

New treatments for Pain

The present invention describes compounds that bind to the Son of Sevenless homolog
5 1 receptor (SOS1) protein thereby inhibiting a cascade pathway, leading to a reduction in pain.

There remains a need for novel treatments for the treatment of pain. Many of the most
efficacious and frequently prescribed pain treatments are opioids. These drugs have a
10 high potential for abuse and addiction. However, to date there are no treatments of
comparable efficacy to replace them as front-line treatments. To provide a paradigm shift
in the treatment of pain requires the identification of new targets and pathways within the
body.

15 This application describes novel SOS1 inhibitors suitable for the treatment of Pain and
cancer.

SOS1 inhibitors have recently been identified capable of mediating several conditions:

20 WO2019/122129 describes benzylamino substituted pyridopyrimidines as SOS1
inhibitors useful in the treatment of cancerous growth in oncology.

WO2018/115380 describes benzylamino substituted quinazolines as SOS1 inhibitors,
similarly useful in the treatment of cancerous growth in oncology.

25 WO2018/172250 describes a genus of 2 methyl quinazolines for use in treating hyper-
proliferative diseases.

WO2019/201848 describes a further genus of 2 methyl quinazolines for use in treating
30 hyper-proliferative diseases.

Further SOS1 inhibitors are taught in Proceedings of the National Academy of Sciences
of the United States of America (2019), 116(7), 2551-2560.

35 The present invention provides novel SOS1 inhibitors, novel SOS1 inhibitors for use in
the treatment of Pain and novel SOS1 inhibitors for use in the treatment of cancer.

Figures

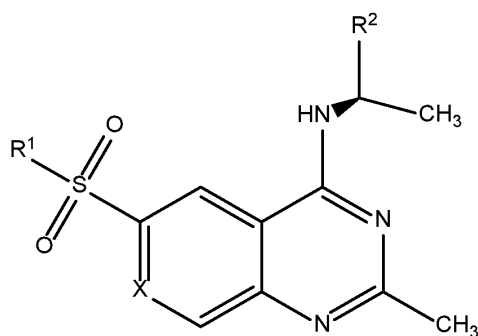
Fig 1. NGF signal transduction pathway leading to pain and the clinical drugs that
 5 validate the pathway. NGF binds to TrkA and subsequent signal transduction culminates
 in the nuclear accumulation of diphosphorylated Extracellular signal-regulated kinase
 (dppERKnuc) in neurons, upregulating pain genes.

Fig 2. Clinical genetic validation of the target. In NF1, patients have a mutation in the
 10 neuronal gap protein (NF1). The mutation causes a loss of function, preventing the
 normal turnover of GTP on RAS_{GTP} to GDP in turn increasing the concentration of
 RAS_{GTP} and leading to excess signalling, tumours and pain.

Summary of invention

15 This application describes novel SOS1 inhibitors, their use to treat pain and their use to
 treat cancer.

The present invention provides compounds of formula (I)
 20



Or a pharmaceutically acceptable salt or solvate thereof, wherein:

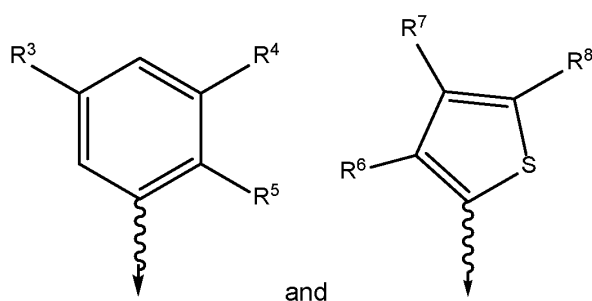
25 X is N or CR²⁵

R¹ is selected from a N containing 4-7 membered saturated heterocycle, optionally
 containing an additional O, N or S atom, or S(O)₂ moiety. Said heterocycle optionally
 containing:

30 (i) an ether bridge, or

- (ii) joining another 4-7membered, N containing, saturated heterocycle to form a spiro bicyclic group; or
- (iii) joining with another 3-6 membered N containing saturated heterocycle, such that the rings share two atoms in common, said saturated heterocycle
- 5 optionally incorporating a C(O) moiety;
- said monocyclic or bicyclic heterocycle optionally substituted by 1-3 substituents, each independently selected from NC(O)C₁₋₆ alkyl, H, N(C₁₋₆ alkyl)(C₁₋₆ alkyl), C₁₋₆ alkyl, C(O)C₁₋₆ alkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, OH and O-C₁₋₆ alkyl, HC(O)C₁₋₆ alkyl, halo and Ph.

10 R² is selected from



R³ is H or NH₂

15

R⁴ is CF₃, CF₂CH₂OH, CN

R⁵ is halo

20 R⁶ is H

R⁷ is H

R⁸ is Ph, ortho substituted by CH₂NHCH₃

25

R²⁵ is H, OCH₃, F and CN

The present invention provides SOS1 inhibitors for use in the treatment of Pain.

The present invention provides SOS1 inhibitors for use in the treatment of Cancer.

30

The present invention provides novel compounds, uses of the compounds as medicaments, pharmaceutical compositions and pharmaceutical products as set out in the appended claims. Other features of the invention will be apparent from the dependent claims, and the description that follows.

5

Unless otherwise stated, the following terms used in the specification and claims have the meanings set out below.

The term "comprising" or "comprises" means including the component(s) specified but not to the exclusion of the presence of other components. The term "consisting essentially of" or "consists essentially of" means including the components specified but excluding other components except for materials present as impurities, unavoidable materials present as a result of processes used to provide the components, and components added for a purpose other than achieving the technical effect of the invention. The term "consisting of" or "consists of" means including the components specified but excluding other components.

Whenever appropriate, depending upon the context, the use of the term "comprises" or "comprising" may also be taken to include the meaning "consists essentially of" or "consisting essentially of", and may also be taken to include the meaning "consists of" or "consisting of".

The optional features set out herein may be used either individually or in combination with each other where appropriate and particularly in the combinations as set out in the accompanying claims. The optional features for each aspect or exemplary embodiment of the invention, as set out herein are also applicable to all other aspects or exemplary embodiments of the invention, where appropriate. In other words, the skilled person reading this specification should consider the optional features for each aspect or exemplary embodiment of the invention as interchangeable and combinable between different aspects and exemplary embodiments.

References to "treating" or "treatment" include prophylaxis as well as the alleviation of established symptoms of a disease or medical condition. "Treating" or "treatment" of a disease or medical condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the disease or medical condition developing in a human that may be afflicted with or predisposed to the disease or medical condition but does not yet experience or display clinical or subclinical symptoms thereof, (2) inhibiting

the disease or medical condition, *i.e.* arresting, reducing or delaying the development of the disease or medical condition, or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, *i.e.* causing regression of the disease or medical condition or at least one of its
5 clinical or subclinical symptoms.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the
10 compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

The term "(C₁₋₆)alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl,
15 *tert*-butyl and *n*-pentyl.

The term "halo" refers to one of the halogens, group 17 of the periodic table. In particular, the term refers to fluoro, chloro, bromo and iodo. Preferably, the term refers to fluoro or chloro, most preferably fluoro.
20

Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted by one or more substituents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a group. Where there are two or more substituents, the
25 substituents may be the same or different.

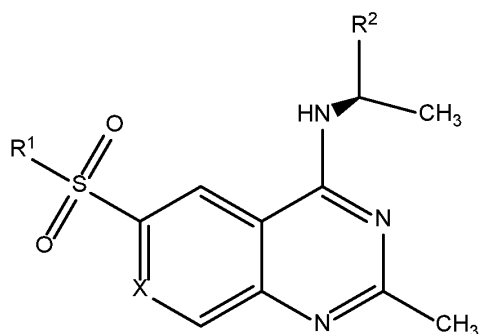
Substituents are only present at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without undue effort which substitutions are chemically possible.
30

The phrase "compound of the invention" means those compounds, *i.e.* of formula (I), that are disclosed herein, both generically and specifically.

Compounds

35

The present invention provides a compound of formula (I):



Or a pharmaceutically acceptable salt or solvate thereof, wherein:

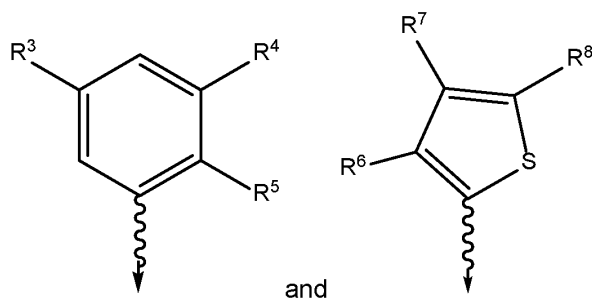
- 5 X is N or CR¹⁹

R¹ is selected from a N containing 4-7 membered saturated heterocycle, optionally containing an additional O, N or S atom, or S(O)₂ moiety. Said heterocycle optionally containing:

- 10 (iv) an ether bridge, or
 (v) joining another 4-7membered, N containing, saturated heterocycle to form a spiro bicyclic group; or
 (vi) joining with another 3-6 membered N containing saturated heterocycle, such that the rings share two atoms in common, said saturated heterocycle
 15 optionally incorporating a C(O) moiety;

said monocyclic or bicyclic heterocycle optionally substituted by 1-3 substituents, each independently selected from NC(O)C₁₋₆ alkyl, H, N(C₁₋₆ alkyl)(C₁₋₆ alkyl), C₁₋₆ alkyl, C(O)C₁₋₆ alkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, OH and O-C₁₋₆ alkyl, HC(O)C₁₋₆ alkyl, halo and Ph.

- 20 R² is selected from



R³ is H or NH₂

R^4 is CF_3 , CF_2CH_2OH , CN

R^5 is halo

5

R^6 is H

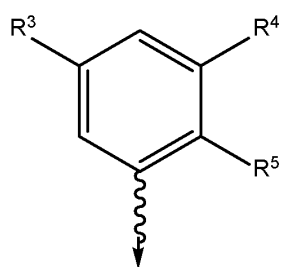
R^7 is H

10 R^8 is Ph, ortho substituted by CH_2NHCH_3

R^{25} is H, OCH_3 , F and CN

In a suitable embodiment R^2 is

15



R^3 is H or NH_2

Preferably R^3 is H

20

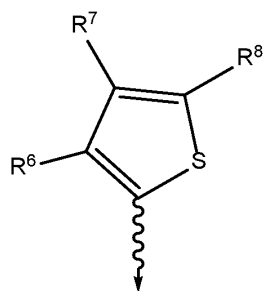
R^4 is CF_3 , CF_2CH_2OH , CN

Preferably R^4 is CF_3

R^5 is halo

25 Preferably R^5 is F

In another suitable embodiment R^2 is



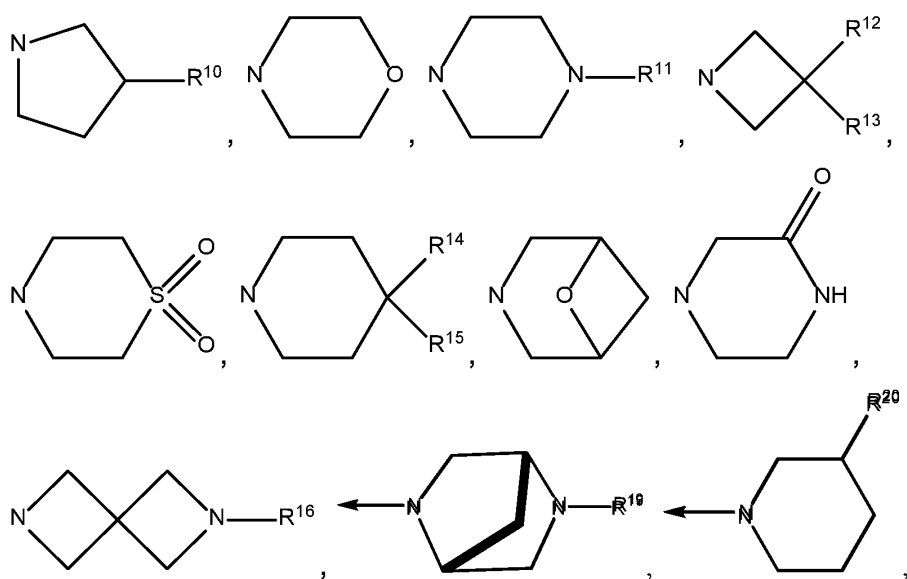
R^6 is H

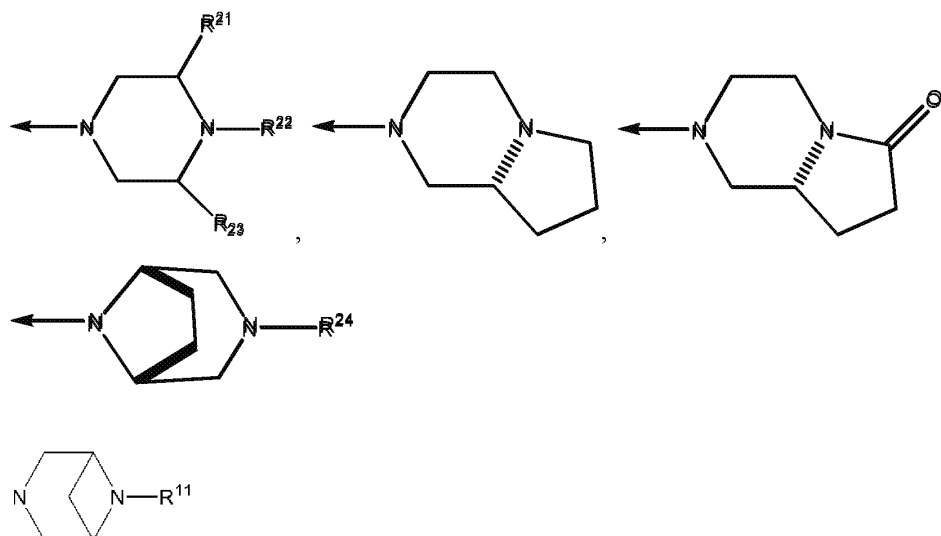
5 R^7 is H

R^8 is Ph, ortho substituted by CH_2NHCH_3

Preferably, R^1 is selected from:

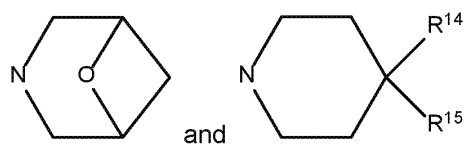
10





5 And $NR^{17}R^{18}$,

Suitably R^1 is selected from



10

Wherein

R^{10} is selected from $NC(O)C_{1-6}$ alkyl, H, $N(C_{1-6}$ alkyl)(C_{1-6} alkyl)

15 Suitably R^{10} is selected from $NC(O)CH_3$, H, $N(CH_3)_2$

R^{11} is selected from C_{1-6} alkyl, $C(O)C_{1-6}$ alkyl, C_{1-6} alkyl-O- C_{1-6} alkyl, OH and O- C_{1-6} alkyl

Suitably, R^{11} is selected from CH_3 , $C(O)CH_3$, CH_2OCH_3 , OH,

20 R^{12} is selected from $NHC(O)C_{1-6}$ alkyl, C_{1-6} alkyl, H

Suitably R^{12} is selected from $NHC(O)CH_3$, CH_3 , H.

R^{13} is selected from $NHC(O)C_{1-6}$ alkyl, C_{1-6} alkyl, H

Suitably R^{13} is selected from $NHC(O)CH_3$, CH_3 , H.

25

R¹⁴ is selected from halo, OH, OC₁₋₆ alkyl, H

Suitably R¹⁴ is selected from F, OH and H.

Most suitably R¹⁴ is H

5

R¹⁵ is selected from halo, OH, OC₁₋₆ alkyl, H

Suitably R¹⁵ is selected from F, OH and H.

Most suitably R¹⁵ is OH

10

R¹⁶ is selected from C(O)C₁₋₆ alkyl

Suitably R¹⁶ is selected from C(O)CH₃

R¹⁷ is selected from C₁₋₆ alkyl, H, Ph

15 Suitably R¹⁷ is selected from CH₃, H & Ph

R¹⁸ is selected from C₁₋₆ alkyl, H, Ph

Suitably R¹⁸ is selected from CH₃, H & Ph

20 R¹⁹ is selected from C(O)C₁₋₆ alkyl

Suitably R¹⁹ is selected from C(O)CH₃

R²⁰ is OH

25 R²¹ is selected from C₁₋₆ alkyl or H

Suitably R²¹ is selected from CH₃ or H

R²² is selected from C₁₋₆ alkyl, H, C(O)C₁₋₆ alkyl and C(O)NHC₁₋₆ alkyl

Suitably R²² is selected from CH₃, H, C(O)CH₃ and C(O)NHCH₃

30

R²³ is selected from C₁₋₆ alkyl and H

Suitably R²³ is selected from CH₃ and H

R²⁴ is C(O)C₁₋₆ alkyl

35 Suitably R²⁴ is C(O)CH₃

In one embodiment R²¹ & R²³ are CH₃ and R²² is H

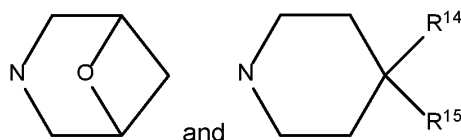
In one embodiment R^{21} & R^{23} are H and R^{22} is $C(O)NHCH_3$

In one embodiment R^{21} & R^{23} are CH_3 and R^{22} is CH_3

In one embodiment R^{21} is CH_3 , R^{23} is H and R^{22} is $C(O)CH_3$

5

In a particularly suitable embodiment R^1 is selected from



10 Wherein R^{14} is H & R^{15} is OH

In a suitable embodiment X is N or CR^{25} , wherein R^{25} is H.

15 A suitable pharmaceutically acceptable salt of a compound of formula (I) is for example an acid-addition salt, such as an acid-additional salt with hydrochloric acid, citric acid, tartaric acid and fumaric acid (particularly hydrochloric acid). An acid-addition salt may be obtained, for example, by reaction of a compound of formula (I) with a suitable acid (such as hydrochloric acid, citric acid, tartaric acid and fumaric acid) using a conventional procedure.

20

A pharmaceutically acceptable salt may alternatively be formed by converting one salt of a compound of the invention to another by reaction with an appropriate acid or base, or by means of a suitable ion exchange column.

25 The preparation of a pharmaceutically acceptable salt is typically conducted in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent.

30 The compounds of formula (I) may form salts *in situ* under physiological conditions, for example when used as a medicament.

It is to be understood that the compounds of formula (I) may exist in solvated or unsolvated forms, such as for example hydrated forms. The invention encompasses all pharmaceutically acceptable solvated forms.

It is to be understood that, insofar as certain of the compounds of formula (I) defined herein may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes within its definition any such optically active or
5 racemic forms.

It is to be understood that the invention relates to compounds of formula (I) that are isotopically-labelled (i.e. radio-labelled). In such compounds, one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic
10 mass or mass number typically found in nature. Examples of radionucleotides that can be included in the compounds of the invention include ^2H (also written as "D" for deuterium), ^3H (also written as "T" for tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}O , ^{17}O , ^{18}O , ^{18}F and the like. The particular radionucleotide used will depend on the specific application of the radio-labelled compound.

15 Some compounds of the invention may contain one or more chiral centres and may therefore exist as stereoisomers. Stereoisomers may be separated using conventional techniques, such as chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for example by fractional crystallisation,
20 resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example by fractional crystallisation, HPLC or flash chromatography. Alternatively, particular stereoisomers may be prepared by chiral synthesis from chiral starting materials under conditions that will not cause racemisation or epimerisation, by derivatisation with a chiral reagent or by
25 asymmetric catalytic synthesis. When a specific stereoisomer is isolated, it is suitably isolated substantially free of other stereoisomers, for example containing less than 20%, such as less than 10%, particularly less than 5%, by weight of other stereoisomers.

It is to be understood that the compounds of formula (I) may exhibit polymorphism and
30 the invention encompasses all such forms.

A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof may be prepared by any process known to be applicable to the preparation of chemically related compounds. Such processes, when used to prepare a compound of formula (I)
35 or a pharmaceutically acceptable salt or solvate thereof are provided as a further feature of the present invention and are illustrated by the following representative process variants. Necessary starting materials are commercially available or may be prepared by

standard procedures of organic chemistry within the ordinary skill of an organic chemist, for example as described in conjunction with the following representative processes and within the accompanying examples.

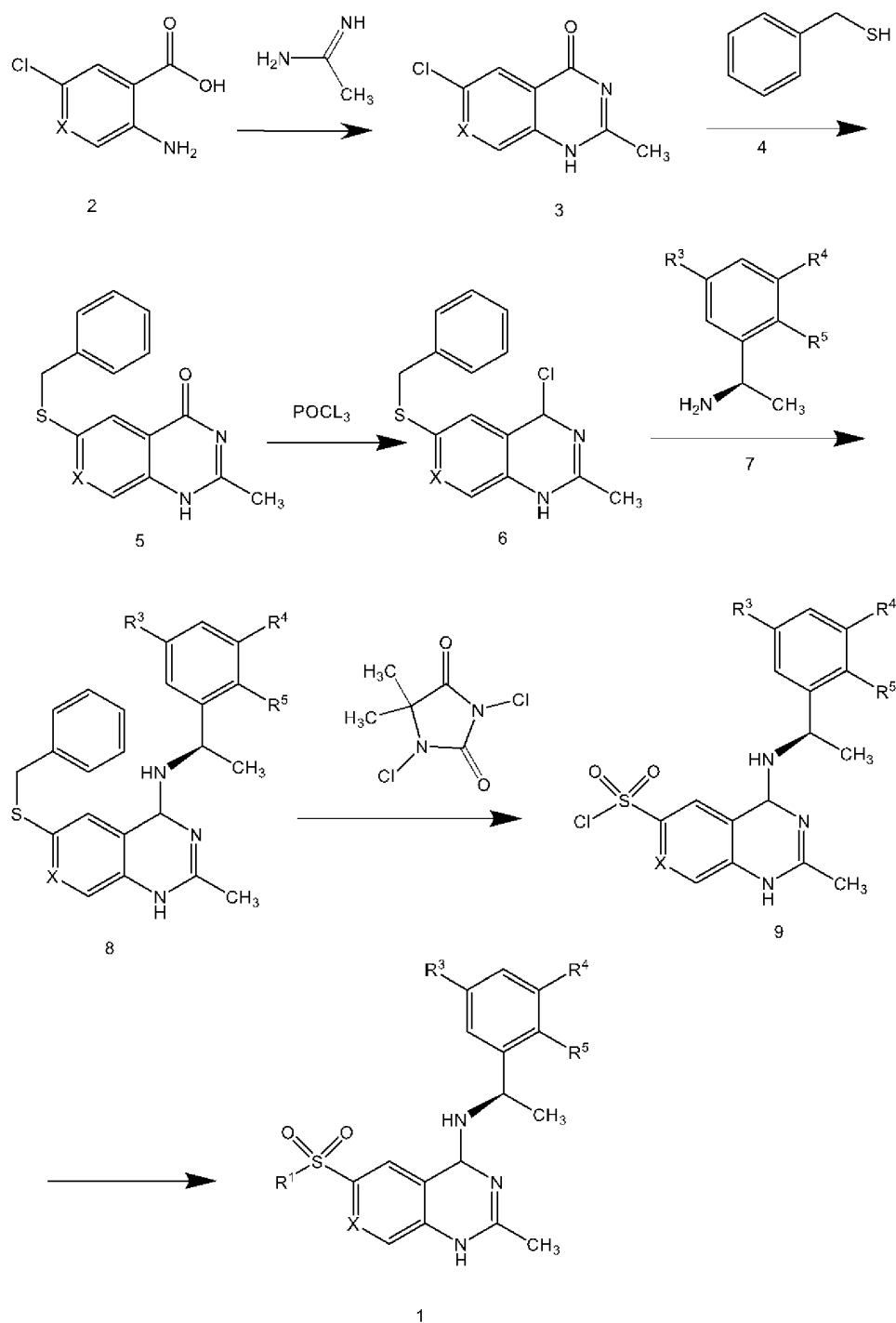
- 5 For example, a compound of formula (I) may be prepared by a process according to Scheme 1:

General Reaction Scheme

- The compounds of the present invention may be prepared using commercially available
10 reagents and intermediates in the synthetic methods and reaction schemes described herein or may be prepared using other reagents and conventional methods well known to those skilled in the art.

- For instance, intermediates for preparing compounds of Template I of the present
15 invention may be prepared according to the General Reaction Scheme I.

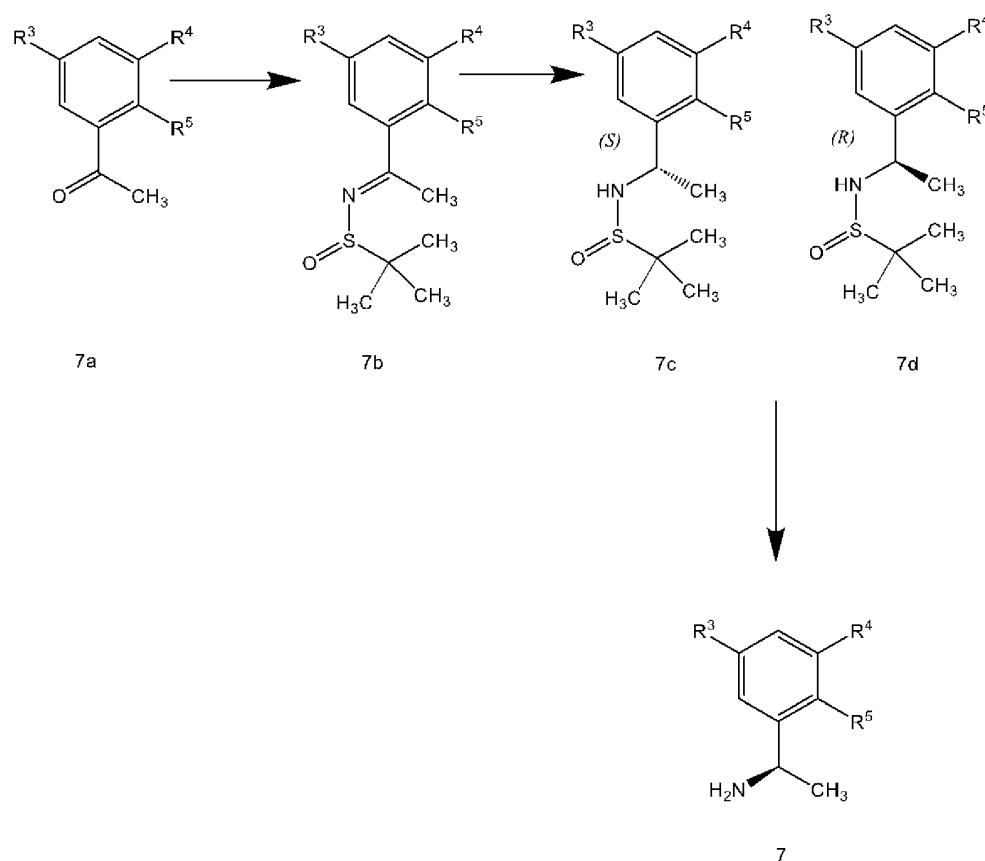
General Reaction Scheme 1



For the General Reaction Scheme 1 is an example of Template I, Compound 2 is reacted with acetamidine hydrochloride to give Compound 3 treatment with phenylmethanethiol 4 in the presence of palladium catalysis and base provides 5 which when treated with a chlorinating reagent such as POCl_3 gives Compound 6. Reaction of

Compound **6** with a suitable amine such as intermediate **7** by either nucleophilic substitution or metal catalysed reaction provides the Compound **8**. Reaction of **8** with 1,3-dichloro-5,5-dimethylhydantoin provides the sulfonyl chloride **9** which when treated with various secondary or primary nucleophilic amines furnishes the title compounds **1**.

5 Scheme 2



The required benzylic amines represented by Compound **7** can be prepared from aromatic aldehydes such as Compound **7a**. There follows formation of a chiral sulfimine **7b** followed by reduction to give a diastereomeric mixture of Compounds **7c** and **7d** that can be separated. The desired diastereoisomer **7d** is then taken to the next step where sulphydryl cleavage is performed to give the title intermediate **7**.

The compounds of the present invention are suitable for use as a medicament.

The present invention also provides for the compounds of the present invention for use in treating pain.

The SOS1 inhibitors have numerous advantages as a pain treatment; they don't have the addiction potential of opiates and they show great efficacy. They also don't appear to have the side effects that make tanezumab and other anti-NGFs almost impossible to use at therapeutically effective doses.

5

The SOS1 compounds of the present invention also benefit from a high degree of selectivity for SOS1 inhibitors over other targets, boosting efficacy, improving safety and minimising off target effects which can be a source of side effects in patients.

- 10 Suitably, the SOS1 inhibitors of the present invention show selectivity of greater than or equal to 100 fold over one or more of the following targets: MEK 1, MEK 2, TrkA kinase, TrkB kinase, TrkC kinase, C-Raf, B-Raf, PI3 kinase, AKT and ERK.

- When determining whether a compound of the present invention has a selectivity of
15 more than a 100 fold for SOS1 over another target the following assays and methods may be used:

MEK 1 and 2 can be assayed using MEK assay kit, product code CS0490, Sigma, St Louis, USA.

- 20 Trk receptor kinase activity can be assayed as described in Wang et al, Curr Chem Genomics. 2008; 1: 27–33.

B-Raf can be assayed using the B-Raf Kinase Assay Kit, product code 17-359, Sigma, St Louis, USA.

- C-Raf can be assayed using the BPS bioscience assay kit catalogue number 79570,
25 San Diego, CA 92121. United States.

PI3 kinase can be assayed via the method described by Fry, Methods Mol Biol, 2009;462:345-62.

AKT can be assayed using the abcam kit Akt Kinase Activity Assay Kit (ab139436), abcam plc, Cambridge, USA.

- 30 ERK can be assayed using the Promega ERK2 kinase kit, catalogue number V1961, Promega corporation, Madison, USA.

- The compounds PK makes them particularly suitable for use in the present invention.
35

The compounds have good bioavailability, permeability, solubility, stability and numerous other qualities associated with a druggable molecule.

Without being bound by theory, it is believed that SOS1 inhibitors act to treat pain in the following way:

5

Nerve growth factor (NGF) is a protein that binds to the NGF receptor (TrkA), leading to the upregulation of genes involved in nociception. NGF is known to be an important contributor to the development of chronic pain. The NGF binding to TrkA and subsequent signal transduction culminates in the nuclear accumulation of diphosphorylated

10 Extracellular signal-regulated kinase (dppERKnuc) in neurons, upregulating pain genes, as shown in Fig 1.

Levels of SOS1 & molecules influenced by it downstream such as Ras feed into this cascade, with greater levels of SOS and RAS leading to higher levels of bRAF and MEK,
15 leading to the accumulation of diphosphorylated Extracellular signal-regulated kinase (dppERKnuc), leading to higher levels of Pain. By inhibiting this pathway it is possible to control the formation of RAS GTP. By lowering levels of RAS GTP, pain is reduced.

The compounds are suitable for use in the treatment of pain.

20

The compounds provide a method for treating pain.

The term pain includes but is not limited to: acute pain; chronic pain; inflammatory pain; nociceptive pain; neuropathic pain; hyperalgesia; allodynia; central pain; cancer pain;
25 post-operative pain; visceral pain; musculo-skeletal pain; heart or vascular pain; head pain including migraine; orofacial pain, including dental pain; and back pain.

In more detail, suitable pain for treatment includes but is not limited to:

- (a) acute pain and/or spontaneous pain,
- 30 (b) chronic pain and or on-going pain,
- (c) inflammatory pain including any one of arthritic pain, pain resulting from osteoarthritis or rheumatoid arthritis, resulting from inflammatory bowel diseases, psoriasis and eczema
- (d) nociceptive pain,
- 35 (e) neuropathic pain, including painful diabetic neuropathy or pain associated with post-herpetic neuralgia,
- (f) hyperalgesia,

- (g) allodynia,
- (h) central pain, central post-stroke pain, pain resulting from multiple sclerosis, pain resulting from spinal cord injury, or pain resulting from Parkinson's disease or epilepsy,
- (i) cancer pain,
- 5 (j) post-operative pain,
- (k) visceral pain, including digestive visceral pain and non-digestive visceral pain, pain due to gastrointestinal (GI) disorders, pain resulting from functional bowel disorders (FBD), pain resulting from inflammatory bowel diseases (IBD), pain resulting from dysmenorrhea, pelvic pain, cystitis, interstitial cystitis or pancreatitis,
- 10 (l) musculo-skeletal pain, myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, Glycogenolysis, polymyositis, pyomyositis,
- (m) heart or vascular pain, pain due to angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma, scleredoma or skeletal muscle
- 15 ischemia,
- (n) head pain including migraine, migraine with aura, migraine without aura cluster headache, tension-type headache.
- (o) orofacial pain, including dental pain, temporomandibular myofascial pain or tinnitus, or
- 20 (p) back pain, bursitis, menstrual pain, migraine, referred pain, trigeminal neuralgia, hypersensitisation, pain resulting from spinal trauma and/or degeneration or stroke.

Treatment of pain includes, but is not limited to, preventing, ameliorating, controlling, reducing incidence of, or delaying the development or progression of pain.

25

Particularly suitable pain indications include Osteoarthritis and cancer pain.

In another embodiment a suitable indication is osteoarthritis.

- 30 According to another aspect of the invention there is provided the compounds of the present invention for separate, sequential or simultaneous use in a combination combined with a second pharmacologically active compound. Preferably the second pharmacologically active compound of the combination may include but is not limited to;
- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone,
 - 35 levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;

- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, 5 phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, 10 diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H₁ antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- 15 • a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4- 20 (phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone};
- 25 • an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- 30 • an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), 35 aprepitant,

- lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium;
 - 5 • a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
 - a coal-tar analgesic, in particular paracetamol;
 - a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine,
 - 10 risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclizine, Miraxion® or sarizotan;
 - a vanilloid receptor agonist (e.g. resiniferatoxin) or antagonist (e.g. capsaizine);
 - 15 • a beta-adrenergic such as propranolol;
 - a local anaesthetic such as mexiletine;
 - a corticosteroid such as dexamethasone;
 - a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
 - 20 • a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
 - a cholinergic (nicotinic) analgesic, such as isopropyl (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
 - 25 • Tramadol®;
 - a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-
 - 30 5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,
 - 35 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,
 - 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-

- (hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
- a cannabinoid;
 - 5 • a metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
 - a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine,
 - 10 dapoxetine, nefazodone, cericlamine and trazodone;
 - a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as
 - 15 reboxetine, in particular (S,S)-reboxetine;
 - a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
 - an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-
 - 20 4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;
 - 30 • an acetylcholinesterase inhibitor such as donepezil;
 - a prostaglandin E₂ subtype 4 (EP4) antagonist such as N-[(2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino]-carbonyl]-4-methylbenzenesulfonamide or 4-[(1S)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
 - 35 • a leukotriene B₄ antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-

methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,

- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or
5 2,3,5-trimethyl-6-(3-pyridylmethyl), 1,4-benzoquinone (CV-6504);
 - a sodium channel blocker, such as lidocaine; or
 - a 5-HT₃ antagonist, such as ondansetron;
- and the pharmaceutically acceptable salts and solvates thereof.

- 10 In a further embodiment of the present invention, SOS1 inhibitors have been found to be particularly suitable for use in the treatment of pain when administered in combination with an anti NGF antibody.

The present invention provides a method of treating pain by administering a
15 therapeutically effective amount of a compound of the present invention in combination with an anti-NGF antibody.

Tanezumab is an example of an anti-NGF antibody. Its a promising and highly
efficacious pain therapy, but patients frequently suffer unpleasant side effects at dosage
20 levels sufficient to provide pain relief.

The combination provides a cooperative level of efficacy, with the advantage that the anti-NGF antibody can be administered at a dosage levels sufficient to provide pain relief without reaching a level where an adverse event may be seen. In cooperative systems,
25 two independent agents are able to show a level of activity equivalent to one of the agents at a much higher dose. Its surprising to find two agents combining to have such an effect.

It is possible to lower the dose of Tanezumab in humans and as a result reduce the
30 propensity for side effects that limit use if of this class of drug. The combination of SOS1 inhibition with NGF blocking via monoclonal antibodies such as Tanezumab will deliver increased pain efficacy with reduced side effects when compared to the use of higher doses of Tanezumab alone.

35 Combinations of SOS1 inhibitors with NGF monoclonal antibodies, or other blockers/modulators of the NGF pathway, have the potential to deliver greater pain

efficacy with reduced side effects leading to improved and enhanced treatment of pain in conditions such as osteoarthritis.

Accordingly, the present invention provides for the use of a compound of the present invention in combination with an anti NGF, wherein one or both components is

- 5 administered at a sub-therapeutic dose for the treatment of pain.

The term sub therapeutic dose is used to describe to describe a dose lower than that at which the component shows efficacy as a monotherapy.

- 10 Other advantages for the combination include the potential for oral dosing instead of intravenous or sub-cutaneous dosing. The combination may also result in a lower cost of treatment and provide a lower risk of immunogenicity.

Particularly suitable anti NGF antibodies include Tanezumab, Fasinumab, Fulranumab
15 and *MEDI735*.

Particularly suitable anti-NGF antibodies are Tanezumab and Fasinumab.

- 20 In a particularly preferred embodiment, the present invention provides for the use of compounds of the present invention in combination with a sub therapeutic dose of Tanezumab, for the treatment of pain. Optionally, both the compound of the present invention and Tanezumab are administered at a sub therapeutic dose.

- 25 Compounds which act as SOS1 inhibitors are known to be effective in the treatment in cancer. The present invention provides compounds of the present invention for the treatment of cancer. The compounds provide a method of treating cancer.

- 30 Suitable cancers may be selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, cholangiocarcinoma, multiple myeloma, melanoma, uterine cancer, endometrial cancer, thyroid cancer, acute myeloid leukaemia, bladder cancer, urothelial cancer, gastric cancer, cervical cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, oesophageal cancer, chronic lymphocytic leukaemia, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, renal cancer and sarcomas.

35

In another aspect the suitable cancers are selected from the group consisting of pancreatic cancer, lung cancer (preferably non-small cell lung cancer (NSCLC)), cholangiocarcinoma and colorectal cancer.

- 5 In another aspect the present invention provides SOS1 inhibitors of formula (I) for conditions selected from RASopathy, preferably selected from the group consisting of Neurofibromatosis type 1 (NF1), Noonan Syndrome (NS), Noonan Syndrome with Multiple Lentigines (NSML) (also referred to as LEOPARD syndrome), Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM), Costello Syndrome (CS),
- 10 Cardio-Facio-Cutaneous Syndrome (CFC), Legius Syndrome (also known as NF1-like Syndrome) and Hereditary gingival fibromatosis.

In another aspect the disease/condition/cancer to be treated/prevented with the compounds of the present invention is a disease/condition/cancer defined as exhibiting

15 one or more of the following molecular features:

1. KRAS alterations:
 - a. KRAS amplification (wt or mutant);
 - b. KRAS overexpression (wt or mutant);
 - c. KRAS mutation(s):
 - 20 i. G12 mutations (e.g. G12C, G12V, G12S, G12A, G12V, G12R, G12F, G12D);
 - ii. G13 mutations (e.g. G13C, G13D, G13R, G13V, G13S, G13A) iii. T35 mutation (e.g. T35I);
 - iv. 136 mutation (e.g. I36L, I36M);
 - 25 v. E49 mutation (e.g. E49K);
 - vi. Q61 mutation (e.g. Q61 H, Q61 R, Q61 P, Q61 E, Q61 K, Q61 L, Q61 K);
 - vii. K1 17 mutation (e.g. K1 17N);
 - viii. A146 mutation (e.g. A146T, A146V);
- NRAS alterations:
 - 30 a. NRAS amplification (wt or mutant);
 - b. NRAS overexpression (wt or mutant);
 - c. NRAS mutation(s):
 - G12 mutations (e.g. G12A, G12V, G12D, G12C, G12S, G12R); G13 mutation (e.g. G13V, G13D, G13R, G13S, G13C, G13A); Q61 mutation (e.g. Q61 K, Q61 L, Q61 H, Q61 P, Q61
 - 35 R);
 - iv. A146 mutation (e.g. A146T, A146V);
- HRAS alterations:

- a. HRAS amplification (wt or mutant);
- b. HRAS overexpression (wt or mutant);
- c. HRAS mutation(s);
 - i. G12 mutation (e.g. G12C, G12V, G12S, G12A, G12V, G12R, G12F, G12D);
 - 5 ii. G13 mutation (e.g. G13C, G13D, G13R, G13V, G13S, G13A);
 - iii. Q61 mutation (e.g. Q61 K, Q61 L, Q61 H, Q61 P, Q61 R);
- EGFR alterations:
 - a. EGFR amplification (wt or mutant);
 - b. EGFR overexpression (wt or mutant);
 - 10 c. EGFR mutation(s)
 - i. e.g. exon 20 insertion, exon 19 deletion (Del19), G719X (e.g. G719A, G719C, G719S), T790M, C797S, T854A, L858R, L861 Q, or any combination thereof;
- ErbB2 (Her2) alterations:
 - a. ErbB2 amplification;
 - 15 b. ErbB2 overexpression; c. ErbB2 mutation(s)
 - i. e.g. R678, G309, L755, D769, V777, P780, V842, R896, c.2264_2278del (L755_T759del), c.2339_2340ins (G778_P780dup), S310;
- 6. c-MET alterations:
 - a. c-MET amplification;
 - 20 b. c-MET overexpression;
 - c. c-MET mutation(s)
 - i. e.g. E168, N375, Q648, A887, E908, T1010, V1088, H1 1 12, R1 166, R1 188, Y1248, Y1253, M1268, D1304, A1357, P1382;
- 7. AXL alterations:
 - 25 a. AXL amplification;
 - b. AXL overexpression;
- 8. BCR-ABL alterations:
 - a. chromosomal rearrangements involving the ABL gene;
- 9. ALK alterations:
 - 30 a. ALK amplification;
 - b. ALK overexpression;
 - c. ALK mutation(s)
 - i. e.g. 1 151Tins, L1 152R, C1 156Y, F1 174L, L1 196M, L1 198F, G1202R, S1206Y, G1269A;
 - 35 d. chromosomal rearrangements involving the ALK gene;
- 10. FGFR1 alterations:
 - a. FGFR1 amplification;

- b. FGFR1 overexpression;
- 11. FGFR2 alterations:
 - a. FGFR2 amplification;
 - b. FGFR2 overexpression;
- 5 12. FGFR3 alterations:
 - a. FGFR3 amplification;
 - b. FGFR3 overexpression;
 - c. chromosomal rearrangement involving the FGFR3 gene;
- 13. NTRK1 alterations:
 - a. chromosomal rearrangements involving the NTRK1 gene;
- 10 14. NF1 alterations:
 - a. NF1 mutation(s);
- 15. RET alterations:
 - a. RET amplification;
 - b. RET overexpression;
- 15 c. chromosomal rearrangements involving the RET gene
- 16. ROS1 alterations:
 - a. ROS1 amplification;
 - b. ROS1 overexpression;
 - c. ROS1 mutation(s)
- 20 i. e.g. G2032R, D2033N, L2155S;
- d. chromosomal rearrangements involving the ROS1 gene;
- 17. SOS1 alterations
 - a. SOS1 amplification;
 - b. SOS1 overexpression;
 - c. SOS1 mutation(s);
- 25 18. RAC1 alterations
 - a. RAC1 amplification;
 - b. RAC1 overexpression;
 - c. RAC1 mutation(s);
- 19. MDM2 alterations
- 30 a. MDM2 amplification
- b. MDM2 overexpression
- c. MDM2 amplification in combination with functional p53
- d. MDM2 amplification in combination with wild-type p53
- 20. RAS wild-type
- 35 a. KRAS wild-type
- a. HRAS wild-type

b. N RAS wild-type Particularly preferred, the cancer to be treated/prevented with the SOS1 inhibitor compound, SOS1 inhibitor compound for use, compound of formula (I), compound of formula (I) for use, use for preparing and method for the treatment and/or prevention as herein (above and below) defined is selected from the group consisting of:

- 5 · lung adenocarcinoma harboring a KRAS mutation selected from the group consisting of G12C, G12V, G12D and G12R;
- colorectal adenocarcinoma harboring a KRAS mutation selected from the group consisting of G12D, G12V, G12C, G12R and G13D; and
- pancreatic adenocarcinoma harboring a KRAS mutation selected from the group
- 10 consisting of G12D, G12V, G12R, G12C and Q61 H.

According to another aspect of the invention there is provided the compounds of the present invention for separate, sequential or simultaneous use in a combination combined with a second pharmacologically active compound. Preferably the second

15 pharmacologically active compound of the combination may include but is not limited to;

- 1. inhibitors of EGFR and/or of mutants thereof
 - a. e.g. afatinib, erlotinib, gefitinib, lapatinib, cetuximab, panitumumab, osimertinib, olmutinib, EGF-816; b. preferred are afatinib, osimertinib and cetuximab;
 - 20 c. most preferred is afatinib
- 2. inhibitors of ErbB2 (Her2) and/or of mutants thereof
 - a. e.g. afatinib, lapatinib, trastuzumab, pertuzumab;
 - b. preferred are afatinib and trastuzumab;
 - c. most preferred is trastuzumab;
- 25 3. inhibitors of ALK and/or of mutants thereof
 - a. e.g. crizotinib, alectinib, entrectinib, brigatinib;
 - b. preferred are crizotinib and alectinib;
 - c. most preferred is crizotinib;
- 4. inhibitors of MEK and/or of mutants thereof
 - 30 a. e.g. trametinib, cobimetinib, binimetinib, selumetinib, refametinib;
 - b. preferred are trametinib and cobimetinib;
 - c. most preferred is trametinib;
- 5. inhibitors of KRAS G12C
 - a. e.g. ARS-853 (compound V-64 in WO 2014/152588), example I-272 in WO
 - 35 2016/044772;
- 6. inhibitors of BCR-ABL and/or of mutants thereof
 - a. e.g. imatinib, dasatinib, nilotinib;

- b. preferred are imatinib and nilotinib;
- c. most preferred is imatinib;
- 7. inhibitors of FGFR1 and/or FGFR2 and/or FGFR3 and/or of mutants thereof
 - a. e.g. nintedanib;
- 5 8. inhibitors of ROS1 and/or of mutants thereof
 - a. e.g. crizotinib, entrectinib, lorlatinib, ceritinib, merestinib;
 - b. preferred are crizotinib and entrectinib;
 - c. most preferred is crizotinib;
- 9. inhibitors of c-MET and/or of mutants thereof
- 10 10. inhibitors of AXL and/or of mutants thereof
 - 11. inhibitors of NTRK1 and/or of mutants thereof 12. inhibitors of RET and/or of mutants thereof
 - 13. taxanes
 - a. e.g. paclitaxel, nab-paclitaxel, docetaxel;
 - 15 b. preferred is paclitaxel;
 - 14. platinum-containing compounds
 - a. e.g. cisplatin, carboplatin, oxaliplatin;
 - 15. an/-'-metabolites
 - a. e.g. 5-fluorouracil, capecitabine, floxuridine, cytarabine, gemcitabine, combination of
 - 20 trifluridine and tipiracil (= TAS102);
 - b. preferred is gemcitabine;
 - 16. mitotic kinase inhibitors
 - a. e.g. CDK4/6 inhibitors
 - e.g. palbociclib, ribociclib, abemaciclib;
 - 25 preferred are palbociclib and abemaciclib;
 - iii. most preferred is abemaciclib;
 - 17. immunotherapeutic agents
 - a. e.g. immune checkpoint inhibitors
 - i. e.g. an/-'-CTLA4 mAb, an/-'-PD1 mAb, anti-PD- mAb, an/-'-PD-L2 mAb, an/-'-LAG3 mAb,
 - 30 an/-'-TIM3 mAb;
 - ii. preferred are an/-'-PD1 mAb;
 - iii. e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, pidilizumab, PDR-001 (BAP049-Clone-E disclosed and used in WO 2017/019896);
 - iv. preferred are nivolumab, pembrolizumab and PDR-001 ;
 - 35 v. most preferred is pembrolizumab;
 - 18. an/-'-angiogenic drugs
 - a. e.g. bevacizumab, nintedanib;

- b. most preferred is bevacizumab;
- 19. topoisomerase inhibitors
 - a. e.g. irinotecan, liposomal irinotecan, topotecan;
 - b. most preferred is irinotecan;
- 20. inhibitors of A-Raf and/or B-Raf and/or C-Raf and/or of mutants thereof
 - a. e.g. RAF-709 (= example 131 in WO 2014/151616), LY-3009120 (= example 1 in WO 2013/134243);
- 21. inhibitors of ERK and/or of mutants thereof
 - a. e.g. ulixertinib;
- 22. apoptosis regulators
 - a. e.g. inhibitors of the interaction between p53 (preferably functional p53, most preferably wt p53) and MDM2 ("MDM2 inhibitors");
 - i. e.g. HDM-201, NVP-CGM097, RG-7112, MK-8242, RG-7388, SAR405838, AMG-232, DS-3032, RG-7775, APG-115;
 - ii. preferred are HDM-201, RG-7388 and AMG-232
- 23. inhibitors of mTOR
 - a. e.g. rapamycin, temsirolimus, everolimus, ridaforolimus;
- 24. epigenetic regulators
 - a. e.g. BET inhibitors
 - i. e.g. JQ-1, GSK 525762, OTX 015 (= MK8628), CPI 0610, TEN-010 (= RO6870810);
 - b. e.g. CDK9 inhibitors;
- 25. inhibitors of IGF1/2 and/or of IGF1-R
 - a. e.g. xentuzumab (antibody 60833 in WO 2010/066868), MEDI-573 (= dusigitumab);
- 25. Within this invention it is to be understood that the combinations, compositions, kits, methods, uses or compounds for use according to this invention may envisage the simultaneous, concurrent, sequential, successive, alternate or separate administration of the active ingredients or components.
- 30. Literature data indicates that integrin and Ab1-42 RAS/ERK signalling can be linked to tau hyperphosphorylation, focal adhesion development and other Alzheimer's disease neuropathology. Consistent with this, inhibitors of the pathway, such as MEK inhibitors, have been shown to ameliorate neuropathological related outcomes in cell disease models. In addition, in neurofibromatosis patients, a disease caused by excess signalling via SOS/RAS/ERK, the hazard ratio risk of AD is significantly increased. Hence, SOS1 inhibitors, that inhibit in the same pathway as MEK, could also provide benefit and offer additional efficacy and safety features both in Alzheimer's disease and other dementias.

The compounds of the present invention are also useful in the treatment of dementia, including:

Alzheimers, Mild cognitive impairment (MCI), Creutzfeldt-Jakob disease (CJD), Dementia
5 with Lewy bodies (DLB), Vascular dementia, Alcohol-related brain damage (ARBD),
Young-onset dementia, Frontotemporal dementia (FTD) & HIV-related cognitive
impairment.

Alzheimers includes, Mild Alzheimer's, Moderate Alzheimer's, Severe Alzheimer's,
10 Inflammatory, Non-Inflammatory, Cortical, Early-Onset Alzheimer's & Late-Onset
Alzheimer's.

Various literature data suggest that MAPK signaling pathways contribute to Parkinson's
disease-related pathological processes, such as oxidative stress, neuro-inflammation,
15 autophagy, and neuronal death. In addition, MEK inhibitors have demonstrated important
neuroprotective properties upstream of the execution of apoptosis in dopaminergic
neurons. It is expected that SOS1 inhibitors, that inhibit in the same pathway as MEK,
could also have neuroprotective properties, with enhanced potency and safety versus
MEK inhibitors.

20

The compounds of the present invention are also useful in the treatment of parkinsonism
also known as parkinsons disease. This includes, idiopathic Parkinson's, Vascular
parkinsonism (also known as arteriosclerotic parkinsonism), drug-induced parkinsonism,
multiple system atrophy, progressive supranuclear palsy, normal pressure hydrocephalus,
25 tremors, including essential tremor & Wilsons disease.

The compounds of the present invention are also useful in the treatment of
neurofibromatosis. Suitably neurofibromatosis is neurofibromatosis 1.

30 The invention further provides a pharmaceutical formulation comprising a compound of
formula I, as defined above, or a pharmaceutically acceptable salt or solvate thereof, and
a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical
formulation may further comprise one or more additional active agents for the treatment of
a disorder mentioned above.

35

The invention further provides a pharmaceutical kit comprising a compound of formula I,
as defined above, or a pharmaceutically acceptable salt or solvate thereof, and one or

more additional active agents, as a combined preparation for separate, simultaneous or sequential administration in the treatment of a disorder mentioned above.

5 The invention further provides a method of treatment of a disorder mentioned above in a mammal (especially a human), comprising administration of a therapeutically effective amount of a compound of formula I, as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a mammal in need of such treatment.

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

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

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

ORAL ADMINISTRATION

30 The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

35 Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled),

chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

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

10

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

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

25 Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol,
30 dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface

active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

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

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

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

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

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

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

30

The compound of the invention may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20

weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of the invention may be in the form of multiparticulate beads.

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

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

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

- Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-,
20 controlled-, targeted and programmed release.

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

PARENTERAL ADMINISTRATION

- 30 The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral,

intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

- 5 Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

10

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

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

- Formulations for parenteral administration may be formulated to be immediate and/or
20 modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*D*-lactic-co-glycolic)acid (PLGA) microspheres.

25

TOPICAL ADMINISTRATION

- The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels,
30 hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol.

Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, 5 phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, 10 targeted and programmed release.

INHALED/INTRANASAL ADMINISTRATION

The compounds of the invention can also be administered intranasally or by inhalation, 15 typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a 20 suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or 25 suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

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

milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

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

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

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

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include
25 delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 to 10,000 µg of
30 the compound of the invention. The overall daily dose will typically be in the range 1µg to 10 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

RECTAL/INTRA VAGINAL ADMINISTRATION

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository
5 base, but various alternatives may be used as appropriate.

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

10

OCULAR/AURAL ADMINISTRATION

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

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

OTHER TECHNOLOGIES

30

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing

polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

5 Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO
10 98/55148.

KIT-OF-PARTS

Inasmuch as it may be desirable to administer a combination of active compounds, for
15 example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

20 Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula I in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

25

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

DOSAGE

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.5 mg to 3000 mg depending, of course, on the mode

of administration. For example, oral administration may require a total daily dose of from 3 mg to 3000 mg, while an intravenous dose may only require from 0.5 mg to 500 mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

- 5 These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

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

10

Experimental

Materials and Methods.

- 15 The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18 to 25°C;
- (ii) final products had satisfactory proton and carbon nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
- 20 (iii) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- (iv) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using perdeuterio dimethyl sulfoxide (DMSO-d₆) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet, dd doublet of doublets;
- 25 (v) chemical symbols have their usual meanings; SI units and symbols are used.

- 30 **List of Abbreviations used in the present invention are given below:**

ACN Acetonitrile

AcOH Acetic acid

- Aq Aqueous
- BSA Bovine Serum Albumin
- CS₂CO₃ Cesium carbonate
- DCM Dichloromethane
- 5 DIPEAN, N-Diisopropylethylamine
- DME Dimethoxy ethane
- DMF Dimethylformamide
- DMF-DMA N,N-Dimethylformamide dimethyl acetal
- DMSO Dimethyl sulfoxide
- 10 DTT Dithiothreitol
- EDA-GTP-DY-647P1 273'-O-(2-Aminoethyl-carbamoyl)-Guanosine-5'- triphosphate,
labeled with DY- 647PI, Triethylammoniumsalt
- EtOAc Ethyl acetate
- EtOH Ethanol
- 15 FRET Fluorescence resonance energy transfer
- GDP Guanosine diphosphate
- GEF Guanine nucleotide exchange factor
- GTP Guanosine triphosphate
- HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide
- 20 hexafluorophosphate
- HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)
- HPLC High-performance liquid chromatography
- HTRF Homogeneous Time Resolved Fluorescence
- IPA Isopropanol
- 25 K₂CO₃ Potassium carbonate
- KRAS Kirsten Rat Sarcoma
- KO^tBu Potassium tert-butoxide
- LC Liquid chromatography

- LiOH.H₂O Lithium hydroxide monohydrate
MeOH Methanol
MeONa Sodium methoxide
MS Mass spectrometry
- 5 NaBH₄ Sodium borohydride
NaN₂ Sodium nitrite
NaIO₄ Sodium periodate
NH₄Cl Ammonium chloride
NiCl₂ .6H₂O Nickel(II) chloride hexahydrate
- 10 nM nanomolar
NMR Nuclear magnetic resonance spectroscopy
O/N Over night
Pd-C Palladium on carbon
Pd(PPh₃)₄ Tetrakis(triphenylphosphine)palladium(0)
- 15 POCl₃ Phosphorus oxychloride
prep Preparative
TEA Triethylamine
THF Tetrahydrofuran
TFA Trifluoroacetic acid
- 20 TiCl₄ Titanium tetrachloride
TLC Thin-layer chromatography

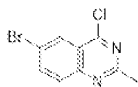
The following intermediates can be used to prepare compounds of the present invention.

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- 25 **Example 1: (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,N,2-trimethylquinazoline-6-sulfonamide**

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Preparation 1: 6-bromo-4-chloro-2-methylquinazoline

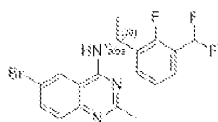


To a stirred solution of 6-bromo-2-methylquinazolin-4(1H)-one (1g, 4.18mmol) was dissolved in Toluene (10mL, 10V) were added DIPEA (2.8mL, 16.73mmol) and POCl₃ (3.9mL, 41.84mmol). The resulting reaction mixture was allowed to stir at 110°C for 6h. TLC (30% EtOAc/Hexane) showed SM was consumed completely. The reaction mixture was diluted with saturated NaHCO₃ solution (50mL) and extracted with EtOAc (2 x 50mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (26:74) ethyl acetate/hexane to yield 6-bromo-4-chloro-2-methylquinazoline (0.6g, 55.70%) as an off white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.322min, m/z =257.0 [M+H]⁺.

¹H-NMR: (400 MHz, CDCl₃): δ 8.40 (s, 1H), 8.01 (dd, J=2.4 Hz, 8.8 Hz, 1H), 8.86 (d, J=9.2 Hz, 1H), 2.86 (s, 3H).

Preparation 2: (R)-6-bromo-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylquinazolin-4-amine



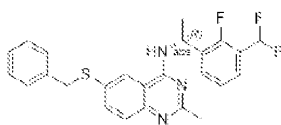
To a stirred solution of (R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethan-1-amine (0.29g, 1.55mmol) in Ethanol (10mL, 20V) was added potassium acetate (0.64g, 6.59mmol) at room temperature and stirred it for 15 minutes. Then 6-bromo-4-chloro-2-methylquinazoline (0.5g, 1.94mmol) was charged in the above reaction mixture and the resulting reaction mixture was stirred for 4h at 110°C. TLC (30% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (26:74) ethyl acetate/hexane to yield (R)-6-bromo-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylquinazolin-4-amine (0.4g, 50.22%) as an off white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.057min, m/z = 411.9 $[M+2H]^+$.

1H -NMR: (400 MHz, DMSO- d_6): δ 8.73 (d, J = 2.00 Hz, 1H), 8.58 (d, J = 7.20 Hz, 1H), 7.85 (dd, J = 2.40, 8.80 Hz, 1H), 7.69 (t, J = 7.20 Hz, 1H), 7.55 (s, 1H), 7.51 (t, J = 6.80 Hz, 1H), 7.29 (t, J = 8.00 Hz, 1H), 7.24 (s, 1H), 5.74-5.81 (m, 1H), 2.38 (s, 3H), 1.60 (d, J = 6.80 Hz, 3H).

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Preparation 3: (R)-6-(benzylthio)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylquinazolin-4-amine

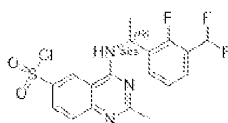


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To a stirred solution of (R)-6-bromo-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylquinazolin-4-amine (0.4g, 0.97mmol) and phenylmethanethiol (0.45g, 1.17mmol) in Dioxane (4mL, 10V) was added DIPEA (0.2g, 0.95mmol). The resulting solution was purged with N_2 for 10 min. Then Xanthphos (0.11g, 0.19mmol) and $Pd_2(dba)_3$ (0.18g, 0.19mmol) were added to the above reaction mixture and allowed to stir at 100°C for 16h. TLC (30% EtOAc/DCM) showed SM was consumed completely. The reaction mixture was diluted with water (20mL) and extracted with EtOAc (2 x 50mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (20:80) ethyl acetate/hexane to yield (R)-6-(benzylthio)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylquinazolin-4-amine (0.4g, 90.46%) as an off white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.198min, m/z = 454.0 $[M+H]^+$.

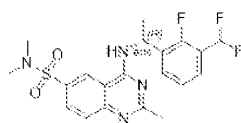
Preparation 4: (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylquinazoline-6-sulfonyl chloride



To a stirred solution of (R)-6-(benzylthio)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylquinazolin-4-amine (0.4g, 0.88mmol) was dissolved in Acetonitrile (4mL, 10V) were added Acetic acid (0.01mL) and water (0.01mL). Then 1,3-Dichloro-5,5-dimethylhydantoin (0.87g, 4.41mmol) was added portion wise to above solution at 0°C. The resulting reaction mixture was allowed to stir at 0°C for 1h. TLC (30% EtOAc/Hexane) showed SM was consumed completely. The reaction mixture was diluted with saturated NaHCO₃ solution (10mL) and extracted with DCM (2 x 10mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced vacuum to get crude of (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylquinazoline-6-sulfonyl chloride (0.4g, Quantitative) as an yellow solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.351min, m/z =not supported.

Example 1, Preparation 5: (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,N,2-trimethylquinazoline-6-sulfonamide



To a stirred solution of dimethyl amine (2M in THF) (0.13mL, 0.28mmol) in THF (0.5mL) was added TEA (0.1 mL, 0.69mmol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylquinazoline-6-sulfonyl chloride (0.10g, 0.23mmol) in THF (1mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (30% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (5mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by prep. HPLC to yield (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,N,2-trimethylquinazoline-6-sulfonamide (0.01g, 10.78%) as an off white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.927min, m/z =439.2 [M+H]⁺.

HPLC t_R (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 4.91min.

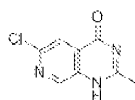
¹H-NMR: (400 MHz, DMSO-d₆): δ 9.08 (d, *J*=7.2 Hz, 1H), 8.95 (s, 1H), 8.01-7.96 (m, 1H), 7.76 (d, *J*=8.8 Hz, 1H), 7.69 (t, *J*=7.2 Hz, 1H), 7.51 (t, *J*=6.8 Hz, 1H), 7.30 (t, *J*=7.6 Hz, 1H), 7.25 (s, 1H), 5.84-5.80 (m, 1H), 2.66 (s, 6H), 2.39 (s, 3H), 1.64 (d, *J*=7.2 Hz, 3H).

5

Example 2: (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,N,2-trimethylpyrido[3,4-d]pyrimidine-6-sulfonamide

Preparation 1: 6-chloro-2-methylpyrido[3,4-d]pyrimidin-4(1H)-one

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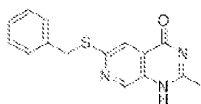
To a solution of 5-amino-2-chloroisonicotinic acid (10g, 58.1mmol) and ethanimidamide hydrochloride (16.3 g, 174mmol) in 2-methoxyethanol (1.2 L) was added sodium acetate (14.3 g, 174mmol) at room temperature. The reaction mixture was stirred at 130 °C for 48 hours. TLC (100% EtOAc) showed SM was consumed completely. The reaction mixture was concentrated to remove 2-methoxyethanol under reduced pressure. The residue was poured into water, brown solid was precipitated. The precipitates were filtered and collected over Buchner funnel and dried under reduced vacuum to give 6-chloro-2-methylpyrido[3,4-d]pyrimidin-4(1H)-one (9.5 g, 83.81%) as a brown solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.265min, m/z =195.2 [M+H]⁺.

¹H-NMR: (400 MHz, DMSO-d₆): δ 12.69 (s, 1H), 8.83 (s, 1H), 7.94 (s, 1H), 2.39 (s, 3H)

Preparation 2: 6-(benzylthio)-2-methylpyrido[3,4-d]pyrimidin-4(1H)-one

25



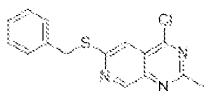
To a stirred solution of 6-chloro-2-methylpyrido[3,4-d]pyrimidin-4(1H)-one (5g, 25.64mmol) was dissolved in DMF (50mL, 10V) was added K₂CO₃ (10.61g, 76.92mmol).

Then phenylmethanethiol (3.17g, 25.64mmol) in was added to the above reaction mixture and allowed to stir at 100°C for 48h. TLC (90% EtOAc/DCM) showed SM was consumed completely. The reaction mixture was diluted with water (100mL) solid was precipitated. The precipitates were filtered and collected over Buchner funnel and dried under reduced
 5 pressure to give 6-(benzylthio)-2-methylpyrido[3,4-d]pyrimidin-4(1H)-one (5 g, 69.03%) as a off white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.997min, m/z =284.3 $[M+H]^+$.

1H -NMR: (400 MHz, DMSO- d_6): δ 12.50 (s, 1H), 8.88 (s, 1H), 7.73 (s, 1H), 7.44-7.42 (m,
 10 2H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 1H), 4.48 (s, 2H), 2.36 (s, 3H).

Preparation 3: 6-(benzylthio)-4-chloro-2-methylpyrido[3,4-d]pyrimidine



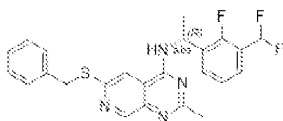
15

To a stirred solution of 6-(benzylthio)-2-methylpyrido[3,4-d]pyrimidin-4(1H)-one (2g, 7.06mmol) was dissolved in Toluene (20mL, 10V) were added DIPEA (1.84mL, 10.60mmol) and POCl₃ (2.16mL, 14.13mmol). The resulting reaction mixture was allowed to stir at 110°C for 13h. TLC (70% EtOAc/Hexane) showed SM was consumed completely.
 20 The reaction mixture was concentrated under reduced vacuum to get crude of 6-(benzylthio)-4-chloro-2-methylpyrido[3,4-d]pyrimidine (2g, 93.89%) as a brown sticky solid.

Note: Crude was directly used for next step.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.664min, m/z =302.1 $[M+H]^+$
 25

Preparation 4: (R)-6-(benzylthio)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine

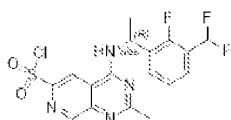


To a stirred solution of (R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethan-1-amine (1.25g, 6.64mmol) in THF (20mL, 10V) was added DIPEA (3.5mL, 19.9mmol) at room temperature and stirred it for 15 minutes. Then 6-(benzylthio)-4-chloro-2-methylpyrido[3,4-d]pyrimidine (2g, 6.64mmol) was charged in the above reaction mixture and the resulting reaction mixture was stirred for 3h at 80°C. TLC (70% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (100mL) and extracted with ethyl acetate (3 x 100mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (30:70) ethyl acetate/hexane to yield (R)-6-(benzylthio)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (1.5g, 50%) as a brown solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.335min, m/z =455.3 [M+H]

¹H-NMR: (400 MHz, DMSO-d₆): δ 8.94 (s, 1H), 8.72 (d, J=7.2 Hz, 1H), 8.25 (s, 1H), 7.67 (t, J=7.6 Hz, 1H), 7.52 (t, J=6.8 Hz, 1H), 7.43-7.41 (m, 2H), 7.32-7.10 (m, 5H), 5.78-5.74 (m, 1H), 4.51 (s, 2H), 2.38 (s, 3H), 1.60 (d, J=6.8 Hz, 1H).

Preparation 5: (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride

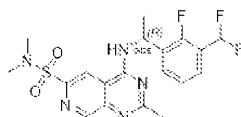


To a stirred solution of (R)-6-(benzylthio)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (1g, 2.20mmol) was dissolved in Acetic acid (40mL, 40V) and water (10mL, 10V). N-Chlorosuccinimide (1.55g, 11.62mmol) was added portion wise to above solution at room temperature. The resulting reaction mixture was allowed to stir at room temperature for 1h. TLC (50% EtOAc/Hexane) showed SM was consumed completely. The reaction mixture was diluted with saturated NaHCO₃ solution (100mL) and extracted with DCM (2 x 50mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced vacuum to get crude of (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (1.1g, Quantitative) as a yellow solid.

Note: Crude was directly used for next step.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.126min, m/z =413.12 (Acid mass observed).

5 Example 2 : Preparation 6: (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,N,2-trimethylpyrido[3,4-d]pyrimidine-6-sulfonamide



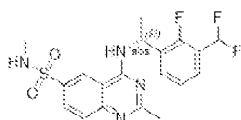
To a stirred solution of dimethyl amine (2M in THF) (0.20mL, 0.42mmol) in THF was added
 10 TEA (0.1 mL, 0.69mmol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.15g, 0.34mmol) in THF (3mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (60% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and
 15 ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (32:68) ethyl acetate/hexane to yield (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,N,2-trimethylpyrido[3,4-d]pyrimidine-6-sulfonamide (0.008g, 5.23%) as an off white solid.

20 LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.189min, m/z =440.3 [M+H]⁺.

HPLC t_R (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.336min.

¹H-NMR: (400 MHz, DMSO-*d*₆): δ 9.34 (d, *J* = 6.8 Hz, 1H), 9.07 (s, 1H), 9.03 (s, 1H), 7.71(t, *J*=7.2 Hz, 1H), 7.53 (t, *J*=5.6 Hz, 1H), 7.32 (t, *J*=7.2 Hz, 1H), 7.25 (s, 1H), 5.80-5.77
 25 (m, 1H), 2.84 (s, 6H), 2.45 (s, 3H), 1.63(d, *J*=6.8 Hz 3H).

Example 3 : (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,2-dimethylquinazoline-6-sulfonamide



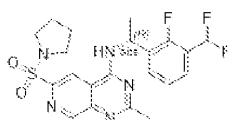
To a stirred solution of (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylquinazoline-6-sulfonyl chloride (0.1g, 0.23mmol), in DCM (10V), methanamine(2M in THF)(0.23mL, 0.46mmol, 2.0eq.) was added. The resulting mixture was allowed to stir at RT for 1h. TLC (70% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (50mL) and ethyl acetate (50mL). The combined organics were dried over Na₂SO₄, filtered and evaporated. The residue was purified by Prep-HPLC, eluting with 0.1% M.NH₃ in MEOH:CAN(50:50) to obtained (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-N,2-dimethylquinazoline-6-sulfonamide (0.004g, 4%) as a white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.859min, m/z =425 [M+H]⁺.

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 4.790min.

¹H NMR (400 MHz, DMSO): δ 9.06 (d, J = 7.0 Hz, 1H), 8.96 (d, J = 1.5 Hz, 1H), 8.00 (dd, J = 8.8, 1.9 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.52 – 7.49 (m, 2H), 7.38 – 7.24 (m, 2H), 5.82 (t, J = 7.1 Hz, 1H), 2.46(s, 3H), 2.38 (s, 3H), 1.63 (d, J = 7.0 Hz, 3H).

Example 4 : (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methyl-6-(pyrrolidin-1-ylsulfonyl)pyrido[3,4-d]pyrimidin-4-amine



To a stirred solution of pyrrolidine (0.29g, 0.42mmol) in THF (1.5mL, 10V) was added TEA (0.1 mL, 0.69mmol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.15g, 0.34mmol) in THF (1.5mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (50:50) ethyl acetate/hexane to yield (R)-N-(1-(3-

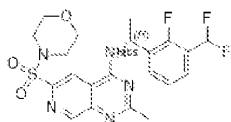
(difluoromethyl)-2-fluorophenyl)ethyl)-2-methyl-6-(pyrrolidin-1-ylsulfonyl)pyrido[3,4-d]pyrimidin-4-amine (0.025g, 15.43%) as a pale yellow solid.

LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.303min, m/z =466.3 [M+H]⁺.

5 HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.522min.

¹H-NMR: (400 MHz, DMSO-d₆): δ 9.34 (d, J = 6.8 Hz, 1H), 9.05 (s, 1H), 9.03 (s, 1H), 7.71 (t, J=7.2 Hz, 1H), 7.53 (t, J=5.6 Hz, 1H), 7.32 (t, J=7.6 Hz, 1H), 7.25 (s, 1H), 5.80-5.77 (m, 1H), 3.41-3.36 (m, 4H), 2.45 (s, 3H), 1.74-1.71 (m, 4H), 1.63 (d, J=7.2 Hz, 3H).

10 **Example 5 : (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methyl-6-(morpholinosulfonyl)pyrido[3,4-d]pyrimidin-4-amine**



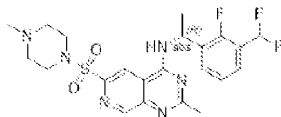
To a stirred solution of Morpholine (0.36g, 0.42mmol) in THF (1.5mL, 10V) was added
 15 TEA (0.1 mL, 0.69mmol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.15g, 0.34mmol) in THF (1.5mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water
 20 (10mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (32:68) ethyl acetate/hexane to yield (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methyl-6-(morpholinosulfonyl)pyrido[3,4-d]pyrimidin-4-amine (0.012g, 7.16%) as a pale yellow solid.

25 LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.176min, m/z =482.4 [M+H]⁺.

HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.331min.

¹H-NMR: (400 MHz, DMSO-d₆): δ 9.35 (d, J = 6.8 Hz, 1H), 9.08 (s, 1H), 9.05 (s, 1H), 7.71 (t, J=7.2 Hz, 1H), 7.53 (t, J=6.4 Hz, 1H), 7.32 (t, J=7.6 Hz, 1H), 7.25 (s, 1H), 5.82-5.75 (m, 1H), 3.65 (t, J=4.4 Hz, 4H), 3.20 (m, 4H), 2.45 (s, 3H), 1.63 (d, J=6.8 Hz, 3H).

Example 6 : (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methyl-6-((4-methylpiperazin-1-yl)sulfonyl)pyrido[3,4-d]pyrimidin-4-amine



5

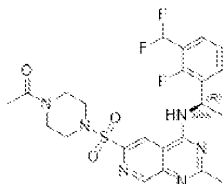
To a stirred solution of 1-methylpiperazine (0.041g, 0.42mmol) in THF (1.5mL, 10V) was added TEA (0.1 mL, 0.69mmol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.15g, 0.34mmol) in THF (1.5mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (5% MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (4:96) MeOH/DCM to yield (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methyl-6-((4-methylpiperazin-1-yl)sulfonyl)pyrido[3,4-d]pyrimidin-4-amine (0.011g, 6.39%) as an pale yellow solid.

LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.176min, m/z =482.4 [M+H]⁺.

HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.331min.

¹H-NMR: (400 MHz, DMSO-d₆): δ 9.35 (d, *J* = 6.8 Hz, 1H), 9.07 (s, 1H), 9.03 (s, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 6.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 5.80-5.76 (m, 1H), 3.22 (m, 4H), 3.45 (s, 3H), 2.40-2.33 (m, 4H), 2.15 (s, 3H), 1.63 (d, *J* = 7.2 Hz, 3H).

Example 7 : (R)-1-(4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)piperazin-1-yl)ethan-1-one



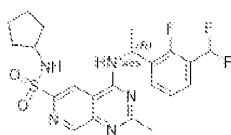
To a stirred solution of 1-(piperazin-1-yl) ethan-1-one (0.030g, 0.0002325mol) in THF (1mL, 10V) was added TEA (0.06 mL, 0.0004651mol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.1g, 0.0002325mol) in THF (1mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 16h. TLC (50% ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by Prep HPLC to yield (R)-1-(4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)piperazin-1-yl)ethan-1-one (0.029g,) as an off white solid.

LCMS Rt (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.067min, m/z =523.3 [M+H]⁺.

HPLC Rt (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 5.983min.

¹H-NMR: (400 MHz, DMSO-d₆): δ 9.34 (d, J = 6.8 Hz, 1H), 9.06 (s, 1H), 9.04 (s, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.53 (t, J=7.2 Hz, 1H), 7.32 (t, J=7.6 Hz, 1H), 7.25 (s, 1H), 5.82-5.75 (m, 1H), 3.60 (brs, 4H), 3.23-3.22 (m, 2H), 3.18-3.15 (m, 2H), 2.44 (s, 3H), 1.95 (s, 3H), 1.64 (d, J=7.2 Hz, 3H).

Example 8 : (R)-N-cyclopentyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonamide



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To a stirred solution of cyclopentanamine (0.035g, 0.42mmol) in THF (1.5mL, 10V) was added TEA (0.1 mL, 0.69mmol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.15g, 0.34mmol) in THF (1.5mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was

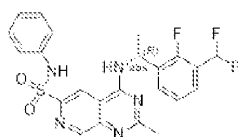
diluted with water (10mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (35:65) ethyl acetate/Hexane to yield (R)-N-cyclopentyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonamide (0.015g, 9%) as a brown solid.

LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.364min, m/z =480.3 [M+H]⁺.

HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.769min.

¹H-NMR: (400 MHz, DMSO-d₆): δ 9.34 (d, J = 6.4 Hz, 1H), 9.06 (s, 1H), 9.03 (s, 1H), 7.94 (d, J=7.6 Hz, 1H), 7.71 (t, J=7.6 Hz, 1H), 7.53 (t, J=6.8 Hz, 1H), 7.32 (t, J=8.0 Hz, 1H), 7.25 (s, 1H), 5.80-5.77 (m, 1H), 3.62-3.57 (m, 1H), 2.45 (s, 3H), 1.63 (d, J=6.8 Hz, 3H), 1.60-1.55 (m, 4H), 1.35-1.29 (m, 4H),.

Example 9 : (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methyl-N-phenylpyrido [3, 4-d]pyrimidine-6-sulfonamide



To a stirred solution of Aniline (0.022g, 0.0002325mol) in THF (1mL, 10V) was added TEA (0.06 mL, 0.00046mol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d] pyrimidine-6-sulfonyl chloride (0.1g, 0.00023mmol) in THF (1mL, 10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 16h. TLC (50% ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by reverse phase chromatography eluting with (40:60) ACN/water to yield (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methyl-N-phenylpyrido[3,4-d]pyrimidine-6-sulfonamide (0.0106g, 8%) as a Gray solid.

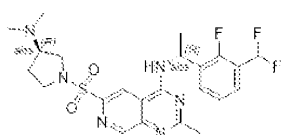
LCMS Rt (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.379min, m/z =488.3 [M+H]⁺.

HPLC Rt (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.909min.

¹H-NMR: (400 MHz, DMSO-d₆): δ 10.60 (s, 1H), 9.33 (d, *J* = 7.2 Hz, 1H), 9.10 (s, 1H), 9.03 (s, 1H), 7.67 (t, *J* = 6.8 Hz, 1H), 7.52 (t, *J* = 6.8 Hz, 1H), 7.37-7.29 (m, 1H), 7.23-7.15 (m, 5H), 7.01-6.98 (m, 1H), 5.78-5.74 (m, 1H), 2.42 (s, 3H), 1.61 (t, *J* = 6.8 Hz, 3H).

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Example 10 : N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(((R)-3-(dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine



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To a stirred solution of (R)-N, N-dimethylpyrrolidin-3-amine (0.15g, 0.348mmol, 2.0eq) in THF (10V) was added TEA (0.15g, 1.046mmol, 3.0eq). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.079g, 0.697mmol, 1.0eq) in THF (10V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% Ethyl acetate/hexane) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and ethyl acetate (2 x 20mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by reverse phase chromatography, eluting with (80:20) Acetonitrile/Water to yield N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(((R)-3-(dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (0.025g, 14.12%) as a light Yellow solid.

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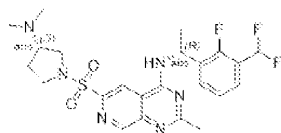
LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.932min, m/z =508.9 [M+H]⁺.

HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 4.952min.

¹H-NMR (400 MHz, DMSO-d₆): δ 9.34 (d, *J*=7.20 Hz, 1H), 9.06 (s, 1H), 9.02 (s, 1H), 7.71 (t, *J*=7.20 Hz, 1H), 7.52 (t, *J*=6.80 Hz, 1H), 7.31 (t, *J*=7.60 Hz, 1H), 7.25 (s, 1H), 5.80-5.76 (m, 1H), 3.63-3.67 (m, 1H), 3.53-3.58 (m, 1H), 3.07 (t, *J*=9.60 Hz, 2H), 2.40 (s, 3H), 2.15 (d, *J*=7.60 Hz, 2H), 2.04 (s, 6H), 1.92-1.95 (m, 1H), 1.63 (d, *J*=6.00 Hz, 3H).

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Example 11 : N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(((S)-3-(dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine



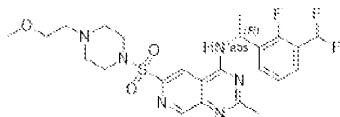
To a stirred solution of (S)-N, N-dimethylpyrrolidin-3-amine (0.026g, 0.23mmol), in THF (10V). To it TEA (0.069g, 0.69mmol) were added to the above mixture. The resulting mixture was allowed to stir at RT for 10 min. To it (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.1g, 0.23mmol), were added to the above mixture. The resulting mixture was allowed to stir at RT for 1h. TLC (10% MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (30mL) and ethyl acetate (60mL). The combined organics were dried over Na₂SO₄, filtered, and evaporated. The residue was purified by reverse phase chromatography, eluting with (50%) ACN/Water to yield N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(((S)-3-(dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (0.018g, 20.61%) as a yellow solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.935min, m/z = 509 [M+H]⁺.

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 4.991min.

¹H NMR (400 MHz, DMSO): δ 9.33 (d, J = 6.80 Hz, 1H), 9.06 (s, 1H), 9.03 (s, 1H), 7.71 (t, J = 7.60 Hz, 1H), 7.53 (t, J = 6.00 Hz, 1H), 7.38- 7.11 (m, 2H), 5.77-5.80 (m, 1H), 3.51-3.63 (m, 1H), 3.11-3.18 (m, 1H), 2.45 (s, 3H), 1.64-2.34 (m, 8H), 1.63 (d, J = 7.20 Hz, 3H), 1.25-1.34 (m, 3H).

Example 12 : (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-((4-(2-methoxyethyl)piperazin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine



To a stirred solution of 1-(2-methoxyethyl)piperazine (0.033g, 0.23mmol), in THF (10V). To it TEA (0.069g, 0.69mmol) were added to the above mixture. The resulting mixture was

allowed to stir at RT for 10 min. To it (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.1g, 0.23mmol), were added to the above mixture. The resulting mixture was allowed to stir at RT for 1h. TLC (10% MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (30mL) and EtOAc (60mL). The combined organics were dried over Na₂SO₄, filtered, and evaporated. The residue was purified by reverse phase chromatography, eluting with (50%) ACN/Water to yield (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-((4-(2-methoxyethyl)piperazin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (0.011g, 12.60%) as a Light yellow solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.974min, m/z = 539 [M+H]⁺.

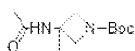
HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 5.088min.

¹H NMR (400 MHz, DMSO): δ 9.33 (d, J = 7.20 Hz, 1H), 9.07 (s, 1H), 9.03 (s, 1H), 7.71 (t, J = 7.60 Hz, 1H), 7.53 (t, J = 7.20 Hz, 1H), 7.31 (t, J = 7.60 Hz, 1H), 7.25 (s, 1H), 5.76-5.80 (m, 1H), 3.33-3.39 (m, 2H), 3.19-3.20 (m, 5H), 2.45-2.47 (m, 11H), 1.63 (d, J = 6.80 Hz, 3H).

Example 13 : (R)-N-(1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-3-methylazetidin-3-yl)acetamide

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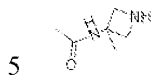
Preparation 1: tert-butyl 3-acetamido-3-methylazetidine-1-carboxylate



To a solution of tert-butyl 3-amino-3-methylazetidine-1-carboxylate (0.5g, 2.68mmol) was dissolved in Tetrahydrofuran (10mL, 20V). Pyridine (1.78mL, 21.40mmol) and Acetyl chloride (0.78mL, 10.70mmol) were added to the above solution at RT. The suspension was stirred at room temperature for 2h. TLC (30:70 hexane/ethyl acetate) showed SM was consumed completely. 1N HCl solution was added to neutralise the solution and then extracted with ethyl acetate. Organics were dried by Na₂SO₄ and concentrated under vacuum. The crude was purified by eluting with 100% ethyl acetate to yield ethyl tert-butyl 3-acetamido-3-methylazetidine-1-carboxylate (0.36g, 58%) as colourless thick oil.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.95min, m/z = 285.2 $[M+H]^+$.

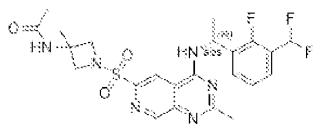
Preparation 2: N-(3-methylazetidin-3-yl) acetamide



To a solution of ethyl tert-butyl 3-acetamido-3-methylazetidine-1-carboxylate (0.5g, 1.57mmol) was dissolved in Dichloromethane (5.4mL, 15V). Trifluoroacetic acid (1.08mL, 3V) was added to the above solution at 0°C. The suspension was stirred at room temperature for 2h. TLC (05:95 DCM/MeOH) showed SM was consumed completely. The resulting mixture was concentrated under vacuum to yield N-(3-methylazetidin-3-yl) acetamide (0.5g, quantitative) as a colourless thick oil.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 0.26min, m/z = 128.9 $[M+H]^+$.

Example 13 : Preparation 3: (R)-N-(1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl)sulfonyl)-3-methylazetidin-3-yl)acetamide



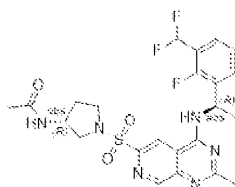
To a stirred solution of N-(3-methylazetidin-3-yl) acetamide (0.066g, 0.52mmol) and DIPEA (0.17mL, 1.04mmol) in dichloromethane (1.5mL, 10V). (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidine-6-sulfonylchloride (0.15g, 0.34mmol) in dichloromethane (1.5mL, 10V) was added dropwise to the above solution at RT. The resulting mixture was allowed to stir at RT for 2h. TLC (05:95 MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (50mL) and extracted with dichloromethane (50mL). The organics were dried and concentrated under vacuum. The residue was purified by PREP-HPLC chromatography to yield (R)-N-(1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methyl pyrido[3,4-d] pyrimidin-6-yl)sulfonyl)-3-methylazetidin-3-yl)acetamide (0.018g, 3%) as a light green solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.06min, m/z = 522.9 $[M+H]^+$

HPLC t_R (Waters Alliance e2695 with 2998 detector, Basic, 17.0min): 6.53min

1H NMR (400 MHz, DMSO): δ 9.38 (d, J = 6.8 Hz, 1H), 9.11 (s, 1H), 9.06 (s, 1H), 8.11 (s, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 6.4 Hz, 1H), 7.12-7.39 (m, 2H), 5.76-5.83 (m, 1H), 4.03-4.10 (m, 2H), 3.81-3.83 (m, 2H), 2.46 (s, 3H), 1.61-1.65 (m, 6H), 1.28 (d, J = 6.8 Hz, 3H).

Example 14 : N-((R)-1-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido [3, 4-d] pyrimidin-6-yl) sulfonyl) pyrrolidin-3-yl) acetamide



To a stirred solution (R)-N-(pyrrolidin-3-yl)acetamide (0.089 g, 0.0007mol) in dry THF at 0°C, TEA (0.141 g, 0.0014mol) was added, followed by addition of (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.150 g, 0.00035mol) solution in dry THF. The resulting reaction mixture was allowed to stir at RT for 2h. TLC (1:9 MeOH/DCM) showed SM was consumed completely. Reaction mixture was diluted with DCM and water. The combined organics were dried over anhydrous Na_2SO_4 , filtered, and evaporated. The residue was purified by normal phase chromatography, eluting with (04/96) MeOH/DCM to yield N-((R)-1-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido [3, 4-d] pyrimidin-6-yl) sulfonyl) pyrrolidin-3-yl) acetamide (0.017 g, 9%) as a pale yellow solid.

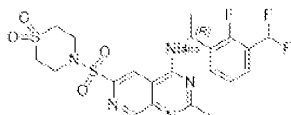
LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.032min, m/z = 522.9 $[M+H]^+$

HPLC t_R (Waters Alliance e2695 with 2998 detector, Basic, 17.0min): 6.557 min

1H NMR (400 MHz, DMSO- d_6): δ 9.34 (d, J = 6.80 Hz, 1H), 9.04 (s, 1H), 9.02 (s, 1H), 7.93 (d, J = 6.00 Hz, 1H), 7.72 (t, J = 7.60 Hz, 1H), 7.53 (t, J = 6.40 Hz, 1H), 7.38-7.11 (m, 2H), 5.77-5.80 (t, J = 7.20 Hz, 1H), 4.05-4.09 (m, 1H), 3.43-3.59 (m, 4H), 3.18-3.25 (m, 1H), 2.45 (s, 3H), 1.93-1.98 (m, 1H), 1.69 (s, 3H), 1.64 (d, J = 6.80 Hz, 3H).

Example 15 : (R)-4-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)thiomorpholine 1,1-dioxide

5



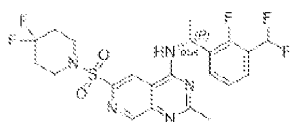
To a stirred solution of thiomorpholine 1,1-dioxide (0.094g, 0.0006976mol) in THF (10V). To it TEA (0.2ml, 0.001398mol) were added to the above mixture. The resulting mixture was allowed to stir at RT for 10 min. To it (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.2g, 0.0004651mol) were added to the above mixture. The resulting mixture was allowed to stir at RT for 1h. TLC (50% ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (30mL) and EtOAC(60mL). The combined organics were dried over Na₂SO₄, filtered, and evaporated. The residue was purified by reverse phase chromatography, eluting with (50%) ACN/Water to yield (R)-4-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)thiomorpholine 1,1-dioxide (0.017g,) as a white solid.

LCMS Rt (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.176min, m/z =529.9 [M+H]⁺.

HPLC Rt (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 7.655min.

¹H-NMR: (400 MHz, DMSO-d₆): δ 9.33 (d, J = 7.20 Hz, 1H), 9.09 (s, 1H), 9.08 (s, 1H), 7.71 (t, J = 7.20 Hz, 1H), 7.53 (t, J = 6.80 Hz, 1H), 7.39-7.11 (m, 2H), 5.82-5.75 (m, 1H), 3.76 (br s, 4H), 3.27 (br s, 4H), 2.45 (s, 3H), 1.63 (d, J = 6.80 Hz, 3H).

Example 16 : (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-((4,4-difluoropiperidin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine



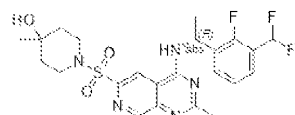
To a stirred solution of 4,4-difluoropiperidine (0.056g, 0.464mmol) in THF (1.0 ml). To this solution, TEA (0.07g, 0.696mmol) and (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.1g, 0.232mmol) were Added at room temperature. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (40% Ethyl Acetate: hexane) showed SM was consumed. The reaction mixture poured in water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was concentrated under reduced vacuum. The crude was purified by Reverse phase chromatography (72% ACN in Water). The yield (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-((4,4-difluoropiperidin-1-yl)sulfonyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (0.011g, 9.19%) as a Light yellow solid material.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.408 min, m/z = 515.9 $[M+H]^+$.

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 8.83 min

400 MHz, DMSO- d_6 : δ 9.34 (d, $J=6.8$ Hz, 1H), 9.07 (s, 2H), 7.71 (t, $J=7.2$ Hz, 1H), 7.52 (t, $J=7.2$ Hz, 1H), 7.31 (t, $J=7.6$ Hz, 1H), 7.24 (s, 1H), 5.79-5.76 (m, 1H), 3.42-3.39 (m, 4H), 2.45 (s, 3H), 2.07-2.02 (m, 4H), 1.63 (d, $J=6.8$ Hz, 3H).

Example 17 : (R)-1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-4-methylpiperidin-4-ol



To a stirred solution of 4-methylpiperidin-4-ol (0.026g, 0.23mmol), in THF (10V). To it TEA (0.069g, 0.69 mmol) were added to the above mixture. The resulting mixture was allowed to stir at RT for 10 min. To it (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.1g, 0.23 mmol), were added to the above mixture. The resulting mixture was allowed to stir at RT for 1h. TLC (10% MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (30mL) and EtOAc (60mL). The combined organics were dried over Na_2SO_4 , filtered, and evaporated. The residue was purified by reverse phase chromatography, eluting with (50%) ACN/Water to yield (R)-1-((4-((1-(3-(difluoromethyl)-2-

fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-4-methylpiperidin-4-ol

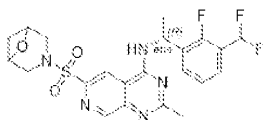
(0.015g, 12.68%) as a Brown solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.121min, m/z = 509.9[M+H]⁺

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 6.74min.

¹H NMR (400 MHz, DMSO): δ 9.32 (d, J = 6.80 Hz, 1H), 9.08 (s, 1H), 9.02 (s, 1H), 7.71 (t, J = 7.20 Hz, 1H), 7.53 (t, J = 7.60 Hz, 1H), 7.32 (t, J = 7.60 Hz, 1H), 7.25 (s, 1H), 5.76-5.80 (m, 1H), 4.29 (s, 1H), 3.43-3.49 (m, 2H), 2.96-3.18 (m, 2H), 2.47 (s, 3H), 1.64 (d, J = 6.80 Hz, 3H), 1.49-1.50 (m, 4H), 1.24 (s, 3H).

Example 18 : 6-((6-oxa-3-azabicyclo [3.1.1] heptan-3-yl) sulfonyl)-N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine



15

To a stirred solution 6-oxa-3-azabicyclo [3.1.1] heptane hydrochloride (0.047g, 0.348 mmol) in dry THF at 0°C. To this solution, TEA (0.105g, 1.04mmol) and (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidine-6-sulfonyl chloride (0.150g, 0.348mmol) were added at 0°C. The resulting reaction mixture was allowed to stir at RT for 2h. TLC (1:9 MeOH/DCM) showed SM was consumed. The reaction mixture poured in water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was concentrated under reduced vacuum. The crude was purified by Prep-HPLC purification. The yield 6-((6-oxa-3-azabicyclo [3.1.1] heptan-3-yl) sulfonyl)-N-((R)-1-(3-(difluoro methyl)-2-fluorophenyl) ethyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine (0.014g, 8.15%) as an off white solid material.

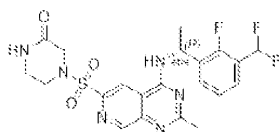
LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.147min, m/z = 493.85 [M+H]⁺

HPLC t_R (Waters Alliance e2695 with 2998 detector, Basic, 17.0min): 6.609 min

¹H NMR (400 MHz, DMSO-d₆): δ 9.78 (s, 1H), 9.11 (d, J = 3.2 Hz, 2H), 7.73 (t, J = 8.0 Hz, 1H), 7.54 (t, J = 6.8 Hz, 1H), 7.39-7.11 (m, 2H), 5.84-5.80 (m, 1H), 4.55 (d, J = 6.4 Hz, 2H), 3.68-3.58 (m, 4H), 3.02-3.00 (m, 1H), 2.45 (s, 3H), 1.77 (d, J = 9.2 Hz, 1H), 1.65 (d, J = 7.2 Hz, 3H).

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Example 19 : (R)-4-((4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido [3, 4-d] pyrimidin-6-yl) sulfonyl) piperazin-2-one



10

To a stirred solution piperazin-2-one (0.071 g, 0.0007mol) in dry THF at 0°C, TEA (0.141 g, 0.0014mol) was added, followed by addition of (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.150 g, 0.00035mol) solution in dry THF. The resulting reaction mixture was allowed to stir at RT for 2h. TLC (1:9 MeOH/DCM) showed SM was consumed completely. Reaction mixture was diluted with DCM and water. The combined organics were dried over anhydrous Na₂SO₄, filtered, and evaporated. The residue was purified by prep-HPLC to yield (R)-4-((4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido [3, 4-d] pyrimidin-6-yl) sulfonyl) piperazin-2-one (0.015 g, 9%) as an off white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.008min, m/z = 494.8 [M+H]⁺

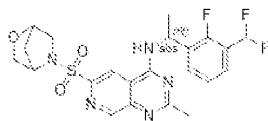
HPLC t_R (Waters Alliance e2695 with 2998 detector, Basic, 17.0min): 6.659 min

¹H NMR (400 MHz, DMSO-d₆): δ 9.35 (d, J = 6.80 Hz, 1H), 9.07 (s, 1H), 9.04 (s, 1H), 8.07 (s, 1H), 7.71 (t, J = 7.60 Hz, 1H), 7.53 (t, J = 7.20 Hz, 1H), 7.12-7.25 (m, 2H), 5.76-5.80 (m, 1H), 3.81 (d, J = 2.00 Hz, 2H), 3.46-3.48 (m, 2H), 3.15-3.17 (m, 2H), 2.45 (s, 3H), 1.64 (d, J = 6.80 Hz, 3H).

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Example 20 :6-((2-oxa-5-azabicyclo [2.2.1] heptan-5-yl) sulfonyl)-N-((R)-1-(3-(difluoromethyl)-2-fluoro phenyl) ethyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine

30



To a stirred solution 2-oxa-5-azabicyclo [2.2.1] heptane hydrochloride (0.047g, 0.348 mmol) in dry THF at 0°C. To this solution, TEA (0.105g, 1.04mmol) and (R)-4-((1-(3-
 5 (difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidine-6-sulfonyl chloride (0.150g, 0.348mmol) were added at 0°C. The resulting reaction mixture was allowed to stir at RT for 2h. TLC (1:9 MeOH/DCM) showed SM was consumed. The reaction mixture poured in water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was concentrated under reduced vacuum. The crude was purified
 10 by Prep-HPLC purification. The yield 6-((2-oxa-5-azabicyclo [2.2.1] heptan-5-yl) sulfonyl)-N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine (0.021g, 12.45%) as an off white solid material.

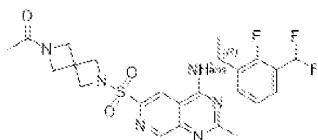
LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.137min, m/z = 493.80 $[M+H]^+$

15 HPLC t_R (Waters Alliance e2695 with 2998 detector, Basic, 17.0min): 7.449min

1H NMR (400 MHz, MeOD): δ 9.03 (s, 1H), 8.96 (s, 1H), 7.64 (t, J =8.0Hz, 1H), 7.50 (t, J = 6.4Hz, 1H), 7.26 (t, J =8.0Hz, 1H), 7.16-6.89 (m, 2H), 5.89-5.83 (m, 1H), 4.66 (s, 1H), 4.56 (s, 1H), 3.90-3.88 (m, 1H), 3.74 (d, J =7.6 Hz, 1H), 3.48-3.47 (m, 2H), 2.52 (s, 3H), 1.80-1.77 (m, 1H), 1.71 (d, J =7.2Hz, 3H), 1.53 (d, J =10.4Hz, 1H).

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Example 21 : (R)-1-(6-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one



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To a stirred solution of 1-(2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one compound with 2,2,2-trifluoro-1,3-ethan-1-one (1:1) (0.162g, 0.58mmol) in THF (2 ml). To this solution,

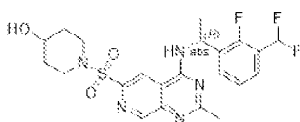
TEA (0.117g, 1.16mmol) and (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.250g, 0.58mmol) were Added at room temperature. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (10% MeOH: DCM) showed SM was consumed. The reaction mixture poured in water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was concentrated under reduced vacuum. The crude was purified by Reverse phase chromatography (50% ACN in Water). The yield (R)-1-(6-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)piperidin-4-ol (0.019g, 6.13%) as a Off white solid material.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.052 min, m/z = 534.91 $[M+H]^+$.

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 6.40 min

400 MHz, DMSO- d_6 : δ 9.38 (d, $J=6.8$ Hz, 1H), 9.11 (s, 1H), 9.06 (s, 1H), 7.72 (t, $J=7.2$ Hz, 1H), 7.53 (t, $J=7.2$ Hz, 1H), 7.39-7.11 (m, 2H), 5.81-5.77 (m, 1H), 4.176 (m, 4H), 4.09 (s, 2H), 2.80 (s, 2H), 2.46 (s, 3H), 1.65-1.62 (m, 6H).

Example 22 : (R)-1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)piperidin-4-ol



To a stirred solution of piperidin-4-ol (0.093g, 0.930mmol) in THF (10V) was added TEA (0.140g, 1.395mmol). (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.2g, 0.465mmol) in THF (10V) was added dropwise to the above solution at 0°C under N_2 atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% Ethyl acetate/hexane) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and ethyl acetate (3 x 10mL). The combined organics were dried over Na_2SO_4 , filtered and concentrated under a reduced vacuum. The residue was purified by PREP-HPLC yield (R)-1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)piperidin-4-ol (0.02g, 8.69%) as an off White solid.

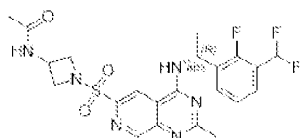
LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.058min, m/z = 495.8 $[M+H]^+$.

HPLC t_R (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.383min.

¹H-NMR: (400 MHz, DMSO- d_6): δ 9.35 (d, J = 6.80 Hz, 1H), 9.07 (s, 1H), 9.03 (s, 1H), 7.71 (t, J = 7.60 Hz, 1H), 7.54 (t, J = 7.20 Hz, 1H), 7.33 (t, J = 8.00 Hz, 1H), 7.26 (s, 1H), 5.80-5.75 (m, 1H), 4.74 (d, J = 4.00 Hz, 1H), 3.50-3.58 (m, 1H), 3.42-3.49 (m, 2H), 3.00-3.02 (m, 2H), 2.46 (s, 3H), 1.74-1.77 (m, 2H), 1.64 (d, J = 7.20 Hz, 3H), 1.38-1.48 (m, 2H).

Example 23 : (R)-N-(1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)azetidin-3-yl)acetamide

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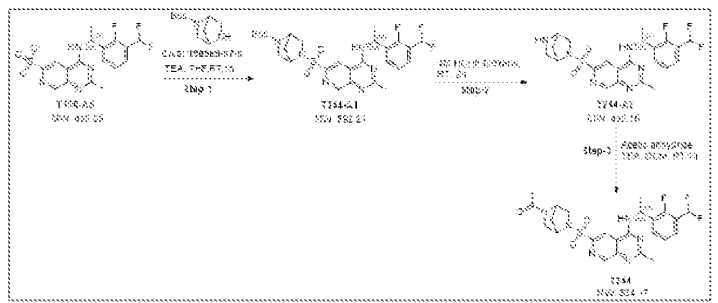
To a stirred solution of N-(azetidin-3-yl)acetamide hydrochloride (0.140g, 0.93mmol) in THF (2 ml). To this solution, TEA (0.215g, 1.86mmol) and (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.2g, 0.46mmol) were Added at room temperature. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% ethyl acetate: Hexane) showed SM was consumed. The reaction mixture poured in water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was concentrated under reduced vacuum. The crude was purified by Reverse phase chromatography (45% ACN in Water). The yield (R)-N-(1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)azeti din-3-yl)acetamide (0.019g, 8.04%) as an off white solid material.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.038 min, m/z = 508.8 $[M+H]^+$.

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 6.408 min.

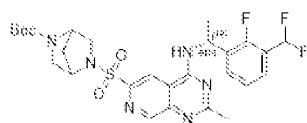
¹H NMR (400 MHz, DMSO- d_6): δ 9.38 (d, J =6.8Hz, 1H), 9.13 (s, 1H), 9.06 (s, 1H), 8.31 (d, J =6.8Hz, 1H), 7.71 (t, J =7.2Hz, 1H), 7.53 (t, J =7.2Hz, 1H), 7.39-7.11 (m, 2H), 5.82-5.76 (m, 1H), 4.37-4.32 (m, 1H), 4.18-4.13 (m, 2H), 3.81-3.77 (m, 2H), 2.47 (s, 3H), 1.72 (s, 3H), 1.64-1.62 (d, J =6.8Hz, 3H)

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T244**Synthetic scheme:**

Example 24: 1-(5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)ethan-1-one

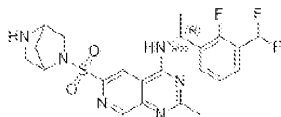
Preparation 1: tert-butyl 5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



To a stirred solution of tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.16g, 0.83mmol) in THF (1.5mL, 5V) was added TEA (0.2mL, 1.39mmol). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-sulfonyl chloride (0.3g, 0.69mmol) in THF (1.5mL, 5V) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% Ethyl acetate/Hexane) showed SM was consumed completely. The resulting solution was diluted with water (20mL) and ethyl acetate (3 x 30mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by normal phase chromatography, eluting with (31:69) ethyl acetate/hexane to yield tert-butyl 5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.25g, 15.43%) as yellow solid.

LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.303min, m/z =466.3 [M+H]⁺.

Preparation 2: 6-((2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine



A solution of tert-butyl 5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.25g, 0.42mmol) in 4M HCl in Dioxane (4.2mL, 10V) was stirred at room temperature for 2h. TLC (100% Ethyl acetate) showed SM was consumed completely. The resulting solution was diluted with saturated NaHCO₃ solution (15mL) and extracted with Ethyl acetate (3 x 25mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by reverse phase chromatography, eluting with (48:52) ACN/Water to yield 6-((2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (0.1g, 48.13%) as yellow solid.

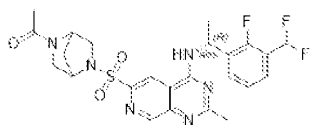
LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.900min, m/z =492.8 [M+H]⁺.

HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 4.022min.

¹H-NMR (400 MHz, DMSO-d₆): δ 9.33 (d, J = 7.2 Hz, 1H), 9.07(s, 1H), 9.02 (s, 1H), 7.71 (t, J=7.6 Hz, 1H), 7.53 (t, J=6.8 Hz, 1H), 7.32 (t, J=8.0 Hz, 1H), 7.25 (s, 1H), 5.80-5.77 (m, 1H), 4.39-4.41 (m, 1H), 3.54 (s, 1H), 3.26 (s, 2H), 2.88-2.79 (m, 2H), 2.45 (s, 3H), 1.63 (d, J=6.8 Hz, 3H), 1.44 (d, J=9.6 Hz, 1H), 1.15 (d, J=9.6 Hz, 1H), 0.88-0.85 (m, 1H).

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Preparation Example 24: 1-(5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)ethan-1-one



A solution of 6-((2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine (0.08g, 0.16mmol) in DCM (2mL) was added TEA (0.033g, (0.05mL) 0.324mmol) at 0°C and stirred it for 10 min. Then acetic anhydride (0.02g, 0.19mmol) in DCM (0.5mL) was added drop wise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (10% MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (5mL) and DCM (3 x 30mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced vacuum. The residue was purified by reverse phase chromatography, eluting with (40:60) ACN/Water to yield 1-(5-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)ethan-1-one (0.043g, 49.52%) as white solid.

LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.038min, m/z =534.9 [M+H]⁺.

HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 6.846min.

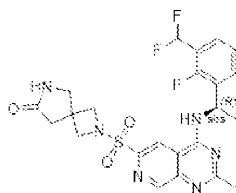
¹H-NMR (400 MHz, DMSO-d₆): δ 9.35 (brs, 1H), 9.08-9.03(m, 2 H), 7.72 (t, J=7.6 Hz, 1H), 7.54 (t, J=6.8 Hz, 1H), 7.35-7.31 (m, 1H), 7.26 (s, 1H), 5.81-5.78(m, 1H), 4.64 (d, J=7.6 Hz, 1H), 4.56 (d, J=7.6 Hz, 1H), 3.48-3.40 (m, 2H), 3.21 (d, J=12.4 Hz, 1H), 2.46 (s, 3H), 1.99 (d, J=2.0 Hz, 2H), 1.79 (d, J=5.6 Hz, 2H), 1.75-1.71 (m, 1H), 1.64 (d, J=6.8 Hz, 3H), 1.55-1.40 (m, 1H).

Example 25: (R)-2-(((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,6-diazaspiro[3.4]octan-7-one

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Preparation 1: (R)-2-(((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,6-diazaspiro[3.4]octan-7-one

-



To a stirred solution of 2,6-diazaspiro[3.4]octan-7-one hydrochloride (0.15g, 0.348mmol, 2.0eq) in THF (10V) was added TEA (0.105g, 1.046mmol, 3.0eq). Then (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-sulfonyl chloride (0.113g, 0.697mmol, 1.0eq) in THF (10V) was added dropwise to the above solution at 0°C under N₂ atmosphere. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% Ethyl acetate/hexane) showed SM was consumed completely. The resulting solution was diluted with water (10mL) and ethyl acetate (3 x 10mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under a reduced vacuum. The residue was purified by reverse phase chromatography, eluting with (80:20) Acetonitrile/Water to yield (R)-2-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,6-diazaspiro[3.4]octan-7-one (0.015g, 8.28%) as a light Yellow solid.

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LCMS tR (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.019min, m/z =520.8[M+H]⁺.

HPLC tR (Waters Alliance e2695 with 2998 detector, Acidic, 17.0min): 5.76min.

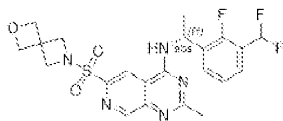
¹H-NMR (400 MHz, DMSO-d₆): δ 9.38 (d, J = 7.20 Hz, 1H), 9.14 (s, 1H), 9.06 (s, 1H), 7.72 (t, J = 7.20 Hz, 1H), 7.51-7.57 (m, 2H), 7.25-7.39 (m, 2H), 5.75-5.82 (m, 1H), 3.98-4.05 (m, 4H), 3.24 (s, 2H), 2.50 (s, 3H), 2.27 (s, 2H), 1.63 (d, J = 7.20 Hz, 3H).

Example 26: (R)-6-((2-oxa-6-azaspiro [3.3] heptan-6-yl) sulfonyl)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine

25

Preparation 1: (R)-6-((2-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpyrido[3,4-d]pyrimidin-4-amine

-



To a stirred solution of 2-oxa-6-azaspiro [3.3] heptane (0.022g, 0.23mmol), in THF (10V). TEA (0.069g, 0.69mmol) was added to the above mixture. The resulting mixture was allowed to stir at RT for 10 min. (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidine-6-sulfonyl chloride (0.1g, 0.23mmol) was added to the above mixture. The resulting mixture was allowed to stir at RT for 1h. TLC (10% MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (30mL) and Ethyl acetate (60mL). The combined organics were dried over Na₂SO₄, filtered, and evaporated. The residue was purified by reverse phase chromatography, eluting with (50%) ACN/Water to yield (R)-6-((2-oxa-6-azaspiro [3.3] heptan-6-yl) sulfonyl)-N-(1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine (0.004g, 3.49%) as a yellow solid.

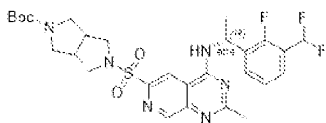
LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.134min, m/z = 494[M+H]⁺.

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 7.43min.

¹H NMR (400 MHz, DMSO) δ: 9.37(d, J = 7.2 Hz, 1H), 9.08 (s, 1H), 9.05 (s, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.40-7.26 (m, 2H), 5.80 (t, J = 7.2 Hz, 1H), 4.52 (s, 4H), 4.24-4.18 (m, 4H), 2.47 (s, 3H), 1.64 (d, J = 7.2 Hz, 3H).

Example 27: 1-(5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl) sulfonyl) hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl) ethan-1-one

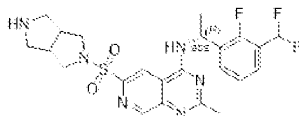
Preparation 1: tert-butyl 5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrid of 3,4-d] pyrimidin-6-yl) sulfonyl) hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate



To a solution of tert-butyl hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate (0.22g, 1.04 mmol) was dissolved in Dichloromethane (3mL, 10V). DIPEA (0.35mL, 2.09mmol) and
 5 (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidine-6-sulfonyl chloride (0.3g, 0.697mmol) were added to the above solution and the suspension was stirred at room temperature for 16h. TLC (70:30 hexane/ethyl acetate) showed SM was consumed completely. Reaction mixture was concentrated to give crude thick oil. The crude was purified by eluting with 70-80% ethyl acetate in hexane to yield
 10 tert-butyl 5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl) sulfonyl) hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate (0.2g, 47%) as sticky light green solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.46min, m/z = 607.1 $[M+H]^+$.

15 Preparation 2: N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-6-((hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl) sulfonyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine

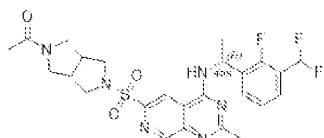


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To a solution of tert-butyl 5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl) sulfonyl) hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate (0.2g, 0.33mmol) was dissolved in Dichloromethane (2mL, 10V). Trifluoroacetic acid (0.6mL, 3V) was added to the above solution at 0°C. The suspension was stirred at
 25 room temperature for 2h. TLC (10:90 DCM/MeOH) showed SM was consumed completely. The resulting mixture was concentrated under vacuum to yield N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-6-((hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl) sulfonyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine (0.18g, quantitative) as an off-white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 1.93min, m/z = 506.9 $[M+H]^+$.

Preparation 3 Example 27: 1-(5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl) sulfonyl) hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl) ethan-1-one



To a stirred solution of N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-6-((hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl) sulfonyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine (0.13g, 0.256mmol) in Dichloromethane (2.6mL, 20V) was added triethylamine (0.10mL, 0.768mmol). Acetic anhydride (0.12mL, 1.28mmol) was added dropwise to the above solution at RT. The resulting mixture was allowed to stir at RT for 1h. TLC (05:95 MeOH/DCM) showed SM was consumed completely. The resulting solution was diluted with water (50mL) and extracted with dichloromethane (50mL). The organics were dried and concentrated under vacuum. The residue was purified by PREP-HPLC chromatography to yield 1-(5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl) sulfonyl) hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl) ethan-1-one (0.0054g, 4%) as an off-white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.02min, m/z = 549.0 $[M+H]^+$.

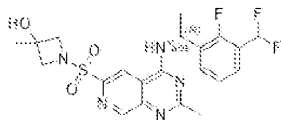
HPLC t_R (Waters Alliance e2695 with 2998 detector, Basic, 17.0min): 5.86min

¹H NMR (400 MHz, DMSO): δ 9.37 (d, J =7.20 Hz, 1H), 9.06 (d, J = 1.60 Hz, 2H), 7.72 (t, J =7.20 Hz, 1H), 7.53 (t, J =7.20 Hz, 1H), 7.13-7.40 (m, 2H), 5.78-5.81 (m, 1H), 3.60-3.67 (m, 4H), 3.19-3.29 (m, 3H), 3.04-3.10 (m, 1H), 2.89-2.93 (m, 1H), 2.78-2.83 (m, 1H), 2.46 (s, 3H), 1.87 (s, 3H), 1.64 (d, J =6.8 Hz, 3H).

Example28: (R)-1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-3-methylazetidin-3-ol

30 -

Preparation 1: (R)-1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-3-methylazetidin-3-ol



- 5 To a stirred solution of 3-methylazetidin-3-ol hydrochloride (0.083g, 0.123mmol) in THF (2.0 ml). TEA (0.156g, 1.34mmol) and (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.145g, 0.337mmol) were Added into reaction mixture at RT. The resulting reaction mixture was allowed to stir at RT for 1h. TLC (50% Ethyl Acetate: hexane) showed SM was consumed.
- 10 The reaction mixture was concentrated under reduced vacuum. The crude was purified by Reverse phase chromatography (40% ACN in Water). The yield (R)-1-((4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-3-methylazetidin-3-ol (0.012g, 7.41%) as a solid as an light yellow material.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.087 min, m/z

15 =481.8 $[M+H]^+$.

HPLC t_R (Waters Alliance e2695 with 2998 detector, basic, 17.0min): 7.13 min

1H NMR (400 MHz, DMSO): δ 9.37 (d, $J=7.2$ Hz, 1H), 9.11 (s, 1H), 9.04 (s, 1H), 7.71 (t, $J=7.6$ Hz, 1H), 7.52 (t, $J=7.2$ Hz, 1H), 7.31 (t, $J=7.6$ Hz, 1H), 7.24 (s, 1H), 5.78-5.79 (m, 1H), 5.56 (s, 1H), 3.78 (s, 4H), 2.46 (s, 3H), 1.63 (d, $J=6.8$ Hz, 3H), 1.24 (s, 3H).

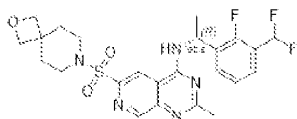
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Example 29: (R)-6-((2-oxa-7-azaspiro [3.5] nonan-7-yl) sulfonyl)-N-(1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methylpyrido [3, 4-d] pyrimidin-4-amine

-

Preparation 1: (R)-6-((2-oxa-7-azaspiro [3.5] nonan-7-yl) sulfonyl)-N-(1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methylpyrido [3, 4-d] pyrimidin-4-amine

25



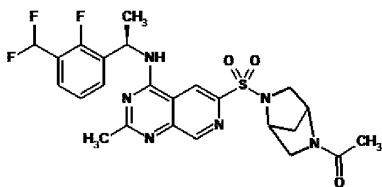
To a stirred solution of 2-oxa-7-azaspiro[3.5]nonane (0.044 g, 0.00035mol) in dry THF at 0°C, Triethylamine (0.106 g, 0.00104mol) was added, followed by addition of (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidine-6-sulfonyl chloride (0.150 g, 0.00035mol) solution in dry THF. The resulting reaction mixture was allowed to stir at RT for 2h. TLC (1:9 MeOH/DCM) showed SM was consumed completely. Reaction mixture was diluted with DCM and water. The combined organics were dried over anhydrous Na₂SO₄, filtered, and evaporated. The residue was purified by reverse phase chromatography, eluting with (46/54) ACN/water to yield (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-6-oxo-1-(1H-pyrazol-4-yl)-1, 6-dihydropyridazine-3-carboxamide (0.047 g, 26%) as an off white solid.

LCMS t_R (Waters Acquity UPLC with QDA mass Detector, Acidic, 4.0min): 2.188 min, m/z = 521.9 [M+H]⁺

HPLC t_R (Waters Alliance e2695 with 2998 detector, Basic, 17.0min): 6.811 min

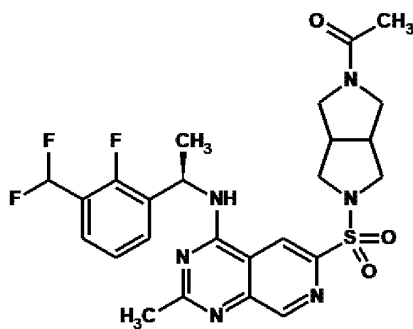
¹H NMR (400 MHz, DMSO-d₆): δ 9.33 (d, *J* = 6.80 Hz, 1H), 9.04 (s, 1H), 9.01 (s, 1H), 7.71 (t, *J* = 7.20 Hz, 1H), 7.53 (t, *J* = 6.80 Hz, 1H), 7.12-7.39 (m, 2H), 5.76-5.80 (m, 1H), 4.22 (s, 4H), 3.13-3.15 (m, 4H), 2.44 (s, 3H), 1.82-1.85 (m, 4H), 1.63 (d, *J* = 6.80 Hz, 3H).

Example 30 - 1-(5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)ethan-1-one



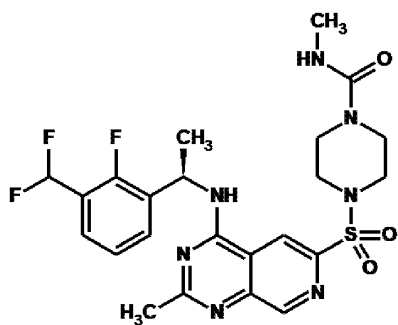
¹H nmr: δ 9.35 (brs, 1H), 9.08-9.03(m, 2 H), 7.72 (t, *J*=7.6 Hz, 1H), 7.54 (t, *J*=6.8 Hz, 1H), 7.35-7.31 (m, 1H), 7.26 (s, 1H), 5.81-5.78(m, 1H), 4.64 (d, *J*=7.6 Hz, 1H), 4.56 (d, *J*=7.6 Hz, 1H), 3.48-3.40 (m, 2H), 3.21 (d, *J*=12.4 Hz, 1H), 2.46 (s, 3H), 1.99 (d, *J*=2.0 Hz, 2H), 1.79 (d, *J*=5.6 Hz, 2H), 1.75-1.71 (m, 1H), 1.64 (d, *J*=6.8 Hz, 3H), 1.55-1.40 (m, 1H).

Example 31 - 1-(5-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl) sulfonyl) hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl) ethan-1-one



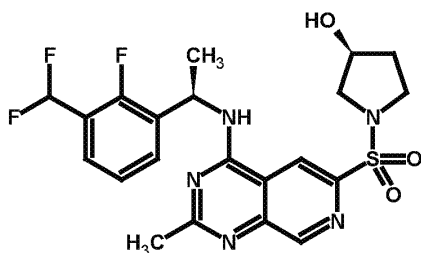
1H nmr: δ 9.37 (d, $J=7.20$ Hz, 1H), 9.06 (d, $J = 1.60$ Hz, 2H), 7.72 (t, $J=7.20$ Hz, 1H), 7.53 (t, $J=7.20$ Hz, 1H), 7.13-7.40 (m, 2H), 5.78-5.81 (m, 1H), 3.60-3.67 (m, 4H), 3.19-3.29 (m, 3H), 3.04-3.10 (m, 1H), 2.89-2.93 (m, 1H), 2.78-2.83 (m, 1H), 2.46 (s, 3H), 1.87 (s, 3H),
 5 1.64 (d, $J=6.8$ Hz, 3H).

Example 32 - (R)-4-((4-((1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido [3, 4-d] pyrimidin-6-yl) sulfonyl)-N-methylpiperazine-1-carboxamide



10 1H nmr: δ 9.33 (d, $J=6.8$ Hz, 1H), 9.04-9.08 (m, 2H), 7.70-7.73 (m, 1H), 7.51-7.55 (m, 1H), 7.12-7.39 (m, 2H), 6.50 (d, $J=4.4$ Hz, 1H), 5.75-5.81 (m, 1H), 3.62 (s, 3H), 3.36-3.47 (m, 4H), 3.15-3.23 (m, 4H), 2.39 (s, 3H), 1.61 (d, $J=7.2$ Hz, 3H).

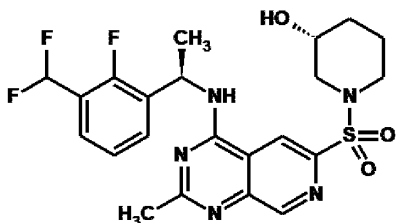
Example 33 - (S)-1-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido [3, 4-d] pyrimidin-6-yl) sulfonyl) pyrrolidin-3-ol



¹H nmr: δ 9.34 (d, J=6.8 Hz, 1H), 9.01-9.04 (m, 2H), 7.70-7.73 (m, 1H), 7.51-7.55 (m, 1H), 7.12-7.39 (m, 2H), 5.75-5.82 (m, 1H), 4.88 (bs, 1H), 4.18 (bs, 1H), 3.51-3.55 (m, 2H), 3.42-3.49 (m, 2H), 2.44 (s, 3H), 1.73-1.82 (m, 1H), 1.69-1.69 (m, 1H), 1.63 (d, J=7.2 Hz, 3H).

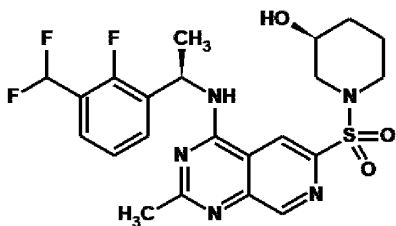
5

Example 34 - (R)-1-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl) sulfonyl) piperidin-3-ol



¹H nmr: δ 9.34 (d, J=7.2 Hz, 1H), 9.02-9.07 (m, 2H), 7.71 (t, J=7.2 Hz, 1H), 7.53 (t, J=6.8 Hz, 1H), 7.25-7.39 (m, 2H), 5.77-5.80 (m, 1H), 5.07 (s, 1H), 4.98 (d, J=4.4 Hz, 1H), 3.62-3.66 (m, 1H), 3.47-3.54 (m, 2H), 2.68-2.78 (m, 1H), 2.45 (s, 3H), 1.71-1.78 (m, 2H), 1.64 (d, J=6.8 Hz, 3H), 1.43-1.46 (m, 1H), 1.15-1.20 (m, 1H).

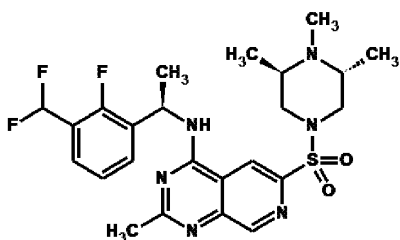
Example 35 - (S)-1-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)piperidin-3-ol



¹H nmr: δ 9.33 (d, J=6.8 Hz, 1H), 9.02-9.06 (m, 2H), 7.71 (t, J=7.6 Hz, 1H), 7.52 (t, J=7.2 Hz, 1H), 7.11-7.38 (m, 2H), 5.74-5.81 (m, 1H), 4.98 (d, J=4.4 Hz, 1H), 3.63-3.65 (m, 1H),

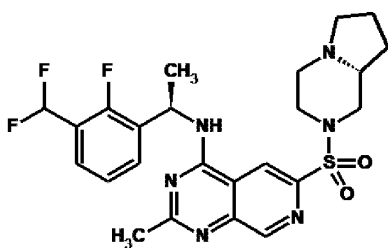
3.47-3.51 (m, 2H), 2.67-2.74 (m, 1H), 2.54-2.59 (m, 1H), 2.44 (s, 3H), 1.70-1.78 (m, 2H), 1.63 (d, J=7.2 Hz, 3H), 1.46-1.47 (m, 1H), 1.10-1.21 (m, 1H)

Example 36 - N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methyl-6-(((3R,5R)-3,4,5-trimethylpiperazin-1-yl) sulfonyl) pyrido[3,4-d] pyrimidin-4-amine



1H nmr: δ 9.31 (d, J=6.8 Hz, 1H), 9.01-9.06 (m, 2H), 7.71 (t, J=7.6 Hz, 1H), 7.52 (t, J=6.8 Hz, 1H), 7.11-7.38 (m, 2H), 5.74-5.81 (m, 1H), 3.19-3.21 (m, 2H), 2.88-2.92 (m, 2H), 2.78-2.81 (m, 2H), 2.45 (s, 3H), 2.14 (s, 3H), 1.63 (d, J=7.2 Hz, 3H), 0.87-0.99 (m, 6H)

Example 37 - N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) -6-(((R)-hexahydropyrrolo [1, 2-a] pyrazin-2 (1H)-yl) sulfonyl)-2-methylpyrido [3, 4-d] pyrimidin-4-amine

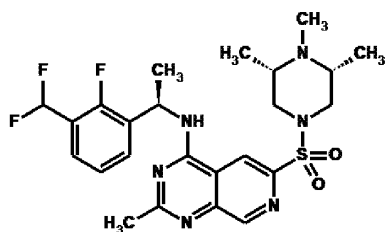


1H nmr: δ 9.33 (d, J=7.2 Hz, 1H), 9.04-9.07 (m, 2H), 7.71 (t, J=7.2 Hz, 1H), 7.53 (t, J=6.8 Hz, 1H), 7.12-7.39 (m, 2H), 5.75-5.82 (m, 1H), 3.86 (d, J=10.4 Hz, 1H), 3.69 (d, J=11.6 Hz, 1H), 2.93-3.00 (m, 2H), 2.75-2.91 (m, 1H), 2.53-2.56 (m, 1H), 2.45 (s, 3H), 2.12-2.15 (m, 1H), 2.07-2.10 (m, 1H), 1.91-2.05 (m, 1H), 1.74-1.81 (m, 1H), 1.63-1.65 (m, 5H), 1.22-1.30 (m, 1H).

20

Example 38 - N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methyl-6-(((3S, 5R)-3, 4, 5-tri

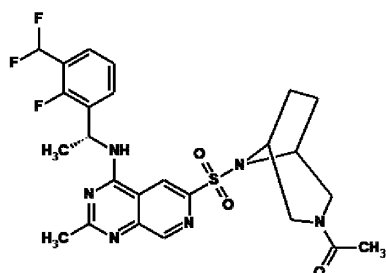
methylpiperazin-1-yl) sulfonyl) pyrido [3, 4-d] pyrimidin-4-amine



¹H nmr: δ 8.93-9.03 (m, 2H), 7.63-7.67 (m, 1H), 7.50-7.53 (m, 1H), 7.27 (t, J=7.6Hz, 1H), 6.90-7.17 (m, 1H), 5.86-5.88 (m, 1H), 3.75 (d, J=11.6 Hz, 2H), 2.54-2.61 (m, 5H), 2.37 (bs, 2H), 2.29 (s, 3H), 1.73 (d, J=7.2 Hz, 3H), 1.12 (d, J=6.4 Hz, 6H).

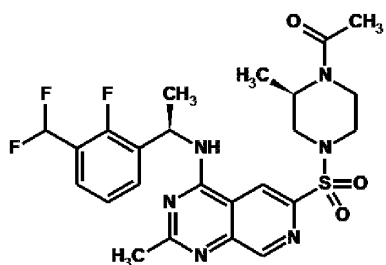
5

Example 39 - 1-(8-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido[3,4-d] pyrimidin-6-yl) sulfonyl)-3,8-diazabicyclo [3.2.1] octan-3-yl) ethan-1-one



10 ¹H nmr: δ 9.32 (d, J=7.2Hz, 1H), 9.04-9.08 (m, 2H), 7.70 (t, J=7.2 Hz, 1H), 7.52 (t, J=7.2 Hz, 1H), 7.11-7.38 (m, 2H), 5.73-5.79 (m, 1H), 4.27-4.30 (m, 2H), 4.20 (d, J=12.8 Hz, 1H), 3.71 (d, J=12.0 Hz, 1H), 3.29 (d, J=13.2Hz, 1H), 2.73-2.77 (m, 1H), 2.44 (s, 3H), 1.98 (s, 3H), 1.64 (d, J=6.8 Hz, 3H), 1.54-1.60 (m, 1H), 1.33-1.41 (m, 3H)

15 Example 40 - 1-((R)-4-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido [3,4-d] pyrimidin-6-yl) sulfonyl)-2-methylpiperazin-1-yl) ethan-1-one

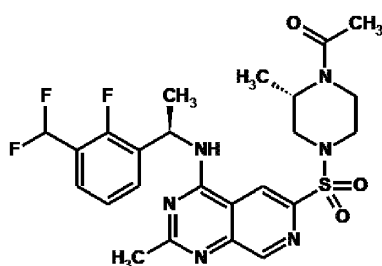


¹H nmr: δ 9.33 (d, J=6.8 Hz, 1H), 9.04(d, J=6.8 Hz, 2H), 7.71 (t, J=7.6 Hz, 1H), 7.53 (t, J=6.8 Hz, 1H), 7.11-7.38 (m, 2H), 5.76-5.81 (m, 1H), 4.66 (bs, 1H), 4.30 (d, J=12.8 Hz, 1H), 4.18 (bs, 1H), 3.72 (bs, 1H), 3.52 (d, J=12.4 Hz, 1H), 2.84-2.89 (m, 1H), 2.74-2.80 (m, 1H), 2.45 (s, 3H), 1.96 (d, J=14.0 Hz, 3H), 1.63 (d, J=6.8 Hz, 3H), 1.10-1.25 (m, 3H).

5

Example 41 - 1-((S)-4-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl) amino)-2-methylpyrido

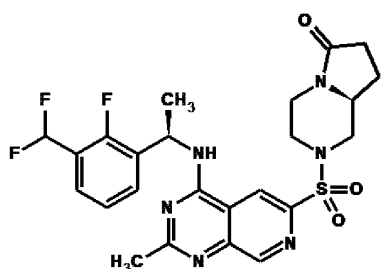
[3, 4-d] pyrimidin-6-yl) sulfonyl)-2-methylpiperazin-1-yl) ethan-1-one



10 ¹H nmr: δ 9.15 (d, J=6.40 Hz, 1H), 9.02 (d, J=10.0 Hz, 2H), 7.73 (t, J=7.6 Hz, 1H), 7.52 (t, J=7.2 Hz, 1H), 7.06-7.33 (m, 2H), 5.80-5.84 (m, 1H), 4.41 (bs, 1H), 3.99 (bs, 1H), 3.75 (d, J=10.4 Hz, 1H), 3.57 (d, J=12.0 Hz, 1H), 3.20-3.23 (m, 1H), 2.89-2.92 (m, 1H), 2.74 (bs, 1H), 2.47 (s, 3H), 1.98 (s, 3H), 1.67 (d, J=7.2 Hz, 3H), 1.19 (d, J=5.6 Hz, 3H).

15

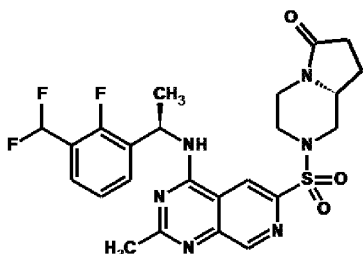
Example 42 - (S)-2-((4-(((R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2-methylpyrido[3,4-d]pyrimidin-6-yl)sulfonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one



20 ¹H nmr: δ 9.34 (d, J=7.2 Hz, 1H), 9.05 (d, J=3.6 Hz, 2H), 7.71 (t, J=7.20 Hz, 1H), 7.53 (t, J=7.2 Hz, 1H), 7.12-7.39 (m, 2H), 5.75-5.82 (m, 1H), 3.87-3.90 (m, 2H), 3.78-3.81 (m, 1H), 3.58-3.65 (m, 1H), 2.80-2.85 (m, 1H), 2.61-2.68 (m, 2H), 2.45 (s, 3H), 2.16-2.29 (m, 2H), 2.08-2.14 (m, 1H), 1.64 (d, J=6.8 Hz, 3H), 1.48-1.57 (m, 1H).

Example 43 - [REDACTED]

[REDACTED]



- 5 ¹H nmr: δ 9.34 (d, J=7.20 Hz, 1H), 9.06 (d, J=3.6 Hz, 2H), 7.71 (t, J=7.2 Hz, 1H), 7.53 (t, J=7.60 Hz, 1H), 7.25-7.42 (m, 2H), 5.79 (t, J=7.2 Hz, 1H), 3.87-3.90 (m, 2H), 3.77-3.79 (m, 1H), 3.59-3.61 (m, 1H), 2.82-2.87 (m, 1H), 2.45 (s, 3H), 2.18-2.26 (m, 2H), 2.09-2.14 (m, 1H), 1.64 (d, J=6.8 Hz, 3H), 1.48-1.57 (m, 2H).

10 Identification of SOS1 Inhibitors:

Compounds were screened using anHTRF KRAS WT/SOS1 PPI kit provided by Cis bio, according to the manufacturer's instructions, with the modifications described below. All reagents were allowed to equilibrate to room temperature and diluted to working stock in Binding Domain Detection buffer (BDD buffer). Stock solutions were prepared by adding

15 1 part Tag1-KRAS WT/GTP to 1 part Tag2-SOS1 and 1 part BDD. Separately, 1 part Anti-Tag1 XL665 antibody premix was added to Anti-Tag2 Tb cryptate antibody premix.

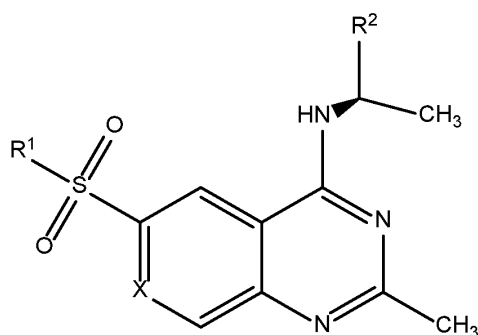
- BI-3406 (Selleck Chemicals) was used as a standard, solubilised to 10mM in DMSO. Test compounds were also solubilised to 10mM in DMSO. Test compounds were then dispensed in a 1/2-log, 10-point dilution series starting at 10μM, using a Labcyte Echo 650
- 20 instrument to dispense 200 nL of compound per well into 384-well microplates (Greiner 784075). Per well, 6uL of Tag1-KRAS WT/GTP premix, 4uL Tag2-SOS1 premix and 10μL of Anti-Tag1 XL665 and Anti-Tag2 Tb cryptate antibodies were then added using a E1-ClipTip™ Electronic Adjustable Multichannel Equalizer Pipette. After the final addition, the plate was covered and placed in the benchtop incubator set at 22°C. The reaction
- 25 was incubated for 60 minutes at room temperature, prior to reading using a Pherastar FSX plate reader.

All the compounds of the present invention had an IC₅₀ of less than 500nM when tested in the assay.

The compound of example 18 : 6-((6-oxa-3-azabicyclo [3.1.1] heptan-3-yl) sulfonyl)-N-((R)-1-(3-(difluoromethyl)-2-fluorophenyl) ethyl)-2-methylpyrido[3,4-d] pyrimidin-4-amine had an IC₅₀ of <100nM.

Claims

- 5 1. A Compound of formula (I)



Or a pharmaceutically acceptable salt or solvate thereof, wherein:

10

X is N or CR²⁵

R¹ is selected from a N containing 4-7 membered saturated heterocycle, optionally containing an additional O, N or S atom, or S(O)₂ moiety. Said heterocycle optionally

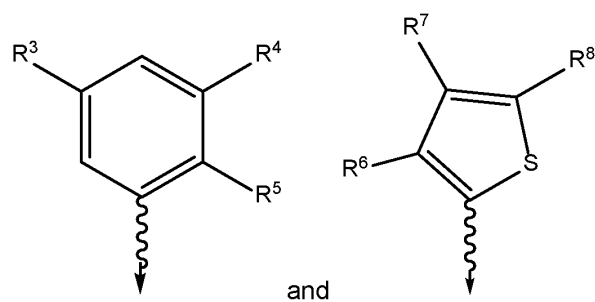
15 containing:

- (i) an ether bridge, or
 - (ii) joining another 4-7membered, N containing, saturated heterocycle to form a spiro bicyclic group; or
 - (iii) joining with another 3-6 membered N containing saturated heterocycle, such
- 20 that the rings share two atoms in common, said saturated heterocycle optionally incorporating a C(O) moiety;

said monocyclic or bicyclic heterocycle optionally substituted by 1-3 substituents, each independently selected from NC(O)C₁₋₆ alkyl, H, N(C₁₋₆ alkyl)(C₁₋₆ alkyl), C₁₋₆ alkyl, C(O)C₁₋₆ alkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, OH and O-C₁₋₆ alkyl, HC(O)C₁₋₆ alkyl, halo and Ph.

25

R² is selected from



R^3 is H or NH_2

5 R^4 is CF_3 , $\text{CF}_2\text{CH}_2\text{OH}$, CN

R^5 is halo

R^6 is H

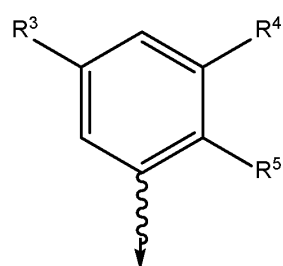
10

R^7 is H

R^8 is Ph, ortho substituted by CH_2NHCH_3

15 R^{25} is selected from H, OCH_3 , F and CN

2. A compound according to claim 1 wherein R^2 is



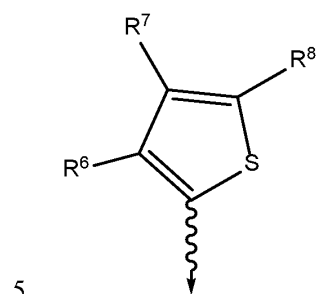
20

R^3 is H or NH_2

R^4 is CF_3 , $\text{CF}_2\text{CH}_2\text{OH}$, CN

25 R^5 is F

3. A compound according to claim 1 wherein R² is



R⁶ is H

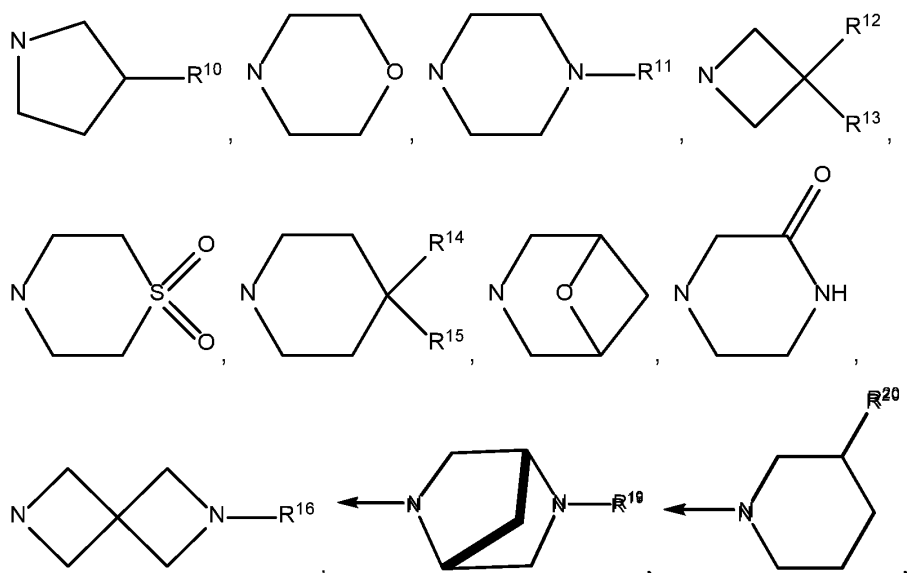
R⁷ is H

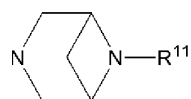
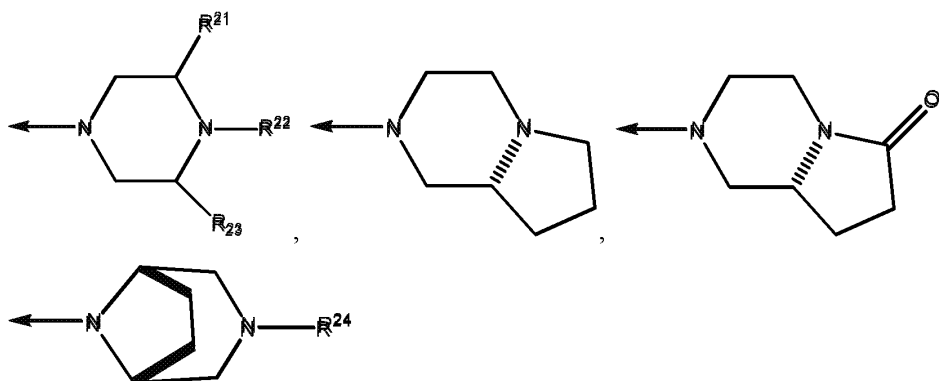
10

R⁸ is Ph, ortho substituted by CH₂NHCH₃

4. A compound according to claims 1-3 wherein R¹ is selected from:

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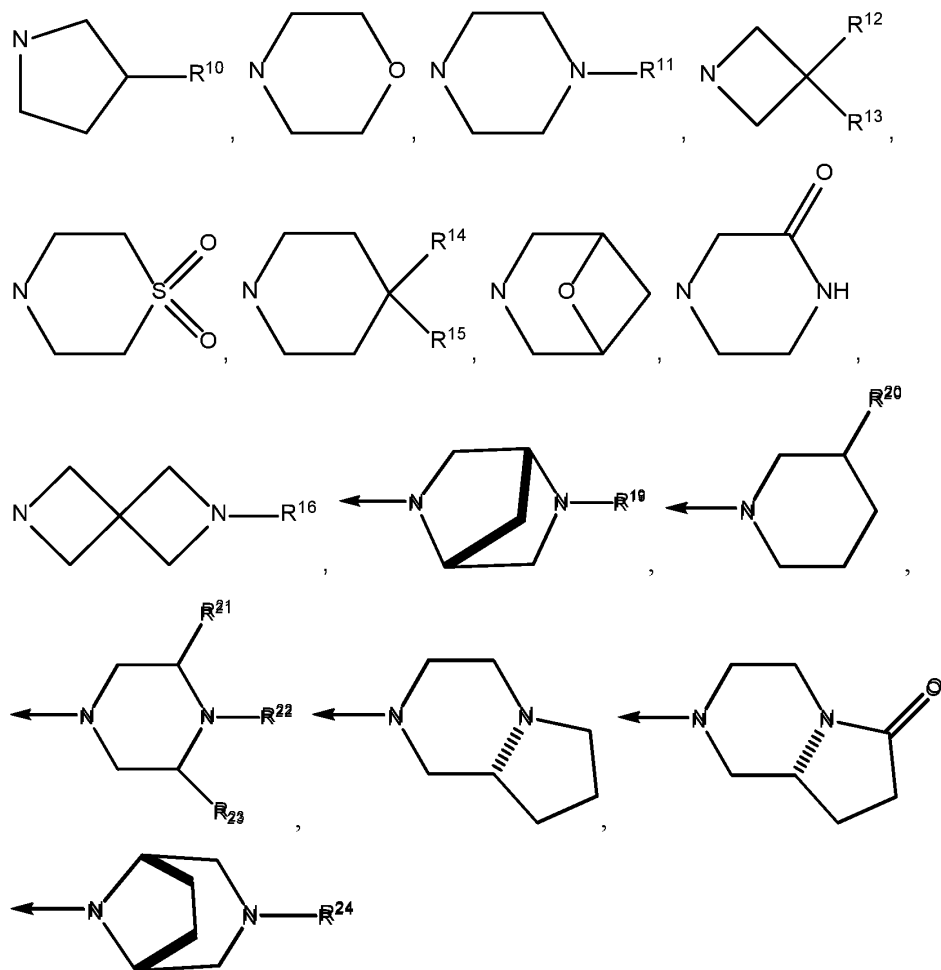
And $\text{NR}^{17}\text{R}^{18}$,

Wherein

- 10 R^{10} is selected from NC(O)C_{1-6} alkyl, H, N(C_{1-6} alkyl)(C_{1-6} alkyl)
 R^{11} is selected from C_{1-6} alkyl, C(O)C_{1-6} alkyl, C_{1-6} alkyl- O-C_{1-6} alkyl, OH and O-C_{1-6} alkyl
 R^{12} is selected from NHC(O)C_{1-6} alkyl, C_{1-6} alkyl, H
 R^{13} is selected from NHC(O)C_{1-6} alkyl, C_{1-6} alkyl, H
 R^{14} is selected from halo, OH, OC_{1-6} alkyl, H
15 R^{15} is selected from halo, OH, OC_{1-6} alkyl, H
 R^{16} is selected from C(O)C_{1-6} alkyl
 R^{17} is selected from C_{1-6} alkyl, H, Ph
 R^{18} is selected from C_{1-6} alkyl, H, Ph
 R^{19} is selected from C(O)C_{1-6} alkyl
20 R^{20} is OH
 R^{21} is selected from CH_3 or H
 R^{22} is selected from C_{1-6} alkyl, H, C(O)C_{1-6} alkyl and C(O)NHC_{1-6} alkyl
 R^{23} is selected from C_{1-6} alkyl and H
 R^{24} is C(O)C_{1-6} alkyl

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5. A compound according to claim 4 wherein R^1 is selected from:



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And $NR^{17}R^{18}$,

Wherein

- 10 R^{10} is selected from $NC(O)CH_3$, H, $N(CH_3)_2$
 R^{11} is selected from CH_3 , $C(O)CH_3$, CH_2-OCH_3 , OH,
 R^{12} is selected from $NHC(O)CH_3$, CH_3 , H.
 R^{13} is selected from $NHC(O)CH_3$, CH_3 , H.
 R^{14} is selected from F, OH and H.
- 15 R^{15} is selected from F, OH and H.
 R^{16} is selected from $C(O)CH_3$
 R^{17} is selected from CH_3 , H & Ph
 R^{18} is selected from CH_3 , H & Ph
 R^{19} is selected from $C(O)CH_3$
- 20 R^{20} is OH

R²¹ is selected from CH₃ or H

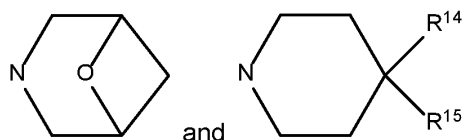
R²² is selected from CH₃, H, C(O)CH₃ and C(O)NHCH₃

R²³ is selected from CH₃ and H

R²⁴ is C(O)CH₃

5

6. A compound according to claim 5 wherein R¹ is selected from



10 R¹⁴ is H

R¹⁵ is OH

7. A compound according to any preceeding claim wherein X is N or CR²⁵, wherein
R²⁵ is H.

15

8. A compound according to claims 1-7 for use as a medicament

9. Use of a compound according to claims 1-7 in the treatment of pain

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10. Use according to claim 9 wherein pain includes acute pain, chronic pain, inflammatory pain, nociceptive pain, neuropathic pain, hyperalgesia, allodynia, central pain, cancer pain, post-operative pain, visceral pain, musculo-skeletal pain, heart or vascular pain, head pain, orofacial pain and back pain.

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11. Use of a compound according to claims 1-7 in the treatment of cancer.

12. Use according to claim 11 wherein cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, cholangiocarcinoma, multiple myeloma, melanoma, uterine cancer, endometrial cancer, thyroid cancer, acute myeloid leukaemia, bladder cancer, urothelial cancer, gastric cancer, cervical cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, oesophageal cancer, chronic lymphocytic leukaemia, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, renal cancer and sarcomas.

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13. Use of a compound according to claims 1-7 for the treatment of neurofibromatosis.