).

NMR (d_6-DMSO): δ (ppm) 8.19 (d, 1H); 7.31-7.18 (m, 5H); 7.08 (m, 2H); 6.94 (dt, 1H); 5.77 (d, 1H); 5.36 (d, 1H); 5.16 (2d, 2H); 3.26 (dd, 1H); 2.32 (d, 1H); 2.26 (s, 3H).

MS (ES/+): m/z=340 $[MH]^+$.

Intermediate 7

2-(4-Fluoro-2-methyl-phenyl)-piperidine-4-one

Method A

2-Methyl-4-fluoro-benzaldehyde (4 g) was added to a solution of 4-aminobutan-2-one ethylene acetal (3.8 g) in dry benzene (50 mL) and the solution was stirred at r.t. under a nitrogen atmosphere. After 1 hour the mixture was heated at reflux for 16 hours and then allowed to cool to r.t. This solution was slowly added to a refluxing solution of p-toluensulphonic acid (10.6 g) in dry benzene (50 mL) previously refluxed for 1 hour with a Dean-Stark apparatus. After 3.5 hours the crude solution was cooled and made basic with a saturated potassium carbonate solution and taken up with AcOEt (50 mL). The aqueous phase was extracted with AcOEt (3 x 50 mL) and Et2O (2 x 50 mL). The organic layer was dried and concentrated *in vacuo* to a yellow thick oil as residue (7.23 g). A portion of the crude mixture (3 g) was dissolved in a 6N hydrochloric acid solution (20 mL) and stirred at 60°C for 16 hours. The solution was basified with solid potassium carbonate and extracted with DCM (5 x 50 mL). The combined organic phases were washed with brine (50 mL), dried and concentrated *in vacuo* to give the title compound (2.5 g) as a thick yellow oil.

Method B

L-selectride (1M solution in dry THF, 210 mL) was added drop-wise, over 80 minutes, to a solution of intermediate **6** (50 g) in dry THF (1065 mL) previously cooled to -72°C under a nitrogen atmosphere. After 45 minutes, 2% sodium hydrogen carbonate solution (994 mL) was added drop-wise and the solution was extracted with AcOEt (3 x 994 mL). The combined organic phases were washed with water (284 mL) and brine (568 mL). The organic phase was dried and concentrated *in vacuo* to get 1-benzyloxycarbonyl-2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one as a pale yellow thick oil (94 g) which was used as a crude.

This material (94 g) was dissolved in AcOEt (710 mL), then 10% Pd/C (30.5 g) was added under a nitrogen atmosphere. The slurry was hydrogenated at 1 atmosphere for 30 minutes. The mixture was filtered through Celite and the organic phase was concentrated *in vacuo* to give the crude 2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one as a yellow oil. This material was dissolved in AcOEt (518 mL) at r.t. and racemic camphorsulphonic acid (48.3 g) was added. The mixture was stirred at r.t for 18 hours, then the solid was filtered off, washed with AcOEt (2 x 50 mL) and dried *in vacuo* for 18 hours to give 2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one, 10-camphorsulfonic acid salt as a pale yellow solid (68.5 g). (M.p.: 167-169°C - NMR (d_6-DMSO): δ (ppm) 9.43 (bs, 1H); 9.23 (bs, 1H); 7.66 (dd, 1H); 7.19 (m, 2H); 4.97 (bd, 1H); 3.6 (m, 2H); 2.87 (m, 3H); 2.66 (m, 1H); 2.53 (m, 2H); 2.37 (s + d, 4H); 2.22 (m, 1H); 1.93 (t, 1H); 1.8 (m, 2H); 1.26 (m, 2H); 1.03 (s, 3H); 0.73 (s, 3H).

This material (68.5 g) was suspended in AcOEt (480 mL) and stirred with a saturated sodium hydrogen carbonate (274 mL). The organic layer was separated and washed with further water (274 mL). The organic phase was dried and concentrated *in vacuo* to give the title compound (31 g) as a yellow-orange oil.

NMR (d_6-DMSO): δ (ppm) 7.49 (dd, 1H); 7.00 (m, 2H); 3.97 (dd, 1H); 3.27 (m, 1H); 2.82 (dt, 1H); 2.72 (bm, 1H); 2.47 (m, 1H); 2.40 (m, 1H); 2.29 (s, 3H); 2.25 (dt, 1H); 2.18 (m, 1H).

MS (ES/+): m/z=208 $[MH]^+$.

Intermediate 8

2-(R)-(4-Fluoro-2-methyl-phenyl)-piperidin-4-one mandelic acid.

A solution of L-(+)-mandelic acid (22.6 g) in AcOEt (308 mL) was added to a solution of intermediate **7** (31 g) in AcOEt (308 mL). Then isopropanol (616 mL) was added and the solution was concentrated *in vacuo* to 274 mL. The solution was then cooled to 0°C and further cold isopropanol (96 mL) was added. The thick precipitate was stirred under

nitrogen for 5 hours at 0°C, then filtered and washed with cold Et2O (250 mL) to give the title compound as a pale yellow solid (20.3 g).

M.p.: 82-85°C.

NMR (d_6-DMSO): δ (ppm) 7.51 (dd, 1H); 7.40 (m, 2H); 7.32 (m, 2H); 7.26 (m, 1H); 7.0 (m, 2H); 4.95 (s, 1H); 4.04 (dd, 1H); 3.31 (m, 1H); 2.88 (m, 1H); 2.49-2.2 (m, 4H); 2.29 (s, 3H).

Chiral HPLC: HP 1100 HPLC system; column Chiralcel OD-H, 25 cm x 4.6 mm; mobile phase: n-hexane/isopropanol 95:5 + 1% diethylamine; flow: 1.3 ml/min; detection: 240/215nm; retention time 12.07 minutes.

Intermediate 9

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (9a) and

2-(S)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (9b)

Method A

A solution of triphosgene (147 mg) dissolved in dry DCM (5 mL) was added drop-wise to a solution of intermediate **7** (250 mg) and DIPEA (860 μL) in dry DCM (15 mL) previously cooled to 0°C under a nitrogen atmosphere. After 2 hours, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (503 mg) and DIPEA (320 μL) in dry acetonitrile (20 mL) were added and the mixture was heated to 70°C for 16 hours. Further [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (170 mg) and DIPEA (100 μL) were added and the mixture was stirred at 70°C for further 4 hours. Next, the mixture was allowed to cool to r.t., taken up with AcOEt (30 mL), washed with a 1N hydrochloric acid cold solution (3 x 15 mL) and brine (2 x 10 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give:

1. intermediate **9a** (230 mg) as a white foam,
2. intermediate **9b** (231 mg) as a white foam.

Intermediate 9a

NMR (d_6-DMSO): δ (ppm) 7.98 (bs, 1H); 7.77 (bs, 2H); 7.24 (dd, 1H); 6.97 (dd, 1H); 6.89 (m, 1H); 5.24 (t, 1H); 5.14 (q, 1H); 3.61 (m, 1H); 3.55 (m, 1H); 2.71 (m, 2H); 2.56 (s, 3H); 2.50 (m, 2H); 2.26 (s, 3H); 1.57 (d, 3H).

Intermediate 9b

NMR (d_6-DMSO): δ (ppm) 7.96 (bs, 1H); 7.75 (bs, 2H); 7.24 (dd, 1H); 6.98 (dd, 1H); 6.93 (dt, 1H); 5.29 (q, 1H); 5.24 (t, 1H); 3.56 (m, 1H); 3.48 (m, 1H); 2.70 (s, 3H); 2.50 (m, 4H); 2.26 (s, 3H); 1.54 (d, 3H).

Intermediate 9a

Method B

A saturated sodium hydrogen carbonate solution (324 mL) was added to a solution of intermediate **8** (21.6 g) in AcOEt (324 mL) and the resulting mixture was vigorously stirred for 15 minutes. The aqueous layer was back-extracted with further AcOEt (216 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give 2-(R)-(4-fluoro-2-methyl-phenyl)-piperidin-4-one as a yellow oil, which was treated with TEA (19 mL) and AcOEt (114 mL). The solution obtained was added drop-wise over 40 minutes to a solution of triphosgene (8 g) in AcOEt (64 mL) previously cooled to 0°C under a nitrogen atmosphere, maintaining the temperature between 0°C and 8°C.

After stirring for 1 hours at 0°C and for 3 hours at 20°C, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (29.7 g), AcOEt (190 mL) and TEA (38 mL) were added to the reaction mixture which was then heated to reflux for 16 hours.

The solution was washed with 10% sodium hydroxide solution (180 mL), 1% hydrochloric acid solution (4 x 150 mL), water (3 x 180 mL) and brine (180 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified through a silica pad (CH/AcOEt 9:1) to give the title compound (21.5 g) as a brown thick oil.

NMR (d_6-DMSO): δ (ppm) 7.97-7.77 (bs + bs, 3H); 7.24 (dd, 1H); 6.97 (dd, 1H); 6.88 (td, 1H); 5.24 (m, 1H); 5.14 (q, 1H); 3.58 (m, 2H); 2.7 (m, 2H); 2.56 (s, 3H); 2.49 (m, 2H); 2.26 (s, 3H); 1.57 (d, 3H).

Representative NK1 antagonist Example 2 (ENK2)

4-(S)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide methanesulphonate

A solution of intermediate **9a** (7.7 g) in acetonitrile (177 mL) was added to a solution of 1-acetyl-piperazine (3.9 g) in acetonitrile (17.7 mL) followed by sodium triacetoxyborohydride (6.4 g) under a nitrogen atmosphere.

The reaction mixture was stirred at room temperature for 24 hours and then quenched with a saturated sodium hydrogen carbonate (23.1 mL) and water (61.6 mL). The resulting solution was concentrated *in vacuo*, then AcOEt (208 mL) was added; the layers were separated and the aqueous layer was back-extracted with further AcOEt (2 x 77 mL). The

collected organic phases were washed with brine (2 x 118 mL), dried and concentrated *in vacuo* to give the crude mixture of syn and anti diastereomers (nearly 1:1) as a white foam (9.5 g).

A solution of this intermediate in THF (85.4 mL) was added to a solution of methansulfonic acid (0.890 mL) in THF (6.1 mL) at r.t.. After seeding, the desired syn diastereomer started to precipitate. The resulting suspension was stirred for 3 hours at 0°C and then filtered under a nitrogen atmosphere. The resulting cake was washed with cold THF (15.4 mL) and dried *in vacuo* at + 20°C for 48 hours to give the title compound as a white solid (4.44 g).

NMR (d_6-DMSO): δ (ppm) 9.52 (bs, 1H); 7.99 (bs, 1H); 7.68 (bs, 2H); 7.23 (m, 1H); 6.95 (dd, 1H); 6.82 (m, 1H); 5.31 (q, 1H); 4.45 (bd, 1H); 4.20 (dd, 1H); 3.99 (bd, 1H); 3.65-3.25 (bm, 5H); 3.17 (m, 1H); 2.96 (m, 1H); 2.88-2.79 (m+m, 2H); 2.73 (s, 3H); 2.36 (s, 3H); 2.30 (s, 3H); 2.13-2.09 (bd+bd, 2H); 2.01 (s, 3H); 1.89-1.73 (m+m, 2H); 1.46 (d, 3H).
m.p 243.0 °C.

The compound is isolated in a crystalline form.

Intermediate 10

1-(Benzyloxycarbonyl)-2-(4-fluoro-2-methyl-phenyl)-2,3-dihydro-4-pyridone

A small amount of iodine was added to a suspension of magnesium turnings (13.2 g) in dry THF (300 mL), at r.t., under a nitrogen atmosphere, then the mixture was vigorously refluxed for 20 minutes. To this suspension, a 15% of a solution of 2-bromo-5-fluoro-toluene (52.5 mL) in anhydrous THF (300 mL) was added. The suspension was heated under vigorous reflux until the brown colour disappeared. The remaining part of the bromide solution was added drop-wise over 1 hour to the refluxing suspension which was then stirred for a further 1 hour. This solution of Grignard reagent was then added drop-wise to the pyridinium salt obtained from benzyl chloroformate (48.7 mL) and 4-methoxypyridine (25 mL) in dry THF (900 mL) at -23°C.

The obtained solution was stirred 1 hour at -20°C then it was warmed up to 20°C, a 10% hydrochloric acid solution (560 mL) was added and the aqueous layer was extracted with AcOEt (2 x 750 mL).

The combined organic extracts were washed with 5% sodium hydrogen carbonate solution (600 mL) and brine (600 mL) then partially concentrated *in vacuo.*

CH (400 mL) was added drop-wise over 1 hour at 20°C and the resulting mixture was stirred 30 minutes and then filtered to give the title compound as a white solid (66 g).

IR (nujol, cm^{-1}): 1726 and 1655 (C=O), 1608 (C=C).

NMR (d_6-DMSO): δ (ppm) 8.19 (d, 1H); 7.31-7.18 (m, 5H); 7.08 (m, 2H); 6.94 (dt, 1H); 5.77 (d, 1H); 5.36 (d, 1H); 5.16 (2d, 2H); 3.26 (dd, 1H); 2.32 (d, 1H); 2.26 (s, 3H).
MS (ES/+): m/z=340 $[MH]^+$.

Intermediate 11

2-(4-Fluoro-2-methyl-phenyl)-piperidine-4-one

Method A:

4-Fluoro-2-methyl-benzaldehyde (4 g) was added to a solution of 4-aminobutan-2-one ethylene acetal (3.8 g) in dry benzene (50 mL) and the solution was stirred at r.t. under a nitrogen atmosphere. After 1 hour the mixture was heated at reflux for 16 hours and then allowed to cool to r.t. This solution was slowly added to a refluxing solution of p-toluenesulphonic acid (10.6 g) in dry benzene (50 mL) previously refluxed for 1 hour with a Dean-Stark apparatus. After 3.5 hours the crude solution was cooled and made basic with a saturated potassium carbonate solution and taken up with AcOEt (50 mL). The aqueous phase was extracted with AcOEt (3 x 50 mL) and Et2O (2 x 50 mL). The organic layer was dried and concentrated *in vacuo* to a yellow thick oil as residue (7.23 g). A portion of the crude mixture (3 g) was dissolved in a 6N hydrochloric acid solution (20 mL) and stirred at 60°C for 16 hours. The solution was basified with solid potassium carbonate and extracted with DCM (5 x 50 mL). The combined organic phases were washed with brine (50 mL), dried and concentrated *in vacuo* to give the title compound (2.5 g) as a thick yellow oil.

Method B

L-selectride (1M solution in dry THF, 210 mL) was added drop-wise, over 80 minutes, to a solution of intermediate **10** (50 g) in dry THF (1065 mL) previously cooled to -72°C under a nitrogen atmosphere. After 45 minutes, 2% sodium hydrogen carbonate solution (994 mL) was added drop-wise and the solution was extracted with AcOEt (3 x 994 mL). The combined organic phases were washed with water (284 mL) and brine (568 mL). The organic phase was dried and concentrated *in vacuo* to get 1-benzyloxycarbonyl-2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one as a pale yellow thick oil (94 g) which was used as a crude.
This material (94 g) was dissolved in AcOEt (710 mL), then 10% Pd/C (30.5 g) was added under a nitrogen atmosphere. The slurry was hydrogenated at 1 atmosphere for 30 minutes. The mixture was filtered through Celite and the organic phase was concentrated *in vacuo* to give the crude 2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one as a yellow oil.

This material was dissolved in AcOEt (518 mL) at r.t. and racemic camphorsulphonic acid (48.3 g) was added. The mixture was stirred at r.t for 18 hours, then the solid was filtered off, washed with AcOEt (2 x 50 mL) and dried *in vacuo* for 18 hours to give 2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one, 10-camphorsulfonic acid salt as a pale yellow solid (68.5 g). (M.p.: 167-169°C - NMR (d_6-DMSO): δ (ppm) 9.43 (bs, 1H); 9.23 (bs, 1H); 7.66 (dd, 1H); 7.19 (m, 2H); 4.97 (bd, 1H); 3.6 (m, 2H); 2.87 (m, 3H); 2.66 (m, 1H); 2.53 (m, 2H); 2.37 (s + d, 4H); 2.22 (m, 1H); 1.93 (t, 1H); 1.8 (m, 2H); 1.26 (m, 2H); 1.03 (s, 3H); 0.73 (s, 3H).

This material (68.5 g) was suspended in AcOEt (480 mL) and stirred with a saturated sodium hydrogen carbonate (274 mL). The organic layer was separated and washed with further water (274 mL). The organic phase was dried and concentrated *in vacuo* to give the title compound (31 g) as a yellow-orange oil.

NMR (d_6-DMSO): δ (ppm) 7.49 (dd, 1H); 7.00 (m, 2H); 3.97 (dd, 1H); 3.27 (m, 1H); 2.82 (dt, 1H); 2.72 (bm, 1H); 2.47 (m, 1H); 2.40 (m, 1H); 2.29 (s, 3H); 2.25 (dt, 1H); 2.18 (m, 1H).

MS (ES/+): m/z=208 $[MH]^+$.

Intermediate 12

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (12a)

and

2-(S)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (12b)

Method A:

A solution of triphosgene (147 mg) dissolved in dry DCM (5 mL) was added drop-wise to a solution of intermediate **11** (250 mg) and DIPEA (860 μL) in dry DCM (15 mL) previously cooled to 0°C under a nitrogen atmosphere. After 2 hours, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (503 mg) and DIPEA (320 μL) in dry acetonitrile (20 mL) were added and the mixture was heated to 70°C for 16 hours. Further [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (170 mg) and DIPEA (100 μL) were added and the mixture was stirred at 70°C for further 4 hours. Next, the mixture was allowed to cool to r.t., taken up with AcOEt (30 mL), washed with a 1N hydrochloric acid cold solution (3 x 15 mL) and brine (2 x 10 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give:

3. intermediate **12a** (230 mg) as a white foam,
4. intermediate **12b** (231 mg) as a white foam.

Intermediate 12a

NMR (d_6-DMSO): δ (ppm) 7.98 (bs, 1H); 7.77 (bs, 2H); 7.24 (dd, 1H); 6.97 (dd, 1H); 6.89 (m, 1H); 5.24 (t, 1H); 5.14 (q, 1H); 3.61 (m, 1H); 3.55 (m, 1H); 2.71 (m, 2H); 2.56 (s, 3H); 2.50 (m, 2H); 2.26 (s, 3H); 1.57 (d, 3H).

Intermediate 12b

NMR (d_6-DMSO): δ (ppm) 7.96 (bs, 1H); 7.75 (bs, 2H); 7.24 (dd, 1H); 6.98 (dd, 1H); 6.93 (dt, 1H); 5.29 (q, 1H); 5.24 (t, 1H); 3.56 (m, 1H); 3.48 (m, 1H); 2.70 (s, 3H); 2.50 (m, 4H); 2.26 (s, 3H); 1.54 (d, 3H).

Intermediate 12a

Method B

A saturated sodium hydrogen carbonate solution (324 mL) was added to a solution of intermediate **13** (21.6 g) in AcOEt (324 mL) and the resulting mixture was vigorously stirred for 15 minutes. The aqueous layer was back-extracted with further AcOEt (216 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give 2-(R)-(4-fluoro-2-methyl-phenyl)-piperidin-4-one as a yellow oil, which was treated with TEA (19 mL) and AcOEt (114 mL). The solution obtained was added drop-wise over 40 minutes to a solution of triphosgene (8 g) in AcOEt (64 mL) previously cooled to 0°C under a nitrogen atmosphere, maintaining the temperature between 0°C and 8°C. After stirring for 1 hours at 0°C and for 3 hours at 20°C, [1-(R)-(3,5-bis-trifluoromethylphenyl)-ethyl]-methylamine hydrochloride (29.7 g), AcOEt (190 mL) and TEA (38 mL)were added to the reaction mixture which was then heated to reflux for 16 hours.

The solution was washed with 10% sodium hydroxide solution (180 mL), 1% hydrochloric acid solution (4 x 150 mL), water (3 x 180 mL) and brine (180 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified through a silica pad (CH/AcOEt 9:1) to give the title compound (21.5 g) as a brown thick oil.

NMR (d_6-DMSO): δ (ppm) 7.97-7.77 (bs + bs, 3H); 7.24 (dd, 1H); 6.97 (dd, 1H); 6.88 (td, 1H); 5.24 (m, 1H); 5.14 (q, 1H); 3.58 (m, 2H); 2.7 (m, 2H); 2.56 (s, 3H); 2.49 (m, 2H); 2.26 (s, 3H); 1.57 (d, 3H).

Intermediate 13

2-(R)-(4-Fluoro-2-methyl-phenyl)-piperidin-4-one L-(+)-mandelate

A solution of L-(+)-mandelic acid (22.6 g) in AcOEt (308 mL) was added to a solution of intermediate **11** (31 g) in AcOEt (308 mL). Then isopropanol (616 mL) was added and the

solution was concentrated *in vacuo* to 274 mL. The solution was then cooled to 0°C and further cold isopropanol (96 mL) was added. The thick precipitate was stirred under nitrogen for 5 hours at 0°C, then filtered and washed with cold Et2O (250 mL) to give the title compound as a pale yellow solid (20.3 g).

M.p.: 82-85°C.

NMR (d_6-DMSO): δ (ppm) 7.51 (dd, 1H); 7.40 (m, 2H); 7.32 (m, 2H); 7.26 (m, 1H); 7.0 (m, 2H); 4.95 (s, 1H); 4.04 (dd, 1H); 3.31 (m, 1H); 2.88 (m, 1H); 2.49-2.2 (m, 4H); 2.29 (s, 3H).

Chiral HPLC: HP 1100 HPLC system; column Chiralcel OD-H, 25 cm x 4.6 mm; mobile phase: n-hexane/isopropanol 95:5 + 1% diethylamine; flow: 1.3 ml/min; detection: 240/215nm; retention time 12.07 minutes.

Intermediate 14

1,4-Dibenzyl-2-piperazinecarboxaldehyde

A solution of ethyl 2,3-dibromopropionate (6 mL) in anhydrous toluene (50 mL) was added to a solution of N,N'-dibenzylethylenediamine (5 g) and DIPEA (12 mL) in anhydrous toluene (50 mL) under a Nitrogen atmosphere. The resulting mixture was heated to 100°C for 21 hours, then allowed to cool to r.t., diluted with AcOEt (100 mL) and washed with brine (3 x 100 mL). The organic extract was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (CH/AcOEt 9:1) to give ethyl 1,4-dibenzyl-piperazine-2-carboxylate (5.65 g) as a yellow oil, which was used without any purification in the next step.

Diisobutylaluminium hydride (1M in toluene – 29 mL) was dropped into a solution of ethyl 1,4-dibenzyl-piperazine-2-carboxylate (5.47 g) in anhydrous toluene (110 mL) previously cooled to -78°C under a Nitrogen atmosphere. The solution was stirred at -78°C for 1 hour, then a 20% sodium hydroxide solution (20 mL) was added and the mixture was allowed to warm to r.t.. Further 20% sodium hydroxide solution (50 mL) was added and the solution was extracted with Et2O (2 x 150 mL). The combined organic extracts were dried and concentrated *in vacuo* to give the title compound (5.33 g) as a crude, which was used without any further purification in the next step.

T.l.c.: CH/AcOEt 8:2, Rf=0.36.

NMR (d_6-DMSO): δ (ppm) 9.62 (s, 1H); 7.4-7.15 (m, 10H); 3.86 (d, 1H); 3.6 (d, 1H); 3.46 (s, 2H); 3.09 (bt, 1H); 2.82 (t, 1H); 2.55-2.45 (m, 2H); 2.4-2.3 (m, 3H).

Intermediate 15

Hexahydro-pyrrolo[1,2-*a*]pyrazin-6-one

Method A:

(Carbethoxymethylene)triphenylphosphorane (11.72 g) was added in two portions to a solution of intermediate **14** (4.95 g) in anhydrous toluene (100 mL) under a Nitrogen atmosphere. The mixture was heated to 80°C for 24 hours, then it was allowed to cool to r.t. and washed with water (100 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 85:15) to give ethyl 1,4-dibenzyl-2-piperazine-3-acrylate (4.2 g - T.l.c.: CH/AcOEt 8:2, Rf=0.36).

A solution of ethyl 1,4-dibenzyl-2-piperazine-3-acrylate (2.84 g) in abs. EtOH (40 mL) was hydrogenated over Pd/C 10% (1.42 g) at 3.5 atm. for 2 days. After filtration, the solution was concentrated to nearly 30 mL and heated to 70°C for 16 hours until complete cyclization occurred. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 7:3) to give the title compound (820 mg) as a pale yellow oil.

Method B:

Diisobutylaluminium hydride (1.2M in toluene – 262 mL) was dropped into a solution of ethyl 1,4-dibenzyl-piperazine-2-carboxylate (48.4g) synthesised as previously described in anhydrous toluene (450 mL) previously cooled to -78°C under a Nitrogen atmosphere (addition of DIBAL-H took 1.5 hours and the internal temperature was always maintained below -70°C). The solution was stirred at -78°C for 2 hour, then a 10% sodium hydroxide solution (500 mL) was added and the mixture was allowed to warm to r.t.. Further 10% sodium hydroxide solution (400 mL) was added and the solution was extracted with toluene (2 x 250 mL). The combined organic extracts were dried and concentrated *in vacuo* until a volume of ~100 mL containing 1,4-dibenzyl-2-piperazinecarboxaldehyde, which was used without any further purification in the next step.

(Carbethoxymethylene)triphenylphosphorane (75 g) was added in two portions to the previous solution of 1,4-dibenzyl-2-piperazine carboxaldehyde in toluene (450 mL) under a Nitrogen atmosphere. The mixture was heated to 80°C overnight, then it was allowed to cool to r.t. and washed with water (2 x 400 mL) and brine (250 mL) The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 85:15) to give ethyl 1,4-dibenzyl-2-piperazine-3-acrylate (44.8 g - T.l.c.: CH/AcOEt 8:2, Rf=0.36).

To a solution of ethyl 1,4-dibenzyl-2-piperazine-3-acrylate (44.8 g) in MeOH (450 mL) under a Nitrogen atmosphere, ammonium formate (23.2 g) and 5% palladium on charcoal

(8.96 g) were added. The resulting mixture was heated to reflux temperature for 6h. After filtration over Celite, the solution was concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 8:2) to give the title compound (14.15 g) as a pale yellow oil.

Method C:

Intermediate **17** (820 g) and toluene (1680 g) were charged in a 5 L stainless steel autoclave and palladium on charcoal (5 %, dry – 50 g) was added. The autoclave was rendered inert with nitrogen, subsequently filled with 100 bar hydrogen, and then heated to 100 °C. When the internal pressure has fallen to 90 bar, the pressure was increased to 100 bar again. After the hydrogen uptake ceased, the autoclave was cooled below 30 °C and the reaction solution was removed. The catalyst was then filtered off with a buchner funnel and washed with toluene (2 x 200 mL). After concentrating the filtrate with a rotatory evaporator, the product was distilled over a 15 cm Vigreux column (bp: 115 to 125 °C @ 0.07 mbar) giving the title compound (574 g) as a slightly yellowish oil.

T.l.c.: DCM/MeOH 7:3, Rf=0.17 (detection with ninhydrin)

NMR (CDCl3): δ (ppm) 4.01(m, 1H); 3.54 (m, 1H); 3.16 (m, 1H); 3.01 (m, 1H); 2.81 (m, 1H); 2.6 (dt, 1H); 2.38 (m, 3H); 2.16 (m, 1H); 1.6 (m, 1H).

MS (ES/+): m/z= 141 $[M+H]^+$

Intermediates 16

(8aS)-Hexahydro-pyrrolo[1,2-*a*]pyrazin-6-one (16a)

and

(8aR)-Hexahydro-pyrrolo[1,2-*a*]pyrazin-6-one (16b)

Method A:

Intermediate **15** (746 mg) was separated into the enantiomers via preparative HPLC (Column: Chiralpack AD 25 x 2 cm; mobile phase: n-hexane/EtOH 8:2; flux=1 mL/min;λ=225 nm). Thus, intermediate **16a** (330 mg) and intermediate **16b** (320 mg) were obtained.

Intermediate 16a (enantiomer 1) :

HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ; mobile phase n-hexane/EtOH 8:2; flux=1 mL/min; λ=225 nm; retention time 10.7 minutes. Ratio **16a**/**16b**=100:0.

Intermediate 16b (enantiomer 2):

HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ; mobile phase n-hexane/EtOH 8:2; flux=1 mL/min; λ=225 nm; retention time 12.8 minutes. Ratio **16a/16b**=0:100.

Intermediate 16b:

Method B:

A solution of L-(+)-mandelic acid (13.03 g) in isopropanol (60 mL) was dropped over 20 minutes into a solution of intermediate **15** (12 g) in isopropanol (60 mL) under a Nitrogen atmosphere. The suspension was stirred at 23°C for 2 hours, then it was filtered off and washed with further isopropanol (120 mL). The solid obtained (ratio enantiomers 20:80) was recrystallized three times from isopropanol (10 volumes) until a complete HPLC enantioselectivity was detected. In this way, (8aR)-hexahydro-pyrrolo[1,2-*a*]pyrazin-6-one L-(+)-mandelate (5.84 g – enantiomer 2) was obtained.

This material (6.469 g) was dissolved in EtOH (40 mL) and water (4 mL) and stirred with a suspension of resin IRA68 (112 g - previously washed with a 0.05N sodium hydroxide solution (370 mL) and water (4 L) until neutral pH) in EtOH (200 mL). The mixture was stirred at 23°C for 1.5 hours, then filtered off. The organic layer was concentrated *in vacuo* to give the title compound (3.1 g) as a white solid.

Intermediate 16b:

HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ; mobile phase n-hexane/EtOH 8:2; flux=1 mL/min; λ=225 nm; retention time 12.8 minutes. Ratio **16a/16b**=0:100.

Intermediate 16a:

Method B:

A part of the mother liquors (3.48 g with ratio **16a**:**16b**=63:37) was treated with a suspension of resin IRA68 (70 g - previously washed with a 0.05N sodium hydroxide solution (150 mL) and water until neutral pH) in EtOH (150 mL) and water (1 mL). The mixture was stirred at 23°C for 2 hours, then filtered off. The organic layer was concentrated *in vacuo* to give the free hexahydro-pyrrolo[1,2-*a*]pyrazin-6-one (1.6 g) as colourless oil. This material (1.6 g) was dissolved in isopropanol (8 mL) and treated with a solution of D-(-)-mandelic acid (1.74 g) in isopropanol (8 mL).

The suspension was stirred at 23°C for 16 hours, then it was filtered off and washed with further isopropanol (120 mL). The solid obtained (ratio enantiomers 86:14) was recrystallized three times from isopropanol (10 volumes) until a complete HPLC enantioselectivity was detected. In this way, (8aS)-hexahydro-pyrrolo[1,2-*a*]pyrazin-6-one D-(-)-mandelate (0.88 g – enantiomer 1) was obtained.

This material (0.88 g) was dissolved in EtOH (10 mL) and water (1 mL) and stirred with a suspension of resin IRA68 (15 g - previously washed with a 0.05N sodium hydroxide solution (50 mL) and water until neutral pH in EtOH (30 mL). The mixture was stirred at

23°C for 1 hour, then filtered off. The organic layer was concentrated *in vacuo* to give the title compound (0.434 g) as a white solid.

Intermediate 16a:

HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ; mobile phase n-hexane/EtOH 8:2; flux=1 mL/min; λ=225 nm; retention time 10.7 minutes. Ratio **16a**/**16b**=100:0.

Intermediate 17

3-Pyrazin-2-yl-propionic acid ethyl ester

Butyl lithium (2.5M in hexane – 2560 mL) was added within 2 hours into a 10 L flask charged with THF (3350 mL) and diisopropylamine (658 g) while the temperature was maintained at 0 – 5°C with an ice bath. The LDA solution was then precooled to –50°C and a mixture of methylpyrazine (606 g) and THF (590 mL) was added within 2 hours under vigorous stirring at –40 to –30°C. The deep red anion solution is then pumped to a cooled (-60°C) mixture of *tert*-butyl bromoacetate (1255 g) and THF (3360 mL) in a 20 L reactor. During the addition of the anion solution, the temperature in the reaction vessel did not exceed –55 °C. After the addition, the mixture is stirred for further 30 min at –55 °C and then transferred to a 30 L reactor (the transesterification and removal of solvents can be done for two runs at once). A solution of sodium ethylate (142 g) dissolved in EtOH (2200 mL) was then added to the orange mixture and about 12 L of solvents were distilled off until a temperature of 80°C was reached in the distillation head and 100°C in the boiling liquid. The mixture was cooled to approximately 30°C and then toluene (840 mL), AcOEt (840 mL), and water (1180 mL) were added. After separation of the phases, the organic layer was extracted three times with AcOEt (420 mL) and toluene (170 mL) each. The combined organic phases were then concentrated *in vacuo* and the residue was distilled over a Vigreux column (bp 115 to 130 °C @ 0.07 mbar) giving the title compound (579 g).

T.l.c.:CH/EtOAc= 1:1, Rf=0.36.

^{1}H-NMR (d_6-DMSO): δ (ppm) 8.57 (d, 1H); 8.52 (dd, 1H); 8.45 (d, 1H); 4.01 (q, 2H); 3.04 (t, 2H); 2.76 (t, 2H); 1.12 (t, 3H).

MS (ES/+): m/z= 181 $[M+H]^+$

Intermediate 18

(8aS)-Hexahydro-pyrrolo[1,2-*a*]pyrazin-6-one S-(+)-O-acetylmandelate (enantiomer 1)

A solution of (S)-(+)-O-acetylmandelic acid (2.77 g) in acetone (12 mL) was added drop-wise to a solution of intermediate **15** (4 g) in acetone (28 mL) at 20°C. The resulting mixture was seeded to initiate the precipitation.

The obtained precipitate was stirred at 20°C over 4 hours then filtered washing with acetone (12 mL). The solid was dried *in vacuo* at 40°C for 18 hours to give the title compound (3.44 g) as a white solid.

HPLC: Column Chiralpack AD 25 x 4.6 x 5µm; mobile phase n-hexane/EtOH=1:1; flow=1ml/min; λ= 210 nm; retention times title compound 5.42min., (8aR) enantiomer 6.06min. E.e.>94%.

^{1}H-NMR (d_6-DMSO): δ (ppm) 9.5 (broad, 1H); 7.42 (m, 2H); 7.32 (m, 3H); 5.62 (s, 1H); 3.79 (dd, 1H); 3.55 (m, 1H); 3.14 -3.02 (2dd, 2H); 2.80 (dt, 1H); 2.52 (dt, 1H); 2.40 (t, 1H); 2.19 (m, 2H); 2.06 (s, 3H); 2.05 (m, 1H); 1.49 (m, 1H).

MS (ES/+): m/z= 141 $[M+H-PhCH(OAc)COOH]^+$.

Representative NK1 antagonist Example 3 (ENK3)

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(R)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (Example 3a) and

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (Example 3b)

Method A:

Intermediate **12a** (168 mg) and sodium triacetoxyborohydride (127 mg) were added to a solution of intermediate **16a** (80 mg) in anhydrous acetonitrile (4 mL) under a Nitrogen atmosphere. The mixture was stirred at 23°C for 14 hours. The solution was diluted with a 5% sodium hydrogen carbonate solution (5 mL) and extracted with AcOEt (2 x 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 9:1) to give three fractions:

1. example **3a** (18 mg) a a white solid
2. mixture of example **3a** and **3b** (160 mg)
3. example **3b** (8 mg) as a white solid.

Method B:

A solution of intermediate **16a** (2.4 g) in anhydrous acetonitrile (80 mL) was added to a solution of intermediate **12a** (5.7 g) in anhydrous acetonitrile (30 mL) under a Nitrogen atmosphere. Sodium triacetoxyborohydride (4.36 g) was added in three portions every 15 minutes and the mixture was stirred at 23°C for 22 hours. The solution was diluted with

water (75 mL) and a saturated sodium hydrogen carbonate solution (25 mL) and extracted with AcOEt (2 x 200 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (CH/AcOEt/MeOH 50:50:8) to give four fractions:

1. mixture example **3a** and example **3b** (1.27 g) in ratio 1:1
2. example **3b** (1.66 g) (ratio **3a**:**3b**=13:87)
3. example **3b** (420 mg) (ratio **3a**:**3b**=5:95)
4. example **3b** (800 mg) (ratio **3a**:**3b**=2:98)

Example 3a:

T.l.c.:AcOEt/MeOH 8:2, Rf=0.55.

MS (ES/+) m/z=629 $[M+H]^+$.

HPLC: Column Supelcosil ABZ Plus 25cm x 4.6mm x 5μ; mobile phase NH_4OAc 10 mmol/CH_3CN from 60:40 to 10:90 in 5 min. then NH_4OAc 10 mmol/CH_3CN for 10 min.; flux=0.8 mL/min; λ=220 nm; retention time 9.27 minutes.

Example 3b:

T.l.c.:AcOEt/MeOH 8:2, Rf=0.48.

MS (ES/+) m/z=629 $[M+H]^+$.

HPLC: Column Supelcosil ABZ Plus 25cm x 4.6mm x 5μ; mobile phase NH_4OAc 10 mmol/CH_3CN from 60:40 to 10:90 in 5 min. then NH_4OAc 10 mmol/CH_3CN for 10 min.; flux=0.8 mL/min; λ=220 nm; retention time 8.84 minutes.

Representative NK1 antagonist Example 4 (ENK4)

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride

A solution of example **3b** (8 mg) in dry Et2O (1 mL) was treated with hydrochloric acid (1M in Et2O – 14 μL) at 0°C under a Nitrogen atmosphere. The resulting mixture was stirred at 0°C for 20 minutes, then the mixture was concentrated *in vacuo*. The precipitate was washed with pentane (2 mL) to give the title compound as a white solid (7.6 mg).

NMR (d_6-DMSO): δ (ppm) 10.22 (bs, 1H); 7.99 (s, 1H); 7.67 (s, 2H); 7.22 (dd, 1H); 6.94 (dd, 1H); 6.81 (t, 1H); 5.31 (q, 1H); 4.2 (dd, 1H); 4.0-3.86 (bm, 2H); 3.6-3.4 (m, 2H); 3.1-2.7 (m, 4H); 2.73 (s, 3H); 2.4-2.0 (m, 5H); 2.35 (s, 3H); 1.94 (m, 1H); 1.74 (q, 1H); 1.57 (d, 3H); 1.46 (d, 3H).

MS (ES/+) m/z=629 $[M+H-HCl]^+$.

HPLC: Column Supelcosil ABZ Plus 25cm x 4.6mm x 5μ, mobile phase NH_4OAc 10 mmol/CH_3CN from 60:40 to 10:90 in 5 min. then NH_4OAc 10 mmol/CH_3CN from 10:90 for 10 min.; flux=0.8 mL/min; λ=220 nm; retention time 8.86 minutes.

Column X-Terra 4.6 x 100mm, RP18 3.5μm; mobile phase: eluant A: NH_4HCO_3 5mM (pH=8)/CH_3CN 90/10 - eluant B: NH_4HCO_3 5mM (pH=8)/ CH_3CN 10/90 - Gradient: from 50% B to 100% B in 7.5min; 100% B for 0.5min then 50% B for 3min.; column temp.: 40°C; flow= 1mL/min; λ= 210 nm; retention time 4.15 minutes.

Representative NK1 antagonist Example 4a (ENK4a)

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride as anhydrous crystalline form

A 2% sodium hydroxide solution (100 mL) was added to a suspension of example **5** (10 g) in AcOEt (150 mL). Then the two phases mixture were stirred for 10 minutes and the layers were separated. The organic phase was washed with water (100 mL) and then concentrated *in vacuo* up to 40 mL. AcOEt (100 mL) was added to the organic phase, which was then concentrated *in vacuo* a second time up to 40 mL. The solution was further diluted with AcOEt (60 mL) and 5-6N hydrochloric acid in isopropanol (3 mL) was added. After 5 minutes the clear solution was seeded. Precipitation occurred in a few minutes and after further 20 minutes stirring, n-heptane (100 mL) was added in 10-15 minutes. The obtained mixture was stirred 2 hours at 20°C.The solid was then filtered, washed with AOEt/n-heptane 1/1 (60 mL) and dried *in vacuo* at 40°C for 16 hours to give the title compound (8.08 g) as a white solid.

X ray podwer diffraction data are reported in table 6

Table 6

The X-ray podwer diffraction pattern of the product of the Example **4a** in terms of d spacing is as follows

Angle(°2 Theta)	d value(A)
3,412	25,87492
6,87	12,85613
9,867	8,95664
12,877	6,86899
14,274	6,19974
15,4	5,74895

16,732	5,29424
17,323	5,11486
17,966	4,93311
18,521	4,78656
19,557	4,53525
22,12	4,01529
22,382	3,96884
24,311	3,65818
27,117	3,28566
27,836	3,20239
28,374	3,14292
28,846	3,0925
29,372	3,03835
33,9	2,64214

Representative NK1 antagonist Example 4b (ENK4b)

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride as dihydrate crystalline form

To a 265 mg of example **4a** , 3 ml of water was added. The suspension was stirred overnight at 25°C and then centrifuged for 5 min at 10000 rpm. The solid was filtered using a centrifugal filter device (Millipore Ultrafree-MC 0.45µm) to obtain the title compound (250mg)

X ray podwer diffraction data are reported in table 7

Table 7

The X-ray podwer diffraction pattern of the product of the Example **4b** in terms of d spacing is as follows

Angle(°2-Theta)	d value(A)
3,233	27,30972
6,353	13,90157
12,14	7,28437
12,647	6,99378
13,282	6,6605

13,5	6,55347
15,48	5,71928
16,324	5,42557
16,779	5,27951
17,825	4,97188
19,022	4,66158
19,414	4,5685
19,901	4,45772
21,339	4,1605
21,915	4,05245
22,21	3,99923
23,161	3,83714
23,521	3,77915
24,179	3,67782
25,417	3,50136
26	3,42415
26,668	3,33994
28,052	3,17821
28,553	3,1236
29,551	3,0203
31,297	2,85568
32,8	2,72816
34,148	2,62353

Representative NK1 antagonist Example 5 (ENK5)

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide maleate

Method A:

Intermediate **18** (25 g) was suspended in acetonitrile (300 mL), then TEA (10.4 mL) was quickly added in order to obtain the free base: the aspect of the slurry did not change as a new precipitate of TEA-acetylmandelate salt was formed. The mixture was kept under stirring for 15-20 minutes. Meanwhile intermediate **12a** (25 g) was dissolved in acetonitrile (125 mL) and the so-obtained solution was quickly added to the slurry. Then Sodium triacetoxyborohydride (15 g) was added all at once and the mixture was kept under

stirring conditions for 22 hours. The white precipitate was filtered off and the mother liquors were evaporated to 100 mL. AcOEt (250 mL) was added to the so-obtained mixture and the resulting solution was washed with aqueous 4% sodium hydrogen carbonate solution (2 x 125 mL) and then with 5% sodium chloride solution (125 mL). The organic layer dried and evaporated to 100 mL. Isopropyl alcohol (150 ml) was added and the mixture was evaporated again to 100 mL. This operation was repeated. The final volume of the mixture was adjusted to 200 mL adding further isopropyl alcohol (100 mL). A solution of maleic acid (5.8 g) in isopropyl alcohol (50 mL) was dropped in ca. 10 minutes. The mixture was seeded and precipitation occurred in few minutes. The slurry was stirred 1 hour at 20°C and isoctane (250 mL) was added in 10 minutes. The resulting suspension was stirred at room temperature for 22 hours. The solid was filtered and washed with isopropanol/isoctane 1/1 (150 mL) and dried *in vacuo* at 40°C for 18 hours giving the title compound (13.75g) as a white solid.

Method B:

Intermediate **18** (1 g) was suspended in acetonitrile (12 mL), then TEA (0.415 mL) was quickly added in order to obtain the free base: the aspect of the slurry did not change as a new precipitate of TEA-acetylmandelate salt was formed. After 30minutes of stirring, the mixture was treated with sodium triacetoxyborohydride (0.6 g) plus formic acid (0.224 mL).

Meanwhile intermediate **12a** (1 g) was dissolved in acetonitrile (6 mL) and the so-obtained solution was quickly added to the slurry and the resulting mixture was kept under stirring conditions for 18 hours. The slurry was evaporated to small volume. AcOEt (10 mL) was added to the so-obtained mixture and the resulting solution was washed with aqueous 4% sodium hydrogen carbonate (2 x 5 mL) and then with 5% sodium chloride solution (5 mL). The organic layer was dried and evaporated to a white foam.

Isopropyl alcohol (10 mL) was added and the mixture was evaporated again to dryness. The resulting foam was, once again, dissolved in isopropyl alcohol (8 mL) and treated drop-wise with a solution of maleic acid (0.232 g) in isopropyl alcohol (2 mL). After 30 minutes the mixture was seeded and precipitation occurred in a few minutes. The slurry was stirred 1 hour at 20°C and then isoctane (10 mL) was added dropwise over 5-10 minutes. The resulting suspension was stirred at room temperature for 19 hours. The solid was filtered and washed with isopropanol/isoctane 1/1 (5 mL) and dried *in vacuo* at 40°C for 18 hours giving the title compound (0.639 g) as a white solid.

HPLC: Column X-Terra 4.6 x 100mm, RP18 3.5µm; mobile phase: eluant A: NH_4HCO_3 5mM (pH=8)/CH_3CN 90/10 - eluant B: NH_4HCO_3 5mM (pH=8)/CH_3CN 10/90 - Gradient:

from 50% B to 100% B in 7.5 minutes; 100% B for 0.5 minutes then 50% B for 3 minutes; column temp. 40°C; flow= 1mL/min; λ= 210 nm; retention times 4.15 minutes, >99%a/a.

^{1}H-NMR (d_6-DMSO): δ (ppm) 7.98 (bs, 1H); 7.68 (bs, 2H); 7.21 (dd, 1H); 6.93 (dd, 1H); 6.81 (dt, 1H); 6.09 (s, 2H); 5.31 (q, 1H); 4.19 (dd, 1H); 3.93 (m, 1H); 3.74 (bm, 1H); 3.46 (m, 1H); 3.45 (bm, 1H); 3.30 (bm, 2H); 2.93 (bt, 1H); 2.79 (t, 1H); 2.73 (s, 3H); 2.73 (bm, 1H); 2.60 (bm, 1H); 2.35 (s, 3H); 2.23 (m, 2H); 2.12 (m, 1H); 2.04 (bd, 1H); 1.98 (bd, 1H); 1.84 (m, 1H); 1.64 (q, 1H); 1.56 (m, 1H); 1.46 (d, 3H).

MS (ES/+): m/z= 629 $[MH\text{-}HOOCCHCHCOOH]^+$

Intermediate 19

[2S]-Phenyl-piperidin-[3S]-ylamine

[2S]-Phenyl-piperidin-[3S]-ylamine [2S,3S]-bis(4-methyl-benzoyloxy)-succinic acid salt (1:1) (6.9g) was taken up in concentrated 0.880 aqueous ammonia solution (100ml) and shaken for a few minutes. The basic solution was extracted with chloroform (3x150ml) , dried (Na_2SO_4), and concentrated *in vacuo* to give [2S]-phenyl-piperidin-[3S]-ylamine (1.85g) as a colourless oil.

$[\alpha]^{20}_D$ (HCl salt) = +65.48° (C=0.006 g/ml)

^{1}H NMR (HCl salt, D_2O) δ 2.05 (m, 2H), 2.30 (m, 2H), 3.36 (m, 1H), 3.74 (m, 1H), 4.16 (q, 1H, J=4Hz), 4.99 (d, 1H, J=4Hz), 7.45 (m, 2H), 7.59 (m, 3H).

A small sample of the free base (50mg) was derivatized as its trifluoroacetyl analogue for chiral HPLC analysis. The sample was dissolved in acetonitrile (4ml) and treated with 1-(trifluoroacetyl)imidazole (0.4ml). The solution was stirred at 65° for 1h, concentrated *in vacuo* and the residue dissolved in dichloromethane (5ml). The organic layer was washed with dilute sulphuric acid(2ml), then the organic layer concentrated and disssolved in hexane-isoproplyalcohol (98:2) for injection onto the HPLC column.

Chiral HPLC (Chiracel-OD-H column, lot no. 09-02-20709, eluent hexane-isopropylalcohol 98:2, flow rate 1ml/min, detection uv 230nm, temperature 40°) retention time 12.93 mins.

Intermediate 20

2-Hydroxy-5-tetrazol-1-yl-benzaldehyde

A solution of 4-tetrazol-1-yl-phenol (0.01mol) in trifluoroacetic acid (20ml) and hexamethylenetetramine (0.04mol) was heated at 70° for 18h, cooled to room temperature and quenched with 2N solution of sulfuric acid (50ml). The mixture was extracted with ethyl acetate (3x100ml), dried ($MgSO_4$), filtered and concentrated to give a

residue which was purified by FCC (dichloromethane/methanol (9:1)) to afford the title compound in 30% yield.
T.l.c. (dichlormethane/methanol (9:1)) Rf 0.6

Intermediate 21 was prepared through a similar procedure to that described for Intermediate 20:

Intermediate 21
2-Hydroxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzaldehyde
From 4-(5-trifluoromethyl-tetrazol-1-yl)-phenol (45mmol) to give the title compound (8.8g) as a pale yellow solid.
T.l.c. (Hexane/ether (2:1)) Rf 0.36

Intermediate 22
2-Methoxy-5-tetrazol-1-yl-benzaldehyde
To a solution of 2-hydroxy-5-tetrazol-1-yl-benzaldehyde (2.63mmol) in dimethylformamide (5ml) was added potassium carbonate (3.95mmol) and iodomethane (3.95mmol) and the mixture was stirred under nitrogen atmosphere for 2h. The mixture was poured into water (100ml) and the white solid formed filtered to afford the title compound in a 67% yield.
T.l.c. (ether) Rf 0.45

Intermediate 23 was prepared through a similar procedure to that described for Intermediate 22:

Intermediate 23
2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzaldehyde
From 2-hydroxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzaldehyde (1.56mmol) to give the title compound as a yellow solid (0.48g).
T.l.c. (ether/hexane (2:1)) Rf 0.38.

Representative NK1 antagonist Example 6 (ENK6)
[2-Methoxy-5-(5-trifuoromethyl-tetrazol-1-yl)-benzyl]-([2S,3S]-2-phenyl-piperidin-3-yl)-amine dihydrochloride
A mixture of [2S]-phenyl-piperidin-[3S]-ylamine (1.14mmol), 2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzaldehyde (1.2mmol), sodium triacetoxyborohydride (2.37mmol) and acetic acid (3 drops) in dichloromethane (25ml) was stirred at 23° under

nitrogen for 64h. 2N sodium carbonate solution (50ml) was added and the mixture extracted with dichloromethane (3x25ml). The combined extracts were washed with saturated brine (50ml), dried ($MgSO_4$) and evaporated. Purification by FCC with dichloromethane/ethanol/ammonia (400:10:1 → 100:10:1) gave a colourless viscous oil. This was dissolved in methanol (10ml) and treated with 2N ethereal hydrogen chloride (~10ml). Evaporation in vacuo and trituration with i-propyl acetate gave the title compound as a white solid (210mg).

T.l.c. (Dichloromethane/ethanol/ammonia (200:10:1)) Rf 0.39

Optical Rotation (c O.OO3g/ml. water) +50.35°.

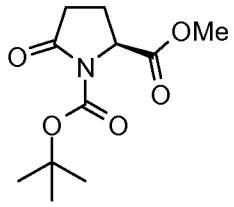
Representative Na Channel blocker Example 7 (ENa7)

3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine is disclosed in US 4,602,017 and EP0021121. Products comprising lamotrigine are marketed under the trade name LAMICTAL™ by the GlaxoSmithKline group of companies.

Intermediate 24

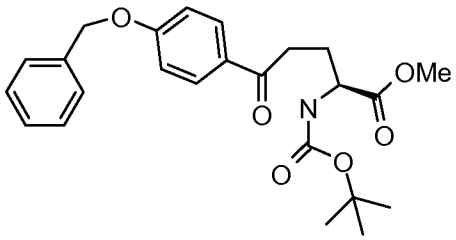
1-(1,1-dimethylethyl) 2-methyl (2*S*)-5-oxo-1,2-pyrrolidinedicarboxylate



To a solution of commercially available methyl 5-oxo-L-prolinate (20g, 140mmol) in DCM (200ml) were added triethylamine (19.6ml, 140mmol), DMAP(17.2g, 140mmol) and then dropwise a solution of BOC_2O (61g, 280mmol) in DCM (100ml). The resulting red mixture was stirred at room temperature for 2 hours. Then the solvent was removed under reduced pressure and the crude material was purified by chromatography on silica gel eluting with cyclohexane / ethyl acetate (7:3 to 4:6) to afford (after a trituration in hexane / diethylether 1:1) the title compound as a white solid (32.4g, 96%); R_f (cyclohexanes:ethyl acetate = 65:35): 0.21; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 4.62 (dd, 1H), 3.78 (s, 3H), 2.68-2.58 (m, 1H), 2.52-2.45 (m, 1H), 2.37-2.27 (m, 1H), 2.08-1.97 (m, 1H), 1.48 (s, 9H).

Intermediate 25

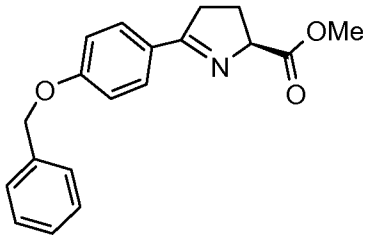
methyl (2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-5-oxo-5-{4-[(phenylmethyl)oxy]phenyl}pentanoate



n-Butyl lithium 1.6M solution in hexanes (0.88ml, 1.4mmol) was added dropwise to a solution of commercially available 1-bromo-4-[(phenylmethyl)oxy]benzene (390mg, 1.48mmol) in dry THF (2ml) at -78°C under nitrogen atmosphere. The resulting suspension was stirred at -78°C for 40 minutes and then it was added dropwise to a solution of 1-(1,1-dimethylethyl) 2-methyl (2*S*)-5-oxo-1,2-pyrrolidinedicarboxylate (300mg, 1.23mmol) in dry THF (2.4ml) previously cooled to -78°C. The mixture was stirred at -78°C for 40 minutes and at -40°C for 1h, then it was quenched at -40°C with an aqueous saturated ammonium chloride solution. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was then washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give the crude material, which was purified by chromatography on silica gel eluting with cyclohexane / ethylacetate (95:5), thus affording the title compound as a white solid (170mg, 32%); R_f (cyclohexane:ethyl acetate = 8:2): 0.30; ^{1}HNMR (300 MHz, $CDCl_3$) δ(ppm): 7.95 (d, 2H), 7.50-7.33 (m, 5H), 7.03 (d, 2H), 5.20 (bs, 1H), 5.15 (s, 2H), 4.45-4.35 (m, 1H), 3.78 (s, 3H), 3.15-2.95 (m, 2H), 2.36-2.26 (m, 1H), 2.16-2.02 (m, 1H), 1.45 (s, 9H).

Intermediate 26:

methyl (2*S*)-5-{4-[(phenylmethyl)oxy]phenyl}-3,4-dihydro-2*H*-pyrrole-2-carboxylate

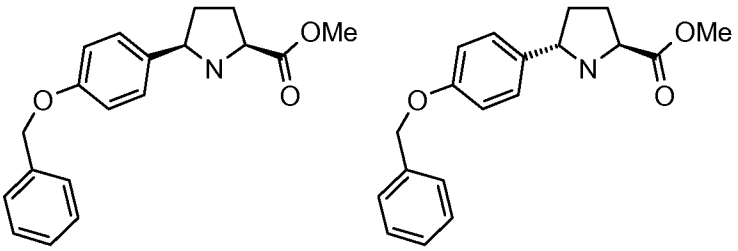


To a solution of methyl (2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-5-oxo-5-{4-[(phenylmethyl)oxy]phenyl}pentanoate (323mg, 0.75mmol) in dry DCM (4ml) at 0°C, under nitrogen atmosphere was added trifluoroacetic acid (1ml) dropwise. The resulting pale pink solution was allowed to warm to room temperature over 1 hour, then it was evaporated under reduced pressure, affording the title compound (D7, 291mg, 0.68mmol,

91%) as a greenish oil which may be used in the next step without any further purification; R_t (HPLC): 3.69min; MS: (ES/+) m/z: 310 [MH^+], C19H19NO3 requires 309.

Intermediate 27: methyl (5*R*)-5-{4-[(phenylmethyl)oxy]phenyl}-L-prolinate (I27)

Intermediate 28: methyl (5S)-5-{4-[(phenylmethyl)oxy]phenyl}-L-prolinate (I28)



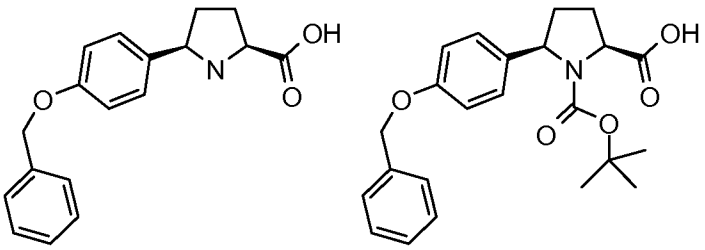
To a solution of methyl (2*S*)-5-{4-[(phenylmethyl)oxy]phenyl}-3,4-dihydro-2*H*-pyrrole-2-carboxylate (13.7g, 32.4mmol) in MeOH (200ml) was added PtO_2 (240mg) and the mixture was stirred under a hydrogen atmosphere (2 atmos) for 6 hours. Then the catalyst was filtered off and the solvent removed under reduced pressure to give a red oil which was dissolved in ethyl acetate and washed with $NaHCO_3$ solution. The resulting crude material was purified by chromatography on silica gel eluting with cyclohexane / ethyl acetate (9:1 to 8:2) to afford the title compounds:

I27, 4.15g, 13.3mmol, Y=41%. MS: (ES/+) m/z: 312 [MH^+]. C19H21NO3 requires 311. Rt (HPLC): 3.80min. Rf (cyclohexane:ethyl acetate = 7:3): 0.18. ^{1}HNMR (300 MHz, $CDCl_3$) δ(ppm): 7.40 (d, 2H); 7.35 (t, 2H); 7.33 (d, 2H); 7.29 (t, 1H); 6.93 (d, 2H); 5.03 (s, 2H); 4.23 (dd, 1H); 4.00 (dd, 1H); 3.71-3.79 (m, 3H); 2.18-2.30 (m, 1H); 2.09-2.18 (m, 2H); 1.67-1.78 (m, 1H). NOE between the proton at C2 and the proton at C5 could be observed.

I28, 0.6g, 1.9mmol, Y=6%. MS: (ES/+) m/z: 312 [MH^+]. C19H21NO3 requires 311; Rt (HPLC): 3.73min. Rf (cyclohexane:ethyl acetate = 7:3): 0.32. ^{1}HNMR (300 MHz, $CDCl_3$) δ(ppm): 7.40 (d, 2H); 7.35 (t, 2H); 7.29 (d, 2H); 7.28 (t, 1H); 6.91 (d, 2H); 4.97-5.07 (m, 2H); 4.29 (dd, 1H); 4.09 (dd, 1H); 3.71-3.75 (m, 3H); 2.29-2.42 (m, 1H); 2.09-2.20 (m, 1H); 1.90-2.02 (m, 1H); 1.69-1.82 (m, 1H). NOE between the proton at C2 and the proton at C5 was not observed.

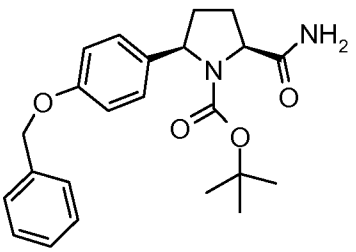
Intermediate 29: (5*R*)-5-{4-[(phenylmethyl)oxy]phenyl}-L-proline (I29):

Intermediate 30: (5*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-5-{4-[(phenylmethyl)oxy]phenyl}-L-proline (I30):



To a solution of methyl (5*R*)-5-{4-[(phenylmethyl)oxy]phenyl}-L-prolinate (120mg, 0.38mmol) in THF (2.3ml) was added LiOH monohydrate (26mg, 0.61mmol) dissolved in water (1.1ml), followed by methanol (1.1ml). The resulting solution was stirred at room temperature for 2.5 hours, then left overnight at -18° C.Then the organic solvent was evaporated under reduced pressure maintaining the temperature at 38°C and the aqueous residue containing the acid intermediate (I28, Rt (HPLC) = 3.63min. MS: (ES/+) m/z: 298 [MH^+]. C18H19NO3 requires 297) was treated with BOC_2O (168mg, 0.77mmol) dissolved in THF (1.1ml). The reaction mixture was stirred at room temperature for 3.5 hours. The organic solvent was evaporated and the basic aqueous solution was acidified at 0°C with aqueous 1N HCl solution to pH=3, this acidic aqueous solution was extracted with ethyl acetate (2x10ml). The organic phase dried over Na_2SO_4 and evaporated under reduced pressure gave a solid, which was titurated in n-hexanes (3x6ml) affording the title compound as a white powder (I29, 137mg, 90% for two steps); Rt (HPLC): 5.81min; Rf (cyclohexane:ethyl acetate = 1:1): 0.34; MS: (ES/+) m/z: 420 [$M+Na^+$] C23H27NO5 requires 397; MS: (ES/-) m/z: 396 [M-H] C23H27NO5 requires 397; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.5-7.3 (m, 5H), 7.10 (bm, 2H), 6.90 (d, 2H), 5.08 (s, 2H), 4.65 (bm, 1H), 4.50 (bm, 1H), 2.58 (bm, 1H), 2.31 (bm, 1H), 2.11-1.90 (m, 2H), 1.16 (s, 9H).

Intermediate 31:
1,1-dimethylethyl (2*S*,5*R*)-2-(aminocarbonyl)-5-{4-[(phenylmethyl)oxy]phenyl}-1-pyrrolidinecarboxylate

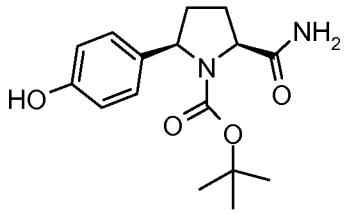


To a solution of (5*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-5-{4-[(phenylmethyl)oxy]phenyl}-L-proline (1.44g, 3.62mmol) in dry DMF (20ml) were added DIPEA (1.26ml, 7.24mmol),

then TBTU (1.23g, 3.98mmol) and after 20 minutes, 1,1,1,3,3,3-hexamethyldisilazane (1.15ml, 5.43mmol). The reaction mixture was stirred at room temperature for 2h, then it was treated with aqueous 5% $NaHCO_3$ solution (30ml) and stirred for further 30 minutes. The resulting mixture was diluted with water and extracted with ethyl acetate. The organic phase was then washed twice with brine/ice, dried over Na_2SO_4 and evaporated to give a colourless oil. This crude material was purified by chromatography on silica gel eluting with cyclohexane / ethyl acetate (7:3 to 5:5) to afford the title compound (1.25g, 87%); R_t (HPLC): 5.51min; R_f (cyclohexane:ethyl acetate = 1:1): 0.29. MS: (ES/+) m/z: 419 [M+Na^+]; C23H28N2O4 requires 396.

Intermediate 32:

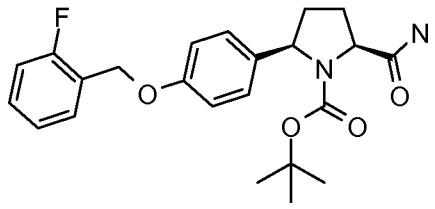
1,1-dimethylethyl (2*S*,5*R*)-2-(aminocarbonyl)-5-(4-hydroxyphenyl)-1-pyrrolidinecarboxylate



To a solution of 1,1-dimethylethyl (2*S*,5*R*)-2-(aminocarbonyl)-5-{4-[(phenylmethyl)oxy]phenyl}-1-pyrrolidinecarboxylate (1.2g, 3.02mmol) in methanol (25ml) was added Pd/C 10% wt (210mg) and the mixture was stirred under hydrogen (1 atm) for 6 hours. The catalyst was filtered off and the solvent removed under reduced pressure to give the title compound as a white solid (870mg, 94%); R_t (HPLC): 3.61min; R_f (cyclohexane:ethyl acetate = 1:1): 0.18; MS: (ES/+) m/z: 329 [M+Na^+]. C16H22N2O4 requires 306; ^{1}H NMR (300 MHz, d_6-DMSO) δ ppm : 9.15 (bs, 1H); 7.40 (bm, 2H); 7.30 (s, 1H); 6.90 (s, 1H); 6.65 (d, 2H); 4.50-4.80 (m, 1H); 4.05-4.28 (m, 1H); 2.07-2.24 (m, 1H); 1.95-2.07 (m, 1H); 1.60-1.89 (m, 2H); 1.00-1.45 (m, 9H).

Intermediate 33:

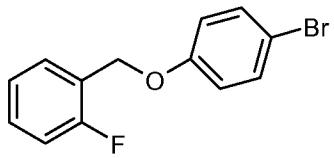
1,1-dimethylethyl (2S,5R)-2-(aminocarbonyl)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1-pyrrolidinecarboxylate



1-(Bromomethyl)-2-fluorobenzene (30µl, 0.220mmol) was added to a solution of 1,1-dimethylethyl (2S,5R)-2-(aminocarbonyl)-5-(4-hydroxyphenyl)-1-pyrrolidinecarboxylate (45mg, 0.146mmol) and potassium carbonate (30mg, 0.217mmol) in acetonitrile (2ml). The mixture was stirred overnight at room temperature. After the reaction was finished, as shown by TLC, ethyl acetate and water were added. The organic phase was then washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude material was purified by chromatography on silica gel using cyclohexane / ethyl acetate (7:3 to 6:4) to afford the title compound (51mg, 85%); Rt (HPLC): 5.56 min; Rf (cyclohexane:ethyl acetate = 1:1): 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.56-7.48 (m, 1H); 7.37-7.28 (m, 1H); 7.24-7.06 (m, 5H); 6.93 (d, 2H); 5.45-5.37 (br. s, 1H); 5.15 (s, 2H); 4.73-4.60 (m, 1H); 4.53-4.45 (m, 1H); 2.58-2.48 (m, 1H); 2.34-2.25 (m, 1H); 2.09-1.93 (m, 2H); 1.28-1.13 (br. s, 9H).

Intermediate 34:

1-[(4-bromophenoxy)methyl]-2-fluorobenzene



Procedure 1: To a solution of 4-bromophenol (502.08g) dissolved in acetone (7322mL) was added K_2CO_3 (570g) and then benzylbromide (523g). The mixture was heated under reflux for 2hrs. The reaction mixture was then cooled at 25°C, filtered and the filter cake was washed with MTBE (1046mL). The combined filtrate was concentrated to 1000mL and MTBE (4184mL) were added. The mixture was washed with an aqueous 1M NaOH solution (1464mL), then with brine (1300mL) and the organic phase was concentrated to dryness. THF (1300mL) was added and the solvent was removed under reduced pressure to afford the title compound (902.1g); ^{1}H NMR (400 MHz, DMSO-d6) δ(ppm): 7.54 (td, 1H); 7.46 (d, 2H); 7.42 (m, 1H); 7.23 (m, 2H); 7.01 (d, 2H); 5.13 (s, 2H).

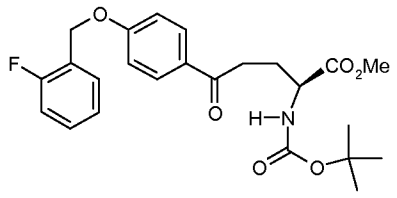
Procedure 2: A stirred mixture of 4-bromophenol (19.22g, 111mmol), orthofluorobenzyl bromide (20g, 105.8mmol) and potassium carbonate (21.9g, 158.4mmol) in acetone

(280ml) was heated at reflux for 6 hours. The reaction mixture was cooled to room temperature and filtered, washing the solid with TBME (40ml). The combined filtrate and washings were concentrated under vacuum to a final volume of about 40ml. The resulting solution was diluted with TBME (160ml) and washed with 1M sodium hydroxide and brine, then concentrated under vacuum to an oil which slowly solidified to give the title compound (28.9g).

1H NMR (300 MHz, CHCl3-*d*). δ(ppm): 5.10 (s, 2H) , 6.86 (m, 2H) , 7.10 (m, 1H) , 7.17 (m, 1H) , 7.29 (m, 1H) , 7.35 (m, 2H) , 7.38 (m, 1H) .

Intermediate 35:

methyl (2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-5-oxopentanoate



Procedure 1: To a stirred suspension of magnesium metal (90g) in dry THF (600mL) under a nitrogen atmosphere at room temperature was added iodine (0.3g). The mixture was heated to an internal temperature of 64 +/- 2°C. A solution of 1-[(4-bromophenoxy)methyl]-2-fluorobenzene (693g) in THF (1500mL) was added in two batches. Firstly 45 mL was added. Secondly, the remaining solution (1455 mL) was added dropwise. After addition, the reaction was heated at reflux for 1h. The reaction mixture was cooled to room temperature. This reaction mixture was then added slowly to a solution of commercially available 1-*tert*-butyl 2-methyl (2*S*)-5-oxopyrrolidine-1,2-dicarboxylate (300g) in THF (1500mL) cooled to -60°C, maintaining the internal temperature below -60°C. The addition was completed in 2 hours. The reaction mixture was stirred for a further 15 minutes after addition. Isopropyl alcohol (300mL) was then added dropwise whilst maintaining the temperature below -60°C. A mixture of aqueous saturated ammonium chloride solution/aqueous saturated sodium chloride solution (2/1; 900mL) was added whilst maintaining the temperature at -50°C. Water (600 mL) was added to dissolve the yellow precipitate. The organic phase was separated and was washed with aqueous 13% NaCl solution (600mL). The organic phase was concentrated to dryness. EtOAc (1500mL) was then added and the solution was evaporated under reduced pressure to remove water. The residue was purified by chromatography on silica

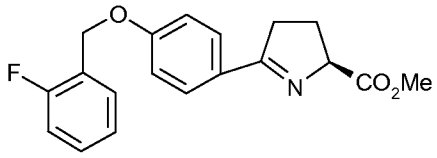
gel eluting with cyclohexane / ethyl acetate (90:10 to 8:2) to afford the title compound (287 g); ^{1}H NMR (600 MHz, DMSO-d6) δ(ppm): 7.93 (d, 2H); 7.57 (td, 1H); 7.44 (m, 1H); 7.27 (m, 3H); 7.14 (d, 2H); 5.24 (s, 2H); 4.04 (m, 1H); 3.61 (s, 3H); 3.03 (m, 2H); 1.94 (m, 2H); 1.38 (s, 9H).

Procedure 2: To a mixture of magnesium turnings (12.79g. 533mol), a trace of iodine and 1,2-dibromoethane in THF (86.ml)at 70-75°C, a solution of (4-bromophenyl (2-fluorophenyl)methyl ether) (100g, 355.6mmol) in THF (216.25ml) was added over about 2 hours. The mixture was heated for a further 2 hours at 70-75°C then cooled to room temperature to give a solution of the Grignard reagent. A solution of 1-(1,1-dimethylethyl) 2-methyl (2*S*)-5-oxo-1,2-pyrrolidinedicarboxylate (43.25g, 177.8mmol) in THF (216.25ml) was cooled to -60°C and the solution of the Grignard reagent was added over 1 hour, then the mixture was stirred for 3 hours at -60°C. Isopropanol (43.25ml) was added dropwise, followed by saturated aqueous ammonium chloride (86.5ml) and brine (43.25ml), then the mixture warmed to room temperature. Water (173ml) and 50% acetic acid (50ml) to pH 6-7, followed by ethyl acetate (129.7ml). The layers were separated and the aqueous extracted with ethyl acetate (2 x 129.7ml). The combined organic layers were washed with brine then concentrated under vacuum. The residue was stirred with hexane (216.2ml), then the solid was filtered and washed with hexane. To the resulting solid, isopropanol (432.5ml) was added and the mixture stirred at 45°C for 15 minutes, then cooled to 5-10°C and stirred for 2 hours. The solid was filtered, washed with isopropanol and dried to give the title compound as a solid.

1H NMR (300 MHz, CHCl3-*d*): δ(ppm): 1.42 (s, 9H); 2.04 (m, 1H); 2.28 (m, 1H); 3.03 (m, 2H); 3.74 (s, 3H); 4.37 (m, 1H); 5.19 (b, 1H); 5.20 (s, 2H); 7.02 (d, 2H); 7.11 (t, 1H); 7.17 (t, 1H); 7.33 (m, 1H); 7.48 (t, 1H); 7.94 (d, 2H).

Intermediate 36:

methyl (2*S*)-5-{4-[(2-fluorobenzyl)oxy]phenyl}-3,4-dihydro-2*H*-pyrrole-2-carboxylate



Procedure 1: To a solution of methyl (2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-5-oxopentanoate (243g) in dry DCM (2430mL) at 0°C was added TFA (461mL) dropwise. The mixture was allowed to warm to room

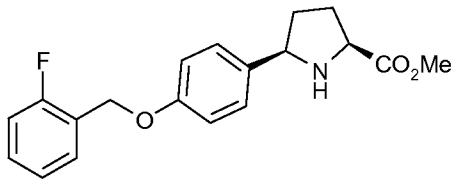
temperature and stirred for 3hrs. Solvent and the excess TFA were removed under vacuum and the resulting dark oil was stripped with EtOAc (2 x 1215mL) and left overnight under a high vacuum. The title compound (392 g) was obtained as a red oil and used in the following step without any further purification; ^{1}H NMR (400 MHz, DMSO-d6) δ(ppm): 8.16 (m, 2H); 7.60 (td, 1H); 7.46 (m, 1H); 7.34 (m, 2H); 7.27 (m, 2H); 5.32 (s, 2H); 5.25 (m, 1H); 3.77 (s, 3H); 3.57 (m, 2H); 2.60 (m, 1H); 2.34 (m, 1H).

Procedure 2: A solution of methyl (2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-5-oxopentanoate (46g, 103mmol) in DCM (437ml) was treated dropwise with trifluoroacetic acid (87.4ml) at 0-5°C, then warmed to room temperature and stirred for 3 hours. The solution was cooled to 0-5°C and sodium hydroxide solution added to a final pH of about 7. The aqueous layer was separated and extracted with DCM (13ml), then the combined organic layers were washed with water, dried over sodium sulphate, then concentrated under vacuum to give the title compound as a solid (33.3g).

1H NMR (300 MHz, CHCl3-*d*): δ(ppm): 2.35 (m, 2H); 2.95 (m, 1H); 3.12 (m, 1H); 3.78 (s, 3H); 4.89 (dd, 1H); 5.18 (s, 2H); 7.00 (d, 2H); 7.10 (m, 1H) ; 7.16 (m, 1H) ; 7.29 (m, 1H) ; 7.5 (t, 1H) ; 7.85 (d, 2H) .

Intermediate 37:

Methyl (5*R*)-5-{4-[(2-fluorobenzyl)oxy]phenyl}-L-prolinate



Procedure 1: Methyl (2*S*)-5-{4-[(2-fluorobenzyl)oxy]phenyl}-3,4-dihydro-2*H*-pyrrole-2-carboxylate (392g) was dissolved in EtOAc (3160mL) in a hydrogenation reactor. 5% platinum on carbon (Engelhard code 44379, moisture content *ca.* 50%, 15.8g) was added, the reactor filled with hydrogen gas to a pressure of 2atm and the reaction mixture was stirred for approximately 1.5 hours. The reactor was depressurised and the spent catalyst filtered through Celite, washing through with EtOAc (2 x 500mL, then further 200mL). Aqueous saturated $NaHCO_3$ solution (600 mL) was added to the filtrate, followed by aqueous 13% w/w Na_2CO_3 solution (up to pH = 9, 1000mL). The mixture was stirred for 10 minutes and phases were then allowed to separate .The aqueous phase was removed

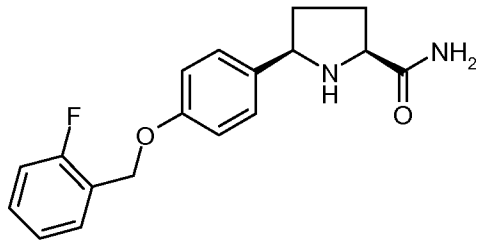
and then the organic layer was washed once with brine (600mL). The resulting solution was concentrated to dryness and the residue was purified by flash chromatography eluting with cyclohexane / ethyl acetate (1:1) to afford the title compound (133 g); ^{1}H NMR (600 MHz, DMSO-d6) δ(ppm): 7.55 (dt, 1H); 7.41 (m, 1H); 7.34 (m, 2H); 7.23 (m, 2H); 6.97 (m, 2H); 5.12 (s, 2H); 4.09 (dd, 1H); 3.83 (dd, 1H); 3.66 (s, 3H); 2.97 (bs, 1H); 2.04 (m, 2H); 1.94 (m, 1H); 1.52 (m, 1H).

Procedure 2: A solution of methyl (2*S*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate (34g, 103.5mmol) in ethyl acetate (272ml) was placed in an autoclave and treated with trifluoroacetic acid (7.2ml). 5% Platinum on carbon catalyst (1.7g) was transferred as a slurry with ethyl acetate (68ml) and the reaction was stirred at room temperature under 50 psi hydrogen pressure for 5 hours. The mixture was filtered through Hyflo, washing with ethyl acetate (272ml), then the filtrate was washed with aq sodium carbonate solution and brine, dried over sodium sulphate, then concentrated under vacuum, and the residue dried to give the title compound as a crude oil (also comprising some of the anti isomer),

1H NMR (300 MHz, CHCl3-*d*): δ(ppm): 1.7 (m, 1H); 2.18 (m, 4H) ; 3.75 (s, 3H); 3.91 (m, 1H) ; 4.15 (m, 1H) ; 5.13 (s, 2H); 6.96 (d, 2H) ; 7.07 (m, 1H); 7.15 (m, 1H); 7.30 (m, 1H) ; 7.38 (d, 2H); 7.5 (t, 1H).

Representative Na Channel blocker Example 8 (ENa8)

(5*R*)-5-(4-{[(2-Fluorophenyl)methyl]oxy}phenyl)-L-prolinamide



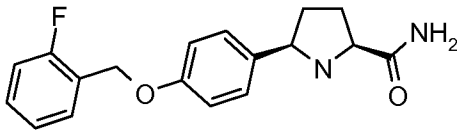
Procedure 1: A solution of methyl (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinate (32.5g, 98.6mmol) in methanol (65ml) was cooled to 0-10°C. A solution of ammonia in methanol (ca 11.2M) was added in four portions over 11 hours (175.4ml, 43.8ml, 43.8ml. 43.8ml) then the reaction stirred at 15-20°C for 22 hours. Ammonia and methanol were removed under vacuum, then toluene (65ml) was added and the mixture heated to 60-65°C to give a solution, which was then concentrated under vacuum and the

residue dried at 60°C. Toluene (130ml) and methanol (0.32ml) were added to the residue and the mixture heated to 70-75°C. The resulting solution was then cooled to 15-20°C and stirred for 1 hour. The solid was filtered, washed with toluene and dried at 45-50°C to give the title compound (21.8g) as a solid.

^{1}H NMR (500 MHz, DMSO-d6) δ(ppm): 1.39 (m, 1H) ; 1.84 (m, 1H) ; 2.04 (m, 2H) ; 3.54 (m, 1H) ; 4.09 (m, 1H) ; 5.12 (s, 2H); 6.96 (d, 2H); 7.15 (m, 1H); 7.25 (m, 2H) ; 7.34 (d, 2H) ; 7.41 (m, 2H) ; 7.55 (t, 1H).

Procedure 2: Methyl (5*R*)-5-{4-[(2-fluorobenzyl)oxy]phenyl}-L-prolinate (127g) was dissolved in 7N NH_3 solution in MeOH (1016mL) and the mixture was stirred at room temperature for 24hrs. Further 7N NH_3 solution in MeOH (63mL) was added and the mixture stirred for a further 15 hours. The solvent was removed under reduced pressure and MeOH (635mL) was added. The solution was evaporated to dryness and the white solid obtained was left under high vacuum over the weekend. The white solid was suspended in a mixture of MTBE/ Toluene 1:1 (254mL) at 20°C and stirred for 1 hr. The suspension was filtered and the solid washed with MTBE (254mL). The white solid was dried at 40°C overnight under vacuum affording 122.4g of material. This material was resuspended in a mixture of MTBE/toluene 1:1 (245mL) and stirred at room temperature for 1 hour. The mixture was filtered and the solid was washed with MTBE (245mL). The white solid obtained was dried at 40°C overnight under vacuum to give the title compound (109g). ^{1}H NMR (600 MHz, DMSO-d6) δ(ppm): 7.54 (td, 1H); 7.41 (m, 1H); 7.38 (m, 2H); 7.34 (d, 2H); 7.24 (m, 2H); 7.13 (bs, 1H); 6.96 (d, 2H); 5.12 (s, 2H); 4.09 (dd, 1H); 3.55 (dd, 1H); 3.24 (bs, 1H); 2.07 (m, 1H); 2.00 (m, 1H); 1.85 (m, 1H); 1.40 (m, 1H).

Representative Na Channel blocker Example 9 (ENa9):
(5R)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide hydrochloride



.HCl

Procedure 1: To a solution of 1,1-dimethylethyl (2S,5R)-2-(aminocarbonyl)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1-pyrrolidinecarboxylate (51mg, 0.123mmol) in a mixture of ethyl acetate (0.9ml) and methanol (1ml) was added acetylchloride (28 µl, 2.5eq) at 0°C. The mixture was shaken for 1.5h and slowly allowed to warm to room temperature. After evaporating the solvent, the residue was triturated with diethyl ether to afford the title

compound as a white solid (42mg, quant.); Chiral HPLC: Column: chiralcel OD 10 um, 250 x 4.6 mm; Mobile phase: A: n-Hexane; B: Ethanol; Gradient: isocratic 30% B; Flow rate: 0.8 ml/min; UV wavelength range: 200-400 nm; Analysis time: 22 min; ret. time: 12.0min. $[\alpha]_D$ = -30.5°. MS: (ES/+) m/z: 315 [MH^+], C18H19FN2O2 requires 314; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.19 (br. s., 1H), 8.13 (br. s., 1H), 7.94 (s, 1H), 7.60 - 7.77 (m, 1H), 7.51 (dt, 1H), 7.43 (d, 2H), 7.34 - 7.41 (m, 1H), 7.23 (d, 1H), 7.18 (dd, 1H), 7.05 (d, 2H), 5.13 (s, 2H), 4.49 - 4.60 (m, 1H), 4.19 - 4.28 (m, 1H), 2.17 - 2.38 (m, 2H), 2.05 - 2.16 (m, 1H), 1.92 - 2.03 (m, 1H).

Procedure 2: ((5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide) (109g) was dissolved in DCM (654mL) and Et_2O (654mL) was added at room temperature. HCl 1N in Et_2O (380.4mL) was added dropwise at room temperature. The suspension was cooled to 0°C and stirred at this temperature for 1 hr. The solid was filtered, washed with Et_2O (2 x 327mL) and dried at 40°C under vacuum overnight to afford Form 1 crystals of the title compound (121.24g). ^{1}H NMR (600 MHz, DMSO-d6) δ(ppm): 10.72 (bs, 1H); 8.10 (bs, 1H); 8.08 (s, 1H); 7.72 (s, 1H); 7.56 (td, 1H); 7.49 (d, 2H); 7.43 (qd, 1H); 7.25 (m, 2H); 7.10 (d, 2H); 5.17 (s, 2H); 4.61 (dd, 1H); 4.30 (dd, 1H); 2.32 (m, 2H); 2.16 (m, 1H); 2.02 (m, 1H).

Procedure 3: ((5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide) (10g, 31.8mmol) was dissolved in DCM (50ml) and stirred with charcoal (1g), then filtered, washing with DCM (30ml). The residue was concentrated under vacuum, removing about 20ml of DCM. Ether (60ml) was added, followed by a solution of HCl in ether (0.84N, 40ml), and the mixture was then stirred at 20-25°C for 30 min, then cooled to 0-5°C and stirred for 2 hours. The solid was filtered, washed with ether, then dried at room temperature to give Form 1 crystals of title compound (10.25g).

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.04 (m, 1H); 2.18 (m, 1H); 2.32 (m, 2H); 4.34 (m, 1H); 4.64 (m, 1H); 5.18 (s, 2H) ; 7.10 (d, 2H) ; 7.25 (m, 2H); 7.40-7.60 (m, 4H); 7.77 (s, 1H) ; 8.24 (s, 1H) ; 11.03 (b, 1H).

Procedure 4: In a round bottom flask, a solution of ((5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide) (1.4g, 4.45mmol) in ethylacetate (14ml) and MeOH (2.5ml) at 0°C was treated with HCl 1M in diethylether (1.1eq, 4.89ml).The precipitation occurred quite soon and the mixture was stirred at 0°C for 1h. The mixture was then diluted with dry diethylether (10ml) and then filtered on a Gooch filter (porosity 4,

diameter 5cm). The cake was washed on the filter with dry diethylether (2x20ml) and the white solid thus obtained was transferred into a round bottom flask, dried under high vacuum at 40°C for 2h and then at room temperature for 18hours. A white solid was obtained (1.51g) of Form 1 crystals of the title compound.

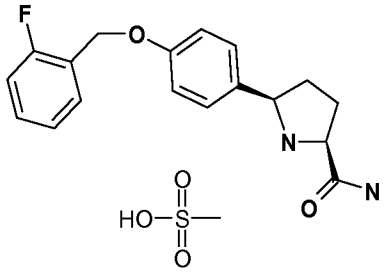
Procedure 5: ((5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide) (25g, 79.5mmol) was dissolved in ethyl acetate (750ml) and stirred with charcoal (2.5g), then filtered, washing with ethyl acetate (125ml). To the filtrate and washings, a solution of HCl in ether (1N, 103ml), was added over 30 minutes at 20-25°C and the mixture was then stirred at 20-25°C for 30 min, then cooled to 0-5°C and stirred for 2 hours. The solid was filtered, washed with ethyl acetate (2 x 70ml), then dried at room temperature to give Form 1 crystals of the title compound. (25.5g).

Unique and discriminating peaks of Form 1 of the title compound of Example 9 have been identified and are illustrated in the table below:

Position [°2Th.]	d-spacing [Å]
4.7	18.6
9.5	9.3
12.6	7.0
14.3	6.2
19.2	4.6
20.3	4.4
20.9	4.2
24.0	3.7
26.4	3.4

Melting point: 230 ^{O} C.

Representative Na Channel blocker Example 10 (ENa10):
(5R)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinamide methanesulfonate

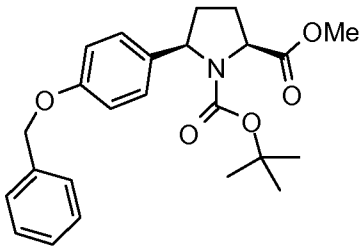


EtOAc (6ml) was added to (5*R*)-5-(4-{[(2-Fluorophenyl)methyl]oxy}phenyl)-L-prolinamide (300 mg) and this was heated at 60°C for an hour to dissolve the compound. Then methanesulfonic acid (65µl, 1.05 eq) was added to the solution and as soon as the acid was added, the solution went cloudy. This was then left to temperature cycle (0-40°C) for 2 days. The compound was isolated by filtration as a white solid, washed with EtOAc and dried *in vacuo* at 40°C overweek-end to afford 335 mg of the title compound.

Melting point: 192° C.

Intermediate 38

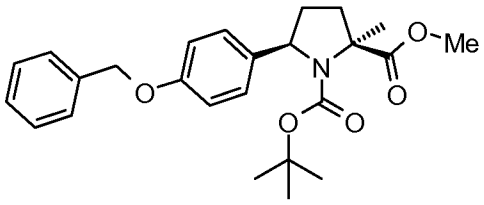
1-(1,1-Dimethylethyl) 2-methyl (2*S*,5*R*)-5-{4-[(phenylmethyl)oxy] phenyl}-1,2-pyrrolidinedicarboxylate



To a solution of methyl (5R)-5-{4-[(phenylmethyl)oxy]phenyl}-L-prolinate (2.6g, 8.35mmol) in DCM (30ml) was added di-tert-butyl dicarbonate (2.0g, 9.18mmol). After stirring for 1h at room temperature, the mixture was evaporated and the residue was purified by chromatography on silica gel using cyclohexane / ethyl acetate (9:1 to 85:15) to afford the title compound (3.29g, 96%) as a white foam; R_t (HPLC): 6.55min; MS: (ES/+) m/z: 434 [M+Na$^+$], 312 [M-BOC]; $C_{24}H_{29}NO_5$ requires 411; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52-7.43 (m, 4H); 7.43-7.37 (m, 2H); 7.37-7.30 (m, 1H); 6.96 (d, 2H); 5.09 and 5.06 (s,s, 2H); 4.99-4.93 and 4.52-4.44 (m,m, 1H); 4.76-4.68 and 4.39-4.32 (m,m, 1H); 3.82 (s, 3H); 2.36-2.26 (m, 1H); 2.26-2.15 (m, 1H); 2.12-2.01 (m, 1H); 2.01-1.88 (m, 1H); 1.42 and 1.17 (s,s, 9H).

Reference Description 39:

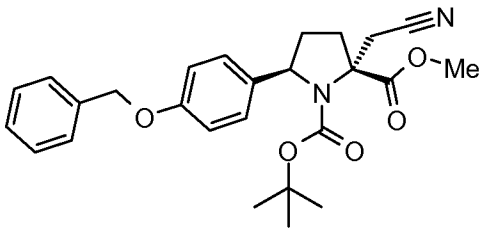
1,1-Dimethylethyl (2*S*,5*R*)-2-(aminocarbonyl)-2-methyl-5-{4-[(phenylmethyl)oxy]phenyl}-1-pyrrolidinecarboxylate



To a solution of 1-(1,1-dimethylethyl) 2-methyl (2*S*,5*R*)-5-{4-[(phenylmethyl)oxy]phenyl}-1,2-pyrrolidinedicarboxylate (1.52g, 3.7mmol) in dry THF (27ml) at -78°C was added LiHMDS (4.0ml, 4.0mmol, 1M solution in THF). The mixture was allowed to warm to -20°C and was stirred for 40min at that temperature. Then the mixture was again cooled to -78°C and methyl iodide (3.15g, 22.1mmol) was added. The mixture was left stirring for another 30min at the same temperature. After standard work up, the organic layer was evaporated. The crude material was purified by chromatography on silica gel using cyclohexanes and ethyl acetate (1:0 to 9:1) affording the title compound (1.23g, 78%); R_t (HPLC): 6.76min; MS: (ES/+) m/z: 448 [M+Na+]; C25H31NO5 requires 425; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.45-7.38 (m, 4H); 7.35 (t, 2H); 7.29 (t, 1H); 6.90 (d, 2H); 5.04 and 5.01 (s,s, 2H); 4.98 and 4.79 (d,d, 1H); 3.79 (s, 3H); 2.50-2.35 (m,1H); 2.34-2.22 (m, 1H); 1.87-1.73 (m, 2H); 1.58 and 1.55 (s,s, 3H); 1.37 and 1.09 (s,s, 9H). NOE between the methyl group and the proton at C5 could be observed.

Intermediate 40

1-(1,1-Dimethylethyl) 2-methyl (2*R*,5*R*)-2-(cyanomethyl)-5-{4-[(phenylmethyl)oxy]phenyl}-1,2-pyrrolidinedicarboxylate

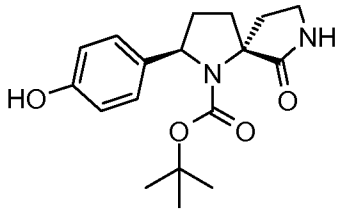


The title compound was prepared (2.71 g, 76%) using a similar procedure to as set out earlier in Reference Description 39 using crude 1-(1,1-dimethylethyl) 2-methyl (2*S*,5*R*)-5-{4-[(phenylmethyl)oxy]phenyl}-1,2-pyrrolidinedicarboxylate (3.25 g, 7.89 mmol) and bromoacetonitrile (3.3 ml, 47.38 mmol in 40ml THF); R_t (HPLC): 6.4 min; R_f (cyclohexane:ethyl acetate = 7:3): 0.40; MS: (ES/+) m/z: 473 [M+Na$^+$]; C26H30N2O5

requires 450; ^{1}H NMR (500 MHz, DMSO-d_6) δ(ppm): 7.46-7.24 (m, 7H); 6.94 (d, 2H); 5.11 (s, 2H); 4.94-4.78 (m, 1H); 3.78 (s, 3H); 3.33 (d, 1H); 3.22 (d, 1H); 2.66-2.52 (m, 1H); 2.42-2.29 (m, 1H); 2.29-2.16 (m, 1H); 1.92-1.77 (m, 1H); 1.38-0.97 (br. s, 9H); NOE between the aromatic protons and the methyl esther could be observed.

Intermediate 41:

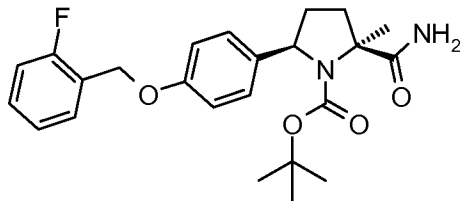
1,1-Dimethylethyl (2*R*,5*R*)-2-(4-hydroxyphenyl)-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate



To a solution of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-2-(cyanomethyl)-5-{4-[(phenylmethyl)oxy]phenyl}-1,2-pyrrolidinedicarboxylate (2.7g, 5.99mmol): in methanol (50ml) was added Raney Nickel (slurry in water) and the mixture was stirred under a hydrogen atmosphere (7 atmospheres) for 14 hours. The catalyst was filtered off, the solvent removed under reduced pressure, and the solid residue was treated with toluene (3x20ml) and dried under vacuum. The dry white solid obtained was refluxed in methanol (40ml) for five hours until cyclization was complete. The solvent was removed under reduced pressure and the crude material purified by chromatography on silica gel using dichloromethane / methanol (95:5 to 90:10) to afford the title compound as a white solid (1.35g, 68%); R_t (HPLC): 3.91min; R_f (dichloromethane:methanol = 9:1): 0.41; MS: (ES/+) m/z: 665 [2M+Na^+], 355 [M+Na^+]; C18H24N2O4 requires 332; ^{1}H NMR (400 MHz, DMSO-d6) δ(ppm): 9.11 (s, 1H); 7.76 and 7.66 (s, s, 1H); 7.43 (dd, 2H); 6.66 (dd, 2H); 4.81-4.70 (m, 1H); 3.29-3.20 (m, 1H); 3.19-3.09 (m, 1H); 2.47-2.20 (m, 2H); 2.08-1.85 (m, 2H); 1.84-1.74 (m, 1H); 1.68-1.52 (m, 1H); 1.33 and 1.08 (s, s, 9H).

Reference Description 42:

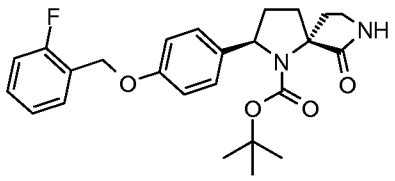
1,1-Dimethylethyl (2*S*,5*R*)-2-(aminocarbonyl)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-methyl-1-pyrrolidinecarboxylate



To a solution of 1,1-dimethylethyl (2*S*,5*R*)-2-(aminocarbonyl)-5-(4-hydroxyphenyl)-2-methyl-1-pyrrolidinecarboxylate (300mg, 0.936mmol) and potassium carbonate (194mg, 1.4mmol) in acetonitrile (4ml) was added 1-(bromomethyl)-2-fluorobenzene (Sigma Aldrich Ltd.) (170µl, 1.4mmol) and the mixture was stirred overnight at room temperature. After the reaction was finished, as shown by TLC, ethyl acetate and water were added. The organic phase was then washed with brine, dried, filtered and evaporated. The crude material was purified by chromatography on silica gel using cyclohexane / ethyl acetate (8:2 to 7:3) to afford the title compound (306mg, 72%); R_t (HPLC): 5.88min; R_f (cyclohexane:ethyl acetate = 1:1): 0.51; ^{1}H NMR (300 MHz, DMSO-d6) δ(ppm): 7.60-7.49 (t, 2H); 7.46-7.32 (m, 2H); 7.29-7.15 (m, 3H); 7.13-7.02 (m, 1H); 6.98-6.88 (m, 2H); 5.11 (s, 2H); 4.87-4.62 (m, 1H); 2.41-2.16 (m, 2H); 1.78-1.64 (m, 1H); 1.64-1.56 (m,1H); 1.52 (s, 3H); 1.32 and 1.03 (s, s, 9H).

Intermediate 43:

1,1-Dimethylethyl (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate



Method a):

The title compound was prepared using a similar procedure as set out earlier in Reference Description 42 starting from 1,1-dimethylethyl (2*R*,5*R*)-2-(4-hydroxyphenyl)-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate (D25, 850 mg, 2.55 mmol) and 2-fluorobenzyl bromide (0.5 ml, 3.83 mmol); R_f (HPLC): 5.72min; R_f (cyclohexane:ethyl acetate = 3:7): 0.45; MS: (ES/+) m/z: 463 [M+Na$^+$]. C25H29FN2O4 requires 440; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.61 (d, 2H); 7.56-7.49 (m, 1H); 7.35-7.28 (m, 1H); 7.20-7.13 (m, 1H); 7.12-7.05 (m, 1H); 7.00-6.94 (dd, 2H); 5.64 and 5.61 (s,s, 1H); 5.14 and 5.12 (s,s, 2H); 5.08 and 4.88 (d, d, 1H); 3.58-3.40 (m, 1H); 3.38-3.24 (m, 1H); 2.82-2.56 (m, 1H); 2.43-2.21 (m, 2H); 2.15-2.00 (m, 1H); 1.95-1.75 (m, 2H), 1.45 and 1.17 (s, s, 9H).

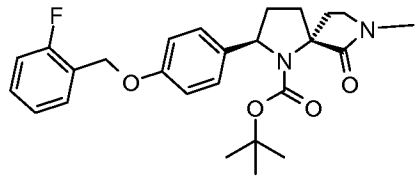
Method b):

To a solution of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-2-(cyanomethyl)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,2-pyrrolidinedicarboxylate (51.3g) in MeOH (~ 500 mL) was added $CoCl_2.6H_2O$ (13.04g). To the resulting purple solution were added three batches of $NaBH_4$ (8.29g, 8.29g and 4.145g respectively; exothermic addition) portionwise every 30 minutes. The reaction mixture was cooled down to ambient temperature, filtered and the resulting solution was heated to reflux overnight. Then the mixture was cooled down and filtered. NH_4Cl saturated solution (513mL) was added and MeOH evaporated in vacuo. The aqueous phase was extracted with EtOAc (2 x 500 mL) and the combined organic phase was evaporated to dryness and the crude material was purified by chromatography on silica gel pad using cyclohexane and ethyl acetate (1:1, 4:6, 3:7) affording the title compound (22.1g) as a white solid.

1H NMR (400 MHz, $CHCl_3$-d) δ(ppm): 7.61 (m, 2 H), 7.53 (m, 1 H), 7.31 (m, 1 H), 7.16 (m, 1 H), 7.09 (m, 1 H), 6.97 (m, 2 H), 5.58 (s, 1 H), 5.14 (m, 2 H), 5.04-4.86 (m, 1 H), 3.58 – 3.42 (m, 1 H), 3.32 (m, 1 H), 2.80-2.58 (m, 1 H), 2.32 (m, 2 H), 2.07 (m, 1 H), 1.93-1.78 (m, 2 H), 1.45 (s, 3H), 1.17 (s, 6H).

Intermediate 44:

1,1-Dimethylethyl (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate

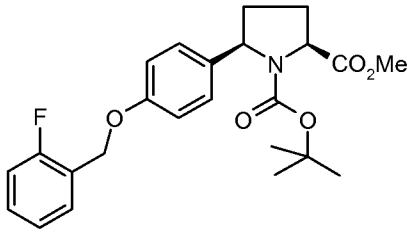


To a solution of 1,1-dimethylethyl (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate (70mg, 0.159 mmol) in dry DMF (1 ml) at 0°C was added NaH 60%wt dispersion in mineral oil (10mg, 0.238 mmol); after 15 minutes of stirring at room temperature, iodomethane (30µl, 0.477 mmol) was added and the resulting mixture was stirred at room temperature for 2.5 hours. The mixture was cooled to 0°C, and water (4 ml) and ethyl acetate (10 ml) were added, the organic layer was washed with ice cold brine (3 x 10 ml), dried over Na_2SO_4 and evaporated. The crude material was purified by chromatography on silica gel using cyclohexanes / ethyl acetate (7:3) to afford the title compound as a white solid (63 mg, 88%); R_t (HPLC): 5.99min; R_f (cyclohexane:ethyl acetate = 1:1): 0.28; MS: (ES/+) m/z: 477 [M+Na^+]; C26H31FN2O4

requires 454. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.66 (d, 2H); 7.56-7.49 (m, 1H); 7.35-7.25 (m, 1H); 7.20-7.13 (m, 1H); 7.12-7.04 (m, 1H); 6.97 (dd, 2H); 5.14 and 5.12 (s, s, 2H); 5.02 and 4.88 (d, d, 1H); 3.52-3.45 and 3.41-3.22 (m, m, 2H); 2.96 and 2.92 (s, s, 3H); 2.67-2.56 and 2.53-2.42 (m, m, 1H); 2.40-2.22 (m, 2H); 2.08-1.79 (m, 2H); 1.77-1.68 (m, 1H), 1.40 and 1.16 (s, s, 9H).

Intermediate 45:

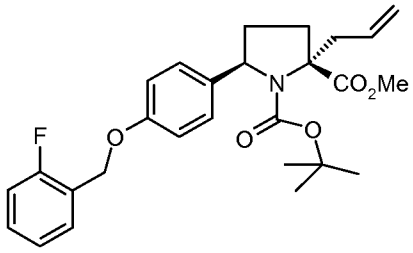
1-(1,1-Dimethylethyl) 2-methyl (2*S*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,2-pyrrolidinedicarboxylate



Methyl (5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-L-prolinate (175g) was dissolved in EtOAc (1000mL) and cooled to 0°C. A solution of di-tert-butyl-dicarbonate (127.5g) in EtOAc (750mL) was added dropwise in about 1hour maintaining the temperature at about 0°C. Then the temperature was increased to 25°C and the reaction stirred at 25°C for 2hours. 28%w/w Racemic malic acid (350mL) was added and the mixture stirred for about 10min. The organic phase was washed with saturated $NaHCO_3$ (700mL). Aqueous pH was ~ 8. The organic phase was concentrated to a low volume then stripped with cyclohexane (3 x 350mL) to afford the title compound (240.8g). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.54 (m, 1H); 7.50 (d, 2H); 7.33 (m, 1H); 7.18 (dt, 1H); 7.11 (m, 1H); 6.98 (d, 2H); 5.16 (2s, 2H); 4.97-4.46 (2bm, 1H); 4.73-4.37 (2t, 1H); 3.83 (s, 3H); 2.32 (m, 1H); 2.21 (m, 1H); 2.08 (m, 1H); 1.96 (m, 1H); 1.43-1.18 (2bs, 9H).

Intermediate 46:

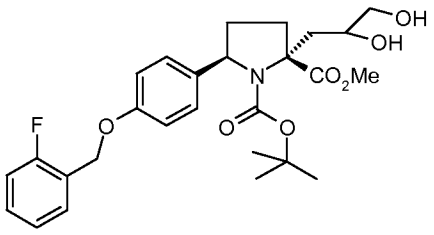
1-(1,1-Dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-(2-propen-1-yl)-1,2-pyrrolidinedicarboxylate



The previous crude of 1-(1,1-dimethylethyl) 2-methyl (2*S*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,2-pyrrolidinedicarboxylate was split in two batches. The first one (100g) was dissolved in dry THF (1000mL) then allyl bromide (42.25g) was added, finally the mixture was cooled to -30°C. 1M LiHMDS in THF (439mL) was added dropwise in about 1.5 hours maintaining the temperature at about -30°C. Water (100mL) was added and temperature allowed to reach 0°C. Saturated NH_4Cl (500mL) was added followed by water (400mL) and EtOAc (500mL). The reaction was warmed to 25°C and the aqueous layer was removed. The organic layer was concentrated to about 700mL and washed with $NaHCO_3$ saturated solution (200mL). Organic layer was dried over Na_2SO_4 and concentrated to afford the title compound as an oil (119.8g). The second batch (135g) was similarly reacted using dry THF (1350mL), allyl bromide (57.04g) and 1M LiHMDS in THF (471.5mL). After work-up, the title compound was isolated as an oil (179g). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 7.53 (m, 1H); 7.39 (m, 3H); 7.22 (m, 2H); 6.95 (m, 2H); 5.82 (m, 1H); 5.12 (m, 4H); 4.80-4.59 (2m, 1H); 3.74-3.71 (2s, 3H); 3.01-1.52 (m, 6H); 1.29-0.98 (2s, 9H).

Intermediate 47:

1-(1,1-Dimethylethyl) 2-methyl (2*R*,5*R*)-2-(2,3-dihydroxypropyl)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,2-pyrrolidinedicarboxylate

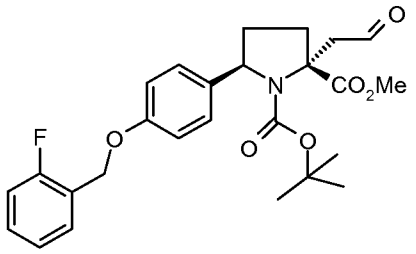


The reaction was performed on the two separated batches of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-(2-propen-1-yl)-1,2-pyrrolidinedicarboxylate obtained from the previous step.The first batch (119.8g) was dissolved in a mixture of 10/1 acetone/water (1200mL). $K_2OsO_4 \cdot 2H_2O$ (4.7g) was added followed by NMO (41.4g) after a few minutes. The mixture was stirred for 7.5 hours. The reaction mixture was treated with EtOAc (1200mL) and washed with saturated NH_4Cl (1200mL) then with saturated $NaHCO_3$ (1200mL). The organic layer was filtered through a celite/activated charcoal pad and concentrated to low volume. EtOAc (500mL) was added and the solution was washed with brine (300mL) and the organic dried over Na_2SO_4, and evaporated to dryness, EtOAc (300mL) was added and filtered through CUNO filter and washed with EtOAc (50mL). The organic was concentrated to dryness to afford the title

compound (135g). The second batch (179g) was dissolved in a mixture of 10/1 acetone/water (1800mL). $K_2OsO_4 \cdot 2H_2O$ (5.5g) was added followed by NMO (56.8g) after a few minutes. The mixture was stirred overnight at room temperature. The reaction mixture was treated with EtOAc (900mL) and washed with saturated NH_4Cl (2 x 900mL) then with saturated $NaHCO_3$ (900mL). The organic layer was filtered through a celite pad and concentrated to low volume to afford the title compound (250g). ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 7.54 (m, 1H); 7.40 (m, 3H); 7.22 (m, 2H); 6.95 (m, 2H); 5.11 (m, 2H); 4.95-4.25 (m, 3H); 3.70 (bm, 3H); 3.50-3.10 (m, 3H); 2.50-1.50 (m, 6H); 1.30-0.95 (4bs, 9H).

Intermediate 48:

1-(1,1-Dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-(2-oxoethyl)-1,2-pyrrolidinedicarboxylate (I48)



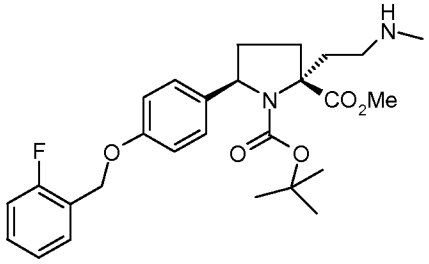
Procedure 1: The reaction was performed on the two separated batches of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-2-(2,3-dihydroxypropyl)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,2-pyrrolidinedicarboxylate obtained from the previous step. The first batch (135g) was dissolved in a mixture of 10/1 acetone/water (2000mL) and $NaIO_4$ (74.54g) was added. The solution turned from brown to yellow and a suspension was formed. The mixture was stirred overnight at 25°C. Further $NaIO_4$ (2 x 5.73g) was added and stirred for further 24 hours. EtOAc (1000mL) was added followed by water (1000mL). After mixing the aqueous phase was removed. The organic phase was concentrated to a yellow oil and stripped with EtOAc (250mL) to afford the title compound (109g). The second batch (250g) was dissolved in a mixture of 10/1 acetone/water (1900mL) and $NaIO_4$ (106g) was added. The solution turned from brown to yellow and a suspension was formed. The mixture was stirred for 6 hours then further $NaIO_4$ (8.15g) was added and stirred overnight. EtOAc (1000mL) was added followed by water (2000mL). After mixing the aqueous phase was removed. The organic phase was concentrated to a yellow oil and stripped with EtOAc (300mL) to afford the title compound (180g).

^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.72 (m, 1H); 7.56 (m, 1H); 7.42 (m, 3H); 7.24 (m, 2H); 6.99 (m, 2H); 5.14 (m, 2H) 4.90-4.79 (2m, 1H); 3.80-3.77 (2s, 3H); 3.02 (m, 1H); 2.83 (m, 1H); 2.55-1.55 (m, 4H); 1.32-1.03 (2s, 9H).

Procedure 2: A solution of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-(2-propen-1-yl)-1,2-pyrrolidinedicarboxylate (15g) in methanol (200ml) was cooled to -10°C. Ozone gas was passed through the solution for 2 hours, then the mixture was warmed to 0-5°C. Dimethylsulphide (7.04ml) was added and the mixture stirred for 1 hours at 0-5°C, then at room temperature for 3 hours. The mixture was then concentrated under vacum at 35-50°C to give a residue. This was treated with water (45ml), then extracted with DCM (2 x 37.5ml). The combined extracts were stirred with a mixture of 60-120 mesh silica gel (45g, DCM (75ml) and 10% oxalic acid (6ml) for 4 hours. The mixture was then filtered and washed with DCM (75ml). The combined flitrates were washed with water (75 ml) and 10% sodium bicarbonate (75ml) and water (75ml). The solution was then dried over sodium sulphate and evaporated, then dried under vacuum to give the title compound as a brownish yellow pasty mass (12.7g).

Intermediate 49:

1-(1,1-Dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-[2-(methylamino)ethyl]-1,2-pyrrolidinedicarboxylate

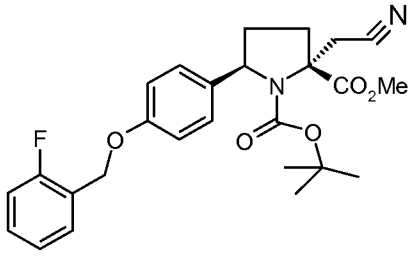


The reaction was performed on the two separated batches of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-(2-oxoethyl)-1,2-pyrrolidinedicarboxylate obtained from the previous step (I48, Procedure 1). The first batch (109g) was dissolved in MeOH (440mL) and $MeNH_2$ in MeOH 2M solution (347mL) was added. AcOH (11mL) was added. $NaBH(OAc)_3$ (49g) was added portion wise after 10 minutes. More $NaBH(OAc)_3$ (14.7g) was added portion wise at 25°C. The reaction mixture was quenched with 28% aqueous malic acid (200mL) followed by AcOEt (1000mL). K_2CO_3 was added up to pH~9. Organic phase was concentrated to dryness, re-dissolved in EtOAc (500mL) and extracted with 20% citric acid (4 x 300mL). The combined aqueous

phases were treated with EtOAc (500mL) and solid K_2CO_3 was added until pH~9. The phases were separated and the organic phase was dried under Na_2SO_4 and evaporated to dryness to afford the title compound (80g). The second batch (180g) was dissolved in MeOH (628mL) and $MeNH_2$ in MeOH 2M solution (300mL) was added. AcOH (31mL) was added. $NaBH(OAc)_3$ (78.8 g) was added portionwise at 0°C after 10 minutes. The reaction mixture was quenched with saturated NH_4Cl (890mL) and EtOAc (890mL). The phases were separated and the aqueous was extracted with EtOAc (4 x 300mL). The organic phase was dried over Na_2SO_4, concentrated to dryness, re-dissolved in EtOAc (500mL) and extracted with 20% citric acid (6 x 150mL). The combined aqueous phases were treated with EtOAc (600mL) and solid K_2CO_3 was added until pH 8/9. The Phases were separated and the organic phase dried over Na_2SO_4 and evaporated to dryness to afford the title compound (78 g). ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 7.55 (m, 1H); 7.42 (m, 3H); 7.25 (m, 2H); 6.98 (m, 2H); 5.14 (m, 2H); 4.85-4.69 (2m, 1H); 3.75-3.73 (2s, 3H); 2.36 (bs, 3H) 2.80-2.25 (m, 2H); 2.20-2.00 (m, 3H); 1.70 (m, 1H); 1.32-1.00 (2s, 9H).

Intermediate 50:

1-(1,1-Dimethylethyl) 2-methyl (2*R*,5*R*)-2-(cyanomethyl)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,2-pyrrolidinedicarboxylate

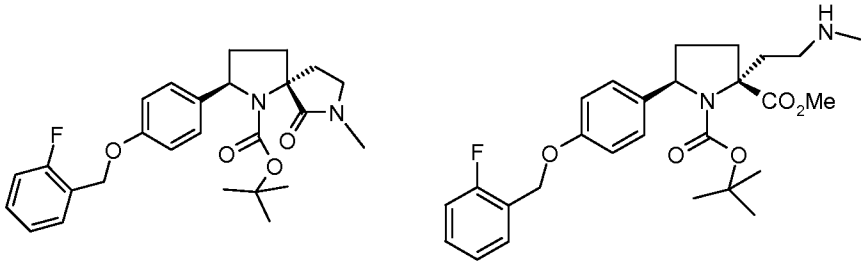


To a solution of 1-(1,1-dimethylethyl) 2-methyl (2*S*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-1,2-pyrrolidinedicarboxylate (45g) in dry THF (450mL) previously cooled to -65°C, was added 1M LiHMDS in THF (115mL) dropwise. The resulting solution was stirred at -35°C for 30 minutes. Then the mixture was again cooled to -65°C and bromoacetonitrile (22mL) dissolved in dry THF (180mL) was added. The mixture was left stirring for a further 30min at the same temperature. The reaction was quenched with saturated ammonium chloride solution (675mL), THF was evaporated in vacuo and the crude mixture was extracted with EtOAc (2 x 675mL). The organic layer was evaporated and the crude material was purified by chromatography on silica gel using cyclohexanes and ethyl acetate (8:2) affording the title compound (51.3g) as a yellow thick oil.

1H NMR (400 MHz, $CDCl_3$-d) δ(ppm): 7.53 (t, 1H), 7.43 (d, 2H), 7.29-7.37 (m, 1H), 7.17 (t, 1H), 7.07-7.13 (m, 1H), 6.97 (d, 2H), 5.16 (s, 2H), 4.88-4.95 (m, 1H), 3.90 (s, 3H), 3.52 (d, 1H), 3.15 (d, 1H), 2.57-2.70 (m, 1H), 2.38-2.50 (m, 1H), 2.23-2.34 (m, 1H), 1.92-2.06 (m, 1H), 1.44 (s, 9H).

Intermediate 51

1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-[2-(methylamino)ethyl]-1,2-pyrrolidinedicarboxylate and 1,1-dimethylethyl (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate

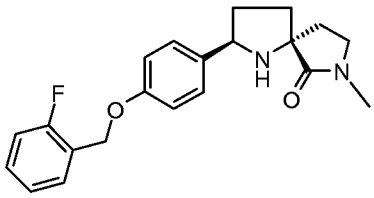


A solution of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-(2-oxoethyl)-1,2-pyrrolidinedicarboxylate (I48, 9.5g) in methanol (38ml) was cooled to 5-10°C. Methylamine in methanol (12.7g of a 24.7% solution) was added and the mixture stirred at 5-10°C for 1 hour. Acetic acid (7.6ml) was added to give a pH of approximately 7, and then the temperature was raised to 20-25°C. Sodium triacetoxyborohydride (6.4g) was added in portions over 1 hour, then the mixture stirred at 20-25°C for a further 2 hours. Methanol was distilled off under vacuum, then the mixture treated with ethyl acetate (50ml) and water (50ml). The layers were separated and the aqueous layer re-extracted with ethyl acetate (25ml). The combined ethyl acetate solutions were extracted with 28% citric acid solution (4 x 50ml), then the combined aqueous layers were treated with 30% sodium carbonate solution (150ml) and ethyl acetate to pH 9. The aqueous layer was re-extracted with ethyl acetate (25ml), then the combined ethyl acetate solution was dried over sodium sulphate and evaporated to give the title compound as a crude (6.6g) also comprising the compound 1,1-dimethylethyl (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate.

MS: (ES/+) m/z: 455 [MH^+] (cyclised product)

Representative Na Channel blocker Example 11 (ENa11):

(2*R*,5*R*)-2-(4-{[(2-Fluorophenyl)methyl]oxy}phenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-6-one



Procedure 1 : The reaction was performed on the two separated batches of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-[2-(methylamino)ethyl]-1,2-pyrrolidinedicarboxylate resulting from procedure decribed for Intermediate 49.

The first batch (80g) was dissolved in MeOH (320mL), 5-6N HCl in IPA (160mL) was added and the mixture stirred overnight at 25°C. 13% aqueous NH_3 (200mL) was added, cooling the reaction to 0°C during addition, until complete conversion. EtOAc (320mL), water (160mL) and $NaHCO_3$ saturated solution (240mL) were added and the phases separated. Aqueous phase was extracted with EtOAc (6 x 80mL) and the organic phase was concentrated to about 400mL then washed with brine (120mL) which was back extracted with EtOAc (80mL). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness to afford the crude (50g).

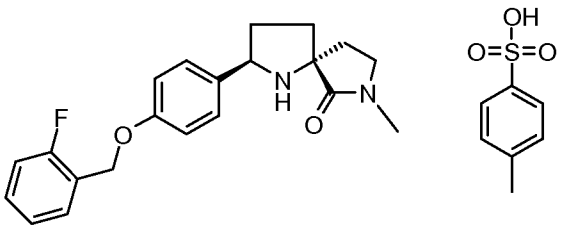
The second batch (81g) was dissolved in MeOH (324mL), 5-6N HCl in IPA (162mL) was added and the mixture stirred overnight at 25°C. Further 5-6N HCl in IPA (20mL) was added and stirred for a further 6 hours. $NaHCO_3$ saturated solution (160mL) and EtOAc (500mL) were added followed by solid $NaHCO_3$ to pH~8. Phases were separated and the aqueous was back extracted with EtOAc (2 x 200mL). Combined organics were concentrated to about 400mL. DCM (300mL) and brine (200mL) were added, the phases were separated and the organic phase was dried over Na_2SO_4 and evaporated to dryness to afford crude (67g). DCM (135mL) was added and stirred overnight at room temperature then heated to reflux for 3 hours then cooled back to room temperature. 2M NH_3 in methanol (12.5mL) was added due to incomplete cyclisation and then aqueous 13% NH_3 was added and stirred for at least 2 hours to reach complete cyclisation. Brine (100mL) was added, phases were separated and organic was dried over Na_2SO_4 and evaporated to dryness to afford the crude (58g).

The two crudes were combined and purified via chromatographic column (DCM/MeOH 25/1) to afford the title compound (85g).

^{1}H NMR (600 MHz, DMSO-d_6) δ(ppm): 7.56 (dt, 1H); 7.41 (m, 3H); 7.25 (t, 1H); 7.23 (t, 1H); 6.97 (d, 2H); 5.12 (s, 2H); 4.18 (m, 1H); 3.28 (m, 1H); 3.21 (m, 1H); 2.77 (s, 3H); 2.50 (bs, 1H); 2.12 (m, 1H); 2.01 (m, 1H); 1.92 (m, 1H); 1.72 (m, 2H).

Procedure 2: A mixture of 1-(1,1-dimethylethyl) 2-methyl (2*R*,5*R*)-5-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-2-[2-(methylamino)ethyl]-1,2-pyrrolidinedicarboxylate and 1,1-dimethylethyl (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate (5.8g) was dissolved in MeOH (23.2mL), HCl in IPA (14.3% solution, 17.7g) was added and the mixture stirred at 25°C for 24 hours. 13% aqueous NH_3 (14.5 ml) and the mixture stirred for 4 hours. EtOAc (60mL) and water (40mL) were added and the phases separated. The aqueous phase was extracted with EtOAc (25ml) then the combined organic phases were dried over Na_2SO_4 and evaporated to dryness to afford the crude (5.52g).The crude was purified via column chromatography (EtOAc to 9:1 EtOAc/MeOH) to afford the title compound (2.1g).

Representative Na Channel blocker Example 12 (ENa12): (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-6-one 4-methylbenzenesulfonate



The compound (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-6-one hydrochloride (57.2g) was suspended in EtOAc (286mL) and $NaHCO_3$ saturated solution (229mL) was added. The layers were separated and the organic layer was dried over Na_2SO_4.

The salt was filtered off and washed with EtOAc (3 x 57mL).

The solvent was evaporated under reduced pressure and the crude stripped with acetone (2 x 171mL), giving 52.7 g of (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-6-one.

This compound was dissolved in acetone (520mL) and the solution was heated to 40°C.

A solution of *p*-toluenesulfonic acid monohydrate (27.84g) in acetone (260mL) was added in 30 min.

A solid precipitated after the addition of approx 50 mL of this solution.

The mixture was stirred at 40°C for 4.5h and then cooled to room temperature.
The solid was collected, washed with acetone (3 x 230 mL) and dried under high vacuum for 16 hours obtaining the Form 1 crystals of the title compound (70.1g).
1H NMR (400 MHz, DMSO-d6) δ(ppm): 9.90 (bs, 1H); 8.91 (bs, 1H); 7.55 (m, 3H); 7.48 (m, 2H); 7.43 (m, 1H); 7.25 (m, 2H); 7.11 (m, 4H); 5.18 (s, 2H); 4.73 (dd, 1H); 3.41 (m, 2H); 2.82 (s, 3H); 2.36 (m, 5H); 2.29 (s, 3H); 2.11 (m, 1H) .

Unique and discriminating peaks of Form 1 of Example 12 have been identified and are illustrated in the table below:

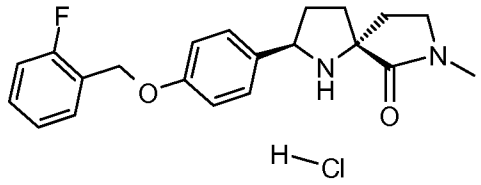
Position [°2Th.]	d-spacing [Å]
6.8	13.0
8.7	10.2
10.8	8.2
12.7	7.0
13.6	6.5
14.6	6.1
17.3	5.1
17.8	5.0
18.3	4.8
20.4	4.4
21.0	4.2
22.0	4.0
22.6	3.9
23.1	3.8
24.1	3.7
24.6	3.6
25.0	3.6
27.2	3.3
27.8	3.2
28.1	3.2
28.7	3.1
29.3	3.0
29.6	3.0
30.2	3.0

34.6	2.6
35.4	2.5
36.1	2.5
44.5	2.0

Melting point: 233 °C.

Representative Na Channel blocker Example 13 (ENa13):

(2*R*,5*R*)-2-(4-{[(2-Fluorophenyl)methyl]oxy}phenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-6-one hydrochloride



Procedure 1: To a solution of 1,1-dimethylethyl (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate (61mg, 0.134mmol) in a mixture of ethyl acetate (1ml) and methanol (0.1ml) at 0°C was added acetyl chloride (60µl, 0.806mmol). The mixture was stirred for 3 hours at room temperature. The solvent was removed under vacuum and the gummy solid was treated with Et_2O (3 x 2ml) obtaining a white solid (53mg). R_t (HPLC): 3.72min; MS: (ES/+) m/z: 355 [MH^+]; C21H23FN2O2 requires 354; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.58 (br. s., 1H), 8.87 (br. s., 1H), 7.59-7.52 (m, 3H), 7.47-7.39 (m, 1H), 7.31-7.20 (m, 2H), 7.11 (d, 2H), 5.17 (s, 2H), 4.80 - 4.66 (m, 1H), 3.43-3.37 (m, 2H), 2.81 (s, 3H), 2.59-2.23 (m, 5H), 2.13-2.03 (m, 1H).

Procedure 2 : The previous crude of (2*R*,5*R*)-2-(4-{[(2-fluorophenyl)methyl]oxy}phenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-6-one (75.85g) was stripped with Et_2O (2 x 150mL), dissolved in DCM (150mL) and 5-6M HCl in IPA (76mL) was added at room temperature. Solvent and excess of HCl were evaporated and then stripped with Et_2O (2 x 76mL) and DCM (2 x 76mL) to get a foam. The foam was suspended in Et_2O (600mL) and DCM (76mL) and stirred overnight at room temperature. Finally the solid was collected, washed with a mixture of Et_2O/DCM 8/1 (3 x 76mL) and dried under high vacuum at 40°C overnight to afford the title compound (79g).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ(ppm): 10.58 (bs, 1H); 8.87 (bs, 1H); 7.55 (m, 3H); 7.43

(m, 1H); 7.25 (m, 2H); 7.11 (d, 2H); 5.17 (s, 2H); 4.73 (m, 1H); 3.40 (m, 2H); 2.81 (s, 3H); 2.60-2.20 (m, 5H); 2.08 (m, 1H).

Intermediate 52

2-(2,3-Dichlorophenyl)-3-ethoxy-4-fluoro-2-butenenitrile

To a suspension of 2,3-dichlorophenylacetonitrile (45 kg, 241.9 mole) in methanol (90 litres) was charged 30% w/w sodium methoxide in methanol solution (113.5 kg, 630.6 mole) then ethylfluoroacetate (29.7 kg, 280.1 mole). The reaction mixture was stirred overnight and the product was precipitated from aqueous hydrochloric acid (63.7 kg, 648 mole) in water (350 litres). The slurry was filtered and the solid was dissolved in ethyl acetate and washed with brine solution. Ethyl acetate (100 litres) was removed by vacuum distillation. DMF (70 litres) was added and the distillation continued to remove the remaining ethyl acetate.

To the resulting enol in DMF was added potassium carbonate (20 kg, 145 mole) over a period of 10 minutes. Alkylation of the potassium enolate was achieved using ethyl iodide (37.7kg, 241.9 mole) at 70°C for 1¼ hours. The reaction mixture was partitioned between toluene (140 litres) and water (75 litres) and the toluene phase was washed with water (50 litres). Toluene (75 litres) was removed by distillation to afford the crude product as a toluene solution.

Intermediate 53

(+/-) 2,4-Diamino-5-(2,3-dichlorophenyl)-6-fluoro methylpyrimidine

To guanidine hydrochloride (25.4 kg, 266 mole) in methanol (60 litres) was added 30% w/w sodium methoxide in methanol solution (49.2 kg, 273.3 mole). The suspension was heated to 55°C±2°C. The toluene solution of 2-(2,3-dichlorophenyl)-3-ethoxy-4-fluoro-2-butenenitrile was added over a period of 45 minutes and the resultant mixture was boiled under reflux for 4 hours, cooled then quenched into water (230 litres). The solid precipitate was washed with 5 portions of methanol (25 litres) to yield the racemate as an off white solid (26.3 kg, 38% yield from 2,3-dichlorophenylacetonitrile).

Representative Na Channel blocker Example 14 (ENa14):

R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine

Procedure 1:

To racemic (+/-)2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine (0.8006g) in a flask was added (-)-dibenzoyl-L-tartaric acid.H_2O (1.0490g). Absolute ethanol (27.7ml) was added, the mixture was warmed and the resulting solution was left overnight. The mother liquor was then decanted from the white crystalline solid that had formed. The solid was dried in a vacuum oven at 50°C overnight. The yield of crystalline material obtained (0.9534g) was about 52%.

The ratio of R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine ("R(-)enantiomer") to S(+)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine ("S(+)enantiomer") was 81:19.

Crystalline material (0.8796g) obtained in the initial resolution step 1 was dissolved under warming in absolute ethanol (36 ml). The solution was left to cool overnight. The mother liquor was decanted. The white crystalline solid obtained was dried in a vacuum oven at 50°C overnight; yield (0.6111g) 69%. The ratio of R(-)enantiomer to S(+)enantiomer was 94:6%.

Recrystallised material (0.5227g) from step 2 was dissolved under warming in absolute ethanol (25ml). The resulting solution was left to cool overnight. The mother liquor was then decanted. The remaining white crystalline solid was washed with ethanol (1ml) and dried at 50°C in a vacuum oven overnight; yield (0.397g) 76%. The ratio of R(-) enantiomer to S(+)enantiomer was 99.8:0.2.

The crystalline salt from step 3 was then basified with 2M NaOH solution. Thus, distilled water was added to the salt. The resulting slurry was stirred at room temperature. Then 2M NaOH was added until pH 12 was maintained. The resulting suspension was left for 1 hour. Then the solid was filtered off and washed with water. The wet solid was dried at 50°C *in vacuo* to give a white solid.

Procedure 2:

To racemic (+/-)2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine (78.83g) in a flask, (-)-dibenzoyl-L-tartaric acid.H_2O (103.27g) was added followed by absolute ethanol (2727ml). The mixture was heated to reflux until all solids were in solution. The solution was left over 18 hours to cool to room temperature. The white solid formed was filtered off and dried *in vacuo* for 3 hours at 50°C. The dried solid was recrystallised from absolute ethanol twice (2 x 1500ml). The white crystalline solid obtained was dried at 50°C *in vacuo* for 6 hours. The ratio of R(-)enantiomer to S(+)enantiomer in the dried crystalline material obtained (22g) was >99:1.

The mother liquors from the recrystallisations were concentrated *in vacuo* and then treated with 2M NaOH (aqueous solution) to basify the salt. Thus, water (100ml) was added to the salt (98g) followed by 2M NaOH solution (250ml) in 50ml portions while the suspension was vigorously stirred. The suspension was maintained at pH 12 for 2 hours. The white solid was filtered off and washed with water (5 x 50 ml) until pH7 was maintained. The solid was dried *in vacuo* at 50°C for 4 hours to afford the free base (39g). The ratio of R(-)enantiomer to S(+)enantiomer in the dried free base was 30:70.

The free base enriched with the S(+) enantiomer was then recycled to the racemate. Thus, toluene (500ml) was added to the free base (39g). The mixture was heated at reflux for 24 hours and then cooled to room temperature. A brown solid was filtered off which was dried *in vacuo* at 50°C for 3 hours. The ratio R(-)enantiomer: S(+)enantiomer in the dried material obtained (33g) was 50:50.

This racemate was then submitted to step 1 to obtain more of the R (-)enantiomer of >99% enantiomeric purity. The combined salts were then basified with 2M NaOH solution. Thus, distilled water (250ml) was added to the salts (86.6g) and the slurry stirred at room temperature. Then 2M NaOH (154ml) was added in 50ml portions and then two 2ml portions until pH 12 was maintained. The resulting suspension was left for 1 hour and then the solid was filtered off and washed with water (7 x 100ml). The wet solid was dried at 50°C *in vacuo* to give, for this batch, a buff-coloured solid (37.9g). Other batches however gave a white solid. The ratio of the R(-)enantiomer to the S(+)enantiomer in the dried material was 99.7:0.3.

Chemical purity = 99.2%

PROPERTIES OF R(-)-2,4-DIAMINO-5-(2,3-DICHLOROPHENYL)-6-FLUOROMETHYL PYRIMIDINE

1. <u>Chemical/Physico-chemical properties</u>

Physical appearance: white solid

Melting point: 215-216°C

Molecular formula: $C_{11}H_9Cl_2FN_4$

Molecular weight: 287.13

Optical rotation: $[\alpha]^{25.5}_{D}$ = -56.75° (c=0.53, EtOH)

$[\alpha]^{25.5}_{Hg546}$ = -72.07° (c=0.53, EtOH)

Optical rotation for

S(+)enantiomer: $[\alpha]^{25.5}_{D}$ = + 59.20° (c=0.52, EtOH)

$[\alpha]^{25.5}_{Hg546}$ = + 70.00° (c=0.52, EtOH)

NMR data:

7.65 (dd, 1H, 4'); 7.39 (t, 1H, 5'); 7.23 (dd, 1H, 6'); 6.15 (s, 2H, 2-NH_2); 5.98 (s, 2H, 4-NH_2); 4.88 (quartet (q), 1H, CH_2F); 4.64 (q, 1H, CH_2F)

Representative Na Channel blocker Example 15 (ENa15): R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine methanesulphonate

Methanesulphonic acid (0.158ml, 0.234g, 2.39 x 10^{-3} mole) was added to a suspension of R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine in dry ether (21 ml). The resulting mixture was stirred at room temperature for 2 hrs. The suspension was filtered, washed well with dry ether (5ml), sucked dry and dried under vacuum at room temperature.

Yield 0.911g (93%)

M.p. 245-247°C

Biological Assays

The ability of a compound to act as an NK1 receptor antagonist may be determined using the gerbill foot tapping model as described by Rupniak & Williams, Eur. Jour. of Pharmacol., 1994.

The compound is orally administered and four hours later an NK1 agonist (e.g. delta-Aminovaleryl^6[Pro^9,Me-Leu^{10}]-substance P (7-11)) (3pmol in 5μL icv) is infused directly in the cerebral ventricules of the animals. The duration of hind foot tapping induced by the NK1 agonist (e.g. delta-Aminovaleryl^6[Pro^9,Me-Leu^{10}]-substance P (7-11)) is recorded continuously for 3 min using a stopclock. The dose of the test compound required to inhibit by 50% the tapping induced by the NK1 agonist (e.g. delta-Aminovaleryl^6[Pro^9,Me-Leu^{10}]-substance P (7-11)) expressed as mg/kg is referred to as the ED50 value. Alternatively the compounds may be administered subcutaneously or intraperitoneally.

The ability of the compounds of the invention to modulate the voltage-gated sodium channel subtype NaV 1.3 may be determined by the following assay.

Cell biology

Stable cell lines expressing hNaV1.3 channels were created by transfecting CHO cells with the pCIN5-hNav1.3 vector using the lipofectamine (Invitrogen) transfection method. pCIN5 is a bicistronic vector for the creation of mammalian cell lines that predisposes all

neomycin resistant cells to express recombinant protein (see Rees S., Coote J., Stable J., Goodson S., Harris S. & Lee M.G. (1996) Biotechniques, **20**, 102-112) by virtue of the recombinant cDNA being linked to the neomycin-selectable marker cDNA downstream of the CMV promoter (for full details see Chen YH, Dale TJ, Romanos MA, Whitaker WR, Xie XM, Clare JJ. Cloning, distribution and functional analysis of the type III sodium channel from human brain Eur J Neurosci, 2000 Dec;**12**, 4281-9). Cells were cultured in Iscove's modified Dulbecco's medium (Invitrogen) comprising, 10% fetal bovine serum, 1% L-glutamine, 1% Penicillin-Streptomycin (Invitrogen), 1% non-essential amino acids, 2% H-T supplement and 1% G418 (Invitrogen) and maintained at 37°C in a humidified environment comprising 5% CO2 in air. Cells were liberated from the T175 culture flask for passage and harvesting using Versene (Invitrogen).

Cell preparation

Cells were grown to 60–95% confluence in a T75 flask. Cells were lifted by removing the growth media and incubating with 1.5 ml of warmed (37°C) Versene (Invitrogen, 15040-066) for 6 min. Lifted cells were suspended in 10 ml of PBS (Invitrogen, 14040-133). Cell suspension was then placed into a 10-ml centrifuge tube and centrifuged for 2 min at 700 rpm. After centrifugation, the supernatant was removed and the cell pellet was resuspended

in 3 ml of PBS.

Electrophysiology

Currents were recorded at room temperature (21–23°C) using the IonWorksHT planar array electrophysiology technology (Molecular Devices Corp.). Stimulation protocols and data acquisition were carried out using a microcomputer (Dell Pentium 4). In order to determine planar electrode hole resistances (Rp), a 10 mV, 160 ms potential difference was applied across each hole. These measurements were performed before cell addition. After cell addition a seal test was performed prior to antibiotic (amphotericin) circulation to achieve intracellular access. Leak subtraction was conducted in all experiments by applying a 160 ms hyperpolarizing (10 mV) prepulse 200 ms before the test pulses to measure leak conductance. Test pulses stepping from the holding potential of -90 mV to 0 mV were applied for 20 ms and repeated 10 times at a frequency of 10 Hz. In all experiments, the test pulse protocol was performed in the absence (pre-read) and presence (post-read) of a compound. Pre- and post-reads were separated by a compound addition followed by a 3–3.5 min incubation.

Solutions and drugs

The intracellular solution contained the following (in m*M*): K-gluconate 100, KCl 40mM, MgCl2 3.2, EGTA 3, HEPES 5, adjusted to pH 7.25. Amphotericin was prepared as 30

mg/ml stock solution and diluted to a final working concentration of 0.1 mg/ml in internal buffer solution. The external solution was Dulbecco's PBS (Invitrogen) and contained the following (in m*M*): CaCl2 0.90, KCl 2.67, K3PO4 1.47, MgCl2 0.50, NaCl 138, Na3PO4 8.10, with a pH of 7.4. Compounds were prepared in DMSO as 10mM stock solutions and subsequent 1:3 serial dilutions performed. Finally the compounds were diluted 1:100 in external solution resulting in a final DMSO concentration of 1%.

Data analysis

The recordings were analysed and filtered using both seal resistance (>40 MΩ) and peak current amplitude (>200pA) in the absence of compound to eliminate unsuitable cells from further analysis. Paired comparisons between pre-drug and post-drug additions were used to determine the inhibitory effect of each compound. The concentrations of compounds required to inhibit current elicited by the 1st depolarising pulse by 50% (tonic pIC50) were determined by fitting of the Hill equation to the concentration response data. In addition the use-dependent inhibitory properties of the compounds were determined by assessing the effect of compounds on the 10th versus 1st depolarising pulse. The ratio of the 10th over 1st pulse was calculated in the absence and presence of drug and the % use-dependent inhibition calculated. The data was fitted using the same equation as for the tonic pIC_{50} and the concentration producing 15% inhibition (use-dependent pUD_{15}) calculated.

PreClinical Experiments

Rat MEST model

Experimental Preparation

This work was conducted in compliance with the Home Office Guidance on the operation of the Animals (Scientific Procedures) Act 1986 and GlaxoSmithKline ethical standards. Male CD rats (100-145g) were supplied by Charles River, UK. Animals were group housed (6 animal per cage) with free access to food (Standard rodent chow; Harlan, UK) and water under a 12 h light/dark cycle (lights on at 0700h). A period of at least one week between arrival at GSK and the study was allowed in all cases.

Experimental Protocol

Animals were administered a test compound at the appropriate dose, route and pre-treatment time and returned to their home cage. Testing occured in a separate room from that used for housing. Testing involved determining the threshold for tonic hindlimb

extensor seizures using a Hugo Sachs Electronik stimulator which delivers a constant current of 0.3 second duration, 50Hz, sinewave form, fully adjustable between 1 and 300 mA. Stimuli were delivered via corneal electrodes (Stean TO, Atkins AR, Heidbreder CA, Quinn LP, Trail BK, Upton N. (2005) Br J Pharmacol.144(5):628-35). Seizure threshold was determined using the 'up and down' method of Kimball et al. (1957)(Kimball AW, Burnett WT Jr, Doherty DG. (1957) Radiat Res. 7(1):1-12). The first animal tested in each group was stimulated with a current that might be expected to be close to the threshold for induction of a seizure. If a tonic seizure was not induced, then then next animal in the group received a stimulus 5 mA higher. If a tonic seizure was induced, then the next animal received a stimulus 5 mA lower. This is repeated for all animals within the control (vehicle) group. In the case of groups treated with a sodium channel blocker steps of 10 to 30 mA were used.

Satellite animals (n=3/group) received the same drugs or combinations of drugs as the test groups, and were culled at the appropriate time after dosing. Blood and brain samples were taken for analysis of the drug concentrations in these compartments.

Drugs and Materials

All doses were calculated as base. **ENa9** and **ENa13** were dosed via the subcutaneous (s.c.) route at 1 ml/kg in a 2% v/v DMSO/saline vehicle 30 minutes prior to test. **ENa7** and **ENa14** were dosed orally (p.o.) in a 1% w/v methylcellulose/water vehicle at 2 ml/kg, 60 minutes before test. Compound **ENK6** was dosed with via the intraperitoneal (i.p.) route 60 minutes before the test or via the s.c. route 15 minutes before test. In both cases **ENK6** was dissolved in saline.

Data Analysis

Induction of seizure is measured as an all-or-nothing effect scored as either present (+) or absent (0) for each animal. The data for each treatment group were recorded as the number of +'s and 0's at each current level employed and this information was then used to calculate the CC50 value (current required for 50% of animals to show seizure behaviour) + standard error of the mean according to the method of Kimball et al. (1957). Drug effects were calculated as the % change in CC50. Significant differences between drug-treated animals and appropriate vehicle treated groups were assessed according to the methods of Litchfield and Wilcoxon (1949). The statistical significance of differences between sodium channel blocker alone or in combination with **ENK6** was assessed using a Student's t test.

ENa9 / ENK6 combination

A dose of 3mg/kg s.c. of **ENa9** gave a small, but significant increase in seizure threshold in the MEST, whereas a lower dose of 1mg/kg s.c. was inactive. **ENK6** (30mg/kg i.p.) had no effect on seizure threshold when administered alone. However, in the presence of **ENK6**, **ENa9** significantly increased seizure threshold at the low dose of 1mg/kg s.c. (133% increase in CC50(mA)) and produced a significantly larger increase at 3mg/kg s.c. (323% increase in CC50(mA)) (Figure 1).

Figure 1

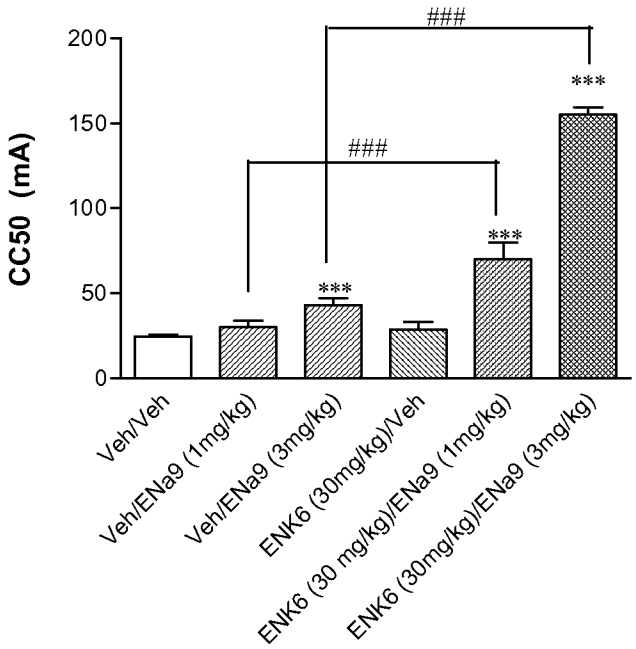


Figure 1: *Effects of* ***ENa9*** *and* ***ENK6*** *in the rat MEST model.* ***ENK6*** *(30 mg/kg, ip, 60 min ptt);* ***ENa9*** *(1.0 & 3.0 mg/kg, sc, 30 min ptt). ***p<0.001 vs corr vehicle, Wilcoxon Test. ### p<0.001 Vs corr vehicle/ENa9 group, t-test.*

No increase in blood or brain concentration of ENa9 was observed in the presence of ENK6 (Table 1), suggesting that a PK interaction does not explain the increased PD effect.

Table 1

		Blood (ng/mL)	Brain (ng/g)

ENK6 (mg/kg)	ENa9 (mg/kg)	ENK6	ENa9	ENK6	ENa9
veh	1		188		1171
veh	3		349		2301
30	veh	631*		1506*	
30	1	471	246	1162	1339
30	3	414	456	881	2621

Table 1: *Blood and brain concentrations of* ***ENa9*** *and* ***ENK6*** *in satellite animals (n=2 per group, except *n=1). Small differences in exposure are within inter-animal variability.*

ENa13/ ENK6 combination

A dose of 3mg/kg s.c. of **ENa13** was found to give a robust and significant increase in seizure threshold, whereas a lower dose of 1mg/kg s.c. was inactive. **ENK6** (30mg/kg i.p.) had no effect on seizure threshold when administered alone. In the presence of **ENK6**, **ENa13** produced a significant increase in seizure threshold at 1mg/kg (118% increase in CC50(mA)) and also a significant increase in seizure threshold at 3mg/kg (129% increase in CC50(mA)) (Figure 2).

Figure 2

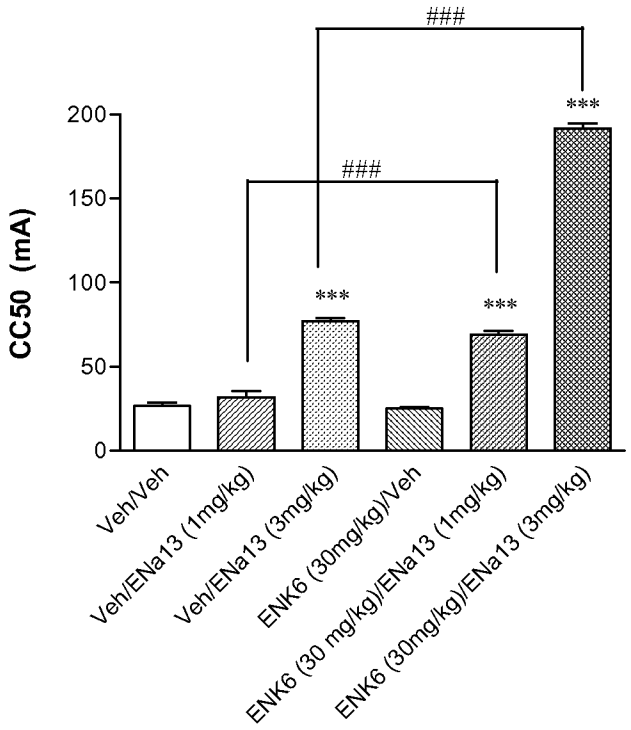


Figure 2: *Effects of* ***ENa13*** *and* ***ENK6*** *in the rat MEST model.* ***ENK6*** *(30 mg/kg, ip, 60 min ptt); GSK1061436A (1.0 & 3.0 mg/kg, sc, 30 min ptt). ***p<0.001 vs corr vehicle, Wilcoxon Test; ### p<0.001 Vs corr vehicle/'ENa13, t-test.*

No increase in the concentration of **ENa13** was observed in the presence of the NK1 antagonist (Table 2); suggesting that a PK interaction does not explain the increased PD effect.

Table 2

		Blood (ng/mL)		Brain (ng/g)	
ENK6 (mg/kg)	**ENa13 (mg/kg)**	**ENK6**	**ENa13**	**ENK6**	**ENa13**
veh	1		499		478
veh	3		1824		1825
30	veh	558*		1263*	
30	1	456	416	1035	508
30	3	1209	1160	4802	1235

Table 2: *Blood and brain concentrations of* ***ENa13*** *and* ***ENK6*** *in satellite animals (n=2 per group, except *n=1). Differences in concentrations of the sodium channel blocker are within inter-animal variability.*

ENa7 / ENK6 Combination

ENa7 was administered orally to rats 60 minutes before the test, whereas **ENK6** was administered subcutaneously 15 minutes before testing. Satellite animals were similarly dosed to provide estimates of blood and brain concentrations of the two drugs. A dose of 1mg/kg p.o. of lamotrigine was tested, as well as a dose of 3mg/kg p.o.. Two independent experiments were conducted, the first using 10mg/kg s.c. of **ENK6** and the second using 30mg/kg s.c. of **ENK6**. In each experiment **ENK6** alone had no effect on seizure threshold, whereas as expected, **ENa7** alone at 1mg/kg produced little or no increase in seizure threshold, the higher dose of 3mg/kg significantly increased seizure threshold by 128 – 205%. In the presence of **ENK6**, lamotrigine significantly increased seizure threshold at the dose of 1mg/kg (61% increase in CC50(mA) in the first experiment and 145% increase in CC50(mA) in the second experiment), and produced a near-maximal increase in threshold with the dose of 3mg/kg (233% increase in CC50(mA) in the second

experiment) (Figures 3 & 4). Blood and brain concentrations of **ENa7**, measured in satellite animals, are reporte in Tables 3 & 4.

Figure 3

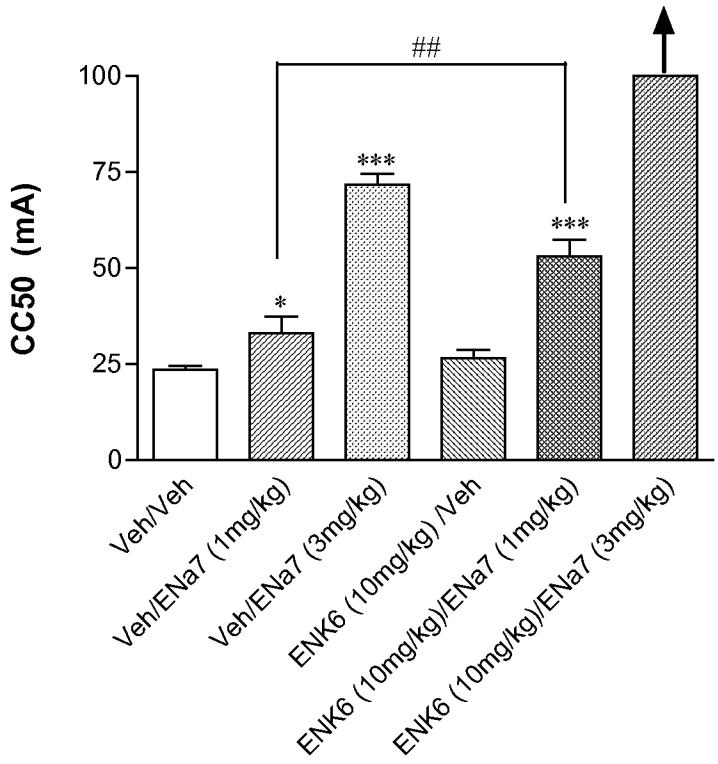


Figure 3: *Effects of **ENa7** and **ENK6** (10mg/kg s.c.) in the rat MEST model. ENK6 (10 mg/kg, sc, 15 min ptt); **Ena7** (1 & 3 mg/kg, po, 60 min ptt). The vertical arrow indicates that the CC50 value could not be determined, but was greater than 180mA (>780% increase). *p<0.05, ***p<0.001 vs corr vehicle, Wilcoxon Test. ##p<0.01 Vs corr vehicle/ENa7 group, t-test.*

Figure 4

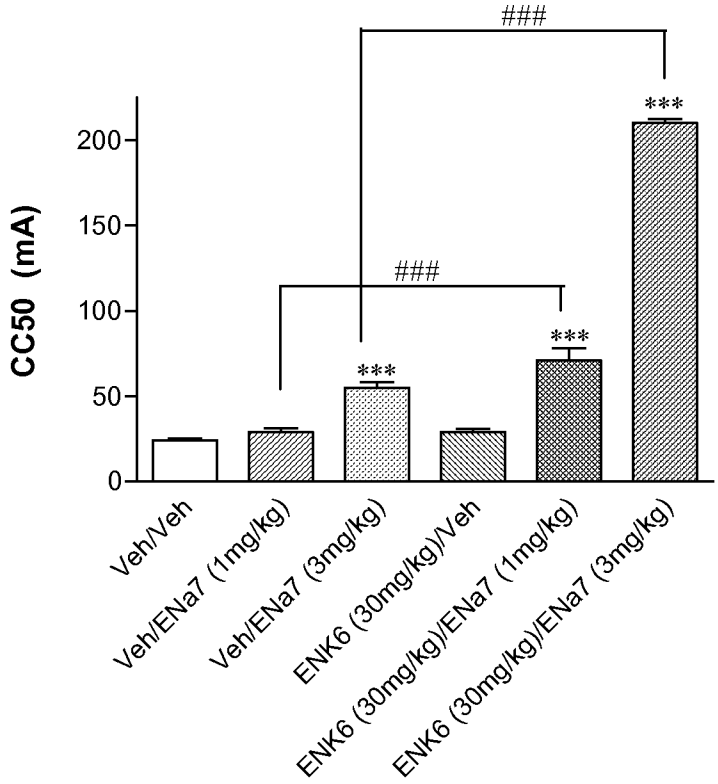


Figure 4: *Effects of **ENa7** and **ENK6** (30mg/kg s.c.) in the rat MEST model. **ENK6** (30 mg/kg, sc, 15 min ptt); Ena7 (1 & 3 mg/kg, po, 60 min ptt). ***p<0.001 vs corr vehicle, Wilcoxon Test. ### p<0.001 Vs corr vehicle/ENa7 group, t-test.*

Blood and brain concentrations of **ENa7**, measured in satellite animals, are reported in Tables 3 & 4.

Table 3

		Blood (ng/mL)		Brain (ng/g)	
ENK6 (mg/kg)	**ENa7 (mg/kg)**	**ENK6**	**ENa7**	**ENK6**	**ENa7**
veh	1	-	311*	-	517*
veh	3	-	1180*	-	2829*
10	veh	839	-	1420	-
10	1	635	581	1254	1125
10	3	732	1603	1504	2855

Table 3: *Blood and brain concentrations of* ***ENa7*** *and* ***ENK6*** *in satellite animals (n=2-3 per group, except *n=1). Differences in concentrations of the sodium channel blocker are within inter-animal variability.*

Table 4

		Blood (ng/mL)		Brain (ng/g)	
ENK6 (mg/kg)	**ENa7 (mg/kg)**	**ENK6**	**ENa7**	**ENK6**	**ENa7**
veh	1	-	352*	-	588*
veh	3	-	1354*	-	2192*
30	veh	1886	-	4495	-
30	1	1542	461	3343	752
30	3	1481	1404	2484	2096

Table 4: *Blood and brain concentrations of* ***ENa7*** *and* ***ENK6*** *in satellite animals (n=2 per group except * n=1). Differences in concentrations of the sodium channel blocker are within inter-animal variability.*

ENa15 + ENK6

ENa15 was administered orally to rats 60 minutes before the test, **ENK6** (30mg/kg) was administered subcutaneously 15 minutes before testing. Satellite animals were similarly dosed to provide estimates of blood and brain concentrations of the two drugs. A dose of 0.3mg/kg p.o. of **ENa15** was tested, as well as a dose of 1mg/kg p.o.. **ENK6** alone had no effect on seizure threshold. **ENa15** alone at 0.3mg/kg produced no increase in seizure threshold, whereas the higher dose of 1mg/kg significantly increased seizure threshold by 292%. In the presence of **ENK6**, **ENa15** significantly increased seizure threshold at the previously inactive dose of 0.3mg/kg (176% increase in CC50(mA)), and also produced a significant increase in threshold at 1mg/kg (51% increase in CC50(mA)) (Figure 5).

Figure 5

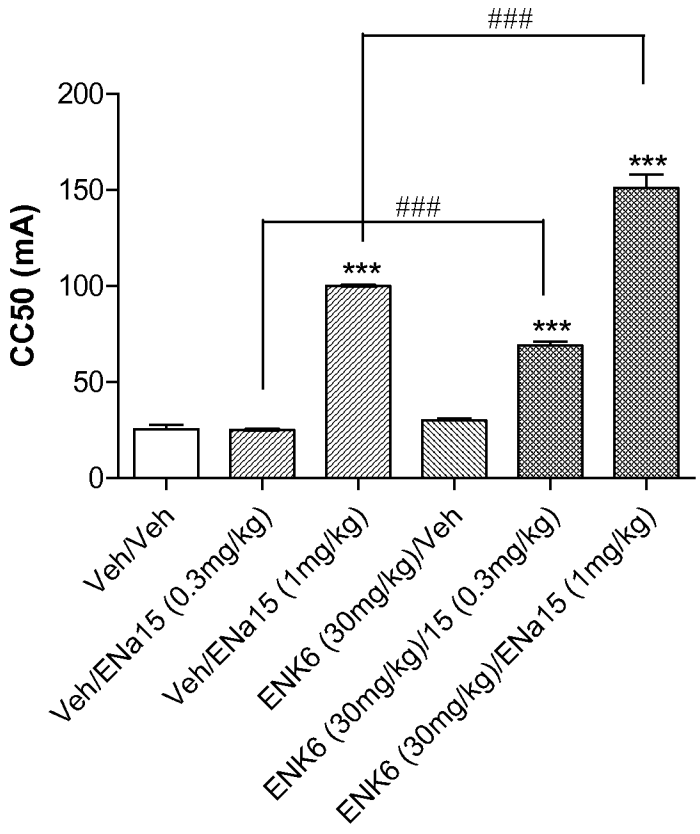


Figure 5: *Effects of* ***ENa15*** *and* ***ENK6*** *(30mg/kg s.c.) in the rat MEST model.* ***ENK6*** *(30 mg/kg, sc, 15 min ptt);* ***ENa15*** *(0.3 & 1 mg/kg, po, 60 min ptt). ***p<0.001 vs corr vehicle, Wilcoxon Test. ### p<0.001 Vs corr vehicle/****ENa15*** *group, t-test.*

FCA (Freunds Complete Adjuvant) model of inflammatory hypersensitivity to pain

This following series of studies demonstrates that the combination of a Sodium Channel compound (ENa7) and an NK1 antagonist (ENK6) produces a synergistic effect in the FCA model of inflammatory hypersensitivity to pain:

a) the effect of ENa7 alone and ENK6 alone on the FCA induced hypersensitivity to pain is tested; the purpose of this study is to determine the ED20 dose for the combination study;

b) then the combination of ENa7 and ENK6 (ED20 doses) on the FCA induced hypersensitivity is evaluated;

c) combination of ENa7 and ENK6 as fixed dose ratio (1:1.25) on the FCA induced hypersensitivity to pain is evaluated.

a)The effect of ENa7 alone and ENK6 alone on the FCA induced hypersensitivity to pain

Method

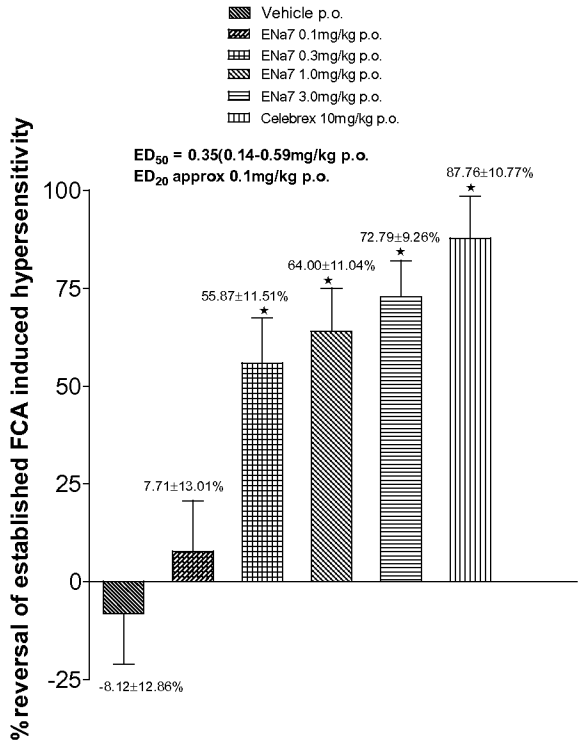
- Naïve weight bearing readings were taken. The hypersensitivity to pain was measured using the Rat incapacitance tester (Linton instruments). This instrument is serviced once a year and should be regularly calibrated
- All rats then received an intraplantar injection of 100ul of FCA (Freund's complete adjuvant) into the left hind paw. The FCA was sonicated for 15 minutes prior to use.
- Approximately 23hrs after administration of the FCA, pre-dose weight bearing readings were taken. All animals were then ranked and randomised for dosing according to their FCA window *(predose difference in grams – naïve difference in grams).* Rats with FCA window less than 30g were excluded from the study.
- Animals were then dosed with vehicle (1% methylcellulose) s.c or, ENK6 0.1-3mgkg s.c or ENa7 0.1-3mg/kg p.o. Celebrex 10mg/kg p.o. (positive control) as appropriate according to ranking and randomisation.
- Animals were assessed in the weight bearing apparatus 1hour post dose.
- The study was blind and randomised by FCA window using the Latin square method.
- % reversals were calculated by using the naïve, pre-dose and post dose values as follows: *% Reversal = [(Pre-dose – Post-dose) / (Pre-dose – Naïve)] x100*
- Graphs and ED50 were calculated where appropriate using Prism4.
- Statistical analysis was carried out using ANOVA followed by calculating the least square means using the statistical package Statistica 6.1
- From the dose response curves the ED20 was determined for the combination study

Results

- Effect of ENa7 alone on the FCA induced hypersensitivity to pain

ENa7 (0.1-3.0mg/kg p.o,) produced a dose related reversal of the FCA induced hypersensitivity with an ED50 of 0.35(0.14-0.59)mg/kg p.o.. The ED20 was 0.2mg/kg p.o. (Figure 6).

Figure 6

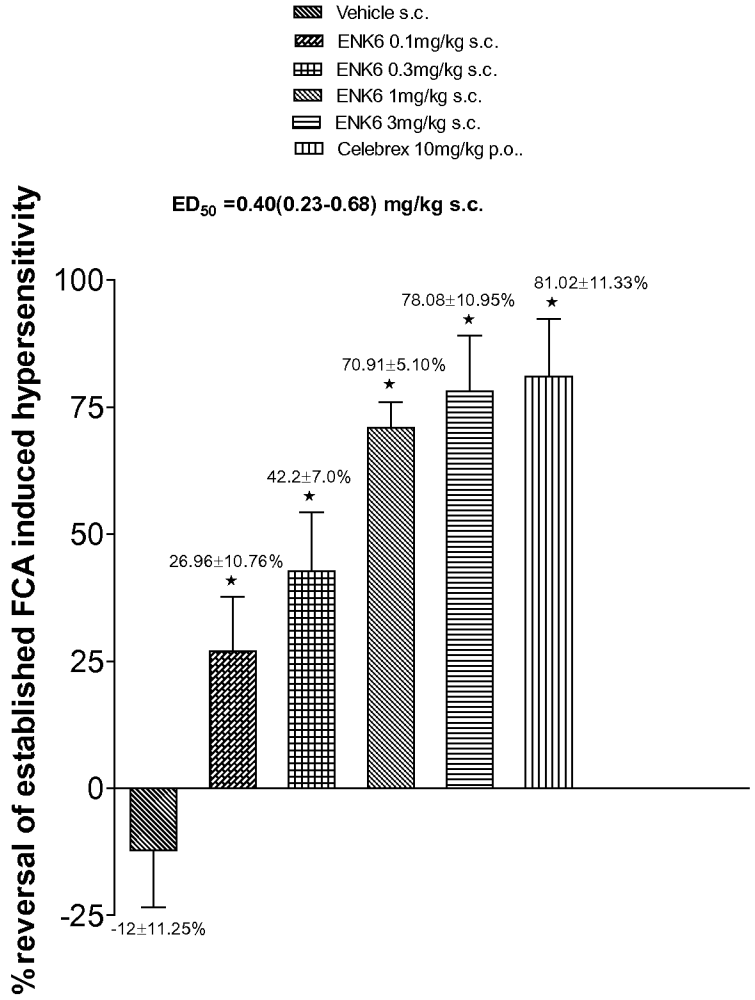


- Effect of ENK6 alone on the FCA induced hypersensitivity to pain

ENK6 (0.1-3.0mg/kg p.o.) produced a dose related reversal of the FCA induced hypersensitivity with an ED50 of 0.40(0.23-0.68)mg/kg p.o.. The ED20 was calculated to be 0.08mg/kg p.o.

(Figure 7)

Figure 7



The fixed dose ratio is therefore calculated to be 1.25:1. This ratio is used to calculate the doses for the fixed dose ratio studies.

b) The effect of combination of ENa7 and ENK6 (ED20doses) on the FCA induced hypersensitivity to pain

Method

- Naïve weight bearing readings were taken. The hypersensitivity to pain was measured using the Rat incapacitance tester (Linton instruments). This instrument is serviced once a year and should be regularly calibrated
- All rats then received an intraplantar injection of 100ul of FCA (Freund's complete adjuvant) into the left hind paw. The FCA was sonicated for 15 minutes prior to use.
- Approximately 23hrs after administration of the FCA, pre-dose weight bearing readings were taken. All animals were then ranked and randomised for dosing according to their FCA window *(predose difference in grams – naïve difference in grams).* Rats with FCA window less than 30g were excluded from the study.
- Animals were then dosed with vehicle with vehicle p.o. or ENa7 0.1mg/kg p.o.. 30mins later animals were dose again with Vehicle or ENK6 0.08mg/kg s.c. according to ranking and randomisation. See table 5 for details of the groups
- Animals were assessed in the weight bearing apparatus 1hour post dose.
- The study was blind and randomised by FCA window using the Latin square method.
- % reversals were calculated by using the naïve, pre-dose and post dose values as follows: *% Reversal = [(Pre-dose – Post-dose) / (Pre-dose – Naïve)] x100*
- Statistical analysis was carried out using ANOVA followed by calculating the least square means using the statistical package Statistica 6.1
- ED50 and ED20 values and graphs were calculated using prism5

Table 5

Treatment	**Dose mg/kg**	**Dose vol.**	**Route**	**n**	**group**
100µl FCA + Vehicle p.o. 30mins later Vehicle s.c..	-	5	p.o.	6	A
100µl FCA + ENa7 0.1mg/kg p.o. 30mins later Vehicle s.c.		5	p.o.	6	B

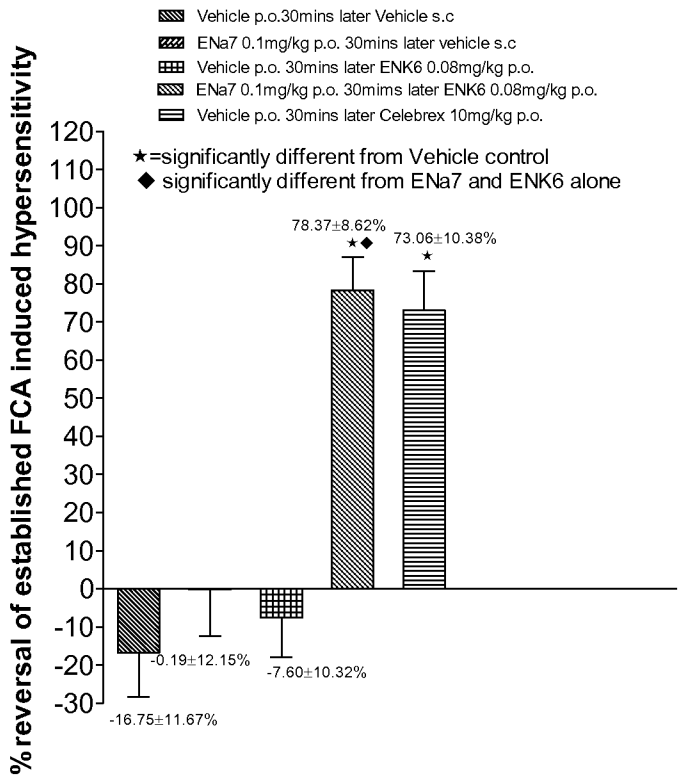
100µl FCA + Vehicle p.o.30mins later ENK6 0.08mg/kg s.c.		5	p.o.	6	C
100µl FCA + Lamotrigine 30mins later ENa7		5	p.o.	6	D
100µl FCA + Vehicle p.o.30mins later Celebrex 10mg/kg p.o.		5	p.o	6	E

Results

- Effect combination of ENa7 and ENK6 (ED20doses) on the FCA induced hypersensitivity to pain

The combination study used a dose of ENa7 of 0.1mg/kg p.o. and ENK6 0.08mg/kg p.o. (ED20 doses); the combination produced a marked reversal of the FCA induced hypersensitivity which was at least additive. (Figure 8)

Figure 8



c) Method for testing ENa7/ENK6 combination at a fixed dose ratio (1:1.25)

- Naïve weight bearing readings were taken. The hypersensitivity to pain was measured using the Rat incapacitance tester (Linton instruments). This instrument is serviced once a year and should be regularly calibrated
- All rats then received an intraplantar injection of 100ul of FCA (Freund's complete adjuvant) into the left hind paw. The FCA was sonicated for 15 minutes prior to use.
- Approximately 23hrs after administration of the FCA, pre-dose weight bearing readings were taken. All animals were then ranked and randomised for dosing according to their FCA window *(predose difference in grams – naïve difference in grams).* Rats with FCA window less than 30g were excluded from the study.
- Animals were then dosed with the following in a fixed dose ratio of 1.25:1according to ranking and randomisation. (Table 6)

Table 6

Treatment **Fixed dose ratio 1.25:1**	**n**	**group**
100µl FCA + Vehicle p.o 30mins later Vehicle s.c.	6	A
100µl FCA + ENa7 0.1mg/kg p.o 30mins later ENK6 0.08mg/kg s.c	6	B
100µl FCA + ENa7 0.03mg/kg p.o. 30mins later ENK6 0.024mg/kg s.c.	6	C
100µl FCA + ENa7 0.01mg/kg p.o. 30mins later ENK6 0.008mg/kg s.c	6	D
100µl FCA + ENa7 0.003mg/kg p.o. 30mins later ENK6 0.0024mg/kg s.c.	6	E
100µl FCA + Vehicle p.o 30mins later Celebrex 10mg/kg p.o.	6	F

- Animals were assessed in the weight bearing apparatus 1hour post dose.
- The study was blind and randomised by FCA window using the Latin square method.
- % reversals were calculated by using the naïve, pre-dose and post dose values as follows: *% Reversal = [(Pre-dose – Post-dose) / (Pre-dose – Naïve)] x100*

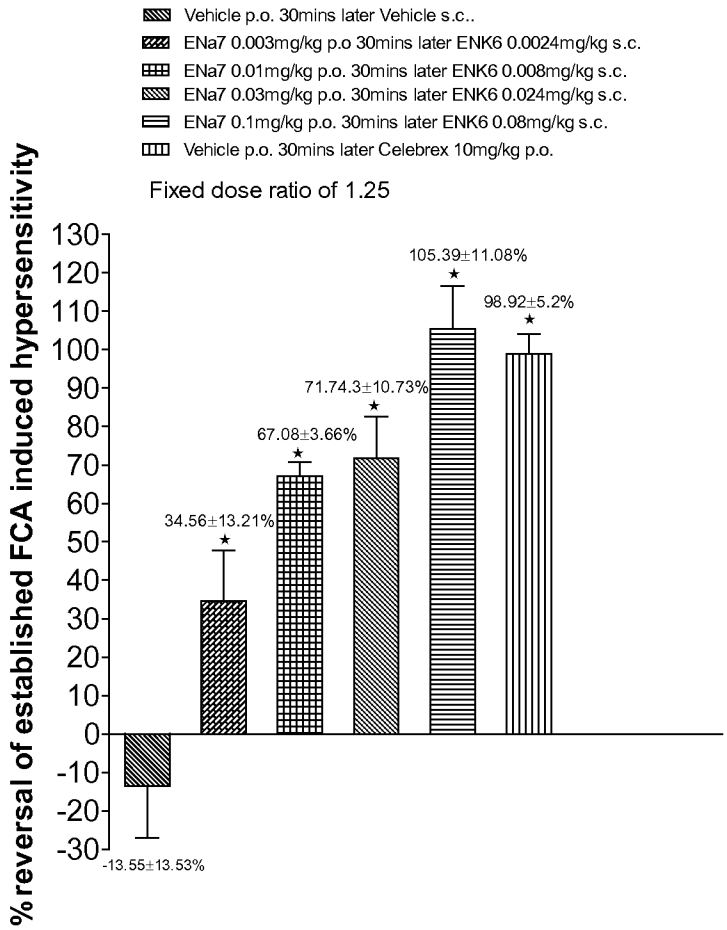
- The data was analysed using the FCA macro written in excel (version 1.5) developed by Paul Lloyd. Graphs and ED50 were calculated where appropriate using Prism5
- Statistical analysis was carried out using ANOVA followed by calculating the least square means using the statistical package Statistica 6.1

Results

- Effect combination of ENa7 and ENK6 (Fixed dose ratio 1.25:1)on the FCA induced hypersensitivity to pain

The combination of ENa7 and ENK6 produced a dose related reversal of the FCA induced hypersensitivity. Analysis of the data using Statistica demonstrated that this effect was highly synergistic(Figure 9).

Figure 9



Summary of Results:

ENK6 produces a dose related reversal of FCA induced hypersensitivity. ED20 is calculated to be approx 0.08mg/kg s.c

ENa7 produces a dose related reversal of FCA induced hypersensitivity. ED20 is calculated to be approx 0.1mg/kg p.o.

The ED20's of ENa7 and ENK6 has no significant effect on the FCA induced hypersensitivity

The combination of ENa7 and ENK6 produces a very marked reversal of FCA induced hypersensitivity which is not significantly different to Celebrex; the effect is at least additive.

The fixed dose ratio is 1.25; the fixed dose ratio study shows there is highly significant synergy when ENa7 is combined with the NK1 antagonist ENK6.

Thus, the data show that ENa7 in combination with ENK6 produces a highly synergistic effect.

Claims

1. A pharmaceutical composition comprising an NK1 receptor antagonist and a sodium channel blocker, wherein at least one of them is at sub therapeutic dose, as a combined preparation for simultaneous or sequential administration.

2. A pharmaceutical composition according to claim 1, wherein the sodium channel blocker is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, or a pharmaceutically acceptable salt, prodrug or solvate thereof.

3. A pharmaceutical composition according to claim 1, wherein the sodium channel blocker is R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, or a pharmaceutically acceptable salt, prodrug or solvate thereof

4. A pharmaceutical composition according to claim 1, for use in therapy.

5. A pharmaceutical composition according to claim 1, for use in the treatment of epilepsy, mood disorders or pain.