

**N-ACYL-{4-[(4-ARYL-PHENYL)SULFONYLMETHYL]PIPERIDINE} COMPOUNDS
AND THEIR THERAPEUTIC USE**

RELATED APPLICATION

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This application is related to United Kingdom (GB) patent application number 1905520.1 filed 18 April 2019, the contents of which are incorporated herein by reference in their entirety.

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TECHNICAL FIELD

The present invention pertains generally to the field of therapeutic compounds. More specifically the present invention pertains to certain N-acyl-{4-[(4-aryl-phenyl)sulfonylmethyl]piperidine} compounds (collectively referred to herein as NASMP compounds) that are useful, for example, in the treatment of disorders (e.g., diseases) including, e.g., multiple myeloma, diffuse large B-cell lymphoma, acute myeloid leukemia, eosinophilic leukemia, glioblastoma, melanoma, ovarian cancer, chemotherapy resistant cancer, radiation resistant cancer, inflammatory arthritis, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus (SLE), lupus nephritis, asthma, chronic obstructive pulmonary disease (COPD), Hidradenitis suppurativa, autoimmune hepatitis, etc. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, for example, in therapy.

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BACKGROUND

A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Each of these publications is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

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Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be

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understood that the particular value forms another embodiment.

This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly

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referenced is prior art.

Cellular Metabolism

Cellular metabolism is a set of complex sequences of biochemical reactions which occur in the cells of living organisms to maintain life. Each sequence of reactions is known as a metabolic pathway, and these pathways act in concert to provide energy, the synthesis of new molecules and the breakdown and removal of other molecules within the cell. One key metabolic pathway is known as oxidative phosphorylation, the process by which energy, in the form of adenosine triphosphate (ATP), is formed by the transfer of

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electrons through carriers known as electron transport complexes. Other examples of metabolic pathways include glycolysis, the process by which glucose is broken down to release ATP, and beta oxidation, the process by which fatty acids are broken down.

Glycolysis occurs in the cytoplasm. Glucose, the substrate for glycolysis, is converted to pyruvate through a series of ten-enzyme-catalysed reactions. This pyruvate is, in turn, converted to lactic acid, the end product of glycolysis. ATP is directly formed through phosphate transfer from substrate to ATP, or substrate phosphorylation. Some of the pyruvate enters the tricarboxylic (TCA) cycle, whereas most of the end product, lactic acid, is flushed out of the cell. Oxidative phosphorylation occurs in the mitochondria of cells. Glutamine, glucose, or fatty acids are the suppliers for the electron transport chain and ATP is formed through a series of redox reactions involving oxygen as the final electron acceptor. The series of oxidative reduction reactions occur through the four complexes of the electron transport chain, which then generates an electrochemical gradient in the inner mitochondrial membrane. Protons return to the mitochondrial matrix through ATP synthase, and this process is coupled to ATP synthesis. A total of 36 mol of ATP are produced per 1 mol of glucose.

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The metabolic properties of certain types of cells can vary greatly. For example, energy production in cancer cells is abnormally skewed towards aerobic glycolysis (a process known as the Warburg Effect), as well as showing increased fatty acid synthesis and increased rates of metabolism of the amino acid glutamine. In addition, changes in the metabolism of cancer cells may render them resistant to therapy and several studies have shown that chemoresistance, at least in part, is driven by mitochondrial metabolism and oxidative phosphorylation, whilst high levels of ATP in cancer cells can lead to increased efflux of chemotherapeutic agents and promote hypoxia-associated drug resistance.

Similar to cancer cells, immune cells show changes in metabolism depending on their activation status and the stimulatory signals they receive. The field of immunometabolism is the investigation of the interface between immunology and metabolism as it relates to both the governance of the function of immune cells, and their role in chronic inflammatory disease and cancer, among others.

Chronic Inflammatory Disease

Inflammation is the immune response of tissues due to bodily injury. Acute inflammation is a normal, protective response that protects and heals the body following physical injury or infection, characterised by heat, swelling, and redness at the site of the injury. However, if inflammation persists for a prolonged period, it becomes chronic. Chronic inflammation is a hallmark of, and a contributing factor to, a range of disease conditions including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis and psoriasis.

The inflammatory process is complex and involves a biological cascade of molecular and cellular signals that alter physiological responses. At the site of the injury, cells release molecular signals such as cytokines and interleukins that cause a number of changes in the affected area including dilation of blood vessels, increased blood flow, increased vascular permeability, invasion by leukocytes (white blood cells), and exudation of fluids containing proteins like immunoglobulins (antibodies). Several different types of leukocytes, including granulocytes, monocytes, and lymphocytes, are involved in the inflammatory cascade. However, chronic inflammation is primarily mediated by monocytes and long-lived macrophages; monocytes mature into macrophages once they leave the bloodstream and enter tissues. Macrophages engulf and digest microorganisms, foreign invaders, and senescent cells and macrophages release several different chemical mediators, including Tumour Necrosis Factor- α (TNF α), interleukins (e.g., IL-1, IL-6, IL-12 and IL-23) and prostaglandins that perpetuate the inflammatory response. At later stages, other cells, including lymphocytes, invade the

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affected tissues. Recent evidence has shown that many aberrant immune responses occur as a result of disruption to metabolic processes and that altering cellular metabolism may either enhance or reduce immune responses. Alterations in metabolism in monocytes, macrophages and lymphocytes (immunometabolism) are hence crucial in driving disease.

There is thus a common pathology underlying a wide variety of chronic inflammatory conditions. In addition, features of chronic inflammation are also observed in other diseases including cancer and metabolic diseases such as obesity, atherosclerosis, and diabetes.

One of the most common chronic inflammatory conditions is rheumatoid arthritis (RA), a condition which affects up to 2% of the population worldwide. Although it is a complex disease, there are a number of physiological, cellular, and biochemical factors associated with the progression of RA that are common to a range of other diseases, including those with a component of autoimmunity (e.g., multiple sclerosis), inflammation (e.g., atherosclerosis and cancer), bone loss (e.g., osteoporosis) and proliferation (e.g., haematological malignancies). This makes the understanding of RA important not only for the study of a much broader range of diseases, but also suggests that pharmaceutical agents that work via modification of these common processes may have utility beyond RA. The latter is borne out by clinical practice where RA drugs have been shown to have broad utility across a variety of other conditions.

Rheumatoid Arthritis and Related Autoimmune / Inflammatory Diseases

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic inflammation of the synovial lining of multiple joints coupled to progressive joint degradation. RA commonly affects the joints of the wrist and hands and may also affect the elbows, shoulders, hips, neck and knees leading to severe pain and disability (see, e.g., Scott *et al.*, 2010). The World Health Organisation (WHO) Global Burden of Disease 2010 update estimated that 23.7 million people suffer from RA, with incidence rising due to the association between the condition and increasing age.

The exact cause of RA, as for all the autoimmune disorders, remains unclear, although possible triggers include reduced self-tolerance, an abnormal response to environmental factors, infectious agents, and hormonal stimulus (see, e.g., Klareskog *et al.*, 2006; Firestein *et al.*, 2005). A central feature of the condition is the dysregulation of innate and adaptive immunity, with an imbalance in pro-inflammatory and anti-inflammatory cytokines and a change in the balance between osteoclast-mediated degradation and osteoblast-mediated deposition in the bone marrow compartment (see, e.g., Kleyer *et al.*, 2014; Jung *et al.*, 2014).

At the cellular level, development of RA usually commences with T-cells infiltrating the synovial membrane lining the affected joint; this then leads to the activation of monocytes, macrophages and synovial fibroblasts by way of cell-cell contact and the subsequent
5 release of various cytokines, including tumour necrosis factor-alpha (TNF α) and pro-inflammatory interleukins such as IL-1, IL-6, IL-12 and IL-23 (see, *e.g.*, Astry *et al.*, 2011). These pro-inflammatory cytokines are then instrumental in orchestrating several complex signal transduction cascades, including the NF κ B, Interferon Regulatory Factor (IRF), Toll-like receptor (TLR), and Jak/STAT pathways (see, *e.g.*, Malemud *et al.*, 2010)
10 which lead to the induction of genes coding for various products that propagate the inflammatory response and also promote tissue destruction. These products include tissue-degrading enzymes such as collagenases, matrix metalloproteinases (MMPs), cathepsins, and other pro-inflammatory factors such as selectins, integrins, leukotrienes, prostaglandins, chemokines, and other cytokines (see, *e.g.*, McInnes *et al.*, 2011;
15 Chimenti *et al.*, 2015). In addition, these cells also increase the production of MMPs, leading to the degradation of the extra cellular matrix and loss of cartilage within the joint (see, *e.g.*, Sun, 2010), a process that also involves a specialised class of cells known as osteoclasts and a factor known as Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) (see, *e.g.*, Takayanagi, 2009).

20 RANKL is an essential factor for the generation of osteoclasts, and upregulated RANKL-production leads to increased osteoclast differentiation and ultimately bone destruction (see, *e.g.*, Long *et al.*, 2012). The inflammatory response in RA leads to the accumulation of lymphocytes, dendritic cells, and macrophages, all operating locally to
25 produce cytokines and other pro-inflammatory mediators such as TNF α and IL-6 which further potentiate the effects of RANKL on bone destruction. In addition, the inflammatory cascade leads to the hyperplasia of synoviocytes (see, *e.g.*, Takayanagi, 2009), which in turn leads to the thickening and vascularisation of the synovium into a destructive and aggressive tissue known as a pannus. The pannus contains both osteoclasts, which
30 destroy bone, and metalloproteinases, which are involved in the destruction of cartilage. As such, the RANKL axis is critical to the progression and pathology of RA as well as to the osteoimmune system (the interplay between the immune and bone systems), which is central to the pathology of a number of different disease conditions.

35 The Role of Immune Metabolism in RA

All cells produce adenosine triphosphate (ATP), a high-energy molecule which acts as fuel, and synthesize macromolecules to maintain their basic cellular functions, whether they are active, replicating, or quiescent (see, *e.g.*, Spies *et al.*, 2012). These
40 bioenergetic needs are met by interconnected metabolic pathways within the cell: glycolysis (the first step in the breakdown of glucose), the tricarboxylic acid cycle (a series

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of reactions releasing stored energy from carbohydrates, fats, and proteins), and oxidative phosphorylation (the process of forming ATP by the transfer of electrons). Changes in these pathways drive the effector functions of immune cells from lymphocytes to monocytes and macrophages and dendritic cells, and are also able to modulate cell fate.

In chronic inflammatory diseases including RA, very large amounts of energy (up to 2,000 kJ/day) are consumed by the activation of the immune system (see, e.g., Straub *et al.*, 2010). This energy is used, at least in part, by the immune system to maintain the chronic inflammatory state in response to environmental signals (see, e.g., Procaccini *et al.*, 2012; Nutsch *et al.*, 2011) and the interplay between immunology and metabolism hence plays a central role in the pathophysiology of chronic inflammatory diseases (see, e.g., Perl, 2017; Ganeshan *et al.*, 2014).

Several metabolic changes in cells that participate in inflammation are seen in immune cells in RA (see, e.g., Weyand *et al.*, 2017a). Chronic stimulation and the synovial microenvironment alters T cell and macrophage metabolism in RA. For example, T cells from patients with RA show reduced expression of 6-phosphofructo 2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), an enzyme involved in ATP generation, and autophagy (see, e.g., Yang *et al.*, 2013), whilst macrophages from patients with RA produce higher levels of ATP than cells from healthy individuals (see, e.g., Weyand *et al.*, 2017b). In addition to direct changes in cells, the hypoxic environment in the RA synovium (see, e.g., Fearon *et al.*, 2016) creates a chronic mitochondrial hyperpolarization, which is also seen in systemic lupus erythematosus (SLE) and in fibroblast-like synoviocytes from RA patients; there is a shift to glycolysis compared with cells from non-inflammatory settings (see, e.g., Garcia-Carbonnel *et al.*, 2016). Thus, there is great potential for agents that modulate ATP or alter immune cell metabolism to be useful in the treatment of chronic inflammatory diseases such as RA, SLE, inflammatory bowel disease (IBD), psoriasis, and atherosclerosis.

Cellular Metabolism and Cancer

Cellular energy in the form of ATP is generated through two major pathways: mitochondrial oxidative phosphorylation and cytoplasmic glycolysis. In normal cells, glycolysis is followed by oxidation of pyruvate using the oxidative phosphorylation machinery of the mitochondria and this is the predominant pathway to generate ATP. However, in cancer cells glycolysis is upregulated and lactic acid is fermented in the cytosol of the cell in a process known as the Warburg effect. Thus, reprogrammed metabolism is a hallmark of cancer, and facilitates the growth and proliferation of cells under stressed conditions.

- Mitochondrial metabolism is also important for the generation of building blocks required for cancer cell proliferation and cancer cells also require mitochondrial oxidative metabolism to maintain their redox balance. The majority of cancer cells display functional mitochondria and are able to generate ATP through mitochondrial metabolism (see, e.g., Koppenol, 2011). Depending on the cellular context, mitochondria substantially contribute to the generation of cellular reactive oxygen species (ROS) as a natural by-product of mitochondrial ATP generation. ROS formation occurs due to the incomplete reduction of molecular oxygen and in cancer cells, ROS have been shown to promote tumour development and progression by inducing oncogenic signalling, genetic instability and DNA mutations (see, e.g., Weinberg *et al.*, 2010). However, when ROS production exceeds the capacity of intracellular ROS-detoxifying systems, cellular toxicity results. As such, cancer cells have to tightly control their metabolic machinery in order to maintain the balance between ROS generation and scavenging.
- Changes in cellular and mitochondrial metabolism are thus critical for the growth and proliferation of tumours. Indeed, mitochondrial biogenesis and the associated increases in oxidative phosphorylation have been shown to promote tumour metastasis (see, e.g., LeBleu *et al.*, 2014), whilst reducing oxidative phosphorylation has also been proposed as a means to target cancer stem cells (see, e.g., Fiorillo *et al.*, 2016). Data also shows that targeting components of the mitochondrial electron transport chain may have anti-cancer effects. For example, complex I inhibition by the anti-diabetic metformin inhibits tumorigenesis (see, e.g., Evans *et al.*, 2005; Pollak *et al.*, 2014; Wheaton *et al.*, 2014; Bridges *et al.*, 2014) whilst novel small molecule inhibitors of electron transport also show anti-tumour activity in xenograft models of cancer (see, e.g., Ellinghaus *et al.*, 2013).
- Altering cellular metabolism is thus emerging as a means by which to prevent cancer growth and progression, as well as to overcome resistance to chemotherapy and prevent metastasis.

The Osteoimmune System and Bone Disorders

- The osteoimmune system is a term for the combined and related interplay between the immune system and the skeletal system.
- Under normal physiological conditions, the skeletal system provides support, mobility, protection for vital organs, and a mineral reservoir for calcium and phosphate. In order to achieve and adapt to these functions, the skeleton exists in a dynamic equilibrium characterized by continuous osteoclast-mediated bone resorption and osteoblast-mediated bone deposition (see, e.g., Karsenty *et al.*, 2002). This biological process has been termed bone “remodelling” and occurs in coupled fashion with osteoblasts producing the key osteoclast differentiation factors, including RANKL, described above,

and osteoclasts promoting bone formation by producing osteoblastic mediators as they degrade bone.

Both innate and adaptive immune cells exert effects on osteoclasts and osteoblasts through a variety of cell-surface and secreted mediators (see, *e.g.*, Takayanagi, 2009). Activation of the RANKL receptor (RANK) on osteoclast precursors starts a cascade of transcriptional changes which results in the formation of osteoclasts and the expression of the machinery needed for bone resorption including molecules needed for attachment to bone, acid secretion, and proteolysis. Many of the transcription factors important for osteoclast differentiation are key regulators of immune responses, such as NF κ B and nuclear factor of activated T cells c1 (NFATc1) and this process is also potentiated by factors involved in inflammation such as TNF α and IL-6.

In addition to its critical role in the progression and pathogenesis of RA, the osteoimmune system plays a critical role in a number of other diseases including osteoporosis and other bone disorders and cancer (see, *e.g.*, Dallas *et al.*, 2011).

Osteoporosis is a common disease characterised by reduced bone density, deterioration of bone tissue, and an increased risk of fracture. Many factors contribute to the pathogenesis of osteoporosis including poor diet, lack of exercise, smoking, and excessive alcohol intake. Osteoporosis also arises in association with inflammatory diseases such as rheumatoid arthritis, endocrine diseases such as thyrotoxicosis, and with certain drug treatments such as treatment with glucocorticoids. Indeed, osteoporosis-related fragility fractures represent one of the most important complications that may occur in patients with rheumatic diseases such as RA, systemic lupus erythematosus, and ankylosing spondylitis.

Paget's disease of bone is a common condition of unknown cause, characterised by increased bone turnover and disorganised bone remodelling, with areas of increased osteoclastic and osteoblast activity. Although Pagetic bone is often denser than normal, the abnormal architecture causes the bone to be mechanically weak, resulting in bone deformity and increased susceptibility to pathological fracture.

IL-6, TNF α , and RANKL signalling have been shown to play a major role in osteoclast over-activity and a consequent increase in bone loss (see, *e.g.*, Tanaka *et al.*, 2003; Roodman, 2006). The use of drugs which affect these pathways have been validated by the completion of clinical trials of the monoclonal antibody against RANKL, AMG-162 (Denosumab®, Amgen), for the treatment of osteoporosis / multiple myeloma, as well as by an increasing body of evidence that shows that the anti-TNF α and anti-IL-6 therapies also prevent bone loss in arthritic diseases (see, *e.g.*, Ogata *et al.*, 2012; Billiau, 2010).

The Osteoimmune System and Cancer

Many types of cancer affect bone. Cancer-associated bone disease can be manifest by the occurrence of hypercalcaemia or the development of osteolytic and/or osteosclerotic metastases. Increased osteoclastic bone resorption plays a key role in the pathogenesis of both conditions. Whilst almost any cancer can be complicated by bone metastases, the most common sources are multiple myeloma, breast carcinoma, and prostate carcinoma. The most common tumours associated with hypercalcaemia are multiple myeloma, breast carcinoma, and lung carcinoma.

As described above, RANK/RANKL signalling is essential for osteoclast formation and bone resorption that occurs during skeletal remodelling. While physiological levels of RANK/RANKL signalling stimulate the proliferation and cell survival of mammary epithelial cells, aberrant RANK/RANKL signalling in these tissues has recently been shown to influence the onset and progression of breast tumorigenesis and blocking RANKL signalling using denosumab (Xgeva®, Amgen) has been shown to be an effective in preventing the secondary complications of bone metastases, such as pathologic fracture, and hypercalcaemia in patients with breast cancer (see, e.g., Steger *et al.*, 2011).

Therapies that block RANK/RANKL signalling may also decrease the ability of osteotropic cancers to metastasize to bone. Signalling through RANK on the surface of human epithelial tumour cells as well as melanoma cells has been shown to induce a chemotactic response in these tumour cells whilst in a murine model of melanoma metastasis, therapeutic treatment of mice with osteoprotegrin, which neutralizes the RANKL receptor, RANK, significantly reduced tumour burden within the bones but not other organs.

In addition to a role for RANKL in cancer, there is growing evidence that activation of NFκB via molecules such as TNFα can play a major role in the promotion and progression of both haematological malignancies, such as myeloma and lymphomas, and solid tumours, such as breast, prostate, and lung cancer (see, e.g., Baud *et al.*, 2009). There is also rising awareness of the role and importance of inflammation and the osteoimmune system in cancer and in the development of resistance to radiotherapy and to chemotherapeutic agents. Furthermore, it has been suggested that inflammation is in fact one of the basic hallmarks of cancer (see, e.g., Mantovani, 2009). Improving the efficacy of anti-cancer treatments by prevention of NFκB activation is therefore a promising strategy to augment existing therapeutic regimes and is currently under investigation, most notably for the treatment of multiple myeloma.

Defects in the normal apoptotic pathways are also implicated in the development and progression of tumour cell growth as well as in inflammation. Apoptosis (programmed cell death) plays a key role in the removal of abnormal cells; defects in the signalling cascades, which would normally lead to its induction, play a key role in oncogenesis.

- 5 Radiotherapy and many chemotherapeutic agents act by causing cellular damage, which would normally induce apoptosis; defects in the pathway will therefore also reduce the effectiveness of such agents. The most important effector molecules in the signalling pathway leading to apoptosis are known as the caspases, which may be triggered by a number of stimuli, including TNF α binding to its receptor. Mutations in the genes which
- 10 encode for the caspases have been found in a number of tumour types, including gastric, breast, renal cell, and cervical cancers as well as commonly in T-cell lymphoblastic lymphoma and basal cell ameloblastomas (see, *e.g.*, Philchenkov *et al.*, 2004). Compounds which activate caspases, and thus sensitise cells to apoptosis, would be highly effective as cancer therapies either as single agents or in enhancing the
- 15 effectiveness of existing cancer chemotherapy and radiotherapy.

Agents that Modulate Cellular and Immune Metabolism, Prevent Inflammation, and Modify the Osteoimmune System

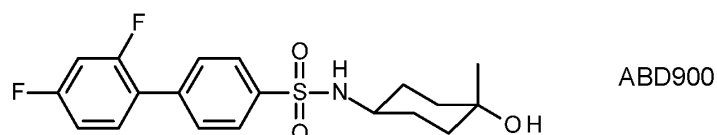
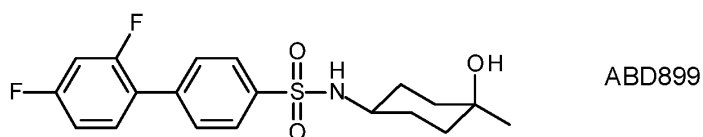
- 20 The inventors have identified new compounds which, for example, modulate cellular and immune metabolism, prevent inflammation, and modify the osteoimmune system, and accordingly are useful in treatment of corresponding disorders, as described herein.

- Without wishing to be bound by any particular theory, the inventors believe that this action
- 25 may be via a mechanism that involves modulating cellular, and immune cell metabolism by reducing cellular ATP, with consequent effects on inflammatory signalling.

Known Compounds

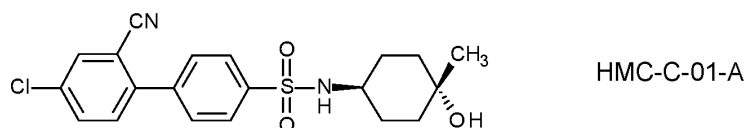
- 30 Greig *et al.*, 2010a, describes certain biphenyl-4-sulfonic acid amides for the treatment of inflammation and/or joint destruction and/or bone loss; disorders mediated by excessive and/or inappropriate and/or prolonged activation of the immune system; inflammatory and autoimmune disorders, for example, rheumatoid arthritis, psoriasis, psoriatic arthritis, chronic obstructive pulmonary disease (COPD), atherosclerosis, inflammatory bowel
- 35 disease, and ankylosing spondylitis; disorders associated with bone loss, such as bone loss associated with excessive osteoclast activity in rheumatoid arthritis, osteoporosis, cancer-associated bone disease, and Paget's disease; and cancer, such as a haematological malignancy and a solid tumour. Examples of compounds shown therein include the following:
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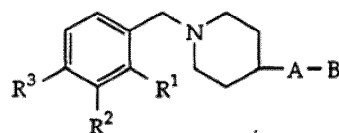
Patel *et al.*, 2014 and Patel *et al.*, 2016 describe certain substituted *N*-(4-hydroxy-4-methyl-cyclohexyl)-4-phenyl-benzenesulfonamide and *N*-(4-hydroxy-4-methyl-cyclohexyl)-4-(2-pyridyl)benzenesulfonamide compounds (e.g., HMC-C-01, shown below)

- 5 for the treatment of inflammation and/or joint destruction and/or bone loss; disorders mediated by excessive and/or inappropriate and/or prolonged activation of the immune system; inflammatory and autoimmune disorders, for example, rheumatoid arthritis; psoriasis; psoriatic arthritis; chronic obstructive pulmonary disease (COPD); asthma; atherosclerosis; inflammatory bowel disease; ankylosing spondylitis; multiple sclerosis;
- 10 systemic lupus erythematosus; Sjogren's syndrome; a disorder associated with bone loss, such as bone loss associated with excessive osteoclast activity in rheumatoid arthritis, osteoporosis, cancer-associated bone disease, or Paget's disease; cancer, such as a haematological malignancy, such as multiple myeloma, leukemia, or lymphoma, or a solid tumour cancer, such as bladder cancer, breast cancer (female and / or male), colon
- 15 cancer, renal cell carcinoma, kidney cancer, lung cancer, pancreatic cancer, gastric cancer, prostate cancer, brain cancer, skin cancer, thyroid cancer, basal cell ameloblastoma, or melanoma; a disorder associated with fibrosis, such as systemic sclerosis or scleroderma; or a rare vasculitide, such as Behçet's disease.



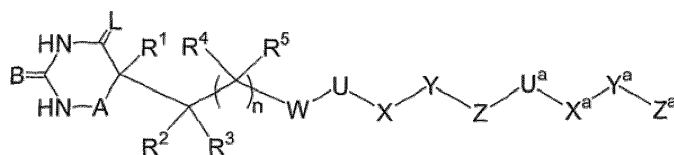
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Riemer *et al.*, 1996, describes certain benzyl piperidine derivatives of the following formula which are allegedly useful in the treatment of psychotic disorders which are caused by damage to the dopamine system.

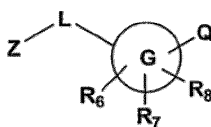


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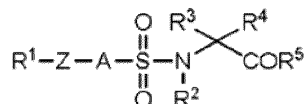
Duan *et al.*, 2003, describes certain barbituric acid derivatives of the following formula which are allegedly useful as TACE inhibitors.



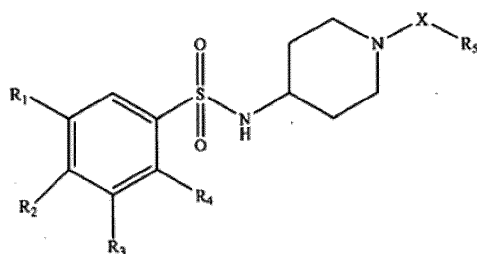
- 10 Li *et al.*, 2006, describes certain compounds of the following formula which are allegedly inhibitors of 11-beta hydroxysteroid dehydrogenase type I (11 β -HSD1).



- 15 Hayashi *et al.*, 2007, describes certain compounds of the following formula which are allegedly useful as MMP-13 selective inhibitors.

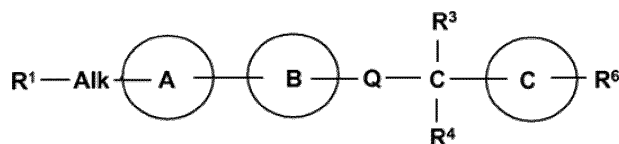


- 20 Moore *et al.*, 2008, describes certain compounds of the following formula which are allegedly useful as modulators of the secreted frizzled related protein-1 for the treatment of osteoporosis, arthritis, COPD, etc.



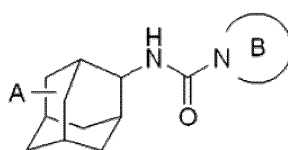
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Fang *et al.*, 2008, describes certain compounds of the following formula which are allegedly useful in the treatment of metabolic disorders such as diabetes mellitus (type I and type II), obesity, and related disorders.



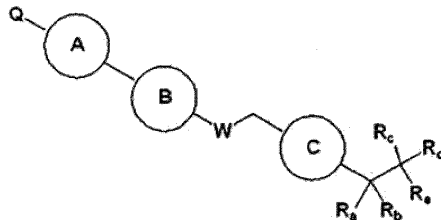
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Horiuchi *et al.*, 2009, describes certain compounds of the following formula which are allegedly useful in the treatment of diabetes.



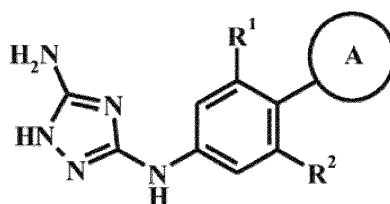
- 10 Lack *et al.*, 2011, describe certain compounds (see Table 1 on page 8566 therein) which are allegedly useful as androgen receptor inhibitors for the treatment of prostate cancer.

Lee *et al.*, 2003, describes certain piperidine derivatives of the following formula which are allegedly useful as GPR119 agonists.



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Bilotta *et al.*, 2014, describes certain compounds of the following formula which are allegedly useful in the treatment of HCV infection.



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New Compounds with Improved Properties

In addition to having excellent biological properties, e.g., similar to or better than the related sulfonamide compounds (for example, as described in Greig *et al.*, 2010a, Patel *et al.*, 2014, and Patel *et al.*, 2016), the NASMP compounds described herein have the additional advantage of forming little or none of an undesirable sulphonamide metabolite.

For example, as demonstrated by the data presented herein, the related sulfonamide compounds (for example, reference compound HMC-C-01-A) give rise to a biaryl sulphonamide metabolite (for example, MET-001) which has a long half-life and therefore persists in the circulation. This biaryl sulphonamide metabolite may induce metabolism in rats, thus complicating the assessment of toxicity in rodents, and potentially, in turn, impacting the developability of the compounds for human use. Therefore, compounds with a *lower* propensity to form a biaryl sulphonamide metabolite have a *greater* potential developability for human use.

As demonstrated by the data presented herein, the NASMP compounds show *greatly reduced* propensity to form a biaryl sulphonamide metabolite, and so have *greatly increased* suitability for development for human use, as compared to the known sulfonamide compounds.

In addition, the NASMP compounds described herein have other advantageous properties, equal to and often better than the properties of the related sulfonamide compounds, including, for example, improved metabolism and solubility.

If a drug is to be used in the clinic, it must have a suitable pharmacokinetic profile. It must show adequate absorption to allow dosing to humans at levels suitable to act at the therapeutic target. Solubility is a key factor in driving absorption of compounds into the circulation from the gastrointestinal tract. In addition, the drug must have an adequate distribution and metabolism profile to ensure dosing can occur at regular intervals, for example, once or twice daily.

The NASMP compounds described herein show good solubility and thus have good propensity to be absorbed from the gastrointestinal tract.

The NASMP compounds described herein also show significant advantages in their *in vitro* metabolic stability and their reduced propensity to form a metabolism inducing biaryl sulphonamide metabolite, e.g., similar to MET-001.

The optimisation of the metabolic and pharmacokinetic properties (Absorption, Distribution, Metabolism, Excretion - ADME) of a drug is a developmental barrier of equal challenge and importance as compared to the optimization of pharmacodynamics (action of the drug on the body) and safety (adverse effects) properties. The NASMP

- 5 compounds described herein provide substantial advantages as oral therapeutic agents (as compared to the known compounds) by improving their metabolic and pharmacokinetic properties with little or no change loss of potency against the biological target.
- 10 The NASMP compounds described herein combine the required characteristics of agents for the treatment of, for example, autoimmune/inflammatory conditions and cancer, as described herein.

SUMMARY OF THE INVENTION

One aspect of the invention pertains to certain substituted N-acyl-{4-[(4-aryl-phenyl) sulfonylmethyl]piperidine} compounds (collectively referred to herein as NASMP
5 compounds), as described herein.

Another aspect of the invention pertains to a composition (e.g., a pharmaceutical composition) comprising a NASMP compound, as described herein, and a carrier, diluent, or excipient (e.g., a pharmaceutically acceptable carrier, diluent, or excipient).
10

Another aspect of the invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising the step of mixing a NASMP compound, as described herein, and a carrier, diluent, or excipient (e.g., a pharmaceutically acceptable carrier, diluent, or excipient).
15

Another aspect of the present invention pertains to a NASMP compound, as described herein, for use in a method of treatment of the human or animal body by therapy, for example, for use a method of treatment of a disorder (e.g., a disease) as described herein.
20

Another aspect of the present invention pertains to use of a NASMP compound, as described herein, in the manufacture of a medicament for treatment, for example, treatment of a disorder (e.g., a disease) as described herein.

Another aspect of the present invention pertains to a method of treatment, for example, of a disorder (e.g., a disease) as described herein, comprising administering to a patient in need of treatment a therapeutically effective amount of a NASMP compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to a kit comprising (a) a NASMP compound, as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the compound.

Another aspect of the present invention pertains to a NASMP compound *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to a NASMP compound *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.
40

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

- 5 Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph of average arthritic index as a function of time (dosing day) for invention compound NASMP-01-A dosed at 10 mg/kg/day by oral gavage (open circles) and control (solid circles).

Figure 2 is a graph of average arthritic index as a function of time (dosing day) for reference compound CHMSA-01-A dosed at 10 mg/kg/day by oral gavage (open circles) and control (solid circles).

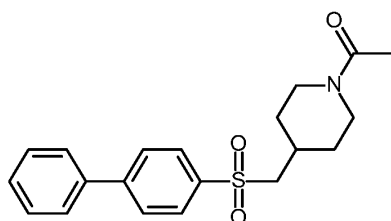
Figure 3 is a graph of average arthritic index as a function of time (dosing day) for test reference CHMSA-03-A dosed at 10 mg/kg/day by oral gavage (open circles) and control (solid circles).

Figure 4 is a graph of arthritic index as a function of time (dosing day) for reference compound ABD899 dosed at 10 mg/kg/day (open circles), control (solid circles), and positive control, the marketed drug etanercept (triangles).

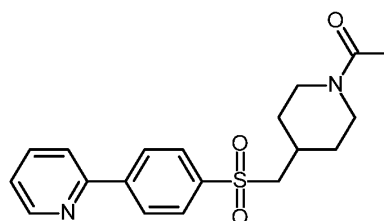
Figure 5 is a graph of arthritic index as a function of time (dosing day) for reference compound HMC-C-01-A dosed at 10 mg/kg/day (open circles), and control (solid circles).

DETAILED DESCRIPTION OF THE INVENTIONCompounds

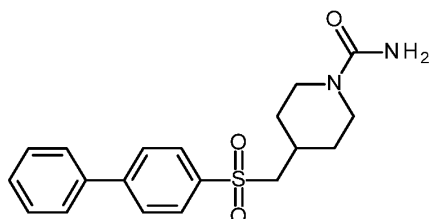
- 5 One aspect of the present invention relates to certain substituted N-acyl-{4-[(4-aryl-phenyl) sulfonylmethyl]piperidine} compounds which are related to the following biphenyl and pyridyl-phenyl compounds:



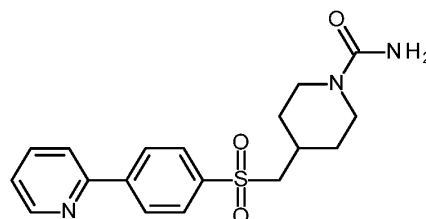
1-[4-[(4-phenylphenyl)
sulfonylmethyl]-
1-piperidyl]ethanone



1-[4-[[4-(2-pyridyl)phenyl]
sulfonylmethyl]-
1-piperidyl]ethanone



4-[(4-phenylphenyl)
sulfonylmethyl]piperidine-
1-carboxamide

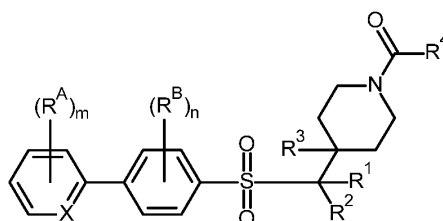


4-[[4-(2-pyridyl)phenyl]
sulfonylmethyl]piperidine-
1-carboxamide

- 20 -

Thus, one aspect of the present invention is a compound of the following formula, or a pharmaceutically acceptable salt or solvate thereof, wherein

=X-, -R¹, -R², -R³, -R⁴, -R^A, -R^B, m, and n are as defined herein (for convenience, collectively referred to herein as “N-acyl-4-[(4-aryl-phenyl)sulfonylmethyl]piperidine} compounds” and “NASMP compounds”):



The Piperidine Ring

Unless otherwise indicated, it is intended that all relative orientations of substituents on the piperidine ring, and all conformations of the piperidine ring (“chair”, “boat”, “twist”, etc.) are encompassed by a reference to a compound that does not specify a particular orientation and/or conformation.

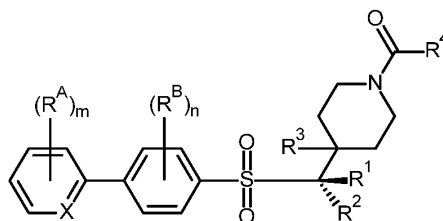
The bond joining the nitrogen atom of the piperidine ring to the C(=O)R⁴ group may be subject to restricted rotation and may give rise to rotamers. Unless otherwise indicated, it is intended that all such rotamers are encompassed by a reference to a compound that does not specify a particular rotamer.

Configuration of Carbon to which -R¹ and -R² are Attached

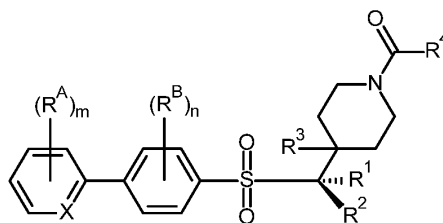
Note that, depending upon the identity of the groups -R¹ and -R², the carbon atom to which they are attached may be chiral, and so may be in the (*R*) or (*S*) configuration.

Unless otherwise indicated, it is intended that all such configurations are encompassed by a reference to a compound that does not specify a particular configuration.

Compounds in one configuration may be indicated as follows:



Compounds in the other configuration may be indicated as follows:

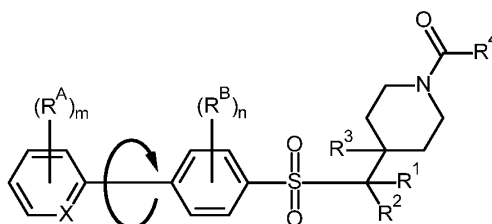


5 Other Substituents on the Piperidine Ring

For the avoidance of doubt, it is intended that, other than $-R^3$ (which may be $-H$) and $-C(=O)R^4$, the piperidine ring has no other non-hydrogen substituents.

10 Conformation of the Biaryl Group

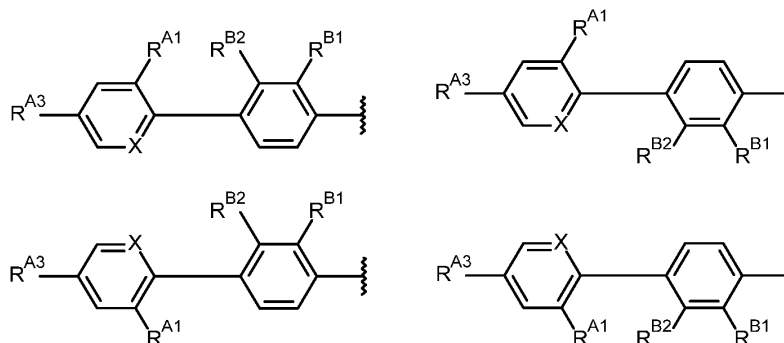
Note that, depending upon the identity of the “m” groups $-R^A$, “n” groups $-R^B$, and X, there may be free rotation about the single bond joining the two aryl groups.



15

For the avoidance of doubt, it is intended that all such rotational conformations (i.e., different rotations about the single bond joining the two aryl groups) are encompassed. For example, the following formulae are intended to be equivalent and represent the same group:

20

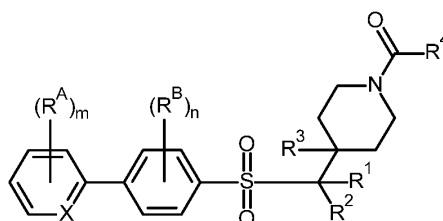


Embodiments

Some embodiments of the invention include the following:

5

(1) A compound of the following formula:



or a pharmaceutically acceptable salt or solvate thereof;
wherein:

10

-X= is independently -CH= or -N=;

"m" is independently 0, 1, 2, or 3;

each -R^A is independently -F, -Cl, -R^{AC}, -R^{AF}, or -CN;

15

-R^{AC} is independently saturated linear or branched C₁₋₃alkyl;

-R^{AF} is independently saturated linear or branched C₁₋₃fluoroalkyl;

"n" is independently 0, 1, or 2;

each -R^B is independently -F, -Cl, -R^{BC}, -R^{BF}, or -CN;

20

-R^{BC} is independently saturated linear or branched C₁₋₃alkyl;

-R^{BF} is independently saturated linear or branched C₁₋₃fluoroalkyl;

-R¹ is independently -H or -R^{1X};

-R^{1X} is independently -F, -R^{1C}, or -R^{1F};

25

-R^{1C} is independently saturated linear or branched C₁₋₃alkyl;

-R^{1F} is independently saturated linear or branched C₁₋₃fluoroalkyl;

-R² is independently -H or -R^{2X};

-R^{2X} is independently -F, -R^{2C}, or -R^{2F};

30

-R^{2C} is independently saturated linear or branched C₁₋₃alkyl;

-R^{2F} is independently saturated linear or branched C₁₋₃fluoroalkyl;

or -R¹ and -R², taken together with the carbon atom to which they are attached,
form saturated C₃₋₆cycloalkyl;

35

- 23 -

- R³ is independently -H or -R^{3X};
- R^{3X} is independently -R^{3C} or -R^{3F};
- R^{3C} is independently saturated linear or branched C₁₋₃alkyl;
- R^{3F} is independently saturated linear or branched C₁₋₃fluoroalkyl;

5

- R⁴ is independently -R^{4C}, -R^{4CC}, or -N(R^{4N1})(R^{4N2});
- R^{4C} is independently saturated linear or branched C₁₋₆alkyl;
- R^{4CC} is independently saturated C₃₋₆cycloalkyl;
- R^{4N1} is independently -H or -R^{4N1C};

10

- R^{4N1C} is independently saturated linear or branched C₁₋₄alkyl;
- R^{4N2} is independently -H or -R^{4N2C}; and
- R^{4N2C} is independently saturated linear or branched C₁₋₄alkyl.

- or -N(R^{4N1})(R^{4N2}) is independently azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and is optionally substituted with one or more saturated linear or branched C₁₋₄alkyl groups.

- Unless otherwise indicated, where a compound is shown or described which has one or more chiral centres, and two or more stereoisomers are possible, all such stereoisomers are disclosed and encompassed, both individually (e.g., as isolated from the other stereoisomer(s)) and as mixtures (e.g., as equimolar or non-equimolar mixtures of two or more stereoisomers). For example, unless otherwise indicated, where a compound has one chiral centre, each of the (*R*) and (*S*) enantiomers are disclosed and encompassed, both individually (e.g., as isolated from the other enantiomer) and as a mixture (e.g., as equimolar or non-equimolar mixtures of the two enantiomers).

For the avoidance of doubt, when -X= is -CH=, and "m" is non-zero, then -X= may be -C(R^A)=.

- The term "saturated linear or branched C₁₋₃alkyl" means -CH₃ (methyl), -CH₂CH₃ (ethyl), -CH₂CH₂CH₃ (n-propyl), and -CH(CH₃)₂ (iso-propyl).

- The term "saturated linear or branched C₁₋₄alkyl" additionally includes -CH₂CH₂CH₂CH₃ (n-butyl), -CH₂CH(CH₃)₂ (iso-butyl), -CH(CH₃)CH₂CH₃ (sec-butyl), and -C(CH₃)₃ (tert-butyl).

The term "saturated linear or branched C₁₋₆alkyl" additionally includes, e.g., -CH₂CH₂CH₂CH₂CH₃ (n-pentyl), -CH₂CH₂CH(CH₃)₂ (iso-pentyl), -CH₂CH₂CH₂CH₂CH₂CH₃ (n-hexyl), -CH₂CH₂CH₂CH(CH₃)₂ (iso-hexyl), *etc.*

40

- 24 -

The term "saturated linear or branched C₁₋₃fluoroalkyl" means a saturated linear or branched C₁₋₃alkyl group substituted with one or more fluoro groups. Accordingly, C₁₋₃fluoroalkyl includes, e.g., -CF₃, -CH₂F, -CHF₂, -CH₂CF₃, -CH₂CH₂F, *etc.*

- 5 The term "saturated C₃₋₆cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The Group =X-

- 10 (2) A compound according to (1), wherein -X= is -CH=.

(3) A compound according to (1), wherein -X= is -N=.

The Index "m"

- 15 (4) A compound according to any one of (1) to (3), wherein "m" is independently 0, 1, or 2.

(5) A compound according to any one of (1) to (3), wherein "m" is 1 or 2 or 3.

20

(6) A compound according to any one of (1) to (3), wherein "m" is 1 or 2.

(7) A compound according to any one of (1) to (3), wherein "m" is 1.

- 25 (8) A compound according to any one of (1) to (3), wherein "m" is 2.

(9) A compound according to any one of (1) to (3), wherein "m" is 3.

The Group -R^A

30

(10) A compound according to any one of (1) to (9), wherein each -R^A, if present, is independently -F, -Cl, or -CN.

(11) A compound according to any one of (1) to (9), wherein each -R^A, if present, is -F.

35

(12) A compound according to any one of (1) to (9), wherein each -R^A, if present, is -Cl.

The Group -R^{AC}

- 40 (13) A compound according to any one of (1) to (12), wherein each -R^{AC}, if present, is -CH₃.

The Group -R^{AF}

- 5 (14) A compound according to any one of (1) to (13), wherein each -R^{AF}, if present, is -CF₃.

The Index "n"

- 10 (15) A compound according to any one of (1) to (14), wherein "n" is independently 1 or 2.
- (16) A compound according to any one of (1) to (14), wherein "n" is 0.
- (17) A compound according to any one of (1) to (14), wherein "n" is 1.
- 15 (18) A compound according to any one of (1) to (14), wherein "n" is 2.

The Group -R^B

- 20 (19) A compound according to any one of (1) to (18), wherein each -R^B, if present, is independently -F, -Cl, or -CN.
- (20) A compound according to any one of (1) to (18), wherein each -R^B, if present, is -F.
- (21) A compound according to any one of (1) to (18), wherein each -R^B, if present, is -Cl.
- 25

The Group -R^{BC}

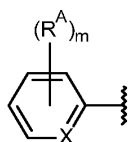
- (22) A compound according to any one of (1) to (21), wherein each -R^{BC}, if present, is -CH₃.
- 30

The Group -R^{BF}

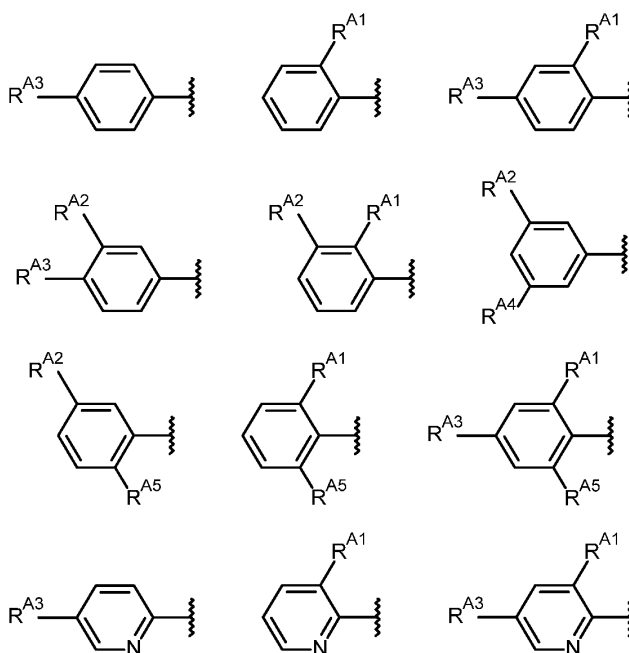
- (23) A compound according to any one of (1) to (22), wherein each -R^{BF}, if present, is -CF₃.
- 35

The Terminal Aryl Group

(24) A compound according to (1), wherein the group:



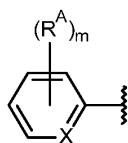
5 is independently selected from:



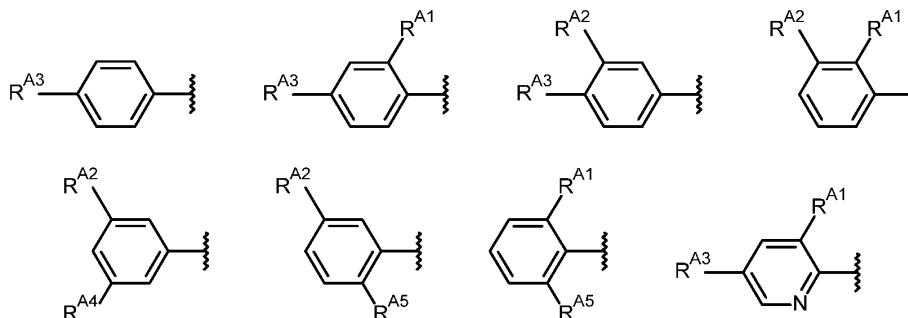
10 wherein each of $-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, and $-R^{A5}$ is independently as defined for $-R^A$.

- 27 -

(25) A compound according to (1), wherein the group:



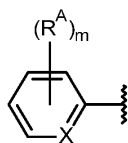
is independently selected from:



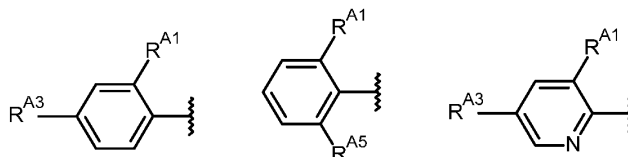
5

wherein each of $-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, and $-R^{A5}$ is independently as defined for $-R^A$.

(26) A compound according to (1), wherein the group:



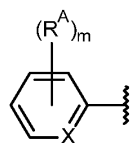
10 is independently selected from:



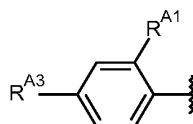
wherein each of $-R^{A1}$, $-R^{A3}$, and $-R^{A5}$ is independently as defined for $-R^A$.

- 28 -

(27) A compound according to (1), wherein the group:



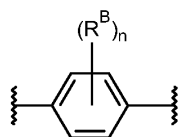
is:



- 5 wherein each of $-R^{A1}$ and $-R^{A3}$ is independently as defined for $-R^A$.

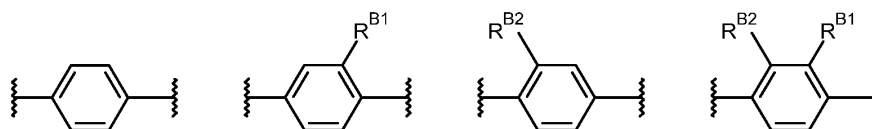
The Linking Phenylene Group

(28) A compound according to any one of (1) and (24) to (27), wherein the group:



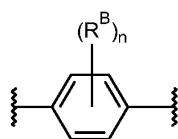
10

is independently selected from:

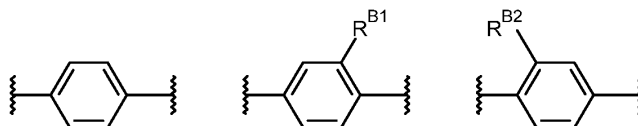


wherein each of $-R^{B1}$ and $-R^{B2}$ is independently as defined for $-R^B$.

- 15 (29) A compound according to any one of (1) and (24) to (27), wherein the group:



is independently selected from:

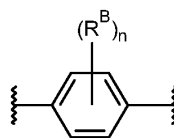


wherein each of $-R^{B1}$ and $-R^{B2}$ is independently as defined for $-R^B$.

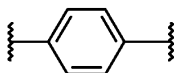
20

- 29 -

(30) A compound according to any one of (1) and (24) to (27), wherein the group:

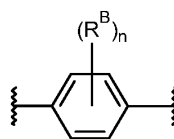


is:



5

(31) A compound according to any one of (1) and (24) to (27), wherein the group:



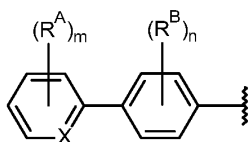
is independently selected from:



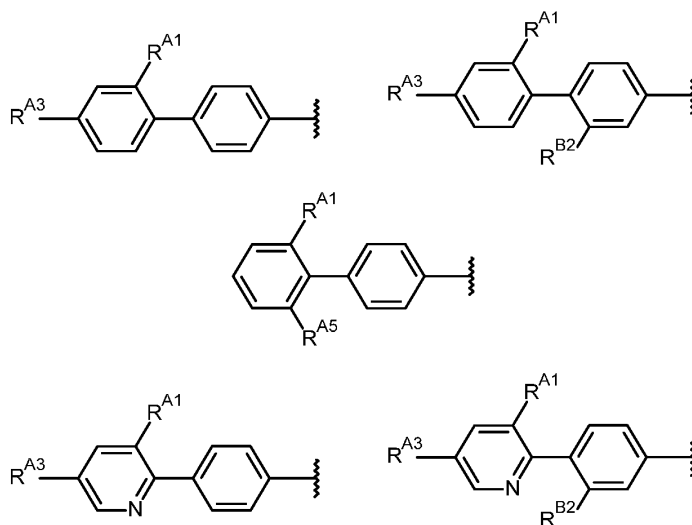
10 wherein each of $-R^{B1}$ and $-R^{B2}$ is independently as defined for $-R^B$.

The Biaryl Group

(32) A compound according to (1), wherein the group:



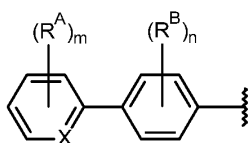
5 is independently selected from:



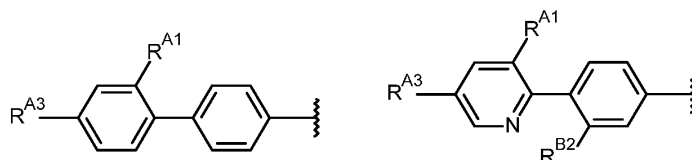
wherein:

- 10 each of -R^{A1}, -R^{A3}, and -R^{A5} is independently as defined for -R^A; and
-R^{B2} is independently as defined for -R^B.

(33) A compound according to (1), wherein the group:



15 is independently selected from:

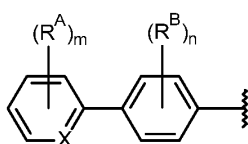


wherein:

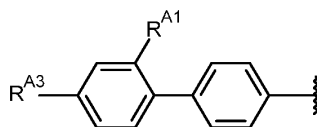
each of -R^{A1} and -R^{A3} is independently as defined for -R^A; and
-R^{B2} is independently as defined for -R^B.

- 31 -

(34) A compound according to (1), wherein the group:



is:



5 wherein each of $-R^{A1}$ and $-R^{A3}$ is independently as defined for $-R^A$.

The Group $-R^{A1}$

(35) A compound according to any one of (24) to (34), wherein $-R^{A1}$, if present, is
10 independently $-F$, $-Cl$, $-R^{A1C}$, $-R^{A1F}$, or $-CN$.

(36) A compound according to any one of (24) to (34), wherein $-R^{A1}$, if present, is independently $-F$, $-Cl$, or $-CN$.

15 (37) A compound according to any one of (24) to (34), wherein $-R^{A1}$, if present, is $-F$.

(38) A compound according to any one of (24) to (34), wherein $-R^{A1}$, if present, is $-Cl$.

(39) A compound according to any one of (24) to (34), wherein $-R^{A1}$, if present, is $-CN$.

20

(40) A compound according to any one of (24) to (34), wherein $-R^{A1}$, if present, is $-R^{A1C}$.

(41) A compound according to any one of (24) to (34), wherein $-R^{A1}$, if present, is $-R^{A1F}$.

25 The Group $-R^{A1C}$

(42) A compound according to any one of (24) to (41), wherein $-R^{A1C}$, if present, is $-CH_3$.

The Group $-R^{A1F}$

30

(43) A compound according to any one of (24) to (42), wherein $-R^{A1F}$, if present, is $-CF_3$.

The Group -R^{A2}

- (44) A compound according to any one of (24) to (43), wherein -R^{A2}, if present, is independently -F, -Cl, -R^{A2C}, -R^{A2F}, or -CN.
- 5 (45) A compound according to any one of (24) to (43), wherein -R^{A2}, if present, is independently -F, -Cl, or -CN.
- (46) A compound according to any one of (24) to (43), wherein -R^{A2}, if present, is -F.
- 10 (47) A compound according to any one of (24) to (43), wherein -R^{A2}, if present, is -Cl.
- (48) A compound according to any one of (24) to (43), wherein -R^{A2}, if present, is -CN.
- 15 (49) A compound according to any one of (24) to (43), wherein -R^{A2}, if present, is -R^{A2C}.
- (50) A compound according to any one of (24) to (43), wherein -R^{A2}, if present, is -R^{A2F}.

The Group -R^{A2C}

- 20 (51) A compound according to any one of (24) to (50), wherein -R^{A2C}, if present, is -CH₃.

The Group -R^{A2F}

- 25 (52) A compound according to any one of (24) to (51), wherein -R^{A2F}, if present, is -CF₃.

The Group -R^{A3}

- (53) A compound according to any one of (24) to (52), wherein -R^{A3}, if present, is independently -F, -Cl, -R^{A3C}, -R^{A3F}, or -CN.
- 30 (54) A compound according to any one of (24) to (52), wherein -R^{A3}, if present, is independently -F, -Cl, or -CN.
- 35 (55) A compound according to any one of (24) to (52), wherein -R^{A3}, if present, is -F.
- (56) A compound according to any one of (24) to (52), wherein -R^{A3}, if present, is -Cl.
- (57) A compound according to any one of (24) to (52), wherein -R^{A3}, if present, is -CN.
- 40 (58) A compound according to any one of (24) to (52), wherein -R^{A3}, if present, is -R^{A3C}.

(59) A compound according to any one of (24) to (52), wherein $-R^{A3}$, if present, is $-R^{A3F}$.

The Group $-R^{A3C}$

5

(60) A compound according to any one of (24) to (59), wherein $-R^{A3C}$, if present, is $-CH_3$.

The Group $-R^{A3F}$

10 (61) A compound according to any one of (24) to (60), wherein $-R^{A3F}$, if present, is $-CF_3$.

The Group $-R^{A4}$

15 (62) A compound according to any one of (24) to (61), wherein $-R^{A4}$, if present, is independently $-F$, $-Cl$, $-R^{A4C}$, $-R^{A4F}$, or $-CN$.

(63) A compound according to any one of (24) to (61), wherein $-R^{A4}$, if present, is independently $-F$, $-Cl$, or $-CN$.

20 (64) A compound according to any one of (24) to (61), wherein $-R^{A4}$, if present, is $-F$.

(65) A compound according to any one of (24) to (61), wherein $-R^{A4}$, if present, is $-Cl$.

(66) A compound according to any one of (24) to (61), wherein $-R^{A4}$, if present, is $-CN$.

25

(67) A compound according to any one of (24) to (61), wherein $-R^{A4}$, if present, is $-R^{A4C}$.

(68) A compound according to any one of (24) to (61), wherein $-R^{A4}$, if present, is $-R^{A4F}$.

30 The Group $-R^{A4C}$

(69) A compound according to any one of (24) to (68), wherein $-R^{A4C}$, if present, is $-CH_3$.

The Group $-R^{A4F}$

35

(70) A compound according to any one of (24) to (69), wherein $-R^{A4F}$, if present, is $-CF_3$.

The Group $-R^{A5}$

40 (71) A compound according to any one of (24) to (70), wherein $-R^{A5}$, if present, is independently $-F$, $-Cl$, $-R^{A5C}$, $-R^{A5F}$, or $-CN$.

(72) A compound according to any one of (24) to (70), wherein $-R^{A5}$, if present, is independently -F, -Cl, or -CN.

5 (73) A compound according to any one of (24) to (70), wherein $-R^{A5}$, if present, is -F.

(74) A compound according to any one of (24) to (70), wherein $-R^{A5}$, if present, is -Cl.

(75) A compound according to any one of (24) to (70), wherein $-R^{A5}$, if present, is -CN.

10

(76) A compound according to any one of (24) to (70), wherein $-R^{A5}$, if present, is $-R^{A5C}$.

(77) A compound according to any one of (24) to (70), wherein $-R^{A5}$, if present, is $-R^{A5F}$.

15 The Group $-R^{A5C}$

(78) A compound according to any one of (24) to (77), wherein $-R^{A5C}$, if present, is $-CH_3$.

The Group $-R^{A5F}$

20

(79) A compound according to any one of (24) to (78), wherein $-R^{A5F}$, if present, is $-CF_3$.

The Group $-R^{B1}$

25 (80) A compound according to any one of (28) to (79), wherein $-R^{B1}$, if present, is independently -F, -Cl, $-R^{B1C}$, $-R^{B1F}$, or -CN.

(81) A compound according to any one of (28) to (79), wherein $-R^{B1}$, if present, is independently -F, -Cl, or -CN.

30

(82) A compound according to any one of (28) to (79), wherein $-R^{B1}$, if present, is -F.

(83) A compound according to any one of (28) to (79), wherein $-R^{B1}$, if present, is -Cl.

35 (84) A compound according to any one of (28) to (79), wherein $-R^{B1}$, if present, is -CN.

(85) A compound according to any one of (28) to (79), wherein $-R^{B1}$, if present, is $-R^{B1C}$.

(86) A compound according to any one of (28) to (79), wherein $-R^{B1}$, if present, is $-R^{B1F}$.

40

The Group -R^{B1C}

(87) A compound according to any one of (28) to (86), wherein -R^{B1C}, if present, is -CH₃.

5 The Group -R^{B1F}

(88) A compound according to any one of (28) to (87), wherein -R^{B1F}, if present, is -CF₃.

The Group -R^{B2}

10

(89) A compound according to any one of (28) to (88), wherein -R^{B2}, if present, is independently -F, -Cl, -R^{B2C}, -R^{B2F}, or -CN.

15 (90) A compound according to any one of (28) to (88), wherein -R^{B2}, if present, is independently -F, -Cl, or -CN.

(91) A compound according to any one of (28) to (88), wherein -R^{B2}, if present, is -F.

20 (92) A compound according to any one of (28) to (88), wherein -R^{B2}, if present, is -Cl.

(93) A compound according to any one of (28) to (88), wherein -R^{B2}, if present, is -CN.

(94) A compound according to any one of (28) to (88), wherein -R^{B2}, if present, is -R^{B2C}.

25 (95) A compound according to any one of (28) to (88), wherein -R^{B2}, if present, is -R^{B2F}.

The Group -R^{B2C}

30 (96) A compound according to any one of (28) to (95), wherein -R^{B2C}, if present, is -CH₃.

The Group -R^{B2F}

(97) A compound according to any one of (28) to (96), wherein -R^{B2F}, if present, is -CF₃.

35 The Group -R¹

(98) A compound according to any one of (1) to (97), wherein -R¹ is -R^{1X}.

(99) A compound according to any one of (1) to (97), wherein -R¹ is -H.

40

The Group -R^{1X}

(100) A compound according to any one of (1) to (99), wherein -R^{1X}, if present, is independently -F, -R^{1C}, or -R^{1F}.

5

(101) A compound according to any one of (1) to (99), wherein -R^{1X}, if present, is -F.

(102) A compound according to any one of (1) to (99), wherein -R^{1X}, if present, is -R^{1C}.

10 (103) A compound according to any one of (1) to (99), wherein -R^{1X}, if present, is -R^{1F}.

The Group -R^{1C}

(104) A compound according to any one of (1) to (103), wherein -R^{1C}, if present, is -CH₃.

15

The Group -R^{1F}

(105) A compound according to any one of (1) to (104), wherein -R^{1F}, if present, is -CF₃.

20 The Group -R²

(106) A compound according to any one of (1) to (105), wherein -R² is -R^{2X}.

(107) A compound according to any one of (1) to (105), wherein -R² is -H.

25

The Group -R^{2X}

(108) A compound according to any one of (1) to (107), wherein -R^{2X}, if present, is independently -F, -R^{2C}, or -R^{2F}.

30

(109) A compound according to any one of (1) to (107), wherein -R^{2X}, if present, is -F.

(110) A compound according to any one of (1) to (107), wherein -R^{2X}, if present, is -R^{2C}.

35 (111) A compound according to any one of (1) to (107), wherein -R^{2X}, if present, is -R^{2F}.

The Group -R^{2C}

(112) A compound according to any one of (1) to (111), wherein -R^{2C}, if present, is -CH₃.

40

The Group -R^{2F}

(113) A compound according to any one of (1) to (112), wherein -R^{2F}, if present, is -CF₃.

5 The Groups -R¹ and -R² Taken Together

(114) A compound according to any one of (1) to (97), wherein -R¹ and -R², taken together with the carbon atom to which they are attached, form saturated C₃₋₆cycloalkyl.

10 (115) A compound according to any one of (1) to (97), wherein -R¹ and -R², taken together with the carbon atom to which they are attached, form cyclopropyl.

(116) A compound according to any one of (1) to (97), wherein -R¹ and -R², taken together with the carbon atom to which they are attached, form cyclobutyl.

15 (117) A compound according to any one of (1) to (97), wherein -R¹ and -R⁶², taken together with the carbon atom to which they are attached, form cyclopentyl.

20 (118) A compound according to any one of (1) to (97), wherein -R¹ and -R², taken together with the carbon atom to which they are attached, form cyclohexyl.

The Group -R³

25 (119) A compound according to any one of (1) to (118), wherein -R³ is -R^{3X}.

(120) A compound according to any one of (1) to (118), wherein -R³ is -H.

The Group -R^{3X}

30 (121) A compound according to any one of (1) to (120), wherein -R^{3X}, if present, is -R^{3C}.

(122) A compound according to any one of (1) to (120), wherein -R^{3X}, if present, is -R^{3F}.

The Group -R^{3C}

35 (123) A compound according to any one of (1) to (122), wherein -R^{3C}, if present, is -CH₃.

The Group -R^{3F}

40 (124) A compound according to any one of (1) to (123), wherein -R^{3F}, if present, is -CF₃.

The Group -R⁴

(125) A compound according to any one of (1) to (124), wherein -R⁴ is -R^{4C}.

5 (126) A compound according to any one of (1) to (124), wherein -R⁴ is -R^{4CC}.

(127) A compound according to any one of (1) to (124), wherein -R⁴ is -N(R^{4N1})(R^{4N2}).

The Group -R^{4C}

10

(128) A compound according to any one of (1) to (127), wherein -R^{4C}, if present, is saturated linear or branched C₁₋₄alkyl.

15 (129) A compound according to any one of (1) to (127), wherein -R^{4C}, if present, is saturated linear or branched C₁₋₃alkyl.

(130) A compound according to any one of (1) to (127), wherein -R^{4C}, if present, is -CH₃ or -CH₂CH₃.

20 (131) A compound according to any one of (1) to (127), wherein -R^{4C}, if present, is -CH₃.

The Group -R^{4CC}

25 (132) A compound according to any one of (1) to (131), wherein -R^{4CC}, if present, is cyclopropyl.

(133) A compound according to any one of (1) to (131), wherein -R^{4CC}, if present, is cyclobutyl.

30 (134) A compound according to any one of (1) to (131), wherein -R^{4CC}, if present, is cyclopentyl.

35 (135) A compound according to any one of (1) to (131), wherein -R^{4CC}, if present, is cyclohexyl.

The Group -R^{4N1}

40 (136) A compound according to any one of (1) to (135), wherein -R^{4N1}, if present, is -R^{4N1C}.

(137) A compound according to any one of (1) to (135), wherein -R^{4N1}, if present, is -H.

The Group -R^{4N1C}

- 5 (138) A compound according to any one of (1) to (137), wherein -R^{4N1C}, if present, is saturated linear or branched C₁₋₃alkyl.
- (139) A compound according to any one of (1) to (137), wherein -R^{4N1C}, if present, is -CH₃ or -CH₂CH₃.
- 10 (140) A compound according to any one of (1) to (137), wherein -R^{4N1C}, if present, is -CH₃.

The Group -R^{4N2}

- 15 (141) A compound according to any one of (1) to (140), wherein -R^{4N2}, if present, is -R^{4N2C}.
- (142) A compound according to any one of (1) to (140), wherein -R^{4N2}, if present, is -H.
- 20 The Group -R^{4N2C}
- (143) A compound according to any one of (1) to (142), wherein -R^{4N2C}, if present, is saturated linear or branched C₁₋₃alkyl.
- 25 (144) A compound according to any one of (1) to (142), wherein -R^{4N2C}, if present, is -CH₃ or -CH₂CH₃.
- (145) A compound according to any one of (1) to (142), wherein -R^{4N2C}, if present, is -CH₃.

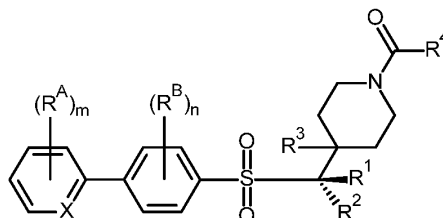
30

The Group -N(R^{4N1})(R^{4N2}) (when cyclic)

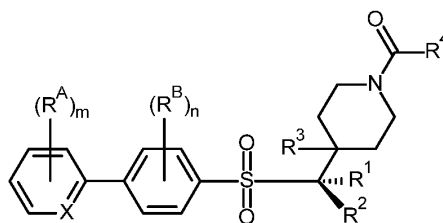
- (146) A compound according to any one of (1) to (127), wherein -N(R^{4N1})(R^{4N2}), if present, is independently pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl; and is optionally
- 35 substituted with one or more saturated linear or branched C₁₋₄alkyl groups.
- (147) A compound according to any one of (1) to (127), wherein -N(R^{4N1})(R^{4N2}), if present, is independently pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl.

Configuration of Carbon to which -R¹ and -R² are Attached

- (148) A compound according to any one of (1) to (147), wherein -R¹ and -R² are different, and the compound is a compound of the following formula, or a pharmaceutically acceptable salt or solvate thereof:



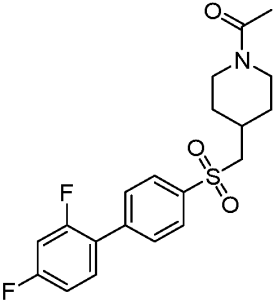
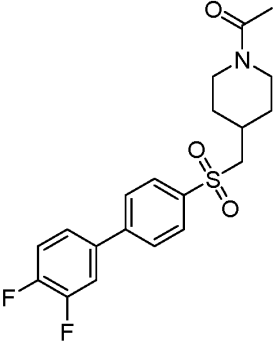
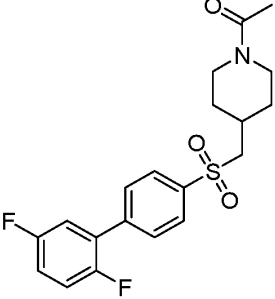
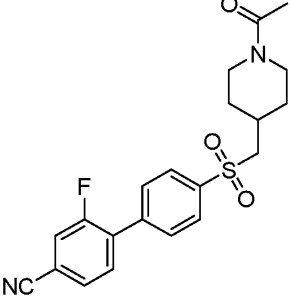
- (149) A compound according to any one of (1) to (147), wherein -R¹ and -R² are different, and the compound is a compound of the following formula, or a pharmaceutically acceptable salt or solvate thereof:

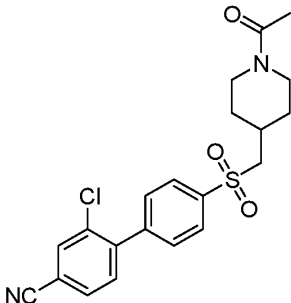
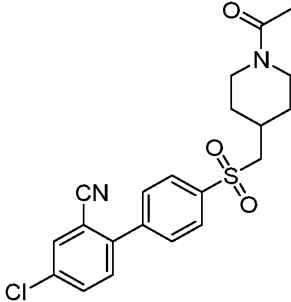
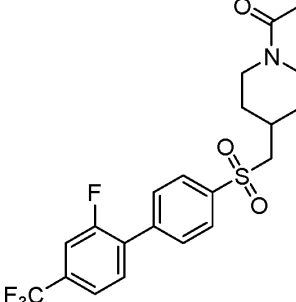
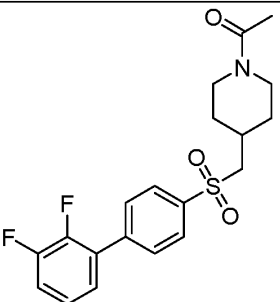


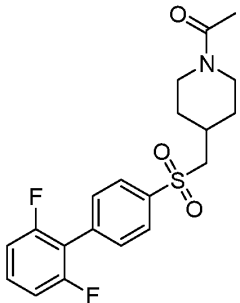
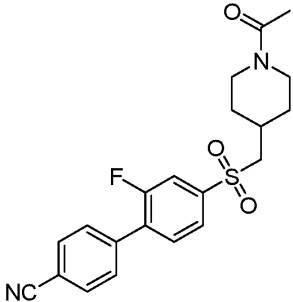
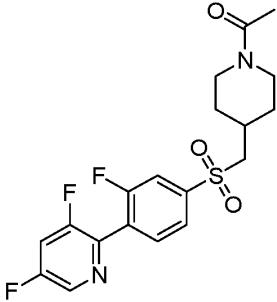
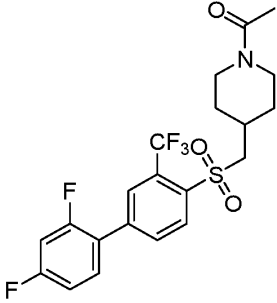
Some Preferred Compounds

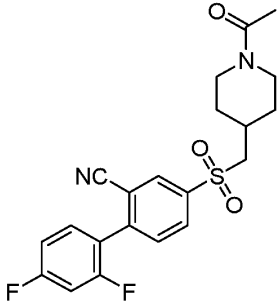
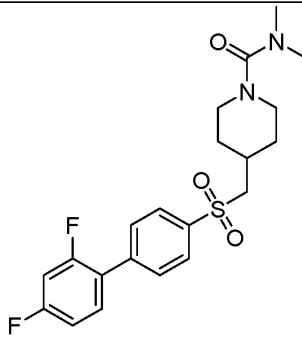
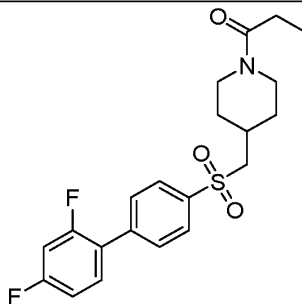
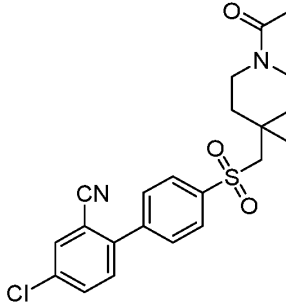
(150) A compound according to (1), which is a compound of one of following formulae, or a pharmaceutically acceptable salt or solvate thereof:

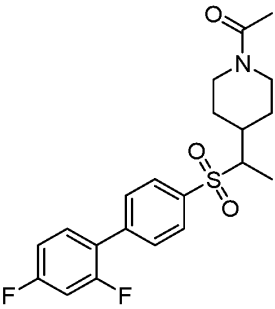
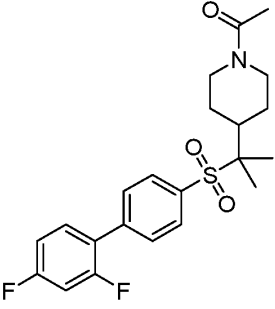
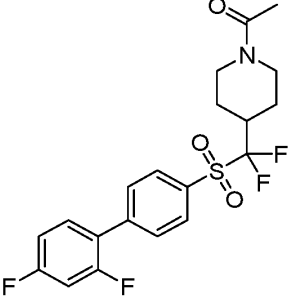
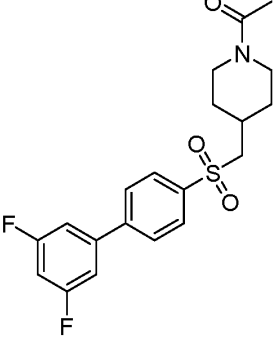
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Compound	Structure
NASMP-01	
NASMP-02	
NASMP-03	
NASMP-04	

Compound	Structure
NASMP-05	
NASMP-06	
NASMP-07	
NASMP-08	

Compound	Structure
NASMP-09	
NASMP-10	
NASMP-11	
NASMP-12	

Compound	Structure
NASMP-13	
NASMP-14	
NASMP-15	
NASMP-16	

Compound	Structure
NASMP-17	
NASMP-18	
NASMP-19	
NASMP-20	

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Compound	Structure
NASMP-21	

Combinations

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., =X-, m, -R^A, -R^{AC}, -R^{AF}, n, -R^B, -R^{BC}, -R^{BF}, -R^{A1}, -R^{A1C}, -R^{A1F}, -R^{A2}, -R^{A2C}, -R^{A2F}, -R^{A3}, -R^{A3C}, -R^{A3F}, -R^{A4}, -R^{A4C}, -R^{A4F}, -R^{A5}, -R^{A5C}, -R^{A5F}, -R^{B1}, -R^{B1C}, -R^{B1F}, -R^{B2}, -R^{B2C}, -R^{B2F}, -R¹, -R^{1X}, -R^{1C}, -R^{1F}, -R², -R^{2X}, -R^{2C}, -R^{2F}, -R³, -R^{3X}, -R^{3C}, -R^{3F}, -R⁴, -R^{4C}, -R^{4CC}, -R^{4N1}, -R^{4N1C}, -R^{4N2}, -R^{4N2C}, etc.) are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterised, and tested for biological activity). In this context, the skilled person will readily appreciate that certain combinations of groups (e.g., substituents) may give rise to compounds which may not be readily synthesized and/or are chemically unstable. In addition, all sub-combinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

Substantially Purified Forms

One aspect of the present invention pertains to NASMP compounds, as described herein, in substantially purified form and/or in a form substantially free from contaminants.

In one embodiment, the substantially purified form is at least 50% by weight, e.g., at least 60% by weight, e.g., at least 70% by weight, e.g., at least 80% by weight, e.g., at least 90% by weight, e.g., at least 95% by weight, e.g., at least 97% by weight, e.g., at least 98% by weight, e.g., at least 99% by weight.

Unless otherwise specified, the substantially purified form refers to the compound in any stereoisomeric or enantiomeric form. For example, in one embodiment, the substantially purified form refers to a mixture of stereoisomers, i.e., purified with respect to other
5 compounds. In one embodiment, the substantially purified form refers to one stereoisomer, e.g., optically pure stereoisomer. In one embodiment, the substantially purified form refers to a mixture of enantiomers. In one embodiment, the substantially purified form refers to an equimolar mixture of enantiomers (i.e., a racemic mixture, a racemate). In one embodiment, the substantially purified form refers to one enantiomer,
10 e.g., optically pure enantiomer.

In one embodiment, the contaminants represent no more than 50% by weight, e.g., no more than 40% by weight, e.g., no more than 30% by weight, e.g., no more than 20% by weight, e.g., no more than 10% by weight, e.g., no more than 5% by weight, e.g., no more
15 than 3% by weight, e.g., no more than 2% by weight, e.g., no more than 1% by weight.

Unless specified, the contaminants refer to other compounds, that is, other than stereoisomers or enantiomers. In one embodiment, the contaminants refer to other compounds and other stereoisomers. In one embodiment, the contaminants refer to
20 other compounds and the other enantiomer.

In one embodiment, the substantially purified form is at least 60% optically pure (i.e., 60% of the compound, on a molar basis, is the desired stereoisomer or enantiomer, and 40% is the undesired stereoisomer or enantiomer), e.g., at least 70% optically pure, e.g., at
25 least 80% optically pure, e.g., at least 90% optically pure, e.g., at least 95% optically pure, e.g., at least 97% optically pure, e.g., at least 98% optically pure, e.g., at least 99% optically pure.

Isomers

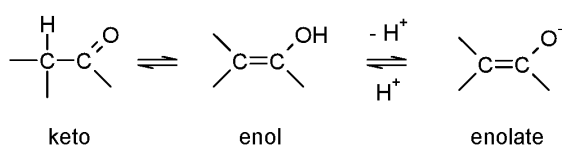
30 Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereoisomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and
35 l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α - and β -forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

40 A reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C₁₋₃alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-,

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sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl). However, reference to a specific group or substitution pattern is not intended to include other structural (or constitutional isomers) which differ with respect to the connections between atoms rather than by positions in space. For example, a reference to a methoxy group, -OCH₃, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, -CH₂OH.

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro. A reference herein to one tautomer is intended to encompass both tautomers.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ¹H, ²H (D), and ³H (T); C may be in any isotopic form, including ¹²C, ¹³C, and ¹⁴C; O may be in any isotopic form, including ¹⁶O and ¹⁸O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including mixtures (e.g., racemic mixtures) thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group, which may be anionic (e.g., -COOH may be -COO⁻), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na⁺ and K⁺, alkaline earth cations such as Ca²⁺ and Mg²⁺, and other cations such

as Al^{3+} as well as the ammonium ion (i.e., NH_4^+). Examples of suitable organic cations include, but are not limited to substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+), for example, where each R is independently linear or branched saturated C_{1-18} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl, and phenyl- C_{1-6} alkyl, wherein the phenyl group is optionally substituted. Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

10

If the compound is cationic, or has a functional group, which upon protonation may become cationic (e.g., $-\text{NH}_2$ may become $-\text{NH}_3^+$), then a salt may be formed with a suitable anion.

15 For example, if a parent structure contains a cationic group (e.g., $-\text{NMe}_2^+$), or has a functional group, which upon protonation may become cationic (e.g., $-\text{NH}_2$ may become $-\text{NH}_3^+$), then a salt may be formed with a suitable anion. In the case of a quaternary ammonium compound a counter-anion is generally always present in order to balance the positive charge. If, in addition to a cationic group (e.g., $-\text{NMe}_2^+$, $-\text{NH}_3^+$), the compound also contains a group capable of forming an anion (e.g., $-\text{COOH}$), then an inner salt (also referred to as a zwitterion) may be formed.

20 Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

25 Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyloxybenzoic, acetic, trifluoroacetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, 1,2-ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pantoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

35 Examples of suitable counter-ions which are especially suitable for quaternary ammonium compounds (e.g., those with a pendant $-\text{NMe}_3^+$ group) include 1-adamantanesulfonate, benzenesulfonate, bisulfate, bromide, chloride, iodide, methanesulfonate, methylsulfate, 1,5-naphthalene-bis-sulfonate, 4-nitrobenzenesulfonate, formate, tartrate, tosylate,

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trifluoroacetate, trifluoromethylsulfonate, sulphate. Again, if the compound also contains a group capable of forming an anion (e.g., -COOH), then an inner salt may be formed.

- 5 Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

Solvates and Hydrates

- 10 It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., compound, salt of compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

- 15 Unless otherwise specified, a reference to a particular compound also includes solvate and hydrate forms thereof.

Chemically Protected Forms

- 20 It may be convenient or desirable to prepare, purify, and/or handle the compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well-known
25 chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (alternatively as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive
30 functional groups can be performed, without affecting the protected group; the protecting group may be removed or the masking group transformed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 4th Edition; John Wiley and Sons, 2006).

- 35 A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore
40 unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired

reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

- For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyl dimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc).

Prodrugs

- It may be convenient or desirable to prepare, purify, and/or handle the compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound, which yields the desired active compound *in vivo*. Typically, the prodrug is inactive, or less active than the desired active compound, but may provide advantageous handling, administration, or metabolic properties.

- For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

- Also, some prodrugs are activated enzymatically to yield the active compound, or a compound, which, upon further chemical reaction, yields the active compound (for example, as in antibody directed enzyme prodrug therapy (ADEPT), gene directed enzyme prodrug therapy (GDEPT), lipid directed enzyme prodrug therapy (LIDEPT), etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

General Chemical Synthesis

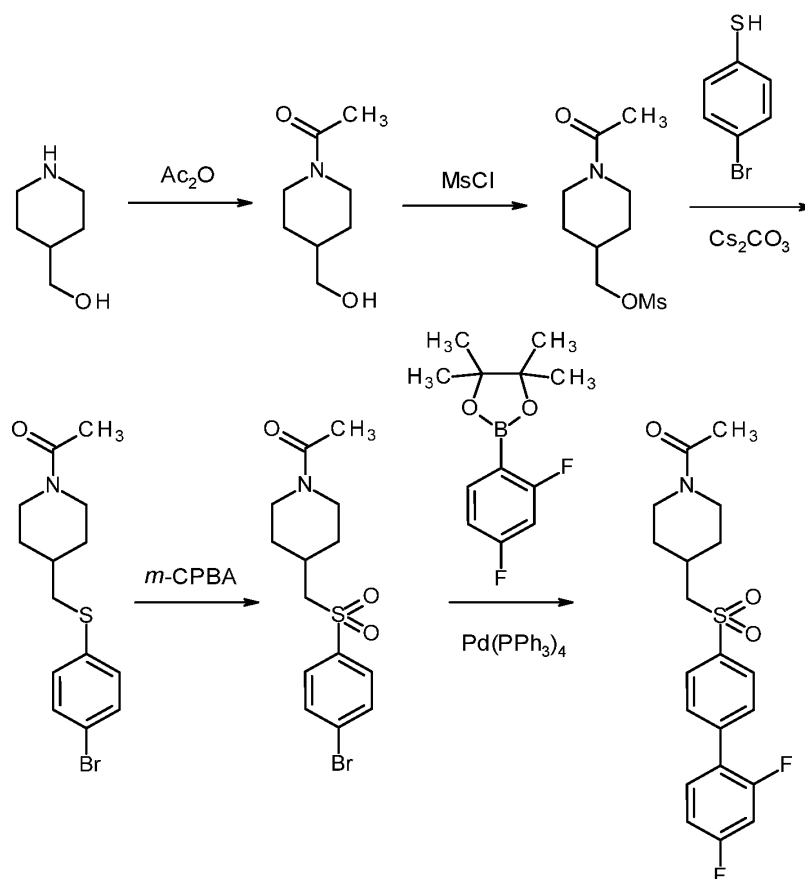
- Methods for the chemical synthesis of the NASMP compounds are described herein. These and/or other well-known methods may be modified and/or adapted in known ways in order to provide additional NASMP compounds and/or alternative or improved methods of synthesis.

- In one approach (as illustrated in Scheme A), a piperidine-4-methanol is N-acylated or N-carbamoylated with, for example acetic anhydride or acetyl chloride in the presence of a base such as trimethylamine. The N-acylated or N-carbamoyl derivative is subsequently converted to the mesylate with methanesulphonyl chloride (MsCl) in the

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- presence of a base such as triethylamine. The mesylate is displaced by an aromatic thiolate anion using a base such as caesium carbonate (Cs_2CO_3) and the sulphide derivative so formed is oxidised to the sulphone using *m*-chloroperbenzoic acid (*m*-CPBA) or potassium permanganate (KMnO_4). The biaryl sulphone is formed by coupling an appropriate aromatic boronic ester or acid to the bromophenyl sulphone using transition metal catalysis such as tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$).

Scheme A

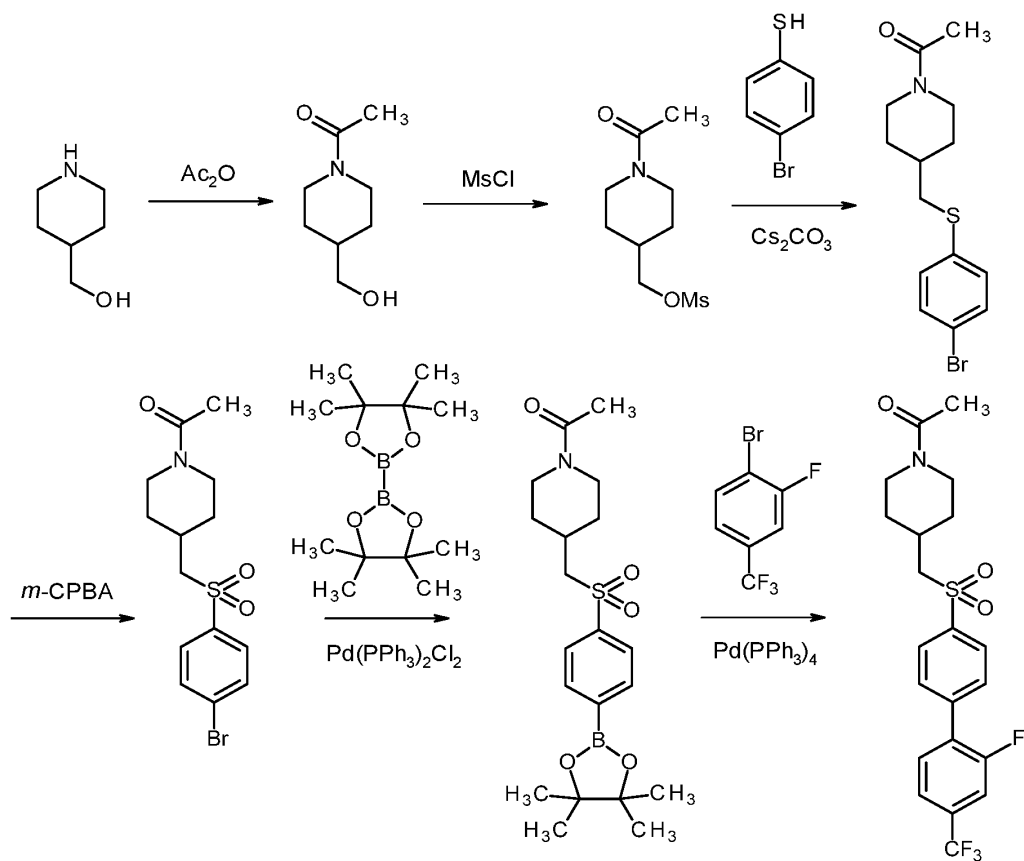


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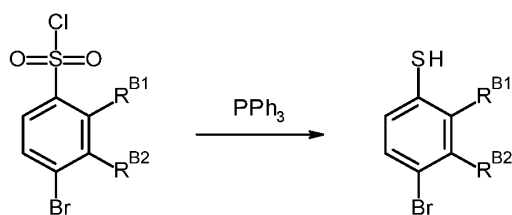
- In a second approach (as illustrated in Scheme B), the bromo(mono)phenyl sulphone formed in Scheme A is converted into a boronic ester using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane and transition metal catalysis such as bis(triphenylphosphine) palladium (II) dichloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$). The biaryl sulphone is formed by coupling the boronic ester with an appropriate aromatic bromide, iodide or triflate using transition metal catalysis such as tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$) or [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($\text{Pd}(\text{dppf})\text{Cl}_2$).

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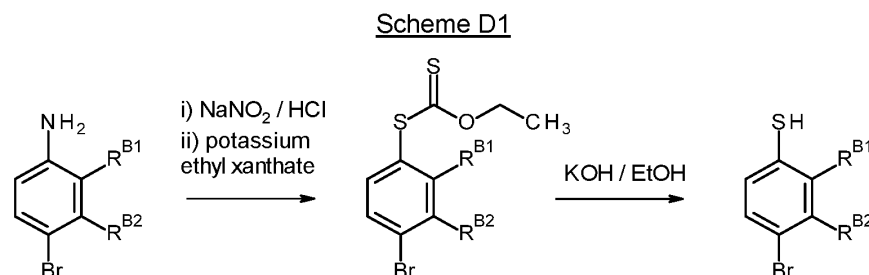
Scheme B

- 5 In instances in which the appropriate aromatic thiol is not readily commercially available, it may be made by reduction of the corresponding sulphonyl chloride with a reducing agent such as triphenylphosphine (PPh_3) (as illustrated in Scheme C).

Scheme C

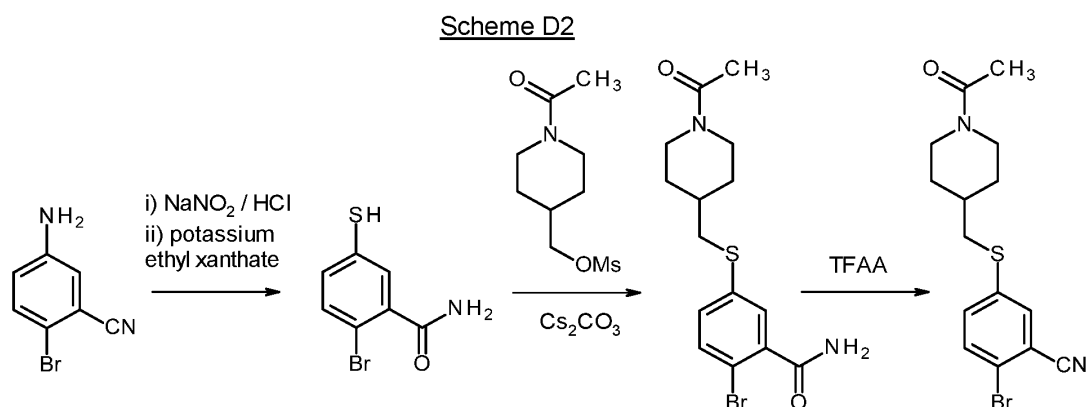
Alternatively (as illustrated in Scheme D1), an appropriately substituted aniline may be diazotised with sodium nitrite (NaNO_2) and acid such as hydrochloric acid (HCl). The diazonium salt is then reacted with potassium ethyl xanthate and subsequently hydrolysed with potassium hydroxide (KOH) to give the aromatic thiol.

5



In the case in which one of the substituents is a nitrile group (as illustrated in Scheme D2), the nitrile may be hydrated to the primary amide during the potassium hydroxide hydrolysis. If this is the case, the aromatic thiol containing the primary amide substituent is coupled with the bromide as in Schemes A and B and then treated with a dehydrating agent such as trifluoroacetic anhydride (TFAA) to regenerate the nitrile from the primary amide.

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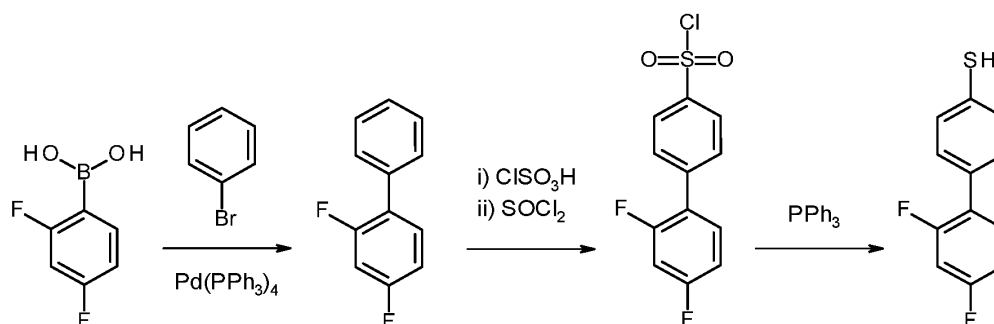


Access to biaryl thiols may be achieved as follows (as illustrated in Scheme E): An appropriate biphenyl compound is prepared from a boronic acid and a halobenzene via a Suzuki coupling. The biphenyl is sulfonylated using chlorosulfonic acid (ClSO_3H) to give the corresponding sulfonic acid. The acid is then reacted with thionyl chloride (SOCl_2) to give the corresponding aryl sulfonyl chloride. Reduction of the sulphonyl chloride with, for example triphenylphosphine (PPh_3), gives the biarylthiol derivative.

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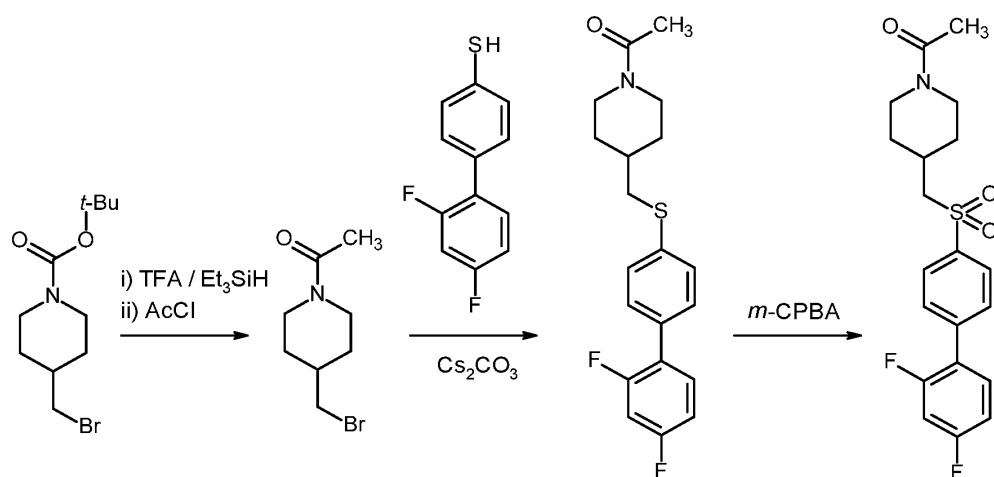
Scheme E



The biaryl thiols may be reacted with the N-acylated / N-carbamoylated-O-mesylated-piperidine-4-methanol derivatives, for example, as in Schemes A and B.

Alternatively (as illustrated in Scheme F), a *tert*-butyl 4-(bromomethyl)piperidine-1-carboxylate may be treated with trifluoroacetic acid (TFA) in the presence of triethylsilane (Et_3SiH) to remove the Boc group. The resulting product may then be N-acylated or N-carbamoylated in the presence of a base such as pyridine. This bromomethylpiperidine may be reacted with the biaryl thiol in the presence of a base such as caesium carbonate (Cs_2CO_3) and the sulphide so formed oxidised with, for example, *m*-chloroperbenzoic acid (*m*-CPBA) or potassium permanganate (KMnO_4) to give the target compound.

Scheme F

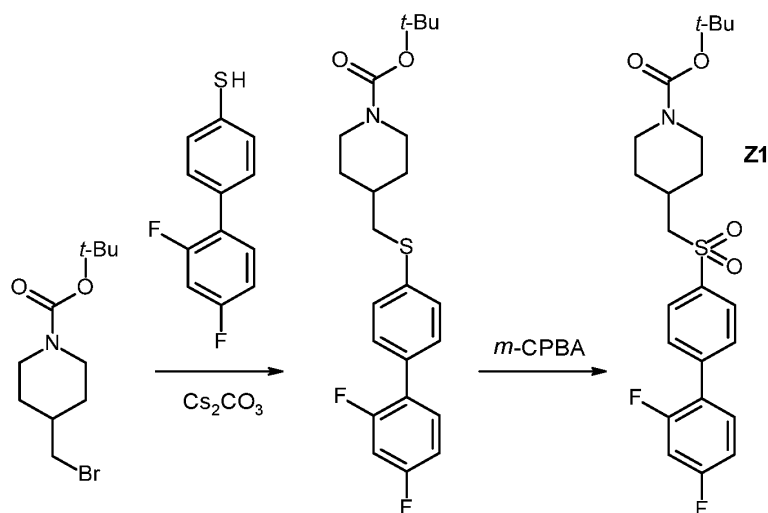


The N-acylated bromomethylpiperidine may also be used in place of the mesylate in Schemes A and B.

In an alternative approach (as illustrated in Scheme G1), a biaryl thiol may be reacted with an N-Boc-4-bromomethylpiperidine or N-Boc-4-methanesulphonyloxymethylpiperidine to give a sulphide which is oxidised with, for example *m*-chloroperbenzoic acid (*m*-CPBA) to give the biaryl sulphone (Z1).

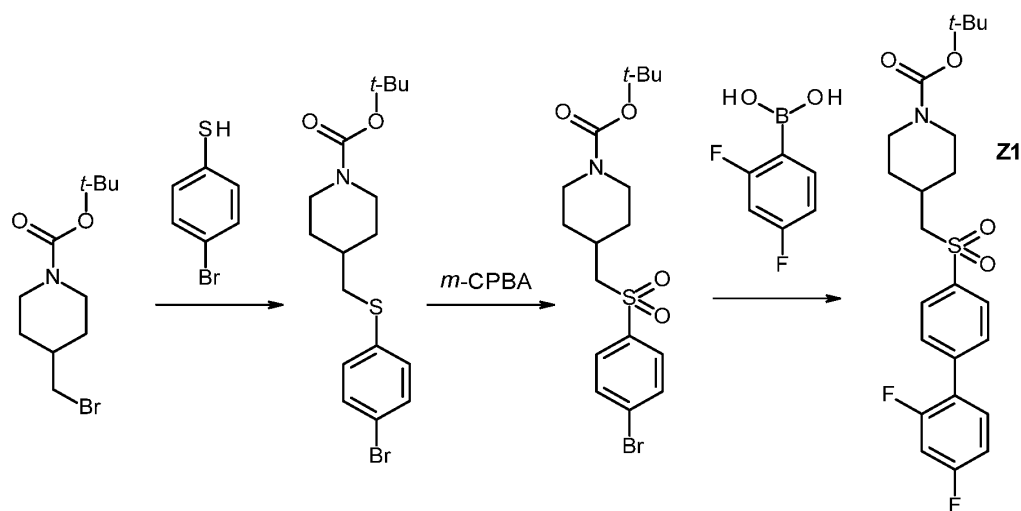
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Scheme G1



10 In an alternative approach (as illustrated in Scheme G2), the biaryl may be built up via reaction of an appropriate monoaryl thiol, oxidation, and coupling with an appropriate boronic acid or ester derivative as in Scheme A.

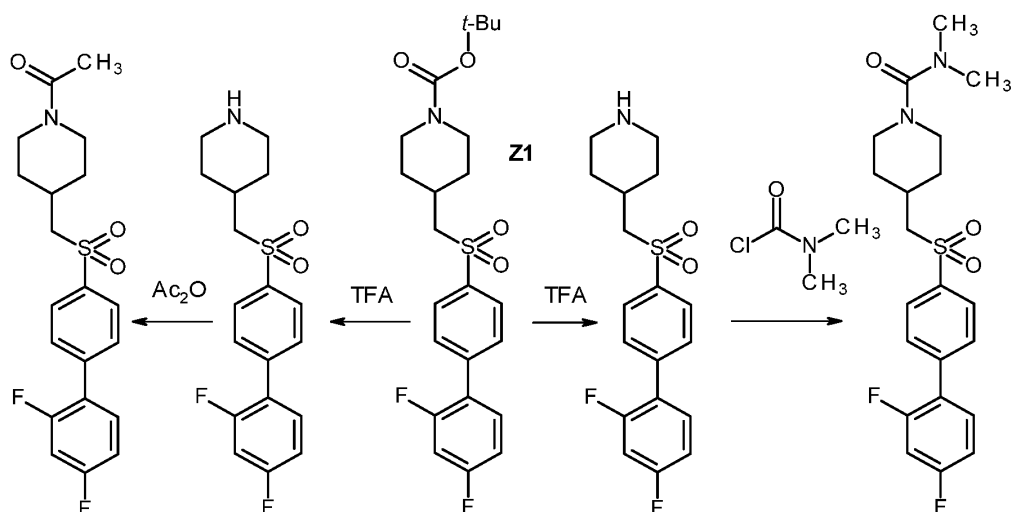
Scheme G2



For compounds where $R_1 = R_2 = H$ in the biaryl sulphone (Z1), the Boc group may be removed by treatment with trifluoroacetic acid and the piperidine so formed may then be N-acylated or N-carbamoylated (for example, as illustrated in Scheme H).

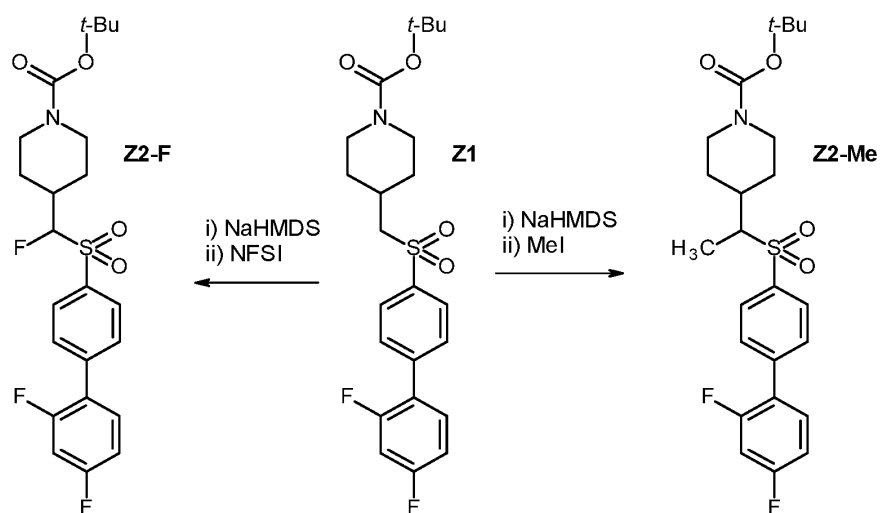
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Scheme H



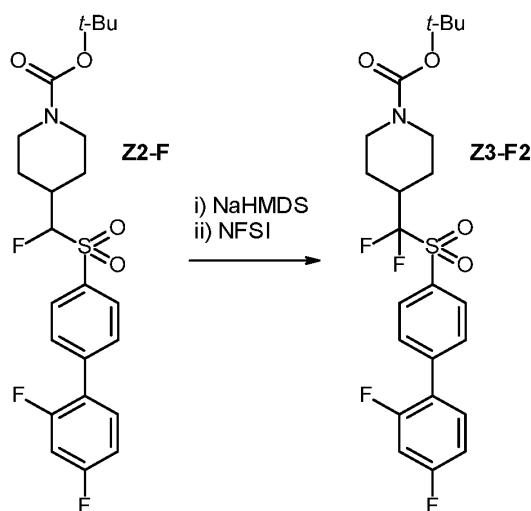
- In addition (as illustrated in Scheme J1), the biaryl sulfone (**Z1**) may be treated with a base such as sodium hexamethyldisilazide (NaHMDS) followed by either a fluorinating agent such as N-fluorobenzenesulfonimide (NFSI) or an alkylating agent such as methyl iodide (MeI) to give the biaryl sulfone with R1 = fluoro (**Z2-F**) or R1 = methyl (**Z2-Me**), respectively. The Boc group may then be removed by treatment with trifluoroacetic acid and the piperidine so formed may then be N-acylated or N-carbamoylated. Isomers may be separated if desired.

Scheme J1



In addition (as illustrated in Scheme J2), the biaryl sulphone with R1= fluoro (Z2-F) may be subsequently treated with a base such as sodium hexamethyldisilazide (NaHMDS) followed by a fluorinating agent such as N-fluorobenzenesulfonimide (NFSI) to give the compound with R1 = R2 = F (Z3-F2). The Boc group may then be removed by treatment with trifluoroacetic acid and the piperidine so formed may then be N-acylated or N-carbamoylated.

Scheme J2



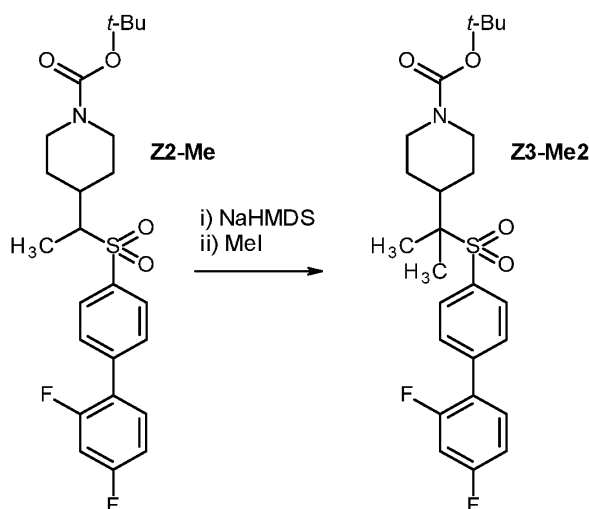
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In a similar manner (as illustrated in Scheme J3), the biaryl sulphone with R1 = alkyl, e.g., methyl (Z2-Me), may be treated with a similar base followed by an alkylating agent such as methyl iodide to give the compound with R1 = R2 = alkyl, e.g., methyl (Z3-Me2). The Boc group may then be removed by treatment with trifluoroacetic acid and the piperidine so formed may then be N-acylated or N-carbamoylated.

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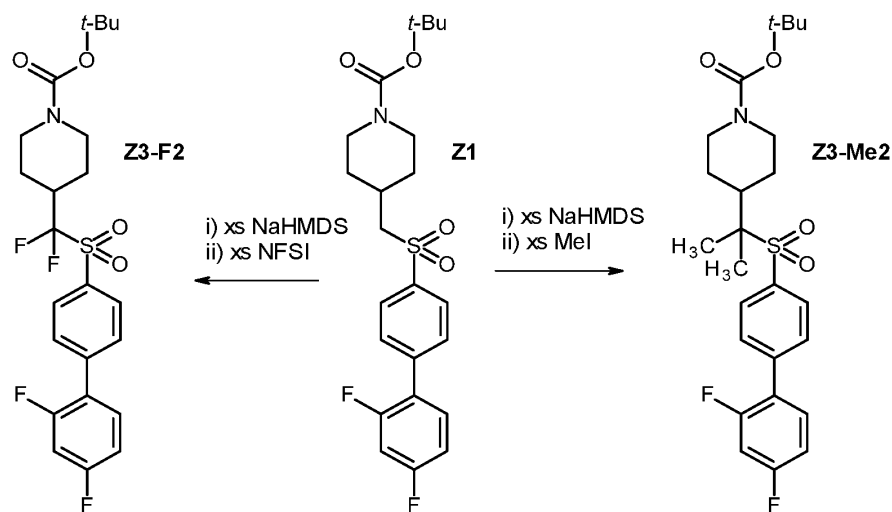
Scheme J3



- Additionally, the biaryl sulphone (e.g., Z2-F, with R1 = fluoro; Z2-Me, with R1 = methyl) may be treated with a base, for example, lithium diisopropylamide (LDA), followed by either a fluorinating agent, for example, N-fluorobenzenesulfonimide (NFSI), or an alkylating agent, for example, MeI, to give the biaryl sulphone with R2 = fluoro or R2 = alkyl (e.g., methyl). In this way, compounds where R1 and R2 are different (e.g., R1 = fluoro and R2 = methyl; R1 = methyl and R2 = ethyl; *etc.*), can be prepared. In the case where R1 is not the same as R2, the isomers may be separated if desired.

- Alternatively (as illustrated in Scheme J4), in the cases in which R1 = R2, the biaryl sulphone (Z1) may be treated with an excess of sodium hexamethyldisilazide (NaHMDS) and an excess of alkyl halide or N-fluorobenzenesulfonimide (NFSI) to lead directly to the disubstituted sulphone with R1 = R2 = alkyl or R1 = R2 = fluoro. The Boc group may then be removed by treatment with trifluoroacetic acid and the piperidine so formed may then be N-acylated or N-carbamoylated.

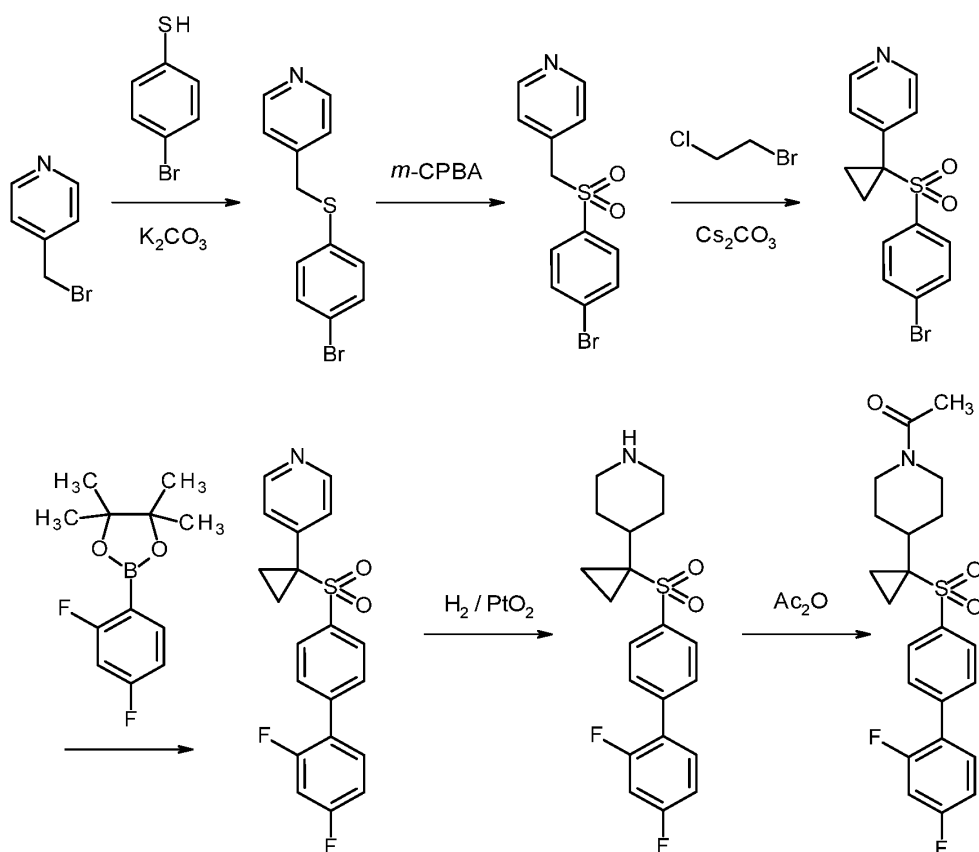
Scheme J4



- In a further approach (as illustrated in Scheme K), 4-chloromethylpyridine is reacted with an aromatic thiolate anion using a base such potassium carbonate (K_2CO_3) and the sulphide derivative so formed is oxidised to the sulphone using *m*-chloroperbenzoic acid (*m*-CPBA). This sulphone is reacted with an alkyl derivative that has a leaving group on each of the terminal carbon atoms, such as 1-bromo-2-chloroethane, in the presence of a base such a caesium carbonate (Cs_2CO_3). The resulting cycloalkyl derivative is then coupled to a suitable aryl partner, such as an aryl boronic ester using transition metal catalysis such as tetrakis(triphenylphosphine)palladium(0), the pyridine ring is reduced using hydrogen (H_2) with a catalyst such as platinum dioxide (PtO_2) and the product of the reduction is then N-acylated or N-carbamoylated as required.

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Scheme K



- These and/or other well-known methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds described herein. See, for example:

Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Wiley) 2010. Ed. R.C.Larock. ISBN: 978-1-118-03758-4.

10

Comprehensive Organic Synthesis, 2nd Edition (Elsevier) 2014. Editor in Chiefs P. Knochel, G.A. Molander. eBook ISBN: 9780080977430. Hardcover ISBN: 9780080977423.

- 15 *Science of Synthesis: Cross Coupling and Heck-Type Reactions*, Workbench Edition (Thieme) 2013. Ed. G. Molander, J.P. Wolfe, Mats Larhed. ISBN 9783131734112.

- 20 *Greene's Protective Groups in Organic Synthesis*, 4th Edition (Wiley) 2006. P.G.M. Wuts, T.W. Greene. Print ISBN: 9780471697541. Online ISBN: 9780470053485.

e-EROS Encyclopedia of Reagents for Organic Synthesis, (Wiley). Online ISBN: 9780470842898. DOI: 10.1002/047084289X.

- 5 *Organic Reactions: Electrophilic Fluorination with N–F Reagents*, (Wiley) 2008.
J. Baudoux, D. Cahard. DOI: 10.1002/0471264180.or069.02.

Compositions

- 10 One aspect of the present invention pertains to a composition (e.g., a pharmaceutical composition) comprising a NASMP compound, as described herein, and a carrier, diluent, or excipient (e.g., a pharmaceutically acceptable carrier, diluent, or excipient).

- In one embodiment, the composition further comprises one or more (e.g., 1, 2, 3, 4)
15 additional therapeutic agents, as described herein.

- Another aspect of the present invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising admixing a NASMP compound, as described herein, and a carrier, diluent, or excipient (e.g., a pharmaceutically acceptable
20 carrier, diluent, or excipient).

- Another aspect of the present invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising admixing a NASMP compound, as described herein; one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described
25 herein; and a carrier, diluent, or excipient (e.g., a pharmaceutically acceptable carrier, diluent, or excipient).

Uses

- 30 The NASMP compounds, as described herein, are useful, for example, in the treatment of disorders (e.g., diseases) including, for example, the disorders (e.g., diseases) described herein.

Use in Methods of Therapy

- 35 Another aspect of the present invention pertains to a NASMP compound, as described herein, for use in a method of treatment of the human or animal body by therapy, for example, for use a method of treatment of a disorder (e.g., a disease) as described herein.
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Another aspect of the present invention pertains to a NASMP compound, as described herein, in combination with one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein, for use in a method of treatment of the human or animal body by therapy, for example, for use in a method of treatment of a disorder (e.g., a disease) as described herein.

Use in the Manufacture of Medicaments

Another aspect of the present invention pertains to use of a NASMP compound, as described herein, in the manufacture of a medicament for treatment, for example, treatment of a disorder (e.g., a disease) as described herein.

In one embodiment, the medicament comprises the NASMP compound.

Another aspect of the present invention pertains to use of a NASMP compound, as described herein, and one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein, in the manufacture of a medicament for treatment, for example, treatment of a disorder (e.g., a disease) as described herein.

In one embodiment, the medicament comprises the NASMP compound and the one or more (e.g., 1, 2, 3, 4) additional therapeutic agents.

Methods of Treatment

Another aspect of the present invention pertains to a method of treatment, for example, of a disorder (e.g., a disease) as described herein, comprising administering to a patient in need of treatment a therapeutically effective amount of a NASMP compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to a method of treatment, for example, of a disorder (e.g., a disease) as described herein, comprising administering to a patient in need of treatment a therapeutically effective amount of a NASMP compound, as described herein, preferably in the form of a pharmaceutical composition, and one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein, preferably in the form of a pharmaceutical composition.

Conditions Treated - Disorders Associated with Changes in Cellular Metabolism

In one embodiment, the treatment is treatment of: a disorder associated with changes in cellular metabolism.

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In one embodiment, the treatment is treatment of: a disorder in which cellular metabolism is dysregulated.

- 5 Examples of such disorders include many of those described below, including, e.g.,
an autoimmune/inflammatory disorder; cancer; and a disorder mediated by osteoclasts.

- 10 In one embodiment, the treatment is treatment of multiple myeloma, diffuse large B-cell lymphoma, acute myeloid leukemia, eosinophilic leukemia, glioblastoma, melanoma, ovarian cancer, chemotherapy resistant cancer, radiation resistant cancer, inflammatory arthritis, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus (SLE), lupus nephritis, asthma, chronic obstructive pulmonary disease (COPD).

Conditions Treated - Autoimmune/Inflammatory Disorders

- 15 In one embodiment, the treatment is treatment of: an autoimmune/inflammatory disorder.

In one embodiment, the treatment is treatment of: an autoimmune disorder.

- 20 In one embodiment, the treatment is treatment of: an inflammatory disorder.

- In one embodiment, the treatment is treatment of: inflammatory arthritis (including, e.g., rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis; spondyloarthritis; reactive arthritis; infectious arthritis; systemic lupus erythematosus; scleroderma; gout; adult-onset
- 25 Still's disease; juvenile idiopathic arthritis); psoriasis; systemic lupus erythematosus; lupus nephritis; systemic sclerosis; scleroderma; hepatitis; endometriosis; adenomyosis; Sjogren's syndrome; inflammatory bowel disease; ulcerative colitis; Crohn's disease; multiple sclerosis; asthma; atherosclerosis; chronic obstructive pulmonary disease (COPD); uveitis; Hidradenitis suppurativa; autoimmune hepatitis; pulmonary fibrosis;
- 30 allergic disease (including, e.g., atopy, allergic rhinitis, atopic dermatitis, anaphylaxis, allergic bronchopulmonary aspergillosis, allergic gastroenteritis, hypersensitivity pneumonitis); an allergy; type I diabetes; rheumatic fever; celiac disease; encephalitis; oophoritis; primary biliary cirrhosis; insulin-resistant diabetes; autoimmune adrenal insufficiency (Addison's disease); acne; acne conglobate; acne fulminans; autoimmune
- 35 oophoritis; autoimmune orchitis; autoimmune haemolytic anaemia; paroxysmal cold hemoglobinuria; Behçet's disease; autoimmune thrombocytopenia; autoimmune neutropenia; pernicious anaemia; pure red cell anaemia; autoimmune coagulopathy; myasthenia gravis; autoimmune polyneuritis; pemphigus; rheumatic carditis; Goodpasture's syndrome; postcardiotomy syndrome; polymyositis; dermatomyositis;
- 40 irritable bowel syndrome; pancreatitis; gastritis, lichen planus; delayed type hypersensitivity; chronic pulmonary inflammation; pulmonary alveolitis; pulmonary

granuloma; gingival inflammation; endodontic disease; periodontal disease; hypersensitivity pneumonitis; hay fever; anaphylaxis; skin allergy; hives; gout; polycystic kidney disease; cryopyrin-associated periodic syndrome (CAPS); Muckle-Wells Syndrome; Guillain-Barre syndrome; chronic inflammatory demyelinating polyneuropathy;

5 organ or transplant rejection; chronic allograft rejection; acute or chronic graft versus-host disease; dermatitis; atopic dermatomyositis; Graves' disease; autoimmune (Hashimoto's) thyroiditis; blistering disorder; vasculitis syndrome; immune-complex mediated vasculitis; bronchitis; cystic fibrosis; pneumonia; pulmonary oedema; pulmonary embolism; sarcoidosis; hypertension; emphysema; respiratory failure; acute respiratory distress

10 syndrome; BENTA disease; or polymyositis.

In one embodiment, the treatment is treatment of: inflammatory arthritis (including, e.g., rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis; spondyloarthritis; reactive arthritis; infectious arthritis; systemic lupus erythematosus; scleroderma; gout; adult-onset

15 Still's disease; juvenile idiopathic arthritis); psoriasis; systemic lupus erythematosus, lupus nephritis; systemic sclerosis; scleroderma; hepatitis; endometriosis; adenomyosis; Sjogren's syndrome; inflammatory bowel disease; ulcerative colitis; Crohn's disease; Hidradenitis suppurativa; autoimmune hepatitis; multiple sclerosis; asthma, atherosclerosis; chronic obstructive pulmonary disease (COPD); uveitis; or pulmonary

20 fibrosis.

In one embodiment, the treatment is treatment of: inflammatory arthritis (including, e.g., rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis; spondyloarthritis; reactive arthritis; infectious arthritis; systemic lupus erythematosus; scleroderma; gout; adult-onset

25 Still's disease; juvenile idiopathic arthritis).

In one embodiment, the treatment is treatment of: psoriasis; psoriatic arthritis; systemic lupus erythematosus, lupus nephritis; systemic sclerosis; scleroderma; hepatitis; endometriosis; adenomyosis; Sjogren's syndrome; inflammatory bowel disease;

30 ulcerative colitis; Crohn's disease; Hidradenitis suppurativa; autoimmune hepatitis; multiple sclerosis; asthma, atherosclerosis; chronic obstructive pulmonary disease (COPD); uveitis; or pulmonary fibrosis.

In one embodiment, the treatment is treatment of: inflammatory arthritis (including, e.g., rheumatoid arthritis; psoriatic arthritis; systemic lupus erythematosus; juvenile idiopathic arthritis); psoriasis; lupus nephritis; systemic sclerosis; inflammatory bowel disease; ulcerative colitis; Crohn's disease; Hidradenitis suppurativa; autoimmune hepatitis; or

35 multiple sclerosis.

40 In one embodiment, the treatment is treatment of: inflammatory arthritis.

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In one embodiment, the treatment is treatment of: rheumatoid arthritis.

In one embodiment, the treatment is treatment of: psoriatic arthritis.

5 In one embodiment, the treatment is treatment of: systemic lupus erythematosus.

In one embodiment, the treatment is treatment of: juvenile idiopathic arthritis.

In one embodiment, the treatment is treatment of: psoriasis.

10

In one embodiment, the treatment is treatment of: lupus nephritis.

In one embodiment, the treatment is treatment of: systemic sclerosis.

15 In one embodiment, the treatment is treatment of: inflammatory bowel disease.

In one embodiment, the treatment is treatment of: ulcerative colitis.

In one embodiment, the treatment is treatment of: Crohn's disease.

20

In one embodiment, the treatment is treatment of: Hidradenitis suppurativa.

In one embodiment, the treatment is treatment of: autoimmune hepatitis.

25 In one embodiment, the treatment is treatment of: multiple sclerosis.

Conditions Treated - Cancer

In one embodiment, the treatment is treatment of: cancer.

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In one embodiment, the treatment is treatment of: multiple myeloma; lymphoma; leukaemia; carcinoma; or sarcoma.

Multiple Myeloma:

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In one embodiment, the treatment is treatment of: multiple myeloma.

Lymphoma:

40 In one embodiment, the treatment is treatment of: lymphoma.

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- In one embodiment, the treatment is treatment of: Hodgkin's lymphoma; non-Hodgkin's lymphoma; lymphocytic lymphoma; granulocytic lymphoma; monocytic lymphoma; diffuse large B-cell lymphoma (DLBCL); mantel cell lymphoma (MCL); follicular cell lymphoma (FL); mucosa-associated lymphoid tissue (MALT) lymphoma; marginal zone lymphoma;
- 5 T-cell lymphoma; marginal zone lymphoma; or Burkitt's lymphoma.

In one embodiment, the treatment is treatment of lymphocytic lymphoma; granulocytic lymphoma; monocytic lymphoma; or diffuse large B-cell lymphoma (DLBCL).

- 10 In one embodiment, the treatment is treatment of: diffuse large B-cell lymphoma (DLBCL).

Leukaemia:

- 15 In one embodiment, the treatment is treatment of: leukaemia.

- In one embodiment, the treatment is treatment of: chronic lymphocytic leukemia (CLL); acute myeloid leukemia (AML); acute lymphocytic leukemia (ALL); lymphoblastic T-cell leukemia; chronic myelogenous leukemia (CML); hairy-cell leukemia; acute lymphoblastic
- 20 T-cell leukemia; acute eosinophilic leukemia; immunoblastic large-cell leukemia; megakaryoblastic leukemia; acute megakaryocytic leukemia; promyelocytic leukemia; erythroleukemia; or plasmacytoma.

- In one embodiment, the treatment is treatment of: chronic lymphocytic leukemia (CLL);
- 25 acute myeloid leukemia (AML); acute lymphocytic leukemia (ALL); lymphoblastic T-cell leukemia; chronic myelogenous leukemia (CML); or acute eosinophilic leukemia.

In one embodiment, the treatment is treatment of: chronic lymphocytic leukemia (CLL).

- 30 In one embodiment, the treatment is treatment of: acute myeloid leukemia (AML).

In one embodiment, the treatment is treatment of: acute lymphocytic leukemia (ALL).

In one embodiment, the treatment is treatment of: lymphoblastic T-cell leukemia.

- 35 In one embodiment, the treatment is treatment of: chronic myelogenous leukemia (CML).

Carcinoma:

- 40 In one embodiment, the treatment is treatment of: carcinoma.

In one embodiment, the treatment is treatment of: colon cancer; breast cancer; ovarian cancer; lung cancer (including, e.g., small cell lung carcinoma and non-small cell lung carcinoma); prostate cancer; cancer of the oral cavity or pharynx (including, e.g., cancer of the lip, tongue, mouth, larynx, pharynx, salivary gland, buccal mucosa); esophageal cancer; stomach cancer; small intestine cancer; large intestine cancer; rectal cancer; liver passage cancer; biliary passage cancer; pancreatic cancer; bone cancer; connective tissue cancer; skin cancer; cervical cancer; uterine cancer; corpus cancer; endometrial cancer; vulval cancer; vaginal cancer; testicular cancer; bladder cancer; kidney cancer; ureter cancer; urethral cancer; urachus cancer; eye cancer; glioma; spinal cord cancer; central nervous system cancer; peripheral nervous system cancer; meningeal cancer; thyroid cancer; adenocarcinoma; astrocytoma; acoustic neuroma; anaplastic astrocytoma; basal cell carcinoma; blastoglioma; choriocarcinoma; chordoma; craniopharyngioma; cutaneous melanoma; cystadenocarcinoma; embryonal carcinoma; ependymoma; epithelial carcinoma; gastric cancer; genitourinary tract cancer; glioblastoma multiforme; head and neck cancer; hemangioblastoma; hepatocellular carcinoma; renal cell carcinoma (RCC); hepatoma; large cell carcinoma; medullary thyroid carcinoma; medulloblastoma; meningioma mesothelioma; myeloma; neuroblastoma; oligodendroglioma; epithelial ovarian cancer; papillary carcinoma; papillary adenocarcinoma; paraganglioma; parathyroid tumour; pheochromocytoma; pinealoma; plasmacytoma; retinoblastoma; sebaceous gland carcinoma; seminoma; melanoma; squamous cell carcinoma; sweat gland carcinoma; synovioma; thyroid cancer; uveal melanoma; or Wilm's tumour.

In one embodiment, the treatment is treatment of: colon cancer; breast cancer; ovarian cancer; lung cancer (including, e.g., small cell lung carcinoma and non-small cell lung carcinoma); prostate cancer; stomach cancer; pancreatic cancer; bone cancer; skin cancer; cervical cancer; uterine cancer; endometrial cancer; testicular cancer; bladder cancer; kidney cancer; eye cancer; liver cancer; glioma; thyroid cancer; adenocarcinoma; astrocytoma; acoustic neuroma; anaplastic astrocytoma; cutaneous melanoma; gastric cancer; glioblastoma multiforme; head and neck cancer; hepatocellular carcinoma; renal cell carcinoma (RCC); melanoma; or squamous cell carcinoma.

In one embodiment, the treatment is treatment of: colon cancer; breast cancer; ovarian cancer; lung cancer (including, e.g., small cell lung carcinoma and non-small cell lung carcinoma); prostate cancer; pancreatic cancer; bone cancer; liver cancer; glioblastoma multiforme; head and neck cancer; or melanoma.

In one embodiment, the treatment is treatment of: melanoma.

In one embodiment, the treatment is treatment of: glioblastoma multiforme.

In one embodiment, the treatment is treatment of: breast cancer.

In one embodiment, the treatment is treatment of: prostate cancer.

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In one embodiment, the treatment is treatment of: bone cancer.

In one embodiment, the treatment is treatment of: pancreatic cancer.

10 In one embodiment, the treatment is treatment of: head and neck cancer.

In one embodiment, the treatment is treatment of: lung cancer (including, e.g., small cell lung carcinoma and non-small cell lung carcinoma).

15 In one embodiment, the treatment is treatment of: ovarian cancer.

In one embodiment, the treatment is treatment of: liver cancer.

Sarcoma:

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In one embodiment, the treatment is treatment of: sarcoma.

In one embodiment, the treatment is treatment of: Askin's tumour; sarcoma botryoides; chondrosarcoma; endotheliosarcoma; Ewing's sarcoma; Malignant

25 hemagioendothelioma; malignant Schwannoma; osteosarcoma; gastrointestinal stromal tumour (GIST); myxosarcoma; alveolar soft part sarcoma; angiosarcoma; cystosarcoma phyllodes; dermatofibrosarcoma; desmoid tumour; desmoplastic small round cell tumour; extraskkeletal chondrosarcoma; osteosarcoma; fibrosarcoma; hemagiopericytoma; hemangiosarcoma; Kaposi's sarcoma; leiomyosarcoma; liposarcoma; lymphangiosarcoma;
30 lymphangioendotheliosarcoma; lymphosarcoma; malignant peripheral nerve sheath tumour; neurofibrosarcoma; plexiform fibrohistiocytic tumour; rhabdomyosarcoma; or synovial sarcoma.

Treatment of Refractory Cancer:

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In one embodiment, the treatment is treatment of: treatment refractory cancer (including, e.g., chemotherapy resistant cancer and radiotherapy resistant cancer); metastatic cancer; metastases; or recurrent cancer.

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In one embodiment, the treatment is treatment of: chemotherapy resistant cancer (including, e.g., chemotherapy resistant multiple myeloma, lymphoma, leukaemia, carcinoma, and sarcoma).

- 5 In one embodiment, the treatment is treatment of: radiotherapy resistant cancer (including, e.g., radiotherapy resistant multiple myeloma, lymphoma, leukaemia, carcinoma, and sarcoma).

In one embodiment, the treatment is treatment of: metastatic cancer.

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In one embodiment, the treatment is treatment of: metastases.

In one embodiment, the treatment is treatment of: recurrent cancer.

- 15 In one embodiment, the treatment is use in: preventing, reducing, or overcoming resistance to radiotherapy or chemotherapy (for example, due to changes in cellular metabolism); preventing or reducing tumour invasion; preventing or reducing tumour metastasis; improving the action of anti-tumour agents; and/or augmenting the action of immunomodulators.

20

In one embodiment, the treatment is use in: preventing, reducing, or overcoming resistance to radiotherapy.

- 25 In one embodiment, the treatment is use in: preventing, reducing, or overcoming resistance to chemotherapy.

In one embodiment, the treatment is use in: preventing or reducing tumour invasion or tumour metastasis; improving the action of anti-tumour agents; and/or augmenting the action of immunomodulators.

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In one embodiment, the treatment is use in: improving the action of anti-tumour agents; and/or augmenting the action of immunomodulators.

In one embodiment, the treatment is use in: improving the action of immunomodulators.

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Conditions Treated - Disorders Mediated by Osteoclasts

In one embodiment, the treatment is treatment of: a disorder mediated by osteoclasts.

- 40 In one embodiment, the treatment is treatment of: rheumatoid arthritis; osteoporosis; Paget's disease; osteopetrosis; osteoarthritis; ectopic bone formation; bone loss

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associated with endometriosis; neoplasia of bones (including, e.g., as a primary tumour or as metastases and including, e.g., bone cancer; osteosarcoma; or osteoma); cancer-associated bone disease (including, e.g., metastatic bone disease associated with, e.g., breast cancer, lung cancer, prostate cancer, or multiple myeloma; changes in bone mineralisation and density associated with cancer, including, e.g., hypercalcaemia associated with cancer); bone metastases (including, e.g., osteolytic bone metastases); hypercalcaemia (including, e.g., hypercalcaemia associated with cancer; hypercalcaemia caused by conditions associated with increased bone resorption (including, e.g., hypercalcaemia caused by vitamin D intoxication, primary or tertiary hyperparathyroidism, immobilisation, or sarcoidosis); or aseptic loosening of prosthetic implants (e.g., artificial joints, e.g., knees, hips, etc.).

In one embodiment, the treatment is treatment of: rheumatoid arthritis; osteoporosis; neoplasia of bones (including, e.g., as a primary tumour or as metastases and including, e.g., bone cancer; osteosarcoma; or osteoma); cancer-associated bone disease (including, e.g., metastatic bone disease associated with, e.g., breast cancer, lung cancer, prostate cancer, or multiple myeloma; changes in bone mineralisation and density associated with cancer, including, e.g., hypercalcaemia associated with cancer); or bone metastases (including, e.g., osteolytic bone metastases).

In one embodiment, the treatment is treatment of: rheumatoid arthritis.

In one embodiment, the treatment is treatment of: osteoporosis.

In one embodiment, the treatment is treatment of: neoplasia of bones (including, e.g., as a primary tumour or as metastases and including, e.g., bone cancer; osteosarcoma; or osteoma).

In one embodiment, the treatment is treatment of: bone cancer; osteosarcoma; or osteoma.

In one embodiment, the treatment is treatment of: cancer-associated bone disease (including, e.g., metastatic bone disease associated with, e.g., breast cancer, lung cancer, prostate cancer, or multiple myeloma; changes in bone mineralisation and density associated with cancer, including, e.g., hypercalcaemia associated with cancer).

In one embodiment, the treatment is treatment of: bone metastases.

Treatment

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, alleviation of symptoms of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included. For example, use with patients who have not yet developed the condition, but who are at risk of developing the condition, is encompassed by the term "treatment."

For example, treatment of inflammation includes the prophylaxis of inflammation, reducing the incidence of inflammation, reducing the severity of inflammation, alleviating the symptoms of inflammation, *etc.*

The term "therapeutically-effective amount," as used herein, pertains to that amount of a compound, or a material, composition or dosage form comprising a compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Combination Therapies

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. For example, the compounds described herein may also be used in combination therapies, e.g., in conjunction with other agents, for example, anti-inflammation agents, *etc.* Examples of treatments and therapies include chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, *etc.*); surgery; radiation therapy; photodynamic therapy; gene therapy; and controlled diets.

One aspect of the present invention pertains to a compound as described herein, in combination with one or more additional therapeutic agents.

The particular combination would be at the discretion of the physician who would select dosages using his common general knowledge and dosing regimens known to a skilled practitioner.

The agents (i.e., the compound described herein, plus one or more other agents) may be administered simultaneously or sequentially, and may be administered individually

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varying dose schedules and via different routes. For example, when administered sequentially, the agents can be administered at closely spaced intervals (e.g., over a period of 5-10 minutes) or at longer intervals (e.g., 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The agents (*i.e.*, the compound described here, plus one or more other agents) may be formulated together in a single dosage form, or alternatively, the individual agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

Other Uses

The NASMP compounds described herein may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

The NASMP compounds described herein may also be used as a standard, for example, in an assay, in order to identify other compounds, other anti-inflammation agents, *etc.*

Kits

One aspect of the invention pertains to a kit comprising (a) a NASMP compound as described herein, or a composition comprising a NASMP compound as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the compound or composition.

In one embodiment, the kit further comprises one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein.

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

Routes of Administration

The NASMP compound or pharmaceutical composition comprising the NASMP compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (*i.e.*, at the site of desired action).

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Routes of administration include oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray, drops or from an atomiser or dry powder delivery device); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

In one preferred embodiment, the route of administration is oral (e.g., by ingestion).

In one preferred embodiment, the route of administration is parenteral (e.g., by injection).

15 The Subject/Patient

The subject/patient may be a chordate, a vertebrate, a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutan, gibbon), or a human. Furthermore, the subject/patient may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject/patient is a human.

Formulations

While it is possible for the NASMP compound to be administered alone, it is preferable to present it as a pharmaceutical formulation (e.g., composition, preparation, medicament) comprising at least one NASMP compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined herein, and methods of making a pharmaceutical composition comprising admixing at

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least one NASMP compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, *e.g.*, carriers, diluents, excipients, *etc.* If formulated as discrete units (*e.g.*, tablets, *etc.*), each unit contains a predetermined amount (dosage) of the compound.

5

The term "pharmaceutically acceptable," as used herein, pertains to compounds, ingredients, materials, compositions, dosage forms, *etc.*, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (*e.g.*, human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, *etc.* must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

10

Suitable carriers, diluents, excipients, *etc.* can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 5th edition, 2005.

15

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the compound with carriers (*e.g.*, liquid carriers, finely divided solid carrier, *etc.*), and then shaping the product, if necessary.

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The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

30

Formulations may suitably be in the form of liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, *e.g.*, coated tablets), granules, powders, lozenges, pastilles, capsules (including, *e.g.*, hard and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories, pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, foams, sprays, mists, or aerosols.

35

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more compounds and optionally one or more other pharmaceutically acceptable ingredients, including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in the form of a depot or reservoir.

40

The compound may be dissolved in, suspended in, or admixed with one or more other pharmaceutically acceptable ingredients. The compound may be presented in a liposome or other microparticulate which is designed to target the compound, for example, to blood components or one or more organs.

Formulations suitable for oral administration (*e.g.*, by ingestion) include liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

Formulations suitable for buccal administration include mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs. Lozenges typically comprise the compound in a flavoured basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the compound in an inert matrix, such as gelatin and glycerin, or sucrose and acacia. Mouthwashes typically comprise the compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, lozenges, pastilles, capsules, and pills.

Formulations suitable for oral transmucosal administration include liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for non-oral transmucosal administration include liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

Tablets may be made by conventional means, *e.g.*, compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (*e.g.*, povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (*e.g.*, lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (*e.g.*, magnesium

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stearate, talc, silica); disintegrants (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); preservatives (e.g., methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and sweeteners.

- 5 Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided
10 with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

Ointments are typically prepared from the compound and a paraffinic or a water-miscible ointment base.

- 15 Creams are typically prepared from the compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol
20 and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

- 25 Emulsions are typically prepared from the compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together,
30 the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

- Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl
35 alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency
40 to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of

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coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids
5 such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for intranasal administration, where the carrier is a liquid, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the compound.

10 Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the
15 powder held close up to the nose.

Formulations suitable for pulmonary administration (*e.g.*, by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane,
20 dichloro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for ocular administration include eye drops wherein the compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the compound.

25 Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.

30 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the compound, such carriers as are known in the art to be appropriate.

35 Formulations suitable for parenteral administration (*e.g.*, by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (*e.g.*, solutions, suspensions), in which the compound is dissolved, suspended, or otherwise provided (*e.g.*, in a liposome or other microparticulate). Such liquids may additionally contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers,
40 bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient.

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Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection.

- Typically, the concentration of the compound in the liquid is from about 1 ng/mL to about 10 µg/mL, for example, from about 10 ng/mL to about 1 µg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Dosage

- It will be appreciated by one of skill in the art that appropriate dosages of the NASMP compounds, and compositions comprising the NASMP compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including the activity of the particular NASMP compound, the route of administration, the time of administration, the rate of excretion of the NASMP compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of NASMP compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

- Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

- In general, a suitable dose of the NASMP compound is in the range of about 10 µg to about 20 mg (more typically about 100 µg to about 10 mg) per kilogram body weight of the subject per day. Where the compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

CHEMICAL SYNTHESISAcronyms and abbreviations

- 5 AcCl : acetyl chloride
 Ac₂O : acetic anhydride
 B₂pin₂ : bis(pinacolato)diboron
 DCM : dichloromethane
 DMAP : 4-dimethylaminopyridine
- 10 DMF : dimethylformamide
 DMSO : dimethyl sulfoxide
 ESI : electrospray ionization
 Et₃N : triethylamine
 EtOAc : ethyl acetate
- 15 HPLC : high-performance liquid chromatography
 LCMS : liquid chromatography-mass spectrometry
 m-CPBA : *meta*-chloroperoxybenzoic acid
 MeOH : methanol
 Ms : mesylate
- 20 *m/z* : mass-to-charge ratio
 NaHMDS : sodium bis(trimethylsilyl)amide
 NFSI : *N*-fluorobenzenesulfonimide
 NMR : nuclear magnetic resonance (spectroscopy)
 rt : room temperature
- 25 TBAB : tetra-*n*-butylammonium bromide
 TES : triethylsilane
 TFA : trifluoroacetic acid
 TFAA : trifluoroacetic anhydride
 THF : tetrahydrofuran
- 30 TLC : thin-layer chromatography

Analytical HPLC (Method A)

Unless specified, the analytical HPLC characterisation of the target compounds (*i.e.*, the “Synthesis Compounds”) was conducted on the following system:

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Column: X-select CSH C18, 4.6 mm x 150 mm, ID 3.5 µm

Injection volume: 5 µL

Flow rate: 1 mL/min

10

Solvents: A: 0.1% formic acid in water:acetonitrile (95:5)

B: acetonitrile

Gradient (B% is increased linearly between 1 minute and 8 minutes):

Time (min)	A%	B%
0	95	5
1	95	5
8	0	100
12	0	100
14	95	5
18	95	5

Analytical HPLC (Method B)

15

The analytical HPLC characterisation of Intermediates 47, 49, 50 and 51 plus the larger scale synthesis of Synthesis Compound 1 was conducted on the following system:

20

Column: Acquity BEH Phenyl, 4.6 mm x 30 mm, ID 1.7 µm

Injection volume: 5 µL

Flow rate: 2 mL/min

Solvents: A: 0.03% TFA in water

B: 0.03% TFA in acetonitrile

Gradient:

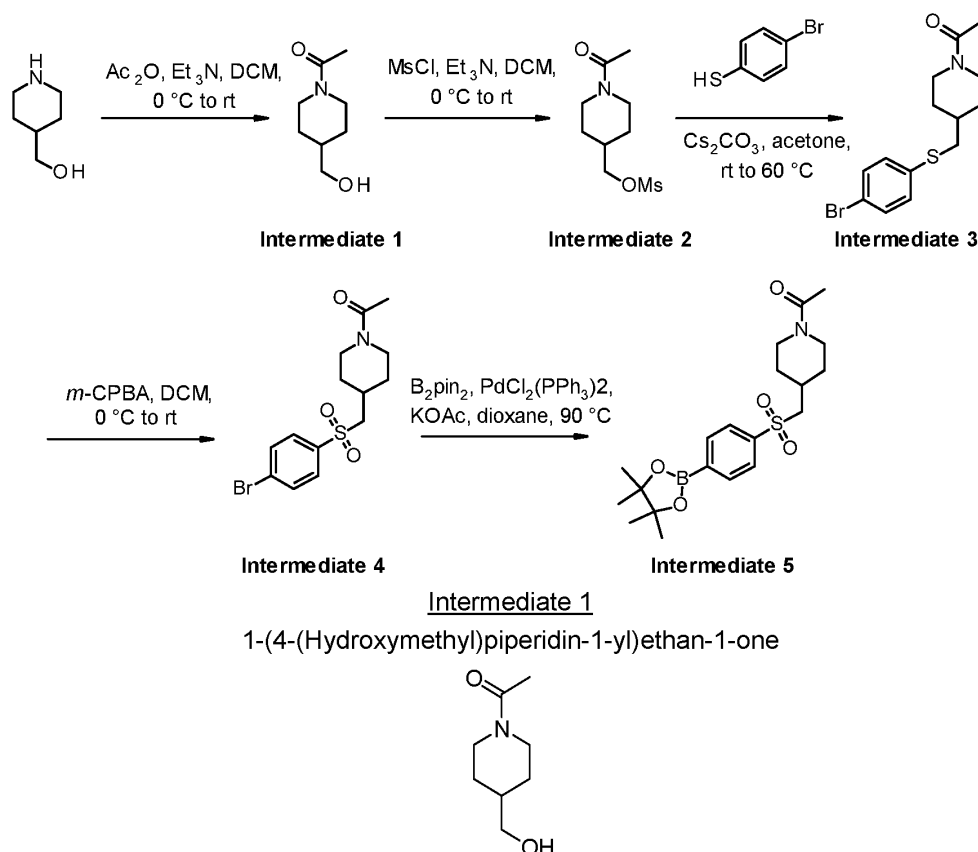
25

Time (min)	A%	B%
0	95	5
5.2	5	95
5.7	5	95
5.8	95	5
6.2	95	5

Thin-Layer Chromatography (TLC)

TLC analyses were carried out using pre-coated TLC sheets with silica gel 60 with fluorescent indicator UV-254 from Loba Chemie.

5

Synthetic Scheme 1

10

To a solution of piperidin-4-yl methanol (25.00 g, 217.05 mmol) in DCM (250 mL), triethylamine (60.50 mL, 434.10 mmol) and acetic anhydride (22.56 mL, 238.75 mmol) were added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion of the reaction, water (250 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with DCM (3 x 250 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 1** (20.00 g, crude) as colorless oil. This compound was carried on to the next step without further purification.

20

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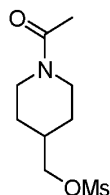
Analytical Data:

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 4.48 (t, *J* = 5.2 Hz, 1H), 4.35 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 1H), 3.25 (t, *J* = 5.6 Hz, 2H), 2.97 (td, *J* = 13.2, 2.8 Hz, 1H), 2.46 (td, *J* = 12.4, 2.4 Hz, 1H), 1.97 (s, 3H), 1.70 – 1.50 (m, 3H), 1.10 – 0.85 (m, 2H).

5

Intermediate 2

(1-Acetylpiperidin-4-yl)methyl methanesulfonate

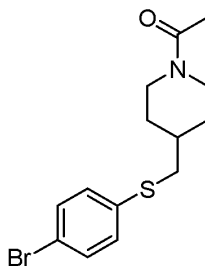


To a solution of 1-(4-(hydroxymethyl)piperidin-1-yl)ethan-1-one **Intermediate 1** (20.00 g, 127.21 mmol) in DCM (200 mL), triethylamine (35.39 mL, 254.43 mmol) and methanesulfonyl chloride (10.83 mL, 139.94 mmol) were added dropwise at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 4 h. The progress of the reaction was monitored by TLC [mobile phase: 10% Methanol in DCM]. After completion of the reaction, the reaction mixture was quenched with water (50 mL) and extracted with DCM (3 x 200 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 2** (25.00 g, crude) as yellow oil. This compound was used in the next step without further purification.

20 Analytical Data:

LCMS (ESI) *m/z* = 235.95 [M + H]⁺.Intermediate 3

1-(4-(((4-Bromophenyl)thio)methyl)piperidin-1-yl)ethan-1-one



25

To a solution of 4-bromobenzenethiol (2.82 g, 14.95 mmol) in acetone (50 mL), caesium carbonate (8.85 g, 27.18 mmol) was added under an argon atmosphere at room temperature and the reaction mixture was stirred for 30 min. Then, (1-acetylpiperidin-4-yl)methyl methanesulfonate **Intermediate 2** (3.20 g, 13.59 mmol) was added to the reaction mixture and the reaction was heated to 60 °C for 16 h under an argon atmosphere. The progress of the reaction was monitored by TLC [mobile phase: 100%

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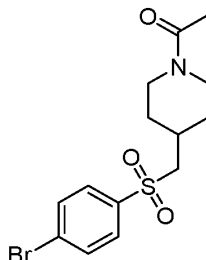
ethyl acetate]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a pad of celite and the filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 10-100% ethyl acetate in hexane to 5% methanol in DCM) to afford the title compound **Intermediate 3** (3.95 g, 80%) as a colorless thick oil.

Analytical Data:

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.39 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 4.61 (d, J = 13.2 Hz, 1H), 3.81 (d, J = 14.0 Hz, 1H), 3.04 – 2.95 (m, 1H), 2.90 – 2.75 (m, 2H), 2.55 – 2.45 (m, 1H), 2.08 (s, 3H), 1.96 – 1.80 (m, 2H), 1.80 – 1.65 (m, 1H), 1.25 – 1.11 (m, 2H).

Intermediate 4

1-(4-(((4-Bromophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one



To a stirred solution of 1-(4-(((4-bromophenyl)thio)methyl)piperidin-1-yl)ethan-1-one **Intermediate 3** (3.90 g, 11.88 mmol) in DCM (60 mL), *meta*-chloroperbenzoic acid (60%) (10.25 g, 35.64 mmol) was added in portions at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion of the reaction, the reaction mixture was quenched with saturated aqueous sodium thiosulfate (50 mL). The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 4** (4.02 g, crude) as an off-white solid. This compound was used in the next step without further purification.

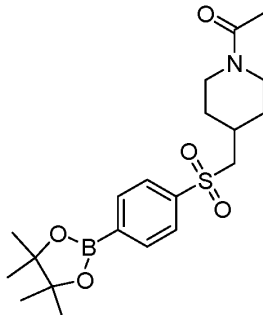
Analytical Data:

LCMS (ESI): m/z = 361.90 [M + H]⁺ (⁸¹Br).

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Intermediate 5

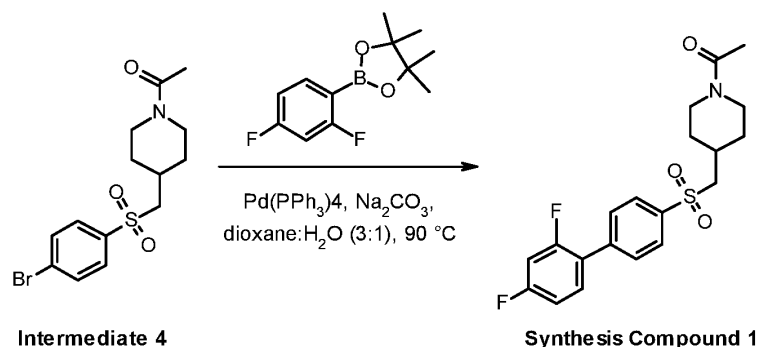
1-(4-(((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one



- 5 To a reaction tube were added a solution of 1-(4-(((4-bromophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 4** (2.00 g, 5.55 mmol), bis(pinacolato)diborane (1.70 g, 6.66 mmol) and potassium acetate (1.63 g, 16.65 mmol) in 1,4-dioxane (30 mL). The tube was sealed and degassed by purging with nitrogen for 15 min. Bis(triphenylphosphine)palladium(II) dichloride (0.060 g, 0.083 mmol) was added to the reaction mixture under a nitrogen atmosphere and the purging with nitrogen was continued for 5 min. The reaction mixture was heated to 90 °C for 4 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-5% methanol in DCM) to afford the title compound **Intermediate 5** (1.50 g, 66%) as a black solid.

Analytical Data:

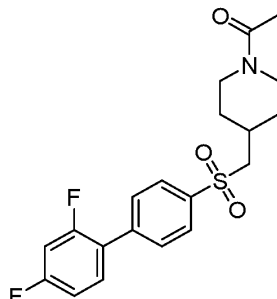
- 20 LCMS (ESI) m/z = 408.21 $[M + H]^+$ (boronic ester), 326.04 $[M + H]^+$ (corresponding boronic acid).

Synthetic Scheme 2

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Synthesis Compound 1

1-(4-(((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-01)



- 5 To a reaction tube were added a solution of 1-(4-(((4-bromophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 4** (0.500 g, 1.39 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.366 g, 1.52 mmol) and sodium carbonate (0.367 g, 3.46 mmol) in a mixture of 1,4-dioxane-water (3:1, 8 mL). The tube was sealed and degassed by purging with argon for 15 min.
- 10 Tetrakis(triphenylphosphine)palladium(0) (0.160 g, 0.139 mmol) was added to the reaction mixture under an argon atmosphere and the purging with argon was continued for 5 min. The reaction mixture was heated at 90 °C for 12 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under
- 15 reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 0-10% methanol in DCM). The compound was further purified by preparative HPLC (mobile phase: 0.5% formic acid in a mixture of acetonitrile/water; solid phase: C₁₈ silica) to afford the title compound **Synthesis Compound 1** (0.220 g, 40%) as an off-white solid.

20

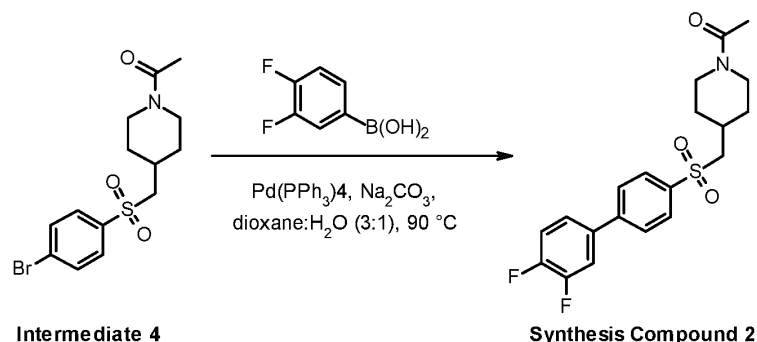
Analytical Data:

LCMS (ESI) m/z = 394.10 [M + H]⁺.

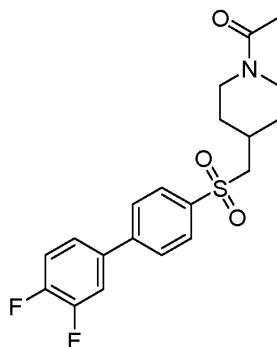
HPLC (see generic method): Retention time: 8.03 min.; Purity: 99.75%.

- 25 ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.97 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.63 – 7.59 (m, 1H), 7.33 – 7.28 (m, 1H), 7.21 – 7.17 (m, 1H), 4.19 (d, J = 13.2 Hz, 1H), 3.71 (d, J = 14.0 Hz, 1H), 3.28 (d, J = 6.0 Hz, 2H), 2.98 (t, J = 8.4 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.10 – 2.02 (m, 1H), 1.93 (s, 3H), 1.87 – 1.72 (m, 2H), 1.32 – 1.20 (m, 1H), 1.20 – 1.07 (m, 1H).

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Synthetic Scheme 3Synthesis Compound 2

- 5 1-((4-((3',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonylmethyl)piperidin-1-yl)ethan-1-one
(NASMP-02)



- To a reaction tube were added a solution of 1-((4-bromophenyl)sulfonylmethyl)piperidin-1-yl ethan-1-one **Intermediate 4** (0.500 g, 1.38 mmol), (3,4-difluorophenyl)boronic acid (0.263 g, 1.66 mmol) and sodium carbonate (0.367 g, 3.46 mmol) in a mixture of 1,4-dioxane: water (3:1, 13 mL). The tube was sealed and degassed by purging with nitrogen for 5 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.159 g, 0.138 mmol) to the reaction mixture under a nitrogen atmosphere and the purging with nitrogen was continued for another 5 min. The reaction mixture was then heated at 90 °C for 16 h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with ethyl acetate (2 x 100 mL). The combined organic layer was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 10-50% ethyl acetate in hexanes). The resulting compound was further purified by stirring with diethyl ether (25 mL) and *n*-pentane (50 mL), the solids were filtered out and dried under reduced pressure to afford the title compound (**Synthesis Compound 2**) (0.410 g, 76%) as an off-white solid.

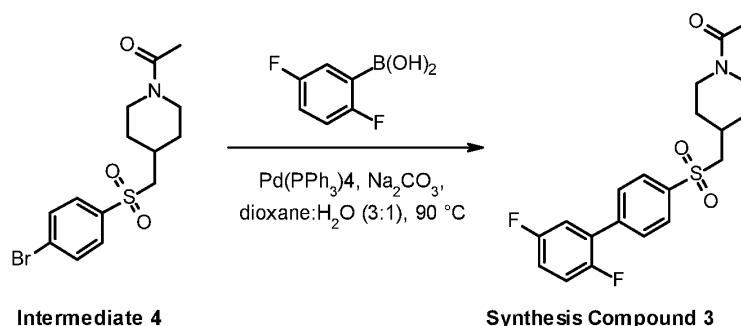
25

Analytical Data:

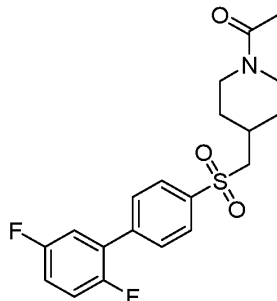
LCMS (ESI) m/z = 393.85 $[M + H]^+$.

HPLC (see generic method): Retention time: 8.06 min.; Purity: 99.22%.

- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.98 (s, 4H), 7.97 – 7.88 (m, 1H), 7.68 – 7.62 (m, 1H), 7.62 – 7.54 (m, 1H), 4.21 (d, J = 13.2 Hz, 1H), 3.72 (d, J = 14.0 Hz, 1H), 3.36 (d, J = 6.4 Hz, 2H), 3.00 (t, J = 11.6 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.10 – 2.00 (m, 1H), 1.94 (s, 3H), 1.84 – 1.70 (m, 2H), 1.30 – 1.19 (m, 1H), 1.19 – 1.05 (m, 1H).

Synthetic Scheme 4Synthesis Compound 3

1-(4-(((2',5'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-03)



- To a reaction tube were added a solution of 1-(4-(((4-bromophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 4** (0.500 g, 1.38 mmol), (2,5-difluorophenyl)boronic acid (0.263 g, 1.66 mmol) and sodium carbonate (0.367 g, 3.46 mmol) in a mixture of 1,4-dioxane: water (3:1, 13 mL). The tube was sealed and degassed by purging with nitrogen for 10 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.159 g, 0.138 mmol) to the reaction mixture under a nitrogen atmosphere and the purging with nitrogen was continued for another 5 min. The reaction mixture was then heated at 90 °C for 16 h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexanes]. After completion of reaction, the reaction mixture was cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with

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ethyl acetate (2 x 100 mL). The combined organic layer was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 10-50% ethyl acetate in hexanes). The obtained compound was further purified by stirring with diethyl ether and *n*-pentane (50 mL), filtered and dried under reduced pressure to afford the title compound (**Synthesis Compound 3**) (0.430 g, 79%) as an off-white solid.

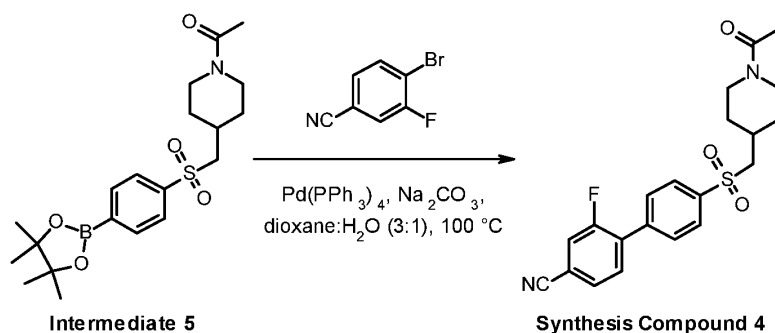
Analytical Data:

LCMS (ESI) m/z = 394.05 $[M + H]^+$.

HPLC (see generic method): Retention time: 7.79 min.; Purity: 99.43%.

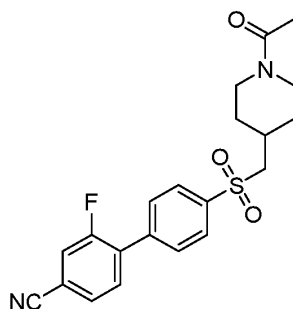
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.02 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 7.2 Hz, 2H), 7.57 – 7.51 (m, 1H), 7.48 – 7.41 (m, 1H), 7.40 – 7.33 (m, 1H), 4.23 (d, J = 12.4 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 3.38 (d, J = 6.0 Hz, 2H), 3.02 (t, J = 11.2 Hz, 1H), 2.57 (t, J = 12.4 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.96 (s, 3H), 1.80 (dd, J = 13.6 & 22.8 Hz, 2H), 1.32 – 1.20 (m, 1H), 1.20 – 1.06 (m, 1H).

Synthetic Scheme 5



Synthesis Compound 4

4'-(((1-Acetylpiperidin-4-yl)methyl)sulfonyl)-2-fluoro-[1,1'-biphenyl]-4-carbonitrile
(NASMP-04)



To a reaction tube were added a solution of 1-(4-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 5** (0.750 g, 1.84 mmol), 4-bromo-3-fluorobenzonitrile (0.405 g, 2.03 mmol) and sodium

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carbonate (0.487 g, 4.60 mmol) in a mixture of 1,4-dioxane-water (3:1, 13 mL). The tube was sealed and degassed by purging with argon for 10 min.

Tetrakis(triphenylphosphine)palladium(0) (0.210 g, 0.180 mmol) was added to the reaction mixture under an argon atmosphere and the purging with argon was continued for 5 min. The reaction mixture was heated at 100 °C for 12 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 0-5% methanol in DCM) to afford the title compound (**Synthesis Compound 4**) (0.210 g, 29%) as a white solid.

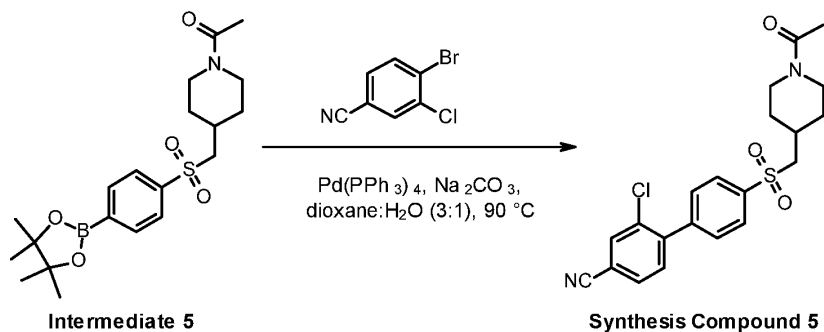
Analytical Data:

LCMS (ESI) m/z = 401.10 $[M + H]^+$.

HPLC (see generic method): Retention time: 7.63 min.; Purity: 99.25%.

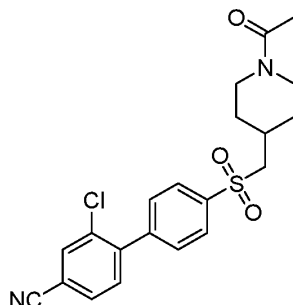
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.08 – 8.03 (m, 3H), 7.91 – 7.81 (m, 4H), 4.23 (d, J = 13.2 Hz, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.39 (d, J = 6.0 Hz, 2H), 3.06 – 2.98 (m, 1H), 2.61 – 2.50 (m, 1H), 2.15 – 2.04 (br m, 1H), 1.96 (s, 3H), 1.87 – 1.73 (m, 2H), 1.31 – 1.20 (m, 1H), 1.20 – 1.07 (m, 1H).

Synthetic Scheme 6



Synthesis Compound 5

4'-(((1-Acetylpiperidin-4-yl)methyl)sulfonyl)-2-chloro-[1,1'-biphenyl]-4-carbonitrile
(NASMP-05)



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To a reaction tube were added a solution of 1-(4-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 5** (0.750 g, 1.84 mmol), 4-bromo-3-chlorobenzonitrile (0.438 g, 2.03 mmol) and sodium carbonate (0.487 g, 4.60 mmol) in a mixture of 1,4-dioxane-water (3:1, 13 mL). The tube

5 was sealed and degassed by purging with argon for 15 min.

Tetrakis(triphenylphosphine)palladium(0) (0.213 g, 0.184 mmol) was added to the reaction mixture under an argon atmosphere and the purging with argon was continued for 10 min. The reaction mixture was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion

10 of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 0-5% methanol in DCM). The product was further purified by preparative HPLC (mobile phase: 0.5% formic acid in a mixture of acetonitrile/water; solid phase: C₁₈ silica) to afford the title compound

15 (**Synthesis Compound 5**) (0.250 g, 32%) as a white solid.

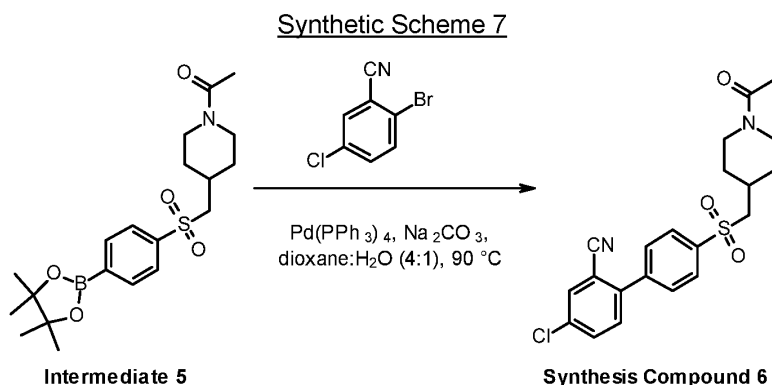
Analytical Data:

LCMS (ESI) m/z = 417.10 [M + H]⁺.

HPLC (see generic method): Retention time: 8.01 min.; Purity: 99.52%.

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.24 (s, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 1H), 4.22 (d, J = 13.6 Hz, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.38 (d, J = 6.0 Hz, 2H), 3.05 – 2.97 (m, 1H), 2.60 – 2.50 (m, 1H), 2.16 – 2.04 (br m, 1H), 1.95 (s, 3H), 1.86 – 1.70 (m, 2H), 1.32 – 1.20 (m, 1H), 1.20 – 1.05 (m, 1H).

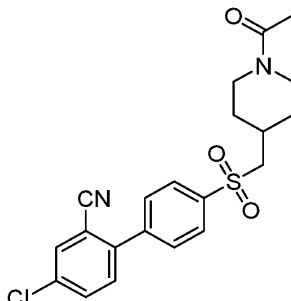
25



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Synthesis Compound 6

4'-(((1-Acetylpiperidin-4-yl)methyl)sulfonyl)-4-chloro-[1,1'-biphenyl]-2-carbonitrile
(NASMP-06)

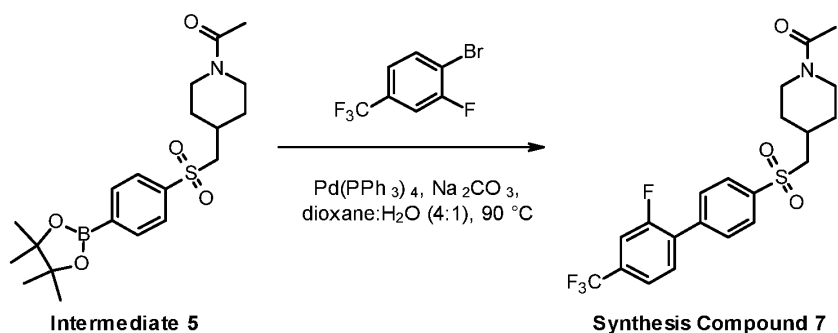


- 5 To a reaction tube were added a solution of 2-bromo-5-chlorobenzonitrile (0.60 g, 2.77 mmol), 1-(4-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 5** (1.35 g, 3.32 mmol) and sodium carbonate (0.68 g, 6.42 mmol) in a mixture of 1,4-dioxane and water (4:1, 15 mL). The tube was sealed and degassed by purging with argon for 15 min, followed by
- 10 addition of tetrakis(triphenylphosphine)palladium(0) (0.32 g, 0.27 mmol) to the reaction mixture under an argon atmosphere and then purged with argon for 5 min. The reaction was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 80% ethyl acetate in hexane]. After completion of the reaction, the mixture was cooled to room temperature, filtered through a pad of celite and the celite pad was
- 15 washed with ethyl acetate (300 mL). The combined filtrates were concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 50% ethyl acetate in hexane then 60% ethyl acetate in DCM) to afford the compound which was stirred in diethyl ether (25 mL). The solids were filtered, washed with diethyl ether (50 mL), pentane (50 mL) and dried under
- 20 reduced pressure to dryness to afford the title compound (**Synthesis Compound 6**) (0.61 g 53%) as an off-white solid.

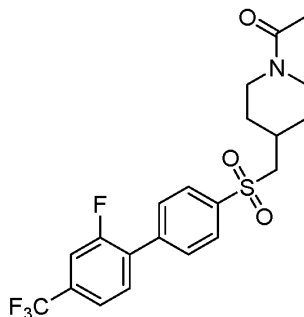
Analytical Data:

- LCMS (ESI) m/z = 416.90 $[M + H]^+$.
- 25 HPLC (see generic method): Retention time: 7.99 min.; Purity: 98.11%.
- ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.23 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.93 (dd, J = 8.4, 2.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.8 Hz, 1H), 4.22 (d, J = 13.2 Hz, 1H), 3.73 (d, J = 13.6 Hz, 1H), 3.41 (d, J = 6.0 Hz, 2H), 3.06 – 2.97 (m, 1H), 2.61 – 2.52 (m, 1H), 2.15 – 2.05 (m, 1H), 1.96 (s, 3H), 1.85 – 1.72 (m, 2H), 1.32 – 1.06 (m, 2H).
- 30

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Synthetic Scheme 8Synthesis Compound 7

- 5 1-(4-(((2'-Fluoro-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-07)



- To a reaction tube were added a solution of 1-bromo-2-fluoro-4-(trifluoromethyl)benzene (0.60 g, 2.47 mmol), 1-(4-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 5** (1.21 g, 2.96 mmol) and sodium carbonate (0.653 g, 6.17 mmol) in a mixture of 1,4-dioxane and water (4:1, 15 mL). The tube was sealed and degassed by purging with argon for 15 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.29 g, 0.25 mmol) to the reaction mixture and then purging with argon for 5 min. The reaction mixture was heated at 90°C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 80% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was filtered through a pad of celite and the celite pad was washed with ethyl acetate (2 x 150 mL). The combined filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 50% ethyl acetate in hexane, then 60% ethyl acetate in DCM) to afford the compound which was stirred in diethyl ether (20 mL) for 15 min. The solids were filtered out and dried under reduced pressure to afford the title compound (**Synthesis Compound 7**) (0.31 g, 28%) as an off-white solid.

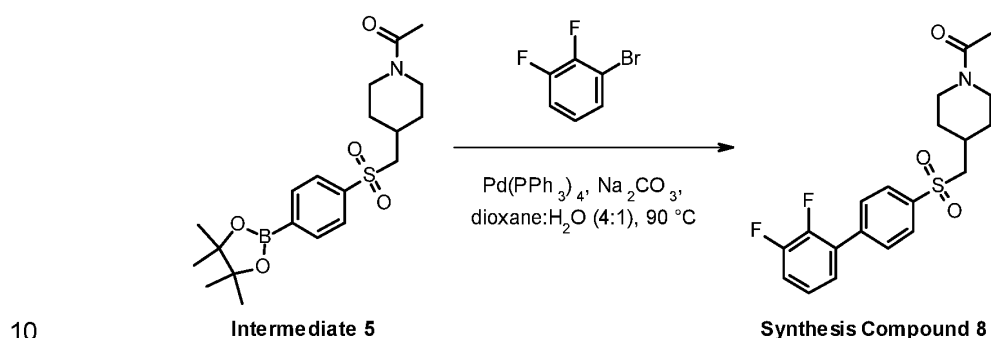
25

Analytical Data:

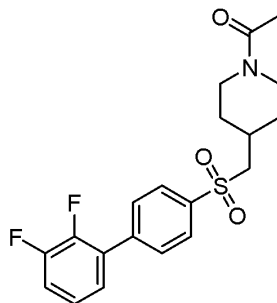
LCMS (ESI) $m/z = 443.90$ $[M + H]^+$.

HPLC (see generic method): Retention time: 8.60 min.; Purity: 99.66%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.06 (d, $J = 8.4$ Hz, 2H), 7.92 – 7.83 (m, 4H), 7.75 (d, $J = 8.0$ Hz, 1H), 4.23 (d, $J = 13.2$ Hz, 1H), 3.74 (d, $J = 13.6$ Hz, 1H), 3.40 (d, $J = 6.0$ Hz, 2H), 3.06 – 2.98 (m, 1H), 2.61 – 2.52 (m, 1H), 2.15 – 2.04 (m, 1H), 1.96 (s, 3H), 1.88 – 1.73 (m, 2H), 1.32 – 1.20 (m, 1H), 1.20 – 1.06 (m, 1H).

Synthetic Scheme 9Synthesis Compound 8

1-(4-(((2,3'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-08)



15 To a reaction tube were added a solution of 1-bromo-2,3-difluorobenzene (0.60 g, 3.11 mmol), 1-(4-(((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 5** (1.52 g, 3.73 mmol) and sodium carbonate (0.82 g, 7.77 mmol) in a mixture of 1,4-dioxane and water (4:1, 15 mL). The tube was sealed and degassed by purging with argon for 30 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.36 g, 0.31 mmol) to the reaction mixture and again purging with argon for 5 min. The reaction mixture was then heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 100% ethyl acetate]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a pad of celite, celite pad was washed with ethyl acetate (50 mL) and the combined filtrate was concentrated under reduced pressure to dryness. The

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crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 0-100% ethyl acetate in hexane) to afford the title compound (**Synthesis Compound 8**) (0.30 g, 25%) as white solid.

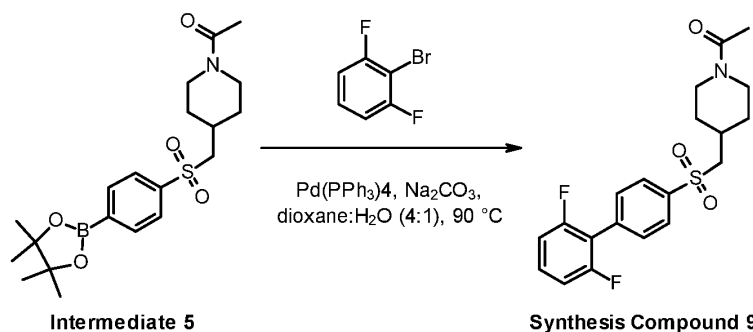
5 Analytical Data:

LCMS (ESI) m/z = 393.95 $[M + H]^+$.

HPLC (see generic method): Retention time: 7.98 min.; Purity: 95.43%.

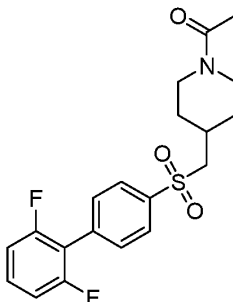
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.01 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 7.2 Hz, 2H), 7.55-7.47 (m, 1H), 7.43 – 7.38 (m, 1H), 7.36 – 7.30 (m, 1H), 4.20 (d, J = 13.2 Hz, 1H), 3.70 (d, J = 13.2 Hz, 1H), 3.35 (d, J = 6.4 Hz, 2H), 3.03 – 2.95 (m, 1H), 2.57 – 2.48 (m, 1H), 2.12 – 2.00 (m, 1H), 1.92 (s, 3H), 1.84 – 1.70 (m, 2H), 1.29 – 1.18 (m, 1H), 1.18 – 1.04 (m, 1H).

Synthetic Scheme 10



Synthesis Compound 9

1-(4-(((2',6'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-09)



To a reaction tube were added a solution of 2-bromo-1,3-difluorobenzene (0.500 g, 2.59 mmol), 1-(4-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 5** (2.109 g, 5.18 mmol) and sodium carbonate (0.686 g, 6.47 mmol) in a mixture of 1,4-dioxane and water (4:1, 50 mL). The tube was sealed and degassed by purging with argon for 10 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.299 g, 0.259 mmol) to the reaction

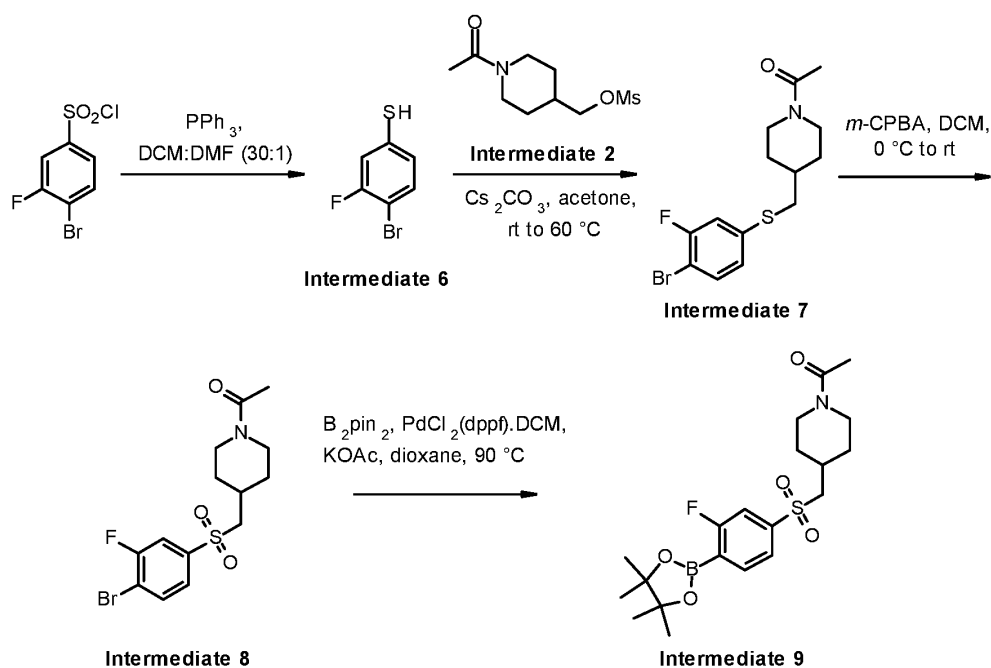
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mixture under an argon atmosphere and the purging with argon was continued for another 5 min. The reaction mixture was then heated at 90 °C for 16 h under an argon atmosphere. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of reaction, the reaction mixture was filtered through
 5 a pad of Celite and the Celite pad was washed with ethyl acetate (2 x 150 mL). The combined filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 100% DCM then 20-50% ethyl acetate in DCM). The obtained compound was further purified by stirring in diethyl ether (20 mL) for 15 min followed by trituration with 10% ethyl acetate in diethyl ether (15 mL). The solids were filtered out and dried under reduced
 10 pressure to afford the title compound (**Synthesis Compound 9**) (0.190 g, 19%) as an off-white solid.

Analytical Data:

15 LCMS (ESI) m/z = 394.00 $[M + H]^+$.
 HPLC (see generic method): Retention time: 7.88 min.; Purity: 98.49%.
 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.04 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.60 – 7.50 (m, 1H), 7.29 (t, J = 8.4 Hz, 2H), 4.23 (d, J = 12.4 Hz, 1H), 3.75 (d, J = 13.2 Hz, 1H), 3.39 (d, J = 6.4 Hz, 2H), 3.03 (t, J = 11.2 Hz, 1H), 2.58 (t, J = 11.6 Hz,
 20 1H), 2.17 – 2.04 (m, 1H), 1.96 (s, 3H), 1.80 (dd, J = 12.4 & 25.2 Hz, 2H), 1.32 – 1.20 (m, 1H), 1.20 – 1.06 (m, 1H).

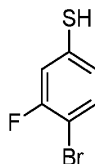
Synthetic Scheme 11



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Intermediate 6

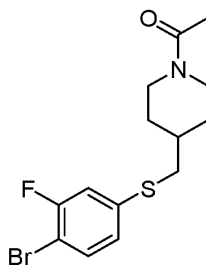
4-Bromo-3-fluorobenzenethiol



To a solution of triphenylphosphine (8.63 g, 32.91 mmol) in DCM (30 mL) and DMF (1 mL), 4-bromo-3-fluorobenzenesulfonyl chloride (3.00 g, 10.97 mmol) was added dropwise at room temperature. The reaction was stirred for 16 h at room temperature. The progress of the reaction was monitored by TLC [mobile phase: 10% ethyl acetate in hexane]. After completion of the reaction, 1 M aqueous HCl (50 mL) was added to the reaction mixture and the layers were separated. The organic layer was concentrated under reduced pressure to dryness. The residue was taken in 1 M aqueous NaOH (50 mL) and the mixture was filtered through a pad of celite. The filtrate was washed with diethyl ether (3 x 50 mL), neutralized with 1 M aqueous HCl (60 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 6** (1.41 g, crude) as colorless oil. This compound was used in the next step without further purification.

Intermediate 7

1-(4-(((4-Bromo-3-fluorophenyl)thio)methyl)piperidin-1-yl)ethan-1-one



To a solution of 4-bromo-3-fluorobenzenethiol **Intermediate 6** (1.30 g, 6.31 mmol) in acetone (40 mL), caesium carbonate (3.73 g, 11.46 mmol) was added under an argon atmosphere at room temperature and the reaction mixture was stirred for 30 min. To the resulting reaction mixture, (1-acetylpiperidin-4-yl)methyl methanesulfonate **Intermediate 2** (1.35 g, 5.73 mmol) was added at room temperature. The reaction mixture was then heated at 60 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a pad of celite and the filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 10-50% ethyl acetate in

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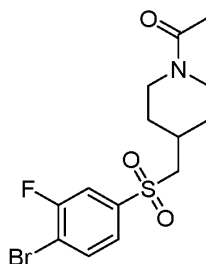
hexane) to afford the title compound **Intermediate 7** (1.63 g, 82%) as pale yellow thick oil.

Analytical Data:

5 LCMS (ESI) m/z = 348.05 $[M + H]^+$ (^{81}Br).

Intermediate 8

1-(4-(((4-Bromo-3-fluorophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one



- 10 To a solution of 1-(4-(((4-bromo-3-fluorophenyl)thio)methyl)piperidin-1-yl)ethan-1-one **Intermediate 7** (1.60 g, 4.62 mmol) in DCM (40 mL), *meta*-chloroperbenzoic acid (60%) (3.98 g, 13.86 mmol) was added in portions at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 5% Methanol in DCM]. After completion of the reaction, the reaction
- 15 mixture was quenched with saturated aqueous sodium thiosulfate (25 mL), the layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 8** (1.63 g, crude) as an off-white solid. This compound was used
- 20 in the next step without further purification.

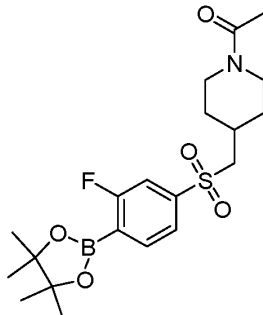
Analytical Data:

LCMS (ESI) m/z = 377.80 $[M + H]^+$ (^{79}Br).

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Intermediate 9

1-(4-(((3-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one

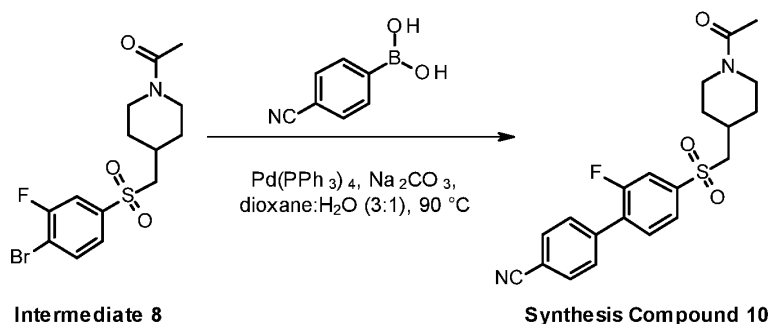


- 5 A reaction tube was charged with a solution of 1-(4-(((4-bromo-3-fluorophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 8** (1.60 g, 4.23 mmol), bis(pinacolato)diborane (1.29 g, 5.07 mmol) and potassium acetate (1.25 g, 12.69 mmol) in 1,4-dioxane (25 mL). The tube was sealed and degassed by purging with nitrogen gas for 15 min followed by addition of 1,1'-bis(diphenylphosphino)ferrocene-palladium (II)
- 10 dichloride, DCM complex (0.104 g, 0.126 mmol) to the reaction mixture under a nitrogen atmosphere and the purging with nitrogen was continued for another 5 min. The reaction mixture was then heated to 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a celite pad and washed with
- 15 ethyl acetate (75 mL). The combined filtrates were concentrated under reduced pressure to dryness. The residue obtained was stirred in pentane (2 x 25 mL), the solvents were decanted and the solids were dried under reduced pressure to dryness to afford the title compound **Intermediate 9** (3.01 g, crude) as dark brown solid. This compound was used in the next step without further purification.

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Analytical Data:

LCMS (ESI) $m/z = 343.90$ $[M + H]^+$ (corresponding boronic acid).

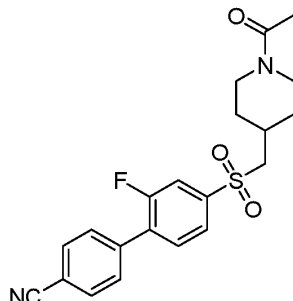
Synthetic Scheme 12

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Synthesis Compound 10

4'-(((1-Acetylpiperidin-4-yl)methyl)sulfonyl)-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile
(NASMP-10)

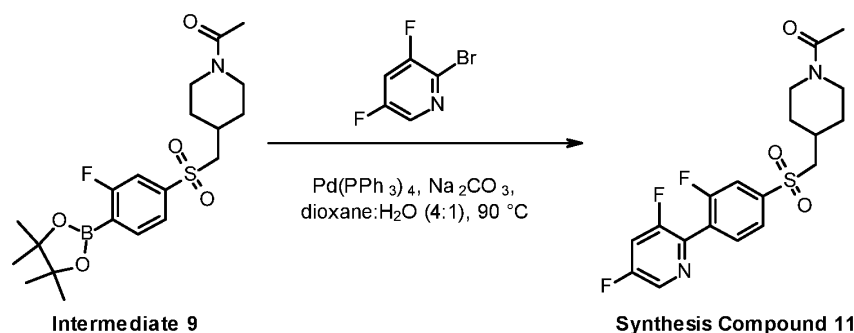


- 5 To a reaction tube were added a solution of 1-(4-(((4-bromo-3-fluorophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 8** (1.00 g, 2.64 mmol), (4-cyanophenyl)boronic acid (0.427 g, 2.91 mmol) and sodium carbonate (0.700 g, 6.61 mmol) in a mixture of 1,4-dioxane-water (3:1, 13 mL). The tube was sealed and degassed by purging with argon for 10 min. Tetrakis(triphenylphosphine)palladium(0) (0.306 g, 0.264 mmol) was added to the reaction mixture under an argon atmosphere and the purging with argon was continued for 10 min. The reaction mixture was heated at 90 °C for 12 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 0-10% methanol in DCM) to afford the title compound (**Synthesis Compound 10**) (0.450 g, 43%) as a white solid.

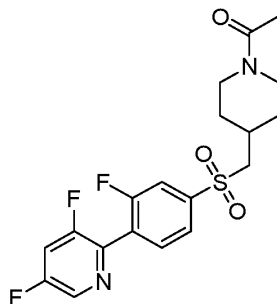
Analytical Data:

- 20 LCMS (ESI) m/z = 401.05 $[M + H]^+$.
HPLC (see generic method): Retention time: 7.86 min.; Purity: 98.37%.
 ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.01 (d, J = 8.4 Hz, 2H), 7.96 – 7.86 (m, 3H), 7.84 (d, J = 7.2 Hz, 2H), 4.23 (d, J = 12.8 Hz, 1H), 3.74 (d, J = 13.6 Hz, 1H), 3.45 (d, J = 6.4 Hz, 2H), 3.07 – 2.98 (m, 1H), 2.62 – 2.52 (m, 1H), 2.15 – 2.04 (br m, 1H), 1.96 (s, 3H), 1.88 – 1.73 (m, 2H), 1.32 – 1.20 (m, 1H), 1.20 – 1.08 (m, 1H).

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Synthetic Scheme 13Synthesis Compound 11

- 5 1-(4-(((4-(3,5-Difluoropyridin-2-yl)-3-fluorophenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-11)



- To a reaction tube were added a solution of 2-bromo-3,5-difluoropyridine (0.60 g, 3.09 mmol), 1-(4-(((3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 9** (1.45 g, 3.40 mmol) and sodium carbonate (0.76 g, 7.17 mmol) in a mixture of 1,4-dioxane-water (4:1, 15 mL). The tube was sealed and degassed by purging with argon gas for 15 min followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.36 g, 0.30 mmol) to the reaction mixture under an argon atmosphere and the purging with argon was continued for another 5 min. The reaction mixture was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 70% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a pad of celite and the celite pad was washed with ethyl acetate (2 x 150 mL). The combined organic layers were concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 50-100% ethyl acetate in hexane). The compound was triturated with diethyl ether (25 mL), the solids were filtered out and dried. The compound was further purified by preparative HPLC (mobile phase: 0.5% formic acid in a mixture of acetonitrile/water; solid phase: C₁₈ silica). The product obtained was dissolved with saturated aqueous sodium bicarbonate (25 mL) and extracted with DCM (3 x 50 mL). The combined organic

layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound (**Synthesis Compound 11**) (0.39 g, 31%) as an off-white solid.

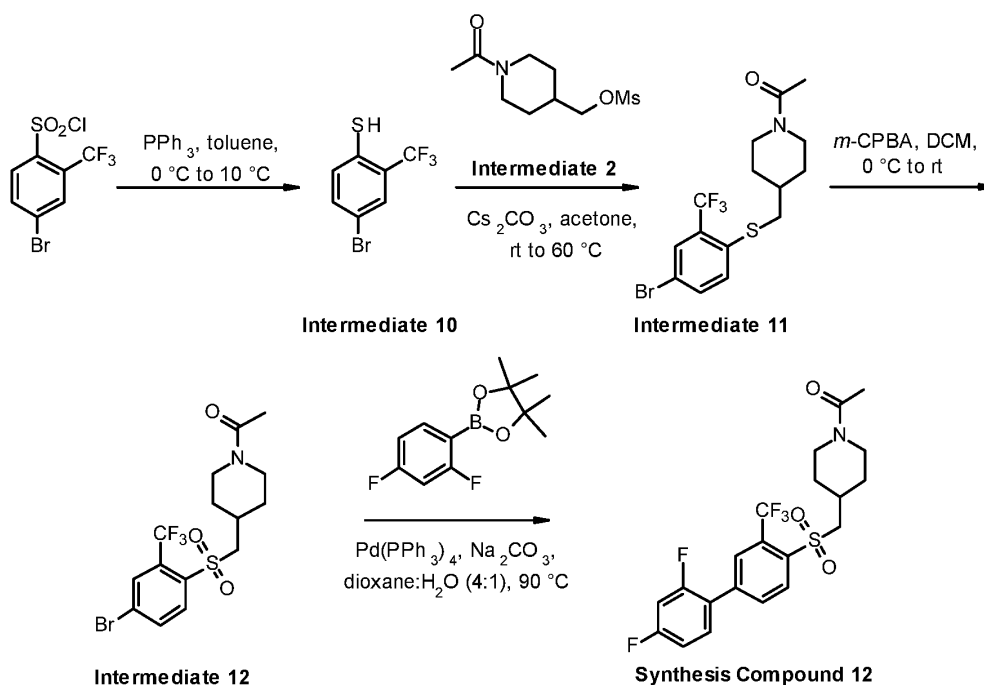
5 Analytical Data:

LCMS (ESI) m/z = 412.90 $[M + H]^+$.

HPLC (see generic method): Retention time: 7.43 min.; Purity: 97.73%.

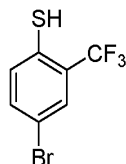
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.71 (d, J = 2.0 Hz, 1H), 8.19 – 8.14 (m, 1H), 7.95 – 7.86 (m, 3H), 4.20 (d, J = 13.2 Hz, 1H), 3.71 (d, J = 13.6 Hz, 1H), 3.44 (d, J = 6.4 Hz, 2H), 3.04 – 2.92 (m, 1H), 2.60 – 2.50 (m, 1H), 2.21 – 2.02 (m, 1H), 1.93 (s, 3H), 1.83 – 1.70 (m, 2H), 1.30 – 1.05 (m, 2H).

Synthetic Scheme 14



Intermediate 10

4-Bromo-2-(trifluoromethyl)benzenethiol



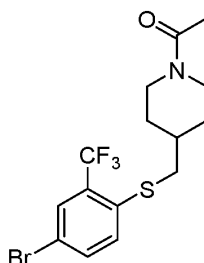
To a stirred solution of 4-bromo-2-(trifluoromethyl)benzenesulfonyl chloride (4.00 g, 12.36 mmol) in toluene (20 mL), a solution of triphenylphosphine (9.72 g, 37.09 mmol) in toluene (8 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 5 °C to

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10 °C for 45 min. The progress of the reaction was monitored by TLC [mobile phase, 25% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was quenched with water (8 mL), the precipitate obtained was filtered and the filtrate was taken into a separating funnel. Then, 1N aqueous KOH (20 mL) was added to the filtrate, three layers were observed, and the upper layer was discarded. The remaining layers were extracted with toluene (2 x 50 mL) and the toluene layer discarded. The aqueous layer was acidified to pH ~3 with citric acid and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 10** (3.00 g, crude) as brown liquid. This compound was used in the next step without further purification.

Intermediate 11

1-(4-(((4-Bromo-2-(trifluoromethyl)phenyl)thio)methyl)piperidin-1-yl)ethan-1-one



To a stirred solution of 4-bromo-2-(trifluoromethyl)benzenethiol **Intermediate 10** (3.00 g, 11.68 mmol) in acetone (20 mL), caesium carbonate (6.92 g, 21.24 mmol) and a solution of (1-acetylpiperidin-4-yl)methyl methanesulfonate **Intermediate 2** (2.50 g, 10.62 mmol) in acetone (5 mL) were added at room temperature. The reaction mixture was then heated at 60 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 70% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a pad of celite and the filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200, gradient 0-70% ethyl acetate in hexane) to afford the title compound **Intermediate 11** (3.50 g 83%) as yellow oil.

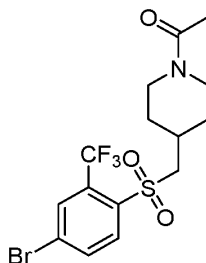
Analytical data:

LCMS (ESI): m/z = 398.15 $[M + H]^+$ (^{81}Br).

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Intermediate 12

1-(4-(((4-Bromo-2-(trifluoromethyl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one

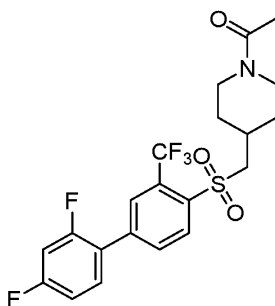


To a stirred solution of 1-(4-(((4-bromo-2-(trifluoromethyl)phenyl)thio)methyl)piperidin-1-yl)ethan-1-one **Intermediate 11** (3.50 g, 8.83 mmol) in DCM (35 mL), *meta*-chloroperbenzoic acid (60%) (4.57 g, 26.49 mmol) was added in portions at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 80% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was quenched with saturated aqueous sodium thiosulfate and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 12** (3.00 g) as yellow oil. This compound was used in the next step without further purification.

Analytical Data:

LCMS (ESI): $m/z = 429.85$ $[M + H]^+$ (^{81}Br).Synthesis Compound 12

1-(4-(((2',4'-Difluoro-3-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(**NASMP-12**)



To a reaction tube were added a solution of 1-(4-(((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 12** (1.00 g, 2.33 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.67 g, 2.80 mmol) and sodium carbonate (0.61 g, 5.83 mmol) in a mixture of 1,4-dioxane and water (4:1, 15 mL). The tube was sealed and degassed by purging with argon for 15 min, followed by addition of

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tetrakis(triphenylphosphine)palladium(0) (0.27 g, 0.23 mmol) to the reaction mixture and again purging with argon for 5 min. The reaction mixture was then heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 70% ethyl acetate in hexane]. After completion of reaction, the reaction mixture was cooled to room temperature and filtered through a pad of celite and the pad of celite was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 0-100% ethyl acetate in hexane) to afford the title compound (**Synthesis Compound 12**) (0.24 g, 22%) as white sticky solid.

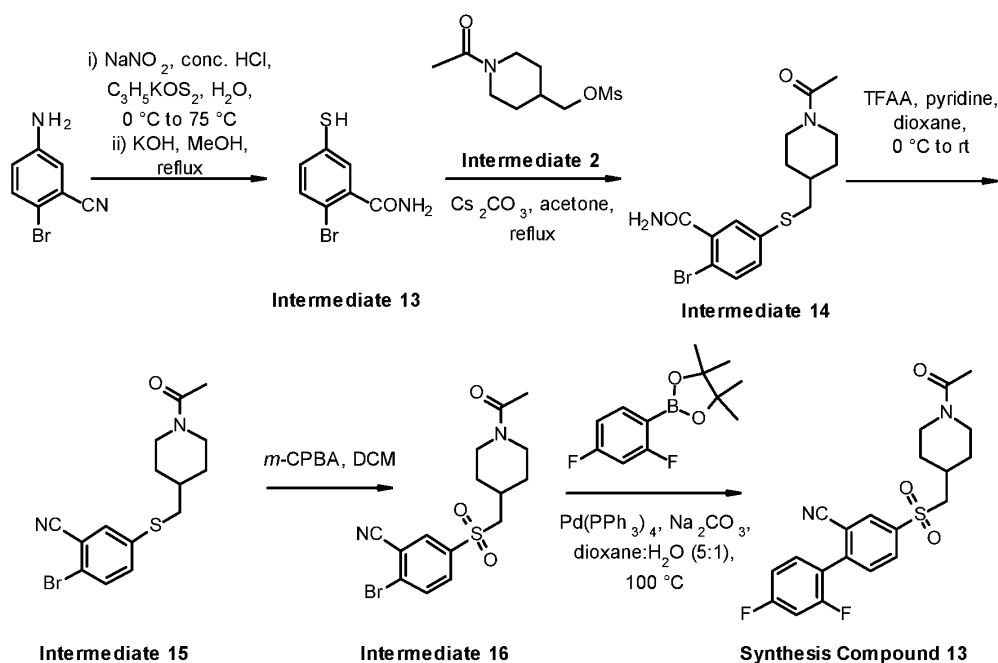
Analytical Data:

LCMS (ESI) m/z = 461.90 $[M + H]^+$.

HPLC (see generic method): Retention time: 8.65 min.; Purity: 98.14%.

^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.31 (d, J = 8.8 Hz, 1H), 8.15 (s, 2H), 7.83 – 7.75 (m, 1H), 7.53 – 7.46 (m, 1H), 7.33 – 7.27 (m, 1H), 4.26 (d, J = 13.2 Hz, 1H), 3.75 (d, J = 13.2 Hz, 1H), 3.40 (d, J = 6.4 Hz, 2H), 3.10 – 3.00 (m, 1H), 2.62 – 2.52 (m, 1H), 2.30 – 2.20 (m, 1H), 1.96 (s, 3H), 1.90 – 1.75 (m, 2H), 1.35 – 1.10 (m, 2H).

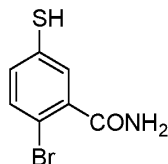
Synthetic Scheme 15



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Intermediate 13

2-Bromo-5-mercaptobenzamide



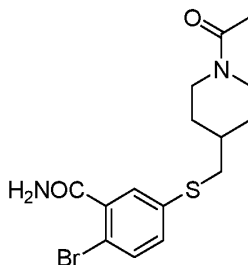
- 5-Amino-2-bromobenzonitrile (2.00 g, 10.15 mmol) was dissolved in conc. HCl (4 mL) and cooled in an ice-bath to 0 °C. A solution of NaNO₂ (0.728 g, 10.55 mmol) in water (6 mL) was added dropwise to the reaction mixture over a period of 10 min. Then, the cold diazonium salt solution was added to a solution of potassium O-ethyl xanthate (3.31 g, 20.30 mmol) in water (6 mL). The reaction mixture was then warmed to room temperature and the mixture was heated at 75 °C for 3 h. The reaction mixture was cooled to 0 °C and basified with saturated aqueous NaHCO₃ to pH 8. The mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was dissolved in methanol (70 mL) and to this was added freshly ground KOH pellets (2.84 g, 50.75 mmol). The reaction mixture was heated at reflux for 17 h under an argon atmosphere. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (40 mL) was added to the residue obtained and the resulting mixture was washed with diethyl ether (50 mL). The aqueous layer was acidified to pH 1-2 by the dropwise addition of 3N H₂SO₄ and extracted with DCM (3 x 50 mL). The combined organic layer was washed with water (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 13** (1.20 g, crude) as yellow oil. This compound was used in the next step without further purification.

Analytical Data:

- LCMS (ESI) m/z = 233.85 [M + H]⁺ (⁸¹Br).

Intermediate 14

5-(((1-Acetylpiperidin-4-yl)methyl)thio)-2-bromobenzamide



- To a stirred solution of 2-bromo-5-mercaptobenzamide **Intermediate 13** (1.10 g, 4.74 mmol) and (1-acetylpiperidin-4-yl)methyl methanesulfonate **Intermediate 2** (1.12 g, 4.74

- 108 -

mmol) in acetone (30 mL), caesium carbonate (1.85 g, 5.69 mmol) was added at room temperature. The reaction mixture was heated at reflux for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water (60 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-50% ethyl acetate in hexane) to afford the title compound **Intermediate 14** (1.55 g, 88%) as brown solid.

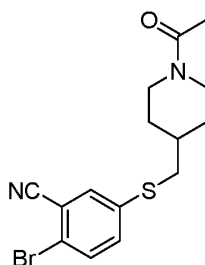
Analytical Data:

LCMS (ESI) m/z = 370.95 $[M + H]^+$ (^{79}Br).

15

Intermediate 15

5-(((1-Acetylpiperidin-4-yl)methyl)thio)-2-bromobenzonitrile



To a stirred solution of 5-(((1-acetylpiperidin-4-yl)methyl)thio)-2-bromobenzonitrile **Intermediate 14** (1.50 g, 4.04 mmol) and pyridine (0.652 mL, 8.08 mmol) in 1,4-dioxane (30 mL), TFAA (0.626 mL, 4.44 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The progress of the reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was quenched with water (60 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-50% ethyl acetate in hexane) to afford the title compound **Intermediate 15** (1.35 g, 95%) as pale yellow thick oil.

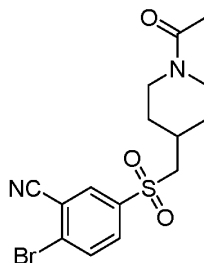
30 Analytical Data:

LCMS (ESI) m/z = 352.95 $[M + H]^+$ (^{79}Br).

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Intermediate 16

5-(((1-Acetylpiperidin-4-yl)methyl)sulfonyl)-2-bromobenzonitrile



To a stirred solution of 5-(((1-acetylpiperidin-4-yl)methyl)thio)-2-bromobenzonitrile

- 5 **Intermediate 15** (1.30 g, 3.69 mmol) in DCM (30 mL), *meta*-chloroperbenzoic acid (55%) (3.47 g, 11.07 mmol) was added in portions at room temperature. The reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was diluted with DCM (70 mL), washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-60% ethyl acetate in hexane) to afford the title compound **Intermediate 16** (1.20 g, 84%) as brown thick oil.

15

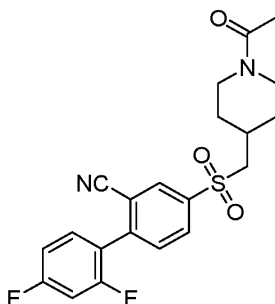
Analytical Data:

- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.44 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.07 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.19 (d, *J* = 13.2 Hz, 1H), 3.69 (d, *J* = 13.6 Hz, 1H), 3.41 (d, *J* = 6.8 Hz, 2H), 3.03 – 2.94 (m, 1H), 2.58 – 2.48 (m, 1H), 2.08 – 1.95 (m, 1H), 1.92 (s, 3H), 1.79 – 1.67 (m, 2H), 1.25 – 1.01 (m, 2H).

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Synthesis Compound 13

4-(((1-Acetylpiperidin-4-yl)methyl)sulfonyl)-2',4'-difluoro-[1,1'-biphenyl]-2-carbonitrile
(NASMP-13)



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To a reaction tube were added a solution of 5-(((1-acetylpiperidin-4-yl)methyl)sulfonyl)-2-bromobenzonitrile **Intermediate 16** (1.20 g, 3.11 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.897 g, 3.73 mmol) and sodium carbonate (0.825 g,

7.78 mmol) in a mixture of 1,4-dioxane: water (5:1, 24 mL). The tube was sealed and degassed by purging with nitrogen for 15 min followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.36 g, 0.30 mmol) under a nitrogen atmosphere and the purging with nitrogen was continued for 5 min. The reaction mixture was heated at 100 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-60% ethyl acetate in hexane) to afford the title compound (**Synthesis Compound 13**) (0.40 g, 31%) as a white solid.

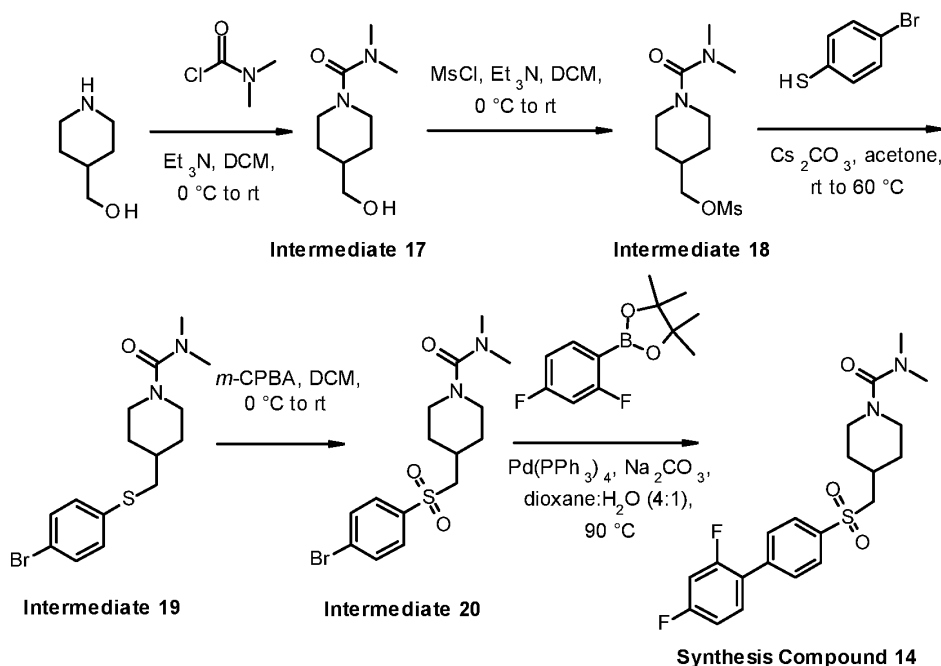
Analytical Data:

LCMS (ESI): $m/z = 419.04$ $[M + H]^+$.

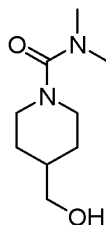
HPLC (see generic method): Retention time: 7.87 min.; Purity: 98.52%.

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.51 (d, $J = 1.6$ Hz, 1H), 8.26 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.70 – 7.62 (m, 1H), 7.56 – 7.48 (m, 1H), 7.34 – 7.28 (m, 1H), 4.20 (d, $J = 14.0$ Hz, 1H), 3.71 (d, $J = 13.6$ Hz, 1H), 3.47 (d, $J = 6.8$ Hz, 2H), 3.06 – 2.96 (m, 1H), 2.64 – 2.52 (m, 1H), 2.16 – 2.05 (m, 1H), 1.93 (s, 3H), 1.85 – 1.70 (m, 2H), 1.30 – 1.19 (m, 1H), 1.17 – 1.05 (m, 1H).

Synthetic Scheme 16



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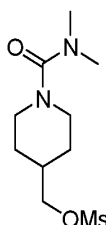
Intermediate 174-(Hydroxymethyl)-*N,N*-dimethylpiperidine-1-carboxamide

To a stirred solution of piperidin-4-ylmethanol (5.00 g, 43.41 mmol) in DCM (50 mL), triethylamine (12.70 mL, 91.16 mmol) was added and the reaction mixture was stirred for 15 min. To the reaction mixture, dimethylcarbamoyl chloride (4.19 mL, 45.50 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was quenched with the addition of ice-water (50 mL) and extracted with DCM (2 x 150 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 17** (5.05 g, crude) as colorless thick oil. This compound was used in the next step without further purification.

Analytical Data:

LCMS (ESI) m/z = 186.95 $[M + H]^+$.Intermediate 18

(1-(Dimethylcarbamoyl)piperidin-4-yl)methyl methanesulfonate



To a stirred solution of 4-(hydroxymethyl)-*N,N*-dimethylpiperidine-1-carboxamide **Intermediate 17** (5.00 g, 26.84 mmol) in DCM (50 mL) cooled at 0 °C was added triethylamine (7.48 mL, 53.68 mmol) followed by the addition of methanesulfonyl chloride (2.28 mL, 29.52 mmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was quenched with water (50 mL), the layers were separated and the organic layer was washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title

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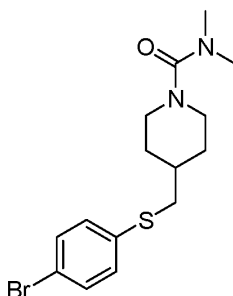
compound **Intermediate 18** (4.54 g, crude) as colorless thick oil. This compound was used in the next step without further purification.

Analytical Data:

5 LCMS (ESI) m/z = 265.20 $[M + H]^+$.

Intermediate 19

4-(((4-Bromophenyl)thio)methyl)-*N,N*-dimethylpiperidine-1-carboxamide



- 10 To a stirred solution of 4-bromobenzenethiol (3.14 g, 16.64 mmol) in acetone (70 mL) was added caesium carbonate (9.85 g, 30.26 mmol) under an argon atmosphere and the reaction mixture was stirred at room temperature for 30 min. To the resulting mixture, (1-(dimethylcarbamoyl)piperidin-4-yl)methyl methanesulfonate **Intermediate 18** (4.00 g, 15.13 mmol) was added and the reaction mixture was heated to 60 °C for 16 h. The
- 15 progress of the reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 50-100% Ethyl acetate in hexane) to afford the title compound **Intermediate 19** (3.20 g, 59%) as white solid.
- 20

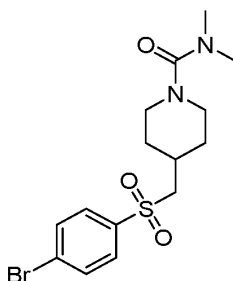
Analytical Data:

LCMS (ESI) m/z = 359.05 $[M + H]^+$ (^{81}Br).

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Intermediate 20

4-(((4-Bromophenyl)sulfonyl)methyl)-*N,N*-dimethylpiperidine-1-carboxamide



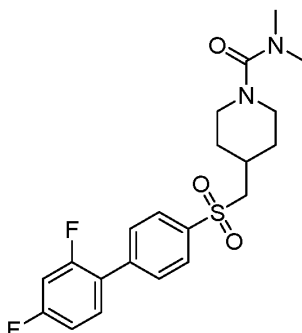
- 113 -

To a stirred solution of 4-(((4-bromophenyl)thio)methyl)-*N,N*-dimethylpiperidine-1-carboxamide **Intermediate 19** (3.10 g, 8.67 mmol) in DCM (50 mL) was added *meta*-chloroperbenzoic acid (60%) (7.48 g, 26.02 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was quenched with saturated aqueous sodium thiosulfate (50 mL), the layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 20** (3.00 g, crude) as an off-white solid. This compound was used in the next step without further purification.

Analytical Data:

LCMS (ESI) m/z = 388.90 $[M + H]^+$ (^{79}Br).Synthesis Compound 14

4-(((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)-*N,N*-dimethylpiperidine-1-carboxamide
(NASMP-14)



To a reaction tube were added a solution of 4-(((4-bromophenyl)sulfonyl)methyl)-*N,N*-dimethylpiperidine-1-carboxamide **Intermediate 20** (1.00 g, 2.56 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.678 g, 2.82 mmol) and sodium carbonate (0.629 g, 5.93 mmol) in a mixture of 1,4-dioxane and water (4:1, 15 mL). The tube was sealed and degassed with argon for 15 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.296 g, 0.25 mmol) under an argon atmosphere and the purging with argon was continued for 5 min. The reaction mixture was then heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was filtered through a pad of celite and the celite pad was washed with ethyl acetate (2 x 150 mL). The combined filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 50-100% ethyl acetate in hexanes) to afford the compound which

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was stirred in diethyl ether (25 mL) for 15 min. The solids were filtered, washed with diethyl ether (15 mL) and pentane (15 mL), and dried under reduced pressure to afford the title compound (**Synthesis Compound 14**) (0.69 g, 64%) as an off-white solid.

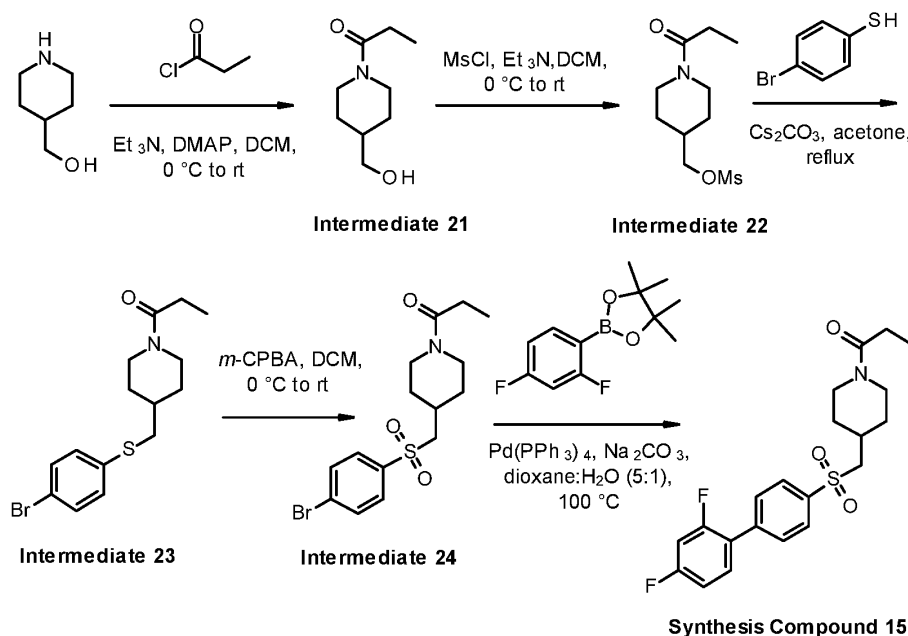
5 Analytical Data:

LCMS (ESI) m/z = 422.95 $[M + H]^+$.

HPLC (see generic method): Retention time: 8.33 min.; Purity: 99.26%.

^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.01 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 7.2 Hz, 2H), 7.72 – 7.58 (m, 1H), 7.48 – 7.41 (m, 1H), 7.29 – 7.23 (m, 1H), 3.46 (d, J = 13.2 Hz, 2H), 3.36 (d, J = 6.4 Hz, 2H), 2.69 (s, 6H), 2.72 – 2.62 (m, 2H), 2.08 – 1.94 (m, 1H), 1.77 (d, J = 12.0 Hz, 2H), 1.32 – 1.20 (m, 2H).

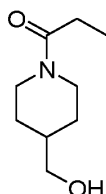
Synthetic Scheme 17



15

Intermediate 21

1-(4-(Hydroxymethyl)piperidin-1-yl)propan-1-one



To a stirred solution of piperidin-4-ylmethanol (5.00 g, 43.41 mmol) in DCM (60 mL), triethylamine (7.87 mL, 56.43 mmol) and DMAP (1.06 g, 8.68 mmol) were added and the reaction mixture was cooled in an ice-bath to 0 °C. To the reaction mixture was then

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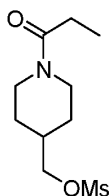
- 115 -

added propionyl chloride (4.17 mL, 47.75 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC [mobile phase: 10% methanol in DCM]. After completion of the reaction, the reaction mixture was diluted with water (100 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 21** (4.25 g, crude) as colourless oil. This compound was used in the next step without further purification.

10 Analytical Data:

LCMS (ESI) m/z = 172.00 $[M + H]^+$.Intermediate 22

(1-Propionylpiperidin-4-yl)methyl methanesulfonate



15

To a stirred solution of 1-(4-(hydroxymethyl)piperidin-1-yl)propan-1-one **Intermediate 21** (4.20 g, 24.53 mmol) in DCM (50 mL), triethylamine (4.44 mL, 31.88 mmol) followed by methanesulfonyl chloride (2.28 mL, 29.43 mmol) were added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was diluted with water (70 mL) and extracted with DCM (2 x 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 22** (4.41 g, crude) as brown oil. This compound was used in the next step without further purification.

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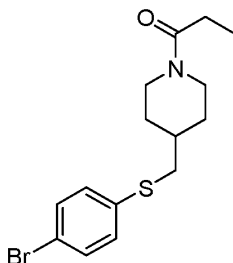
Analytical Data:

LCMS (ESI) m/z = 250.10 $[M + H]^+$.

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Intermediate 23

1-(4-(((4-Bromophenyl)thio)methyl)piperidin-1-yl)propan-1-one



To a stirred solution of (1-propionylpiperidin-4-yl)methyl methanesulfonate **Intermediate**
 5 **22** (4.30 g, 17.25 mmol) and 4-bromobenzenethiol (3.59 g, 18.97 mmol) in acetone (60 mL), caesium carbonate (6.74 g, 20.70 mmol) was added at room temperature. The reaction mixture was heated at reflux for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under
 10 reduced pressure to dryness. Water (80 mL) was added to the residue obtained and the resulting mixture was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-60% ethyl acetate in
 15 hexanes) to afford the title compound **Intermediate 23** (4.85 g, 82%) as sticky yellow oil.

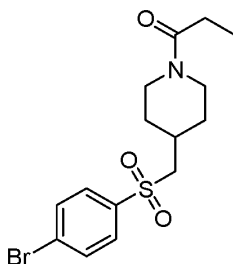
Analytical Data:

LCMS (ESI) m/z = 344.15 $[M + H]^+$ (^{81}Br).

20

Intermediate 24

1-(4-(((4-Bromophenyl)sulfonyl)methyl)piperidin-1-yl)propan-1-one



To a stirred solution of 1-(4-(((4-bromophenyl)thio)methyl)piperidin-1-yl)propan-1-one
Intermediate 23 (4.80 g, 14.02 mmol) in DCM (60 mL), *meta*-chloroperbenzoic acid
 25 (55%) (13.24 g, 42.21 mmol) was added in portions at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 80% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was diluted with DCM (100 mL), washed with saturated aqueous sodium bicarbonate (100 mL) and brine (50 mL). The organic layer was dried

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over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-80% ethyl acetate in hexanes) to afford the title compound

Intermediate 24 (4.30 g, 82%) as yellow thick oil.

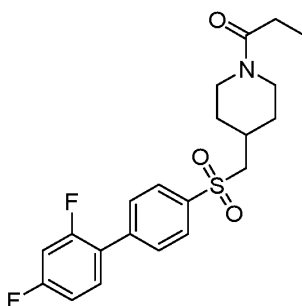
5

Analytical Data:

LCMS (ESI) m/z = 374.10 $[M + H]^+$ (^{79}Br).

Synthesis Compound 15

10 1-(4-(((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)propan-1-one
(NASMP-15)



To a reaction tube were added a solution of 1-(4-(((4-bromophenyl)sulfonyl)methyl)piperidin-1-yl)propan-1-one **Intermediate 24** (1.60 g, 4.27 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.23 g, 5.13 mmol) and sodium carbonate (1.13 g, 10.72 mmol) in a mixture of 1,4-dioxane-water (5:1, 30 mL). The tube was sealed and degassed by purging with argon for 15 min.

Tetrakis(triphenylphosphine)palladium(0) (0.495 g, 0.427 mmol) was added to the reaction mixture under an argon atmosphere and then purging with argon for 5 min. The reaction mixture was heated at 100 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-70% ethyl acetate in hexanes) to afford the title compound (**Synthesis Compound 15**) (0.73 g, 42%) as white solid.

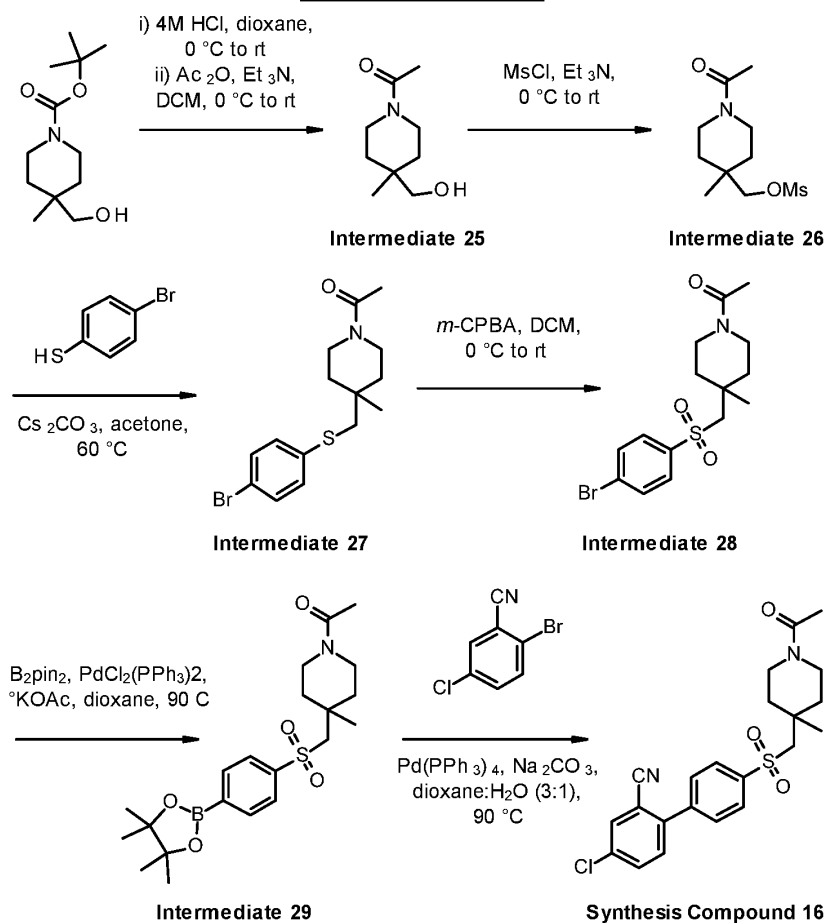
Analytical data:

LCMS (ESI): m/z = 408.10 $[M + H]^+$.

HPLC (see generic method): Retention time: 8.40 min.; Purity: 99.03%.

^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.01 (d, J = 8.4 Hz, 2H), 7.82 (dd, J = 7.6, 0.8 Hz, 2H), 7.72 – 7.65 (m, 1H), 7.48 – 7.46 (m, 1H), 7.29 – 7.23 (m, 1H), 4.25 (d, J = 12.4 Hz, 1H), 3.78 (d, J = 14.0 Hz, 1H), 3.36 (d, J = 6.4 Hz, 2H), 2.99 (t, J = 11.6 Hz, 1H), 2.58 (t, J = 13.2 Hz, 1H), 2.27 (q, J = 7.6 Hz, 2H), 2.14 – 2.02 (m, 1H), 1.87 – 1.73 (m, 2H), 1.30 – 1.06 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H).

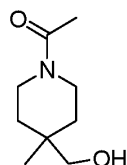
30

Synthetic Scheme 18

5

Intermediate 25

1-(4-(Hydroxymethyl)-4-methylpiperidin-1-yl)ethan-1-one



- To a stirred solution of *tert*-butyl 4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate (2.50 g, 10.90 mmol) in 1,4-dioxane (25 mL), 4 M HCl in 1,4-dioxane (15 mL) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to dryness to afford a white solid (1.90 g, crude). To a stirred solution of the crude compound in DCM (40 mL), triethylamine (6.40 mL, 45.84 mmol) followed by acetic anhydride (1.20 mL, 12.61 mmol) were added at 0 °C. The reaction mixture was warmed

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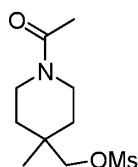
- to room temperature and stirred for 5 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 25** (1.59 g, crude) as yellow oil. This compound was used in the next step without further purification.

Analytical Data:

- LCMS (ESI) m/z = 171.90 $[M + H]^+$.

Intermediate 26

(1-Acetyl-4-methylpiperidin-4-yl)methyl methanesulfonate

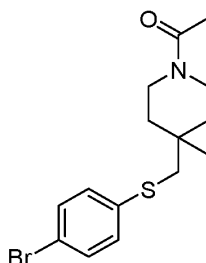


- To a stirred solution of 1-(4-(hydroxymethyl)-4-methylpiperidin-1-yl)ethan-1-one **Intermediate 25** (1.59 g, 9.28 mmol) in DCM (15 mL) was added triethylamine (2.58 mL, 18.57 mmol) followed by methanesulfonyl chloride (0.79 mL, 10.21 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in DCM]. After completion of the reaction, the reaction mixture was diluted with DCM (50 mL), washed with water (50 mL) and brine (25 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 26** (1.88 g, crude) as a yellow oil. This compound was used in the next step without further purification.

Analytical Data:

LCMS (ESI) m/z = 250.00 $[M + H]^+$.Intermediate 27

1-(4-(((4-Bromophenyl)thio)methyl)-4-methylpiperidin-1-yl)ethan-1-one



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To a stirred solution of (1-acetyl-4-methylpiperidin-4-yl)methyl methanesulfonate **Intermediate 26** (1.88 g, 7.54 mmol) and 4-bromobenzenethiol (1.56 g, 8.29 mmol) in acetone (35 mL), caesium carbonate (4.91 g, 15.08 mmol) was added at room temperature. The reaction mixture was then heated at 60 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 70% ethyl acetate in hexane]. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-70% ethyl acetate in hexanes) to afford the title compound **Intermediate 27** (1.00 g, 39%) as yellow oil.

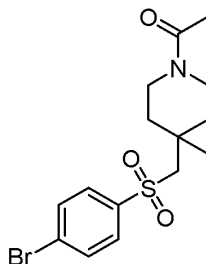
Analytical Data:

LCMS (ESI) m/z = 343.90 $[M + H]^+$ (^{81}Br).

15

Intermediate 28

1-(4-(((4-Bromophenyl)sulfonyl)methyl)-4-methylpiperidin-1-yl)ethan-1-one



To a stirred solution of 1-(4-(((4-bromophenyl)thio)methyl)-4-methylpiperidin-1-yl)ethan-1-one **Intermediate 27** (1.00 g, 2.92 mmol) in DCM (10 mL), *meta*-chloroperbenzoic acid (60%) (2.52 g, 8.76 mmol) was added in portions at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 6 h. The progress of the reaction was monitored by TLC [mobile phase: 70% ethyl acetate in hexanes]. After completion of the reaction, the reaction was quenched with saturated aqueous sodium thiosulfate (10 mL) and stirred until all the solid dissolved. The organic layer was separated, washed with saturated aqueous sodium bicarbonate (2 x 25 mL) and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 28** (1.00 g, crude) as a yellow oil. This compound was used in the next step without further purification.

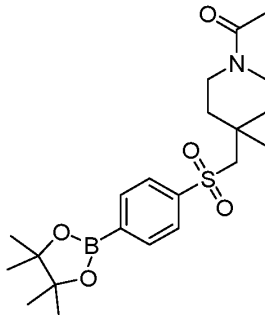
30 Analytical Data:

LCMS (ESI) m/z = 376.05 $[M + H]^+$ (^{81}Br).

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Intermediate 29

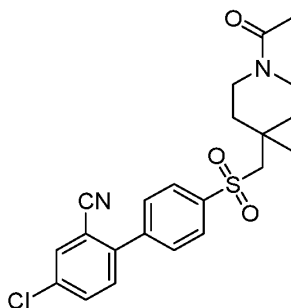
1-(4-Methyl-4-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one



- 5 To a reaction tube were added a solution of 1-(4-(((4-bromophenyl)sulfonyl)methyl)-4-methylpiperidin-1-yl)ethan-1-one **Intermediate 28** (1.00 g, 2.67 mmol), bis(pinacolato)diborane (0.814 g, 3.20 mmol) and potassium acetate (0.786 g, 8.01 mmol) in 1,4-dioxane (10 mL). The tube was sealed and degassed by purging with nitrogen for 15 min followed by addition of bis(triphenylphosphine)palladium (II) dichloride
- 10 (0.038 g, 0.053 mmol) to the reaction mixture under a nitrogen atmosphere and then again purging with nitrogen for 5 min. The reaction mixture was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 100% ethyl acetate]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a pad of celite and the celite pad was washed with ethyl acetate (50 mL).
- 15 The combined filtrate was concentrated under reduced pressure to dryness. The residue was triturated with pentane (2 x 25 mL), the solids were filtered out and dried under reduced pressure to afford the title compound **Intermediate 29** (0.93 g, crude) as brown solid. This compound was used in the next step without further purification.
- 20 Analytical Data:
LCMS (ESI) m/z = 340.05 $[M + H]^+$ (corresponding boronic acid).

Synthesis Compound 16

4'-(((1-Acetyl-4-methylpiperidin-4-yl)methyl)sulfonyl)-4-chloro-[1,1'-biphenyl]-2-carbonitrile
(NASMP-16)



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To a reaction tube were added a solution of 2-bromo-5-chlorobenzonitrile (0.400 g, 1.85 mmol), 1-(4-methyl-4-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one **Intermediate 29** (0.934 g, 2.22 mmol) and sodium carbonate (0.490 g, 4.63 mmol) in a mixture of 1,4-dioxane: water (3:1, 13 mL). The tube was sealed and degassed by purging with argon for 15 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.213 g, 0.184 mmol) to the reaction mixture under an argon atmosphere and then again purging with argon for 5 min. The reaction mixture was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 100% ethyl acetate]. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through a pad of celite and the celite pad was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-100% ethyl acetate in hexane) to afford the title compound (**Synthesis Compound 16**) (0.50 g, 63%) as a white solid.

Analytical Data:

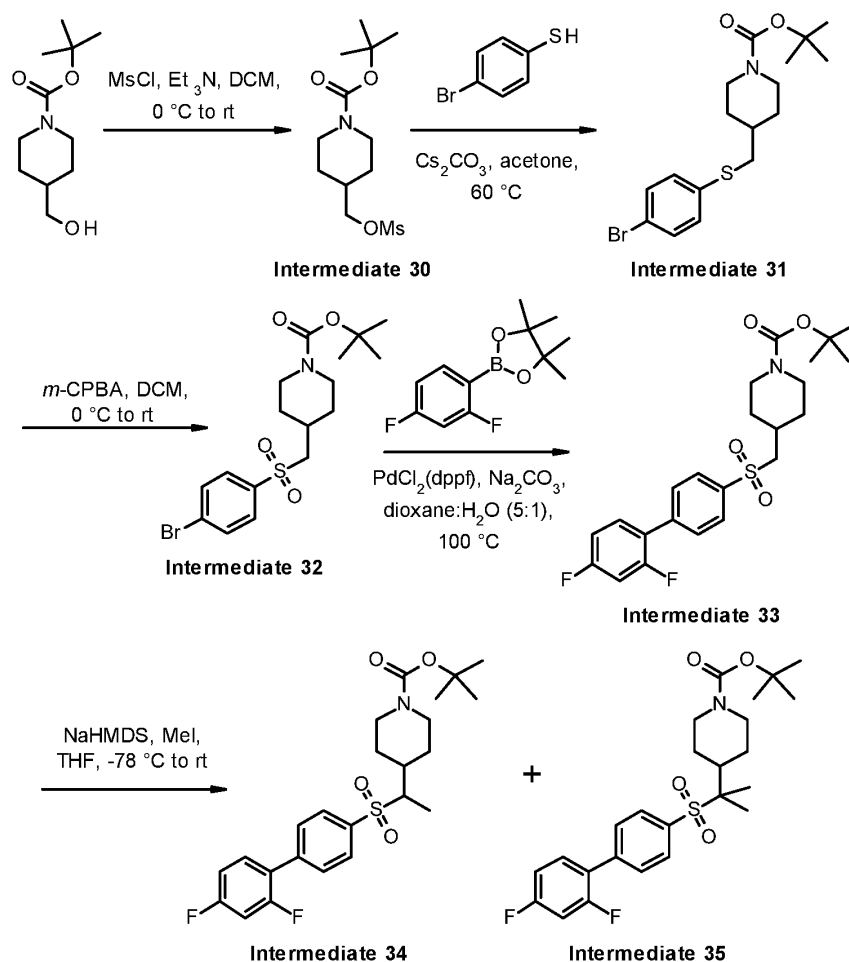
LCMS (ESI): $m/z = 431.05$ $[M + H]^+$.

HPLC (see generic method): Retention time: 8.26 min.; Purity: 98.56%.

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.23 (d, $J = 2.4$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 2H), 7.93 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 1H), 3.58 – 3.42 (m, 2H), 3.50 (d, $J = 4.0$ Hz, 2H), 3.38 – 3.28 (m, 2H), 1.96 (s, 3H), 1.78 – 1.70 (m, 1H), 1.66 – 1.58 (m, 1H), 1.52 – 1.44 (m, 1H), 1.40 – 1.32 (m, 1H), 1.26 (s, 3H).

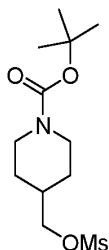
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Synthetic Scheme 19



Intermediate 30

5

tert-Butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (15.0 g, 69.67 mmol) in DCM (80 mL), triethylamine (19.42 mL, 139.34 mmol) was added at 0 °C and stirred for 10 min at the same temperature. Then, methanesulfonyl chloride (5.93 mL, 76.64 mmol) was added dropwise to the reaction at 0 °C. The reaction was warmed to room temperature and stirred for 24 h. The progress of the reaction was monitored by

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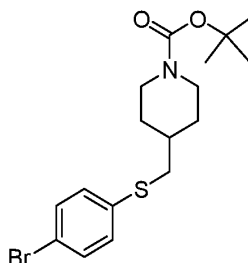
TLC [mobile phase: 30% ethyl acetate in hexanes]. After completion of the reaction, it was quenched with water (100 mL) and extracted with DCM (3 x 60 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 30** (21.0 g, crude) as yellowish viscous oil. This compound was used in the next step without further purification.

Analytical Data:

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 4.06 (d, *J* = 6.4 Hz, 2H), 3.95 (br d, *J* = 11.2 Hz, 2H), 3.17 (s, 3H), 2.70 (br s, 2H), 1.92 – 1.78 (m, 1H), 1.65 (d, *J* = 12.8 Hz, 2H), 1.39 (s, 9H), 1.14 – 1.02 (m, 2H).

Intermediate 31

tert-Butyl 4-(((4-bromophenyl)thio)methyl)piperidine-1-carboxylate



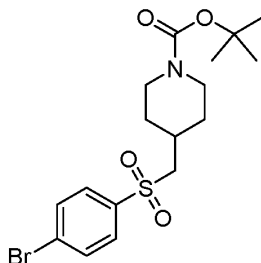
To a stirred solution of *tert*-butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate **Intermediate 30** (21.0 g, 71.57 mmol) in acetone (150 mL), 4-bromobenzenethiol (14.88 g, 78.73 mmol) and caesium carbonate (46.64 g, 143.15 mmol) were added under nitrogen atmosphere at room temperature. The reaction mixture was heated at 60 °C for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (100 mL) was added to the residue obtained and the resulting mixture was extracted with ethyl acetate (3 x 70 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness to afford the title compound **Intermediate 31** (18.0 g, crude) as brown solid. This compound was used in the next step without further purification.

Analytical data:

LCMS (ESI) *m/z* = 332.00 [*M* - *t*Bu + H]⁺ (⁸¹Br).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.43 – 7.39 (m, 2H), 7.21 – 7.17 (m, 2H), 4.11 (br s, 2H), 2.83 (d, *J* = 6.8 Hz, 2H), 2.67 (m, 2H), 1.71 – 1.60 (m, 1H), 1.83 (d, *J* = 13.2 Hz, 2H), 1.47 (s, 9H), 1.24 – 1.12 (m, 2H).

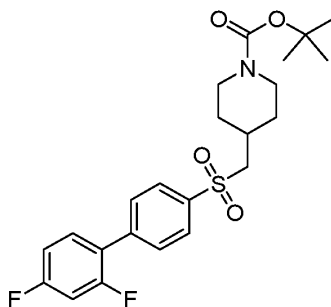
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Intermediate 32*tert*-Butyl 4-(((4-bromophenyl)sulfonyl)methyl)piperidine-1-carboxylate

- To a stirred solution of *tert*-butyl 4-(((4-bromophenyl)thio)methyl)piperidine-1-carboxylate **Intermediate 31** (18.0 g, 46.58 mmol) in DCM (200 mL), *meta*-chloroperbenzoic acid (60%) (40.2 g, 139.76 mmol) was added in portions over a period of 20 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 40% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was diluted with DCM (100 mL) and washed with saturated aqueous sodium thiosulfate (100 mL) and saturated aqueous sodium bicarbonate (100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-40% ethyl acetate in hexanes) to afford the title compound **Intermediate 32** (9.50 g, 49%) as a white solid.

Analytical data:

- ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.82 – 7.71 (m, 4H), 4.07 (br s, 2H), 3.01 (d, J = 6.4 Hz, 2H), 2.75 (t, J = 12.4 Hz, 2H), 2.24 – 2.12 (m, 1H), 1.88 (d, J = 11.6 Hz, 2H), 1.46 (s, 9H), 1.33 – 1.20 (m, 2H).

Intermediate 33*tert*-Butyl 4-(((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidine-1-carboxylate

- To a reaction tube were added a solution of *tert*-butyl 4-(((4-bromophenyl)sulfonyl)methyl)piperidine-1-carboxylate **Intermediate 32** (2.00 g, 4.78 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.37 g, 5.73 mmol) and sodium carbonate (1.51 g, 14.34 mmol) in a mixture of 1,4-dioxane: water (5:1, 12 mL). The tube was sealed and

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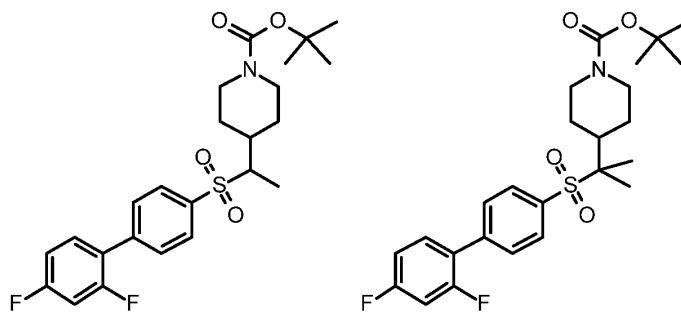
degassed by purging with nitrogen for 10 min followed by addition of [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.349 g, 0.478 mmol) under a nitrogen atmosphere and the purging with nitrogen was continued for 10 min. The reaction mixture was heated at 100 °C for 16 h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC [mobile phase: 40% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-70% ethyl acetate in hexanes) to afford the title compound **Intermediate 33** (1.80 g, 84%) as a brown solid.

Analytical Data:

LCMS (ESI) m/z = 352.05 [M - Boc + H]⁺.

Intermediate 34 and Intermediate 35

tert-butyl 4-(1-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)ethyl)piperidine-1-carboxylate (Intermediate 34) and *tert*-Butyl 4-(2-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)propan-2-yl)piperidine-1-carboxylate (Intermediate 35)



Intermediate 34

Intermediate 35

To a stirred solution of *tert*-butyl 4-(((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidine-1-carboxylate **Intermediate 33** (1.00 g, 2.21 mmol) in THF (100 mL), a solution of NaHMDS (17.72 mL, 17.72 mmol, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Then, methyl iodide (1.10 mL, 17.72 mmol) was added dropwise to the reaction mixture at the same temperature. The reaction was allowed to warm to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 40% ethyl acetate in hexanes]. After completion of the reaction, the reaction was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-40% ethyl acetate in

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hexanes) to afford **Intermediate 35** (0.350 g, 33%) as a white solid along with mono methylated compound **Intermediate 34** (0.055 g, 5%) as a white solid.

Analytical Data:

5 **Intermediate 34:**

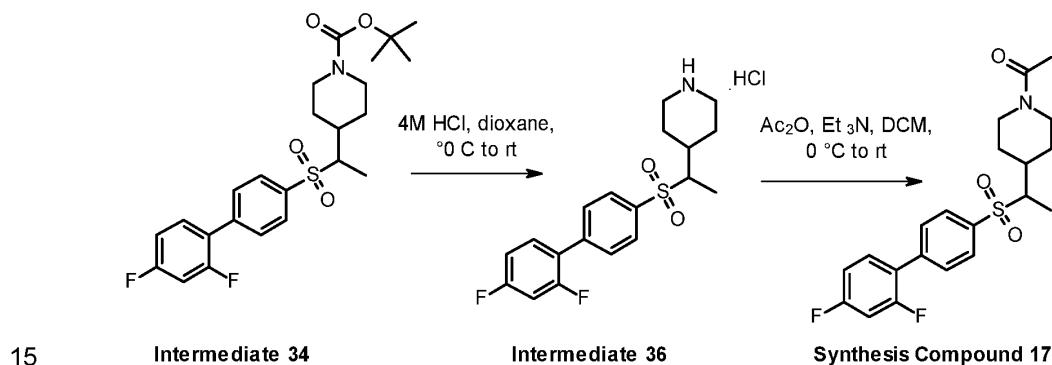
LCMS (ESI) m/z = 488.15 $[M + Na]^+$.

Intermediate 35:

LCMS (ESI) m/z = 502.60 $[M + Na]^+$.

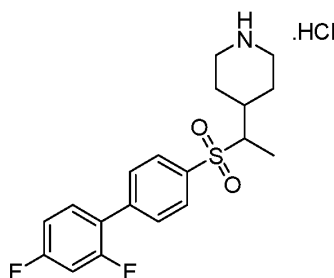
10 ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.91 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.75 – 7.67 (m, 1H), 7.49 – 7.41 (m, 1H), 7.30 – 7.23 (m, 1H), 4.00 (d, J = 10.8 Hz, 2H), 2.76 – 2.55 (m, 2H), 2.00 – 1.88 (m, 3H), 1.39 (s, 9H), 1.30 – 1.18 (m, 2H), 1.18 (s, 6H).

Synthetic Scheme 20



Intermediate 36

4-((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)ethyl)piperidine hydrochloride



20 To a stirred solution of *tert*-butyl 4-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)ethyl)piperidine-1-carboxylate **Intermediate 34** (0.055 g, 0.118 mmol) in 1,4-dioxane (2 mL), a 4 M solution of HCl in 1,4-dioxane (2 mL) was added at 0 °C. The reaction was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexanes]. After

25 completion of the reaction, the reaction mixture was concentrated under reduced pressure to dryness to afford the title compound **Intermediate 36** (0.045 g, crude) as a

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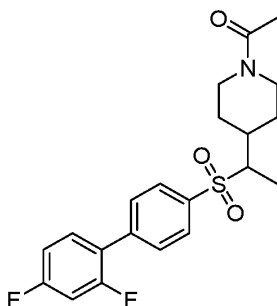
brown solid in the form of hydrochloride salt. This compound was used in the next step without further purification.

Analytical Data:

5 LCMS (ESI) m/z = 366.10 $[M + H]^+$ (free base).

Synthesis Compound 17

1-(4-(1-((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)ethyl)piperidin-1-yl)ethan-1-one
(NASMP-17)



10

To a stirred solution of 4-(1-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)ethyl)piperidine hydrochloride **Intermediate 36** (0.045 g, 0.112 mmol) in DCM (4 mL), triethylamine (0.039 mL, 0.280 mmol) was added at 0 °C and stirred for 10 min. Acetic anhydride (0.011 mL, 0.112 mmol) was then added to the reaction at the same temperature. The reaction was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-50% ethyl acetate in hexanes) to afford the title compound (**Synthesis Compound 17**) (0.012 g, 26%) as a white solid.

20

Analytical Data:

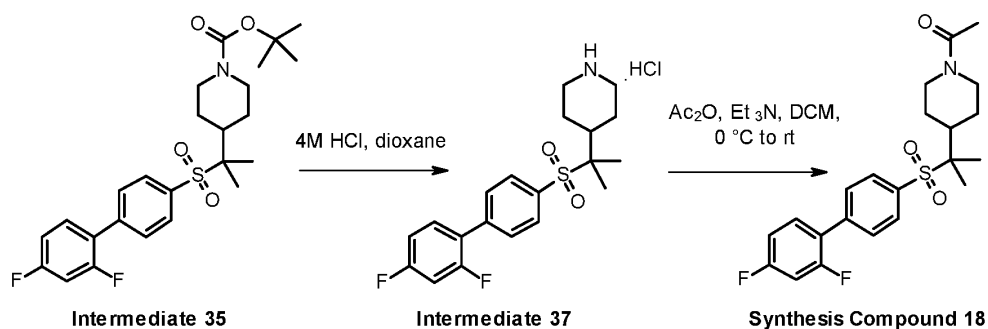
LCMS (ESI) m/z = 408.05 $[M + H]^+$.

HPLC (see generic method): Retention time: 8.26 min.; Purity: 96.98%.

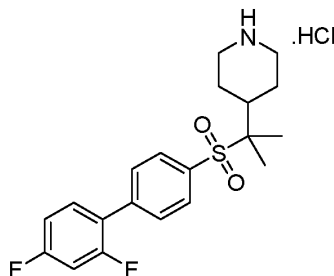
25

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.97 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 7.6 Hz, 2H), 7.73 – 7.66 (m, 1H), 7.48 – 7.42 (m, 1H), 7.26 (dt, J = 2.0 & 8.4 Hz, 1H), 4.42 (d, J = 12.8 Hz, 1H), 3.83 (d, J = 13.6 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.06 – 2.92 (m, 1H), 2.60 – 2.40 (m, 1H; merged with solvent peak), 2.35 – 2.25 (m, 1H), 1.97 (d, J = 1.2 Hz, 3H), 1.81 (t, J = 11.6 Hz, 1H), 1.67 – 1.55 (m, 1H), 1.45 – 1.30 (m, 1H), 1.30 – 1.15 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H).

30

Synthetic Scheme 21Intermediate 37

- 5 4-((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)propan-2-yl)piperidine hydrochloride



- 10 To a stirred solution of *tert*-butyl 4-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)propan-2-yl)piperidine-1-carboxylate **Intermediate 35** (0.350 g, 0.729 mmol) in 1,4-dioxane (2 mL) was added 4 M HCl in 1,4-dioxane (2 mL) at room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC [mobile phase: 40% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to dryness to afford the title compound **Intermediate 37** (0.22 g, crude) as a brown solid in the form of hydrochloride salt. This compound was used in the next step without further purification.

15

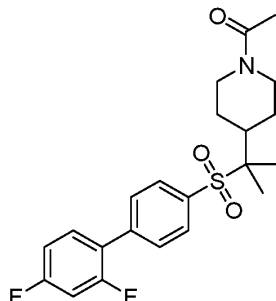
Analytical Data:

LCMS (ESI) m/z = 380.40 $[M + H]^+$ (free base).

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Synthesis Compound 18

1-(4-(2-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)propan-2-yl)piperidin-1-yl)ethan-1-one
(NASMP-18)



- 5 To a stirred solution of 4-(2-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)propan-2-yl)piperidine hydrochloride **Intermediate 37** (0.220 g, 0.529 mmol) in DCM (5 mL), triethylamine (0.184 mL, 1.32 mmol) was added at 0 °C and stirred for 10 min. Then, acetic anhydride (0.050 mL, 0.529 mmol) was added to the reaction mixture at the same temperature. The reaction was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 10-60% ethyl acetate in hexanes) to afford the title compound (**Synthesis Compound 18**) (0.208 g, 93%) as a white solid.

15

Analytical Data:

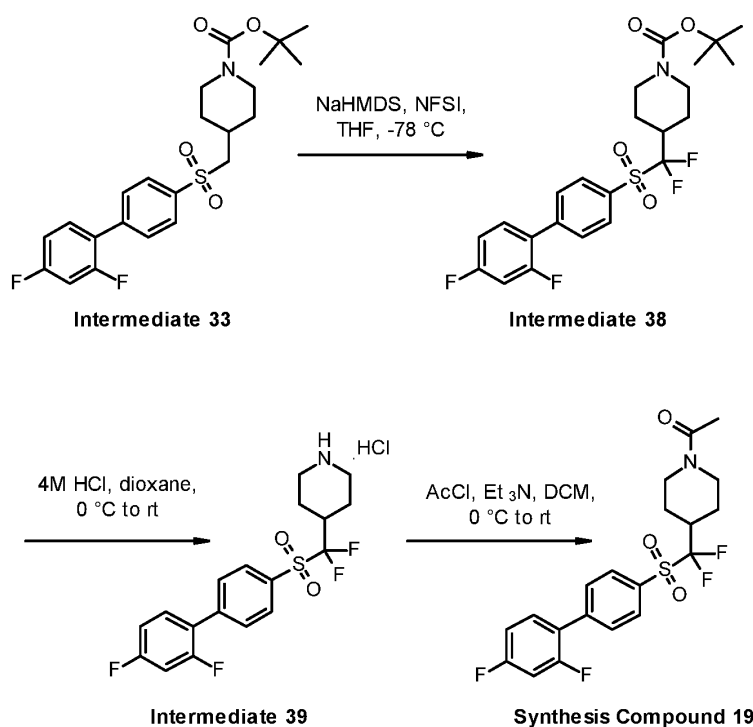
LCMS (ESI) m/z = 422.05 $[M + H]^+$.

HPLC (see generic method): Retention time: 8.48 min.; Purity: 99.53%.

- 20 ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.92 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.75 – 7.67 (m, 1H), 7.49 – 7.42 (m, 1H), 7.30 – 7.24 (m, 1H), 4.45 (d, J = 12.8 Hz, 1H), 3.87 (d, J = 13.2 Hz, 1H), 2.97 (t, J = 12.4 Hz, 1H), 2.43 (t, J = 12.4 Hz, 1H), 2.08 – 1.88 (m, 3H), 1.98 (s, 3H), 1.41 – 1.30 (m, 1H), 1.25 – 1.12 (m, 1H), 1.18 (s, 6H).

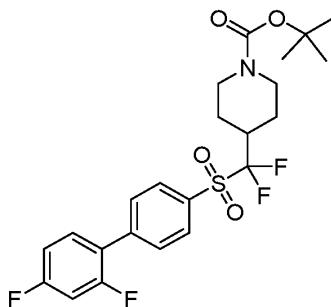
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Synthetic Scheme 22



Intermediate 38

- 5 *tert*-Butyl 4-(((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)difluoromethyl)piperidine-1-carboxylate



- A stirred solution of *tert*-butyl 4-(((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidine-1-carboxylate **Intermediate 33** (0.800 g, 1.77 mmol) in dry THF (20 mL) was cooled to -78 °C. Then, a solution of *N*-fluorobenzenesulfonylimide (NFSI) (2.79 g, 8.85 mmol) in dry THF (5 mL) was added, followed by a solution of NaHMDS (7.08 mL, 14.17 mmol, 2 M in THF) at -78 °C. The reaction mixture was stirred at the same temperature for 1 h. The progress of reaction was monitored by TLC [mobile phase: 30% ethyl acetate in hexanes]. After completion of the reaction, the reaction was warmed to room temperature and quenched with saturated aqueous ammonium chloride (10 mL). The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x

30 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-25% ethyl acetate in hexanes) to afford the title compound **Intermediate 38** (0.665 g, 77%) as a white solid.

5

Analytical Data:

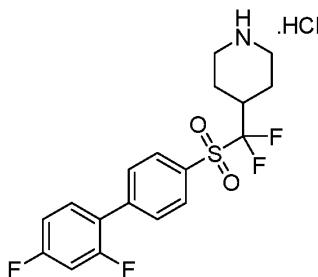
LCMS (ESI) m/z = 432.30 $[M - tBu + H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.50 – 7.43 (m, 1H), 7.06 – 6.95 (m, 2H), 4.26 (br s, 2H), 2.85 – 2.65 (m, 3H), 2.12 (d, J = 12.8 Hz, 2H), 1.70 – 1.55 (m, 2H), 1.48 (s, 9H).

10

Intermediate 39

4-(((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)difluoromethyl)piperidine hydrochloride



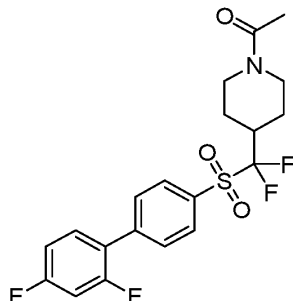
- 15 To a stirred solution of *tert*-butyl 4-(((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)difluoromethyl)piperidine-1-carboxylate **Intermediate 38** (0.660 g, 1.35 mmol) in 1,4-dioxane (20 mL) was added a 4 M solution of HCl in 1,4-dioxane (20 mL) at 0 °C. The reaction was warmed to room temperature and stirred for overnight. The progress of the reaction was monitored by TLC [mobile phase: 70% ethyl acetate in hexanes]. After
- 20 completion of the reaction, the reaction mixture was concentrated under reduced pressure to dryness to afford the title compound **Intermediate 39** (0.500 g, crude) as a yellowish gum in the form of hydrochloride salt. This compound was used in the next step without further purification.

25 Analytical Data:

LCMS (ESI) m/z = 388.30 $[M + H]^+$ (free base).

Synthesis Compound 19

1-(4-(((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)difluoromethyl)piperidin-1-yl)ethan-1-one
(NASMP-19)



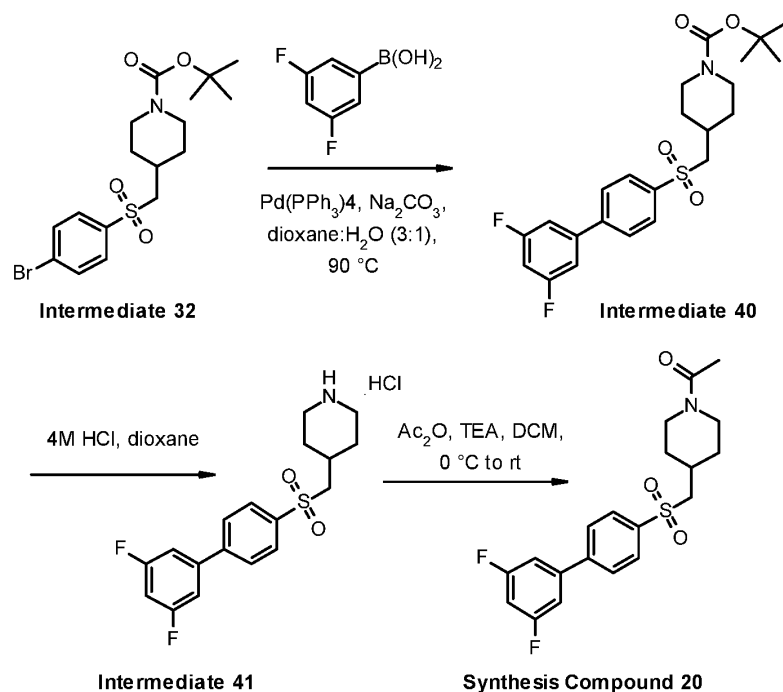
- 5 To a stirred solution of 4-(((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)difluoromethyl)piperidine hydrochloride **Intermediate 39** (0.400 g, 0.943 mmol) in DCM (10 mL) was added triethylamine (0.329 mL, 2.359 mmol) at 0 °C and stirred at the same temperature for 10 min. Then, acetyl chloride (0.081 mL, 1.132 mmol) was added to the reaction at 0 °C. The reaction mixture was warmed to room temperature and
- 10 stirred for 1 h. The progress of reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexanes]. After completion of reaction, the reaction was quenched with water (30 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-50% ethyl acetate in hexanes) to afford (**Synthesis Compound 19**) (0.205 g, 51%) as a white solid.
- 15

Analytical Data:

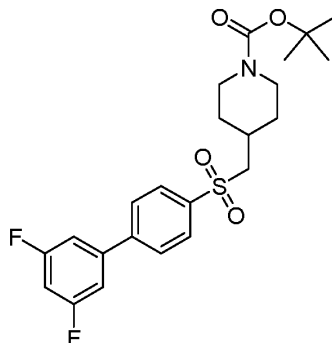
LCMS (ESI) m/z = 430.05 $[M + H]^+$.

- 20 HPLC [Method: Column: X-Select CSH C18 (4.6*150) mm, 5 μ ; Mobile Phase: A - 0.1% TFA in water; B - Acetonitrile; Inj. Vol.: 5.0 μ L; Flow Rate: 1.2 mL/min.; Gradient program: Time (min)/B conc.: 0.01/5, 1.0/5, 8.0/100, 12.0/100, 14.0/5, 18.0/5; Retention time: 8.37 min.; Purity: 95.96%.

- 25 ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.04 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.50 – 7.43 (m, 1H), 7.06 – 6.95 (m, 2H), 4.80 (d, J = 13.2 Hz, 1H), 3.96 (d, J = 13.2 Hz, 1H), 3.16 (t, J = 13.6 Hz, 1H), 2.92 – 2.75 (m, 1H), 2.62 (t, J = 12.0 Hz, 1H), 2.25 (d, J = 13.6 Hz, 1H), 2.17 – 2.10 (m, 1H), 2.14 (s, 3H), 1.74 – 1.55 (m, 2H).

Synthetic Scheme 23Intermediate 40

- 5 *tert*-Butyl 4-(((3',5'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidine-1-carboxylate



- To a reaction tube were added a solution of *tert*-butyl 4-(((4-bromophenyl)sulfonyl)methyl)piperidine-1-carboxylate **Intermediate 32** (1.00 g, 2.39 mmol), (3,5-difluorophenyl)boronic acid (0.566 g, 3.585 mmol) and sodium carbonate (0.633 g, 5.975 mmol) in a mixture of 1,4-dioxane: water (3:1, 21 mL). The tube was sealed and degassed by purging with argon for 10 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.276 g, 0.239 mmol) to the reaction mixture under an argon atmosphere and the purging with argon was continued for 5 min. The reaction mixture was then heated at 90 °C for 16 h under an argon atmosphere. The progress of the reaction was monitored by TLC [mobile phase: 80% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was cooled to room

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temperature and filtered through a pad of Celite. The Celite pad was washed with ethyl acetate (2 x 50 mL). The combined organic layer was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (CombiFlash®, gradient 0-80% ethyl acetate in hexanes) to afford the title compound

5 **Intermediate 40** (0.650 g, 60%) as a yellow oil.

Analytical Data:

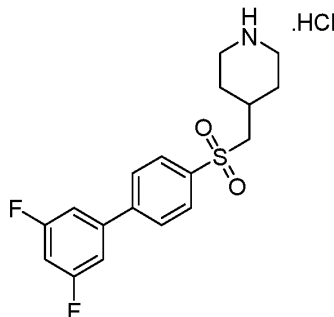
LCMS (ESI) m/z = 351.95 [M - Boc + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.01 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.18 – 7.10 (m, 2H), 6.92 – 6.85 (m, 1H), 4.16 – 4.02 (m, 2H), 3.06 (d, J = 6.4 Hz, 2H), 2.76 (t, J = 10.8 Hz, 2H), 2.30 – 2.18 (m, 1H), 1.91 (br d, J = 11.2 Hz, 2H), 1.46 (s, 9H), 1.35 – 1.22 (m, 2H).

10

Intermediate 41

15 4-(((3',5'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidine hydrochloride



To a stirred solution of *tert*-butyl 4-(((3',5'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidine-1-carboxylate **Intermediate 40** (0.650 g, 1.439 mmol) in 1,4-dioxane (1 mL), a 4 M solution of HCl in 1,4-dioxane (10 mL) was added at room temperature and stirred for 4 h. The progress of the reaction was monitored by TLC [mobile phase: 80% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to dryness to afford the title compound **Intermediate 41** (0.460 g, crude) as a white solid in the form of hydrochloride salt. This compound was used in the next step without further purification.

20

25

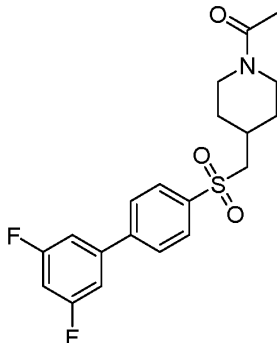
Analytical Data:

LCMS (ESI) m/z = 352.00 [M + H]⁺ (free base).

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Synthesis Compound 20

1-(4-(((3',5'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-20)



- 5 To a stirred solution of 4-(((3',5'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidine hydrochloride **Intermediate 41** (0.460 g, 1.185 mmol) in DCM (10 mL), triethylamine (0.495 mL, 3.555 mmol) followed by acetic anhydride (0.144 mL, 1.422 mmol) were added at 0 °C. The reaction was then warmed to room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC [mobile phase: 5% methanol in
- 10 DCM]. After completion of the reaction, the reaction mixture was diluted with DCM (50 mL), washed with water (2 x 25 mL) and brine (2 x 25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by triturating with diethyl ether (2 x 25 mL), the solids were filtered out and dried under reduced pressure to afford the title compound
- 15 (**Synthesis Compound 20**) (0.310 g, 67%) as an off white solid.

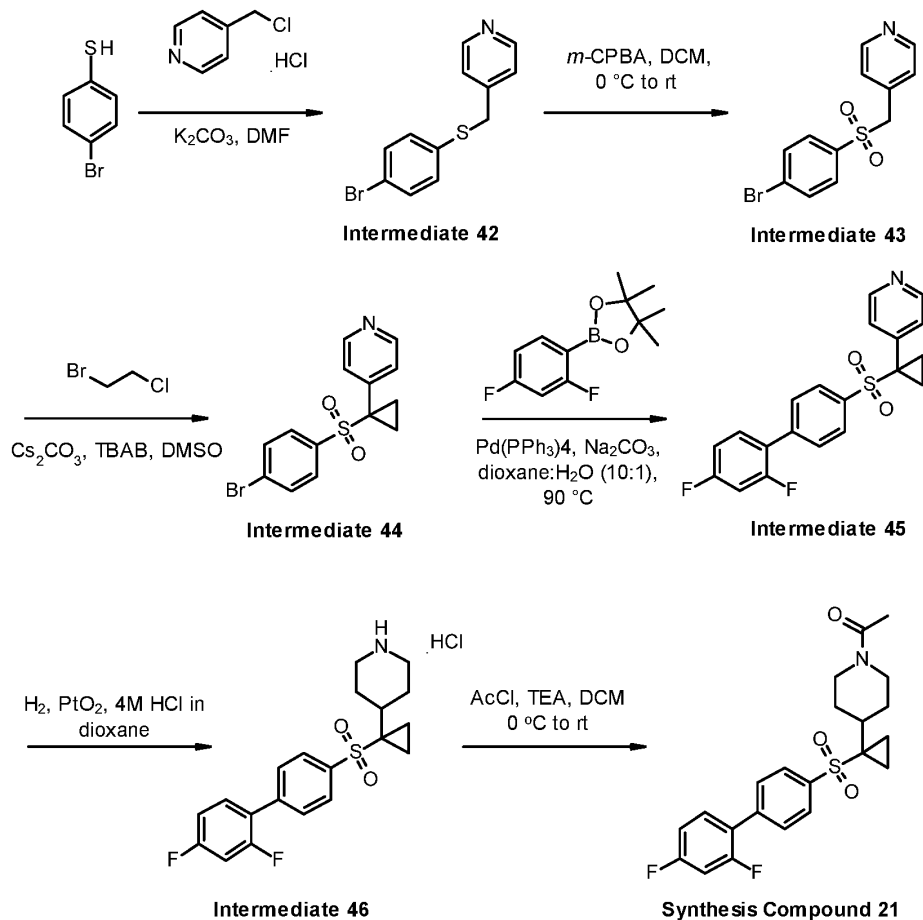
Analytical Data:

LCMS (ESI) m/z = 394.00 $[M + H]^+$.

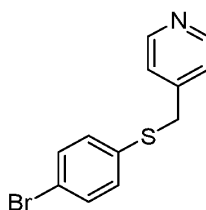
HPLC (see generic method): Retention time: 8.12 min.; Purity: 99.24%.

- 20 ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.06 – 7.98 (m, 4H), 7.58 (d, J = 6.8 Hz, 2H), 7.38 – 7.31 (m, 1H), 4.23 (d, J = 13.2 Hz, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.38 (d, J = 6.4 Hz, 2H), 3.04 – 2.96 (m, 1H), 2.60 – 2.50 (m, 1H), 2.10 – 2.00 (m, 1H), 1.95 (s, 3H), 1.85 – 1.71 (m, 2H), 1.30 – 1.19 (m, 1H), 1.19 – 1.05 (m, 1H).

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Synthetic Scheme 24Intermediate 42

4-(((4-Bromophenyl)thio)methyl)pyridine



To a stirred solution of 4-bromobenzenethiol (5.00 g, 26.44 mmol) in DMF (50 mL), 4-(chloromethyl)pyridine hydrochloride (4.33 g, 26.44 mmol) and potassium carbonate (12.79 g, 92.55 mmol) were added at room temperature and the reaction was stirred for 16 h. Progress of the reaction was monitored by TLC [mobile phase: 30% ethyl acetate in hexanes]. After completion of the reaction, the reaction mixture was quenched with water (200 mL) and extracted with ethyl acetate (4 x 60 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and

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concentrated under reduced pressure to dryness to afford the title compound

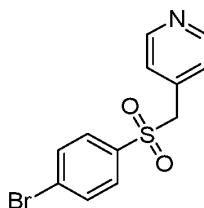
Intermediate 42 (6.00 g, crude) as brown solid. This compound was used in the next step without further purification.

5 Analytical Data:

LCMS (ESI) m/z = 281.75 $[M + H]^+$ (^{81}Br).

Intermediate 43

4-(((4-Bromophenyl)sulfonyl)methyl)pyridine



10

To a stirred solution of 4-(((4-bromophenyl)thio)methyl)pyridine **Intermediate 42** (6.00 g, 21.41 mmol) in DCM (100 mL), cooled at 0 °C, was added in portions *meta*-chloroperbenzoic acid (60%) (13.55 g, 47.11 mmol) over a period of 20 min. The reaction mixture was then warmed to room temperature and stirred for 3 h. The progress of reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexanes]. After completion of reaction, the reaction mixture was diluted with DCM (100 mL) and washed with saturated aqueous sodium thiosulfate (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-40% ethyl acetate in hexanes) to afford the title compound **Intermediate 43** (3.30 g, 49%) as a white solid.

15

20

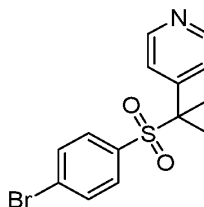
Analytical data:

LCMS (ESI) m/z = 313.85 $[M + H]^+$ (^{81}Br).

25

Intermediate 44

4-(1-((4-Bromophenyl)sulfonyl)cyclopropyl)pyridine



30

To a stirred solution of 4-(((4-bromophenyl)sulfonyl)methyl)pyridine **Intermediate 43** (2.00 g, 6.41 mmol) in DMSO (10 mL), 1-bromo-2-chloroethane (2.76 g, 19.22 mmol), caesium carbonate (6.26 g, 19.22 mmol) and tetra-*n*-butylammonium bromide (0.413 g, 1.28 mmol) were added at room temperature and the reaction was stirred for 3 h. The

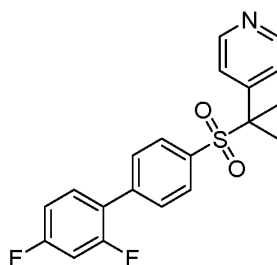
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progress of reaction was monitored by TLC [mobile phase: 50% ethyl acetate in hexanes]. After completion of reaction, the reaction was quenched with water (100 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic layer was washed with water (2 x 40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-25% ethyl acetate in hexanes) to afford the title compound **Intermediate 44** (1.50 g, 69%) as a white solid.

Analytical data:

LCMS (ESI) m/z = 339.75 $[M + H]^+$ (^{81}Br).
 ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.48 (d, J = 6.0 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 6.0 Hz, 2H), 1.90 – 1.84 (m, 2H), 1.47 – 1.40 (m, 2H).

Intermediate 45
 4-(1-((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)cyclopropyl)pyridine



To a reaction tube were added a solution of 4-(1-((4-bromophenyl)sulfonyl)cyclopropyl)pyridine **Intermediate 44** (1.00 g, 2.96 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.851 g, 3.55 mmol) and sodium carbonate (0.783 g, 7.39 mmol) in a mixture of 1,4-dioxane:water (10:1, 11 mL). The tube was sealed and degassed by purging with nitrogen for 10 min, followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.341 g, 0.296 mmol) to the reaction mixture under a nitrogen atmosphere and the purging with nitrogen was continued for 5 min. The reaction mixture was then heated at 90 °C for 16 h under a nitrogen atmosphere. The progress of reaction was monitored by TLC [mobile phase: 60% ethyl acetate in hexanes]. After completion of reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (100-200 mesh, gradient 0-40% ethyl acetate in hexanes) to afford the title compound **Intermediate 45** (0.800 g, 73%) as a brown solid.

Analytical data:

LCMS (ESI) m/z = 372.00 $[M + H]^+$.

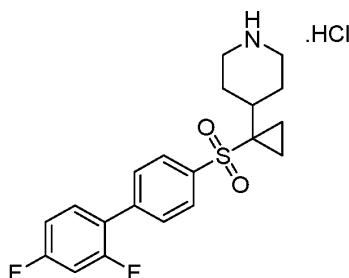
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¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.47 (d, *J* = 4.8 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.68 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.40 (m, 1H), 7.29 – 7.22 (m, 1H), 7.14 (d, *J* = 5.2 Hz, 2H), 1.93 – 1.86 (m, 2H), 1.49 – 1.42 (m, 2H).

5

Intermediate 46

4-(1-((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)cyclopropyl)piperidine hydrochloride



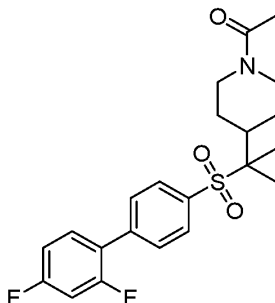
To a Parr reactor was added a solution of 4-(1-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)cyclopropyl)pyridine **Intermediate 45** (0.500 g, 1.35 mmol) in a 4 M solution of HCl in 1,4-dioxane (10 mL). The Parr reactor was evacuated and backfilled with nitrogen. To the reaction mixture was added platinum dioxide (50 mg, 10% w/w) under a nitrogen atmosphere. The Parr reactor was evacuated and backfilled with hydrogen. The reaction was then stirred at room temperature for 16 h under a hydrogen atmosphere at 100 psi. The progress of the reaction was monitored by TLC [mobile phase: 70% ethyl acetate in hexanes]. The reaction mixture was filtered through a pad of Celite and the Celite pad was washed with methanol (100 mL) and water (50 mL). The combined filtrate was concentrated under reduced pressure to dryness to afford the title compound **Intermediate 46** (0.410 g, crude, 35% pure by LCMS) as a viscous liquid as a hydrochloride salt. This compound was used in the next step without further purification.

20

Analytical data:

LCMS (ESI) *m/z* = 378.00 [*M* + *H*]⁺ (free base).Synthesis Compound 21

25 1-(4-(1-((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)cyclopropyl)piperidin-1-yl)ethan-1-one (NASMP-21)



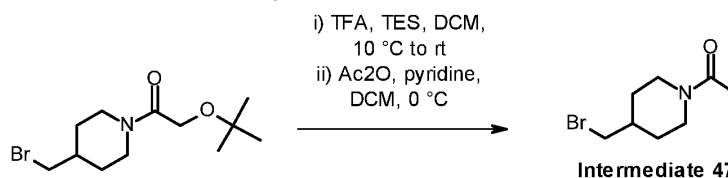
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To a stirred solution of 4-(1-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)cyclopropyl)piperidine hydrochloride **Intermediate 46** [0.410 g (35% pure), 0.346 mmol] in DCM (5 mL) at 0 °C was added triethylamine (0.097 mL, 0.691 mmol) and stirred for 10 min followed by addition of acetyl chloride (0.030 mL, 0.415 mmol) to the reaction. The reaction was then warmed to room temperature and stirred for 1 h. The progress of reaction was monitored by TLC [mobile phase: 80% ethyl acetate in hexanes]. After completion of the reaction, the mixture was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (230-400 mesh, gradient 0-60% ethyl acetate in hexanes). The product was further triturated with diethyl ether (2 x 5 mL) at 0 °C for 15 min. The solids were filtered out and dried under reduced pressure to afford (**Synthesis Compound 21**) (0.073 g, 50%) as a white solid.

Analytical Data:

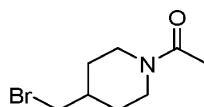
LCMS (ESI) m/z = 420.10 $[M + H]^+$.
 HPLC (see generic method): Retention time: 8.32 min.; Purity: 95.11%.
 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.00 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 7.6 Hz, 2H), 7.75 – 7.67 (m, 1H), 7.48 – 7.41 (m, 1H), 7.29 – 7.23 (m, 1H), 4.32 (d, J = 12.8 Hz, 1H), 3.72 (d, J = 14.0 Hz, 1H), 2.88 (t, J = 12.0 Hz, 1H), 2.33 (t, J = 10.4 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.91 (s, 3H), 1.54 – 1.40 (m, 2H), 1.40 (br s, 2H), 1.08 (br s, 2H), 1.10 – 0.97 (m, 1H), 0.92 – 0.80 (m, 1H).

Synthetic Scheme 25



Intermediate 47

1-[4-(Bromomethyl)piperidin-1-yl]ethanone



To a 2 L flange flask under N_2 was charged 1-[4-(bromomethyl)piperidin-1-yl]-2-(*tert*-butoxy)ethanone (45 g, 0.153 mol), DCM (900 mL) and triethylsilane (21.6 mL, 0.255 mol) at room temperature. The reaction was then cooled to 10 °C and TFA (107.1 mL, 0.631 mol) was charged dropwise over 15 minutes at 10-15 °C. The reaction was warmed to room temperature and stirred for 1 h, where HPLC indicated no starting material remained. The reaction mixture was then concentrated in vacuo to give a crude oil. The oil was taken up in DCM (450 mL) and cooled to 0 °C. Pyridine (39.1 mL, 0.483 mol) was

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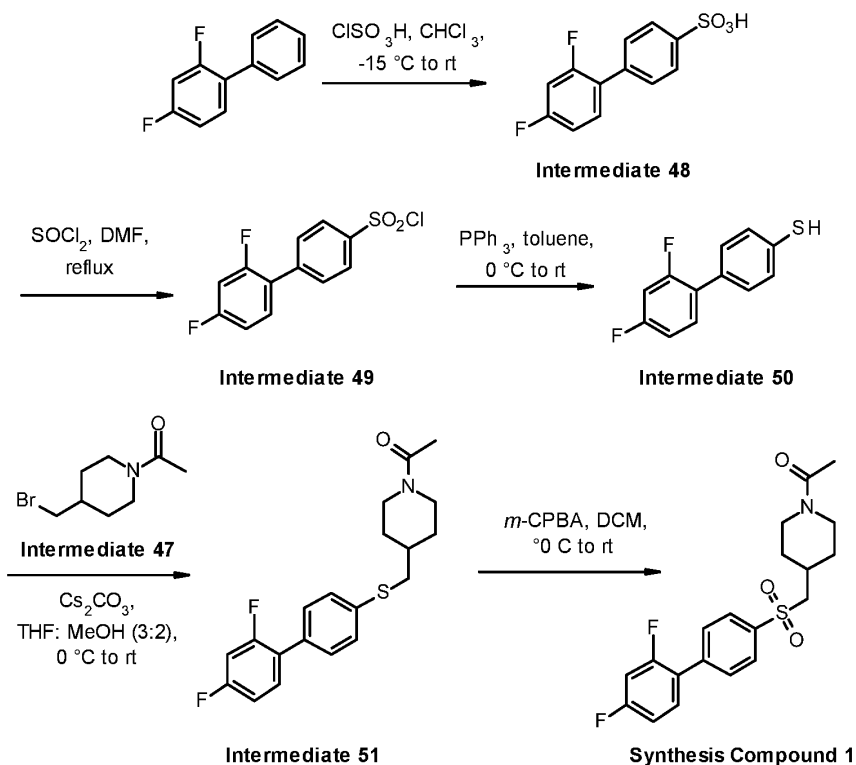
then charged dropwise at 0-5 °C over 15 minutes followed by the addition of Ac₂O (46.1 mL, 0.488 mol) at 0-5 °C over 15 minutes. The reaction was stirred for 30 minutes at 0-5 °C where HPLC indicated 2.0% intermediate and 93.8% product. The reaction mixture was washed with 1 M HCl (225 mL) and the aqueous back extracted with DCM (225mL).

- 5 The organics were combined and washed with water (225 mL x 2) and 10% brine (225 mL x 2). The organics were separated and dried over magnesium sulfate before being concentrated to give 50.4 g of crude in a purity of 94.31% by HPLC. The crude was then purified on silica (2.25 kg) loaded in 1% MeOH/DCM and eluted using 1-3% MeOH/DCM. The clean fractions by TLC were concentrated in vacuo to provide **Intermediate 47** (29.7 g, 88%) in a purity of 98.9% by HPLC and >95% by NMR.
- 10

Analytical Data:

- ¹H NMR (400 MHz, Chloroform-*d*) δ (ppm): 4.67 - 4.61 (m, 1H), 3.87 - 3.82 (m, 1H), 3.30 (dq, *J* = 8.0, 12.0 Hz, 2H), 3.05 (td, *J* = 4.0, 12.0 Hz, 1H), 2.53 (td, *J* = 4.0, 12.0 Hz, 1H), 2.10 (s, 3H), 1.97 - 1.80 (m, 3H), 1.28 - 1.13 (m, 2H).
- 15

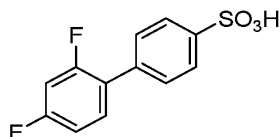
Synthetic Scheme 26



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Intermediate 48

2',4'-Difluoro-[1,1'-biphenyl]-4-sulfonic acid



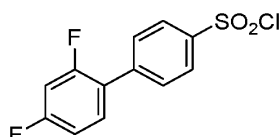
To a 1 L flange flask under N₂ was charged 2,4-difluorobiphenyl (90 g, 0.473 mol) and chloroform (509 mL). Chlorosulfonic acid (53.1 mL, 0.799 mol) was then charged dropwise at -15 °C over 5 minutes. The reaction mixture was then stirred at room temperature for 1 h where HPLC indicated 0.9% starting material and 95.4% product. N₂ was then bubbled through the reaction mixture for 15 minutes before concentrated in vacuo to provide a white solid. The solid was then taken up in EtOAc (422 mL) and quenched with water (333 mL). The aqueous was then separated (poor separation) and saturated brine (422 mL) was charged dropwise to the organics over 15 minutes to provide a thick white suspension. The solids were isolated and washed with EtOAc (90 mL x 2) before drying overnight at 50 °C. This provided **Intermediate 48** (98.8 g, crude) in a purity of >95% by NMR.

Analytical Data:

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.69 - 7.66 (m, 2H), 7.55 (dt, *J* = 6.7, 8.9 Hz, 1H), 7.47 - 7.43 (m, 2H), 7.37 - 7.30 (m, 1H), 7.19 - 7.14 (m, 1H), 4.05 (br s, 1H).

Intermediate 49

2',4'-Difluoro-[1,1'-biphenyl]-4-sulfonyl chloride



To a 2 L flange flask under N₂ was charged 2',4'-difluoro-[1,1'-biphenyl]-4-sulfonic acid **Intermediate 48** (98.8 g, 0.366 mol), thionyl chloride (766 mL, 10.50 mol) and DMF (1 mL, 12.9 mmol). The reaction mixture was then heated to reflux (79 °C) for 8 h where HPLC analysis showed 3.4% starting material remained and 95.0% product. The reaction was cooled to room temperature before being concentrated in vacuo and then azeotroped from toluene (350 mL x 2). The residue was then taken up in EtOAc and washed with water (500 mL) then 10% brine (500 mL). The organics were separated and dried over magnesium sulfate before being concentrated in vacuo. This provided **Intermediate 49** (95.6 g, crude) in a purity of 93.8% by HPLC and >90% by NMR.

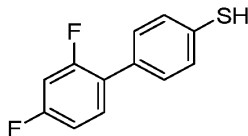
Analytical Data:

¹H NMR (400 MHz, Chloroform-*d*) δ (ppm): 8.11 (d, *J* = 8.0 Hz, 2H), 7.76 (dd, *J* = 4.0, 12.0 Hz, 2H), 7.48 (dt, *J* = 4.0, 8.0 Hz, 1H), 7.08 - 6.95 (m, 2H).

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Intermediate 50

2',4'-Difluoro-[1,1'-biphenyl]-4-thiol



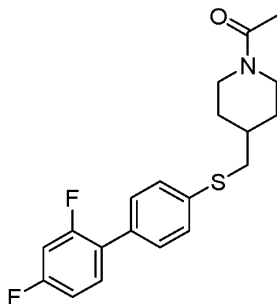
- 5 To a 2 L flange flask under N₂ was charged 2',4'-difluoro-[1,1'-biphenyl]-4-sulfonyl chloride **Intermediate 49** (90.0 g, 0.312 mol) and toluene (900 mL). The reaction mixture was then cooled to 0 °C and a solution of triphenylphosphine (245.5 g, 0.936 mol) in toluene (450 mL) was charged dropwise at 0-5 °C over 30 minutes. The reaction mixture was then stirred at room temperature for 1 h where HPLC indicated no starting material
- 10 remained. The reaction mixture was quenched with 1 M HCl (225 mL) then concentrated in vacuo to remove the toluene. The remaining aqueous layer was then adjusted to pH 10-11 using 2 M potassium hydroxide (450 mL) to provide a suspension. The solids were removed by filtration and washed with water (900 mL x 2). The filtrate was then washed with ether (900 mL x 4). The aqueous was then pH adjusted to pH 3-4 using 1 M HCl (1
- 15 L) before being extracted with ethyl acetate (900 mL + 450 mL). The organics were then separated and dried over magnesium sulfate and concentrated in vacuo. This provided **Intermediate 50** (82.0 g, crude) in a purity of 93.8% by HPLC and 75% by NMR.

Analytical Data:

- 20 ¹H NMR (400 MHz, Chloroform-*d*) δ (ppm): 7.73 - 7.66 (m, 2H), 7.58 - 7.52 (m, 1H), 7.50 - 7.43 (m, 2H), 6.97 - 6.87 (m, 2H), 3.53 (s, 1H).

Intermediate 51

1-[4-({2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfanyl}piperidin-1-yl)ethanone



- 25 To a 500 mL 3-neck flask under N₂ was charged 2',4'-difluoro-[1,1'-biphenyl]-4-thiol **Intermediate 50** (47.7 g, 0.215 mol), THF (180 mL) and MeOH (120 mL). The reaction mixture was then cooled to 0 °C and caesium carbonate (87.7 g, 0.269 mol) was then charged in portions at 0-5 °C over 15 minutes. 1-[4-(Bromomethyl)piperidin-1-yl]ethanone
- 30 **Intermediate 47** (29.5 g, 0.134 mol) in THF (60 mL) was then charged dropwise at 5-10 °C over 10 minutes. The reaction mixture was heated to 60 °C for 45 minutes where

- 145 -

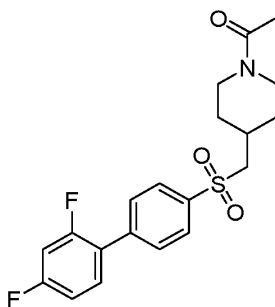
HPLC indicated no 1-[4-(Bromomethyl)piperidin-1-yl]ethanone **Intermediate 47** remained. The reaction mixture was cooled to room temperature and filtered; the solids were washed with THF (150 mL). The filtrate was concentrated in vacuo and the residue partitioned between EtOAc (600 mL) and water (450 mL). The layers were separated and the aqueous back extracted with EtOAc (300 mL). The organics were combined and dried over magnesium sulfate before being concentrated in vacuo. This provided 63.6 g of crude. The crude was purified on silica (3 kg) eluting with 1% MeOH/DCM. The clean fractions were concentrated in vacuo to provide **Intermediate 51** (33.9 g, 70%) in a purity of 97.9% by HPLC and >95% by NMR.

Analytical Data:

¹H NMR (400 MHz, Chloroform-*d*) δ (ppm): 7.44 - 7.33 (m, 5H), 6.97 - 6.86 (m, 2H), 4.66 - 4.59 (m, 1H), 3.85 - 3.78 (m, 1H), 3.05 - 2.96 (m, 1H), 2.95 - 2.81 (m, 2H), 2.57 - 2.47 (m, 1H), 2.08 (s, 3H), 2.01 - 1.86 (m, 2H), 1.85 - 1.74 (m, 1H), 1.27 - 1.13 (m, 2H).

Synthesis Compound 1

1-(4-(((2',4'-Difluoro-[1,1'-biphenyl]-4-yl)sulfonyl)methyl)piperidin-1-yl)ethan-1-one
(NASMP-01)



To a 1 L flange flask under N₂ was charged 1-[4-({2',4'-difluoro-[1,1'-biphenyl]-4-yl}sulfonyl)piperidin-1-yl]ethanone **Intermediate 51** (33.5 g, 0.093 mol) and DCM (400 mL). The reaction mixture was cooled to 0 °C and *m*-CPBA (77%) (45.7 g, 0.278 mol) was charged in portions at 0-5 °C over 45 minutes. The reaction mixture was then warmed to room temperature and stirred for 1 h. HPLC indicated no starting material remained. The reaction mixture was filtered, and the liquors were charged back to the flask. The liquors were then cooled to 0 °C and quenched with saturated sodium bicarbonate (340 mL). The layers were separated, and the organics washed with saturated sodium thiosulfate (340 mL). The organics were then separated and washed with sodium bicarbonate (340 mL x 2 + 170 mL) and sodium thiosulfate (340 mL x 2 + 170 mL). HPLC showed no *m*-CPBA / chlorobenzoic acid remained. The organics were then separated, dried over magnesium sulfate and concentrated in vacuo. This provided (**Synthesis Compound 1**) (31.0g, 84%) in a purity of 95.8% by HPLC and >95% by NMR.

Analytical Data:

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.02 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.69 (td, *J* = 8.0, 12.0 Hz, 1H), 7.48 - 7.40 (m, 1H), 7.29 - 7.21 (m, 1H), 4.28 - 4.20 (m, 1H), 3.78 - 3.70 (m, 1H), 3.40-3.35 (m, 2H), 3.06 - 2.96 (m, 1H), 2.57 (td, *J* = 4.0, 12.0 Hz, 1H), 2.15 - 2.03 (m, 1H), 1.95 (s, 3H), 1.88 - 1.74 (m, 2H), 1.26 (ddd, *J* = 4.0, 12.0 Hz, 1H), 1.13 (ddd, *J* = 4.0, 12.0 Hz, 1H).

BIOLOGICAL STUDIESBiological Study 1

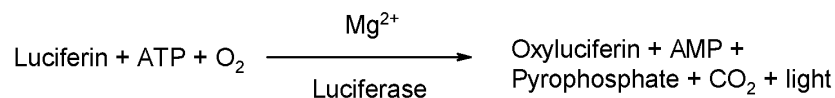
Monocyte ATP Production Assay

5

In vitro potency of test compounds was determined by incubation with Thp1 human monocytic cells and subsequent determination of Adenosine TriPhosphate (ATP) levels using firefly luciferase.

- 10 ATP is present in all metabolically active cells. When cells lose integrity, their ability to synthesise ATP is rapidly lost. ATP concentration is hence reduced when cells undergo necrosis or apoptosis and its concentrations are commonly used as a marker of cell viability or of cellular proliferation. See, e.g., Kang *et al.*, 2015; Jiang *et al.*, 2013. Levels of ATP can be monitored using a system based on firefly (*Photinus pyralis*) luciferase
- 15 (see, e.g., Auld *et al.*, 2009) using commercially available kits. A system known as ATPlite™ was using to measure effects of the test compounds on cellular viability *in vitro*. This one-step assay system is an adenosine triphosphate (ATP) monitoring system based on the production of light caused by the reaction of ATP from the cells with added luciferase and D-luciferin, as illustrated in the reaction scheme below:

20



The emitted light is proportional to the ATP concentration.

- 25 Thp1 cells were plated at 112500 cells per well in 125 µL RPMI-1640 (no glucose) with 1% FBS in 96-well plates. Test compounds were prepared as 100 mM solutions in DMSO. These stock solutions were diluted in DMSO and then diluted 1000x in culture medium (RPMI) before being added directly to the wells so as to give the desired final compound concentration. After a 24 hour incubation at 37°C / 5% CO₂, ATPlite™
- 30 (Perkin Elmer) was added to each well (1 : 10 v/v, 10 µL). The plate was then incubated at room temperature for 5 minutes and the emitted light was quantified on Viewlux with a measurement time of 0.3 seconds and binning 4x4.

- The average results for each test compound were expressed as a percent (%) of the average control value reflecting cell viability. The average values across the concentrations tested were then plotted and the IC₅₀ for was calculated by fitting the data to a 4-parameter IC₅₀ equation using software from Grafit (Erithacus Software). Each experiment was repeated twice and the data are presented as the mean IC₅₀ from both experiments.
- 35

The results are summarised in the following table.

Table 1 Thp1 Monocyte ATP Assay	
Compound	IC ₅₀ (μM) ⁽¹⁾
HMC-C-01-A	0.63
ABD899	0.2
ABD900	1.1
NASMP-01	1.0
NASMP-02	7.9
NASMP-03	3.0
NASMP-04	1.7
NASMP-05	1.1
NASMP-06	0.9
NASMP-07	0.8
NASMP-08	3.8
NASMP-09	1.4
NASMP-10	3.5
NASMP-11	1.6
NASMP-12	0.1
NASMP-13	1.7
NASMP-14	1.4
NASMP-15	0.6
NASMP-16	1.5
NASMP-17	4.6
NASMP-18	28.5 ⁽²⁾
NASMP-19	2.8
NASMP-20	18.1 ⁽²⁾
NASMP-21	6.1

- 5 ⁽¹⁾ Obtained using a 9-point concentration range from 10 μM to 10 nM with n=2 replicates per concentration. Data are the mean from 2 independent experiments.

⁽²⁾ Obtained using an 8-point concentration range from 100 μM to 100 nM with n=2 replicates per concentration. Data are the mean from 2 independent experiments.

- 10 The data demonstrate that many of the NASMP compounds described herein, and particularly compounds NASMP-01, NASMP-07, NASMP-12, and NASMP-15 show excellent potency in the Thp1 monocytic ATP assay, as well as no loss of potency, as compared to the reference compounds.

Biological Study 2
Human Hepatocyte Study

5 Metabolic stability of test compounds was measured by determination of the rate of disappearance of the compound when incubated in the presence of human hepatocytes, a primary source of the most important enzymes (cytochrome P450s) involved in drug metabolism. Study of drug stability in the presence of primary hepatocytes is accepted as a valuable model permitting rapid prediction of *in vivo* drug stability.

10

Human hepatocytes were obtained from a commercial source and viability was assessed using a trypan blue solution prior to use. Test compounds (final concentration 1 µM, 0.1 % DMSO, 0.9 % acetonitrile) or a marker (diclofenac or diltiazem, final assay concentration 1 µM, 0.1 % DMSO, 0.9 % acetonitrile) were incubated with pooled
15 hepatocytes for a 60 minute period and samples removed at up to 6 time points and analysed by LC-MS/MS for the presence/amount of test compounds.

Each compound was incubated for 0, 5, 15, 30, 45, or 60 minutes. The reactions were stopped by the addition of methanol containing an internal standard (1 µM Tolbutamide)
20 at the appropriate time points, mixed and placed at -20°C for ≥ 1 hour to quench and allow protein to precipitate. All samples were centrifuged (2500 x g, 20 minutes, 4°C). The aliquots were analysed using LC-MS/MS. Reactions were performed in duplicate at 37°C.

25 Data were processed, and the results plotted as ln(concentration) vs. time. The elimination rate constant (slope of the regression line, *k*) was calculated using the following formula, where *C(t)* is the concentration at time *t* and *C(0)* is the starting concentration:

$$k = \frac{\ln C(0) - \ln C(t)}{t}$$

30

The half-life (*t*_{1/2}) was calculated using the following formula:

$$t_{1/2} = \frac{\ln 2}{k}$$

35

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The intrinsic clearance (Cl_{int}) was calculated using the following formula, where $[cell]$ is the hepatocyte concentration in the assay:

$$Cl_{int} = \frac{k}{[cell]}$$

5

The data are summarised in the following table.

Table 2 Human Hepatocyte Stability		
Compound	Human $t_{1/2}$ (min)	Human Cl_{int} (uL/min/million cells)
HMC-C-01-A	154	7.6
ABD899	149	9
ABD900	220	6.3
NASMP-01	> 460.0	< 3.0
NASMP-02	> 460.0	< 3.0
NASMP-03	> 460.0	< 3.0
NASMP-05	NC	NC
NASMP-06	> 60.0	NC
NASMP-07	> 60.0	1.1
NASMP-09	> 412.5	< 3.4
NASMP-11	> 60.0	3.3
NASMP-12	NC	NC
NASMP-14	58.2	28.2
NASMP-15	> 60.0	NC
NASMP-16	> 60.0	NC
NASMP-18	352.2	3.8
NASMP-19	114.9	11.7
NASMP-20	> 460.0	< 3.0
NASMP-21	104.2	13.4

(NC = Not calculated due to high stability)

- 10 The data demonstrate that many of the NASMP compounds described herein show metabolic stability greater than that of the reference compounds, with NASMP-01, NASMP-02, NASMP-03, NASMP-05, NASMP-06, NASMP-09, NASMP-12, NASMP-15, NASMP-16, NASMP-18 and NASMP-20 showing exceptionally good stability.

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Biological Study 3

Aqueous Solubility

- 5 Aqueous solubility was measured by equilibration of compounds with fasted state simulated intestinal fluid (FaSSIF) and quantified spectrophotometrically.

FaSSIF was prepared as described below:

- 10 Preparation of blank FaSSIF: 0.21 g of sodium hydroxide (NaOH) pellets, 1.97 g of dihydrogen sodium phosphate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$) and 3.09 g of sodium chloride (NaCl) were dissolved in 400 mL of deionised water. The pH was adjusted to 6.5 using 1 M hydrochloric acid and further deionised water added to a final volume of 500 mL.

- 15 Preparation of FaSSIF: 0.056 g of SIF Powder (containing sodium taurocholate and lecithin) (Phares AG) was dissolved in 25 mL of blank FaSSIF and stirred until the powder was completely dissolved. The solution was allowed to stand for 2 hours during which it became opalescent; it was used within 24 hours. The final solution composition was characterised as follows:

- 20 Sodium taurocholate: 3 mM
Lecithin: 0.75 mM
Osmolarity: 270 ± 10 mOsmol
pH: 6.5

- 25 Aqueous solubility was determined by spiking a known concentration of test compound (dissolved in DMSO) into FaSSIF followed by incubation for 16 hours. The optical density was measured at the end of the incubation period for test compounds and a reference used to determine solubility. In brief, two samples were prepared for each determination: a reference sample consisting of a stock solution of test compound in DMSO diluted in system solution (a phosphate free, low absorption buffer) and propanol; and a test
30 sample (prepared in triplicate) consisting of 0.5 mL FaSSIF spiked with test compound at 0.2 mM. Each sample was incubated at room temperature for 16 hours with constant shaking at 250 rpm. At the end of the incubation period, 0.3 mL of each sample was filtered through a pION filter plate (PION, Woburn MA), diluted 1 : 1 with propanol and scanned using UV spectrophotometry at λ_{max} (190-400 nm) using a Spectra Max Plus –
35 Version 2.1000 (Molecular Devices, Sunnyvale, CA), with μSOL Explorer solubility determination software (pION, Woburn, MA).

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FaSSIF solubility was calculated using the following formula:

$$\text{FaSSIF Solubility} \frac{\text{mg}}{\text{mL}} = \frac{\left[\frac{150}{75} \right] * \left[\frac{\text{OD of sample}}{\text{OD of reference}} \right] * \text{Cr} * \text{molecular weight}}{10^6}$$

5 wherein:

“OD” is the optical density;

“Cr” is the concentration of the reference (33.4 µM); and

“molecular weight” is for the test compound (e.g., 381.44 for ABD735).

10 The data are summarised in the following table.

Table 3 FaSSIF Solubility		
Compound	Solubility (mg/mL) ⁽¹⁾	Solubility (mg/mL) ⁽²⁾
HMC-C-01-A	0.06 ⁽³⁾	
ABD899	0.06 ⁽³⁾	0.13
ABD900		0.12
NASMP-01	0.075	
NASMP-02	0.032	
NASMP-03	0.042	
NASMP-05	0.062	
NASMP-06	0.083	
NASMP-07	0.089	
NASMP-09	0.028	
NASMP-12	0.068	
NASMP-15	0.073	
NASMP-17	0.077	
NASMP-18	0.039	
NASMP-19	0.027	
NASMP-20	0.037	
NASMP-21	0.071	

⁽¹⁾ Two replicates were run per study at pH 6.5.

⁽²⁾ Two replicates were run per study at pH 6.8.

15

⁽³⁾ Three replicates were run for compounds HMC-C-01-A and ABD899.

The data demonstrate that the NASMP compounds described herein show solubility equivalent to that of the reference compounds with compounds NASMP-05, NASMP-06, NASMP-07, NASMP-12, NASMP-15, NASMP-17, and NASMP-21 showing particularly good solubility.

5

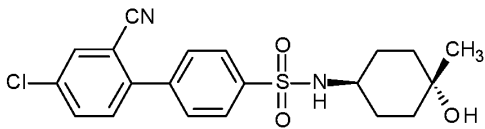
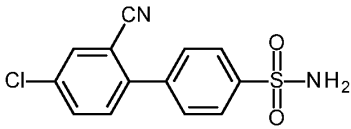
Biological Study 4

Metabolite identification

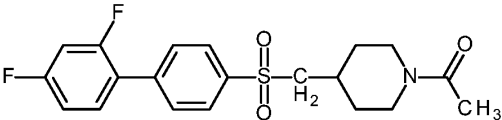
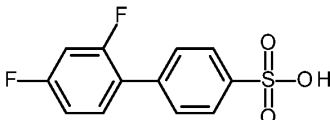
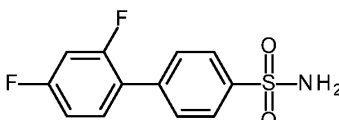
The formation of metabolites in humans, rats and dogs was assessed to determine the propensity of the compounds to form a biaryl metabolite.

The related sulfonamide compounds (for example, reference compound HMC-C-01-A) give rise to a biaryl sulphonamide metabolite (MET-001) which is persistent and has a long half-life. In addition, the metabolite acts as an inducer of metabolism in rats, which may complicate the assessment of toxicity in rodents. Therefore, the *lower* the propensity to form a biaryl metabolite, the *greater* the suitability of the compound for development for human use.

15

Table 4 Reference Compound HMC-C-01-A and Biaryl Sulfonamide Metabolite (MET-001)	
HMC-C-01-A	
MET-001	

20

Table 5 Compound NASMP-01, Postulated Biaryl Metabolite (MET-002), and Biaryl Sulphonamide version of MET-002 (CMPD-003) (MET-002 and CMPD-003 are not predicted, and were not detected)	
NASMP-01	
MET-002	
CMPD-003	

- In vitro* studies on the metabolism of drugs are usually performed using liver preparations such as isolated perfused livers, liver slices, liver homogenates, isolated cryopreserved hepatocytes, subcellular liver fractions (S9, cytosol, and microsomes), or recombinant metabolizing enzymes overexpressed on non-expressing cell systems, particularly CYP enzymes. Cryopreserved hepatocytes contain all the enzymes and co-factors needed for phase I and phase II drug metabolism, making them an excellent *in vitro* model for assessment of drug metabolic stability and metabolite profiling.
- 5
 - 10 Cryopreserved human, rat (Sprague Dawley) and dog (Beagle) hepatocytes were revived from liquid nitrogen and plated at a seeding density of 2×10^6 cells/mL (>95% viability). Following a 15 minute incubation at 37°C a sample was removed for a zero (0) minute time point assessment. Test compound was then added at a final concentration of 10 µM and the reaction initiated by the addition of 250 µL Krebs Henseleit Buffer (KHB, pH 7.4).
 - 15 Samples were incubated for 5, 15, 30 and 60 minutes at 37°C / 5% CO₂.

All samples were processed for analysis by protein precipitation using 500 µL ice-cold acetonitrile and analysed with a fit-for-purpose LC-MS/MS method.

- 20 At the completion of the study, the results were expressed as detection of the biaryl metabolite at the final time point.

The following table shows the presence or absence of the biaryl metabolite in primary hepatocyte incubations for the reference compound HMC-C-01-A and NASMP-01.

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Table 6 Biaryl Metabolite Detection	
Compound	Biaryl metabolite detected?
HMC-C-01-A	Yes (MET-001)
NASMP-01	No

The data demonstrate that the NASMP compounds described herein show *greatly increased* suitability for development for human use, as compared to the reference compound (HMC-C-01-A).

5

Whereas the reference compound HMC-C-01-A gave rise to the biaryl sulphonamide metabolite (MET-001) in large quantities, compound NASMP-01 did not produce either biaryl sulphonamide metabolite, CMPD-03, or biaryl sulphonic acid metabolite, MET-002.

10

Biological Study 5 hERG Ion Channel Assay

Inhibition of the human Ether-à-go-go-Related Gene (hERG) ion channel mediates the repolarizing IKr current in the cardiac action potential, thereby indicating that it contributes to the electrical activity that coordinates the beating of the heart. When the ability of hERG to conduct electrical current across the cell membrane is inhibited or compromised it can result in a potentially fatal disorder called long QT syndrome. This association between hERG and long QT syndrome has made hERG inhibition an important anti-target that must be avoided during drug development.

20

The activity of the compounds against the hERG ion channel was tested using a binding assay in stably transfected Human Embryonic Kidney cells (hERG-HEK293). hERG-HEK293 cells were cultured in MEM medium (Invitrogen) +10% FBS, glutamine and non-essential amino acids at 37°C. To prepare membranes, cells were homogenised on ice, centrifuged at 650 x g for 10 minutes at +4°C, and the resulting supernatant centrifuged at 48000 x g for 10 minutes at +4°C. The pellet was resuspended in ice-cold 50 mM Tris-HCl buffer, 5 mM KCl (pH 8.5) and stored frozen in aliquots until use.

25

For binding assays, membranes were thawed, re-suspended in assay buffer (10 mM HEPES pH 7.4, 0.1% BSA, 5 mM potassium chloride, 0.8 mM magnesium chloride, 130 mM sodium chloride, 1 mM sodium-EGTA, 10 mM glucose) and incubated with ³H astemizole (1.5 nM), and with or without test compound at 25°C for 60 minutes. Binding was determined following filtration of the membranes and washing in Tris-HCl buffer by scintillation counting of ³H astemizole.

35

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The degree of binding of compounds to the hERG ion channel (%) was obtained by measuring the binding of ^3H astemizole and its displacement by test compound. A value of 0% indicates no binding and a value of 100% indicates complete displacement of the radiolabelled ligand.

5

The results are summarised in the following table.

Table 7 hERG Ion Channel Assay Data	
Compound	% inhibition at 30 μM
HMC-C-01-A	18 ⁽¹⁾
NASMP-01	14
NASMP-02	30
NASMP-03	20
NASMP-05	23
NASMP-06	35
NASMP-07	79
NASMP-09	7
NASMP-12	35
NASMP-15	45
NASMP-17	14
NASMP-18	14
NASMP-19	21
NASMP-20	39
NASMP-21	1

⁽¹⁾ Tested at 25 μM .

- 10 The data demonstrate that the NASMP compounds described herein have cardiac safety properties required for an orally active drug, and have safety advantages as compared to the reference compounds, such as HMC-C-01-A, with NASMP-01, NASMP-09, NASMP-17, NASMP-18 and NASMP-21 showing a particularly positive profile.

15

Biological Study 6

Human Cytochrome P450 inhibition Assay

- 20 Inhibition of cytochrome P450 (CYP450) enzymes is one of the major reasons for drug-drug interactions in clinical use, and can complicate, or stop the development of a new drug.

The ability of test compounds to inhibit five of the most relevant cytochrome P450 enzymes was measured by determination of the activity of cytochrome P450 enzymes in

recombinant cytochrome preparations, called Bactosomes (Cypex Ltd, Dundee, Scotland UK DD2 1NH), in the presence of a specific probe substrate. Bactosomes are a highly efficient and cost-effective source of recombinant CYP450s which have a higher specific activity of enzyme compared to other sources, such as liver microsomes. If a compound inhibits enzyme activity, the rate of disappearance of the probe substrate is reduced. The following CYP450 isoforms were assayed: CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The study of CYP450 inhibition potential in Bactosomes is accepted as a valuable model permitting rapid prediction of potential drug-drug interactions *in vivo* (see, e.g., Weaver *et al.*, 2003).

Bactosomes were obtained from a commercial source (Cypex, Scotland, UK). Test compounds were incubated with Bactosomes at 6 concentrations. Samples were incubated for 10 minutes, after which the reaction was stopped and the samples analysed by LC-MS/MS Multiple Reaction Monitoring (MRM) for the presence/amount of substrate probe.

CYP450 enzymes (final protein 75 pmol/mL for CYP1A2; 12.5 pmol/mL for CYP2C19; and 25 pmol/mL for CYP2C9, 2D6 and 3A4), 0.1 M phosphate buffer pH 7.4, probe and test compound (final concentration 50, 15.8, 5, 1.58, 0.5 and 0.158 μ M; diluted from 10 mM stock solution to give a final DMSO concentration of 1%) were pre-incubated at 37°C for 5 minutes. The reaction was initiated by the addition of 20 μ L of 10 mM NADPH in phosphate buffer. The final incubation volume was 200 μ L. The following control inhibitors were used for each CYP450 inhibition assay: CYP1A2: α -naphthoflavone; CYP2C9: sulfaphenazole; CYP2C19: tranilcypromine; CYP2D6: quinidine; CYP3A4: ketoconazole.

Each compound was incubated for 10 minutes at 37°C. The reactions were stopped by the addition of methanol (final composition 1:1, aqueous : methanol). The incubation plates were shaken, chilled at 20°C for 2 hours, and centrifuged at 3500 rpm for 15 minutes at 4°C to precipitate the protein. The supernatant was then transferred to vials for analysis using MS/MRM, with the conditions shown in the following table.

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Table 8 MS Conditions	
HPLC:	Waters Alliance 2790
MS/MS:	Triple Quadrupole Quattro Ultima (Micromass, Manchester)
Software:	Analyst 1.5
Ionisation mode:	ESI+
Scan mode:	Multiple reaction monitoring (MRM)
Column:	Devosil C30
Column Temperature (°C):	40
Phase A:	0.1% formic acid in water
Phase B:	0.1% formic acid in methanol
Gradient	97% A (0-0.3 min), 5% A (0.55-1.55 min), 97% A (1.6 min)
Stop time	2.5 min
Injection volume (µL):	30
Flow Rate (mL/min):	1.2

IC₅₀ values were determined by linear transformation within Microsoft Excel.

The data are summarised in the following table.

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Table 9 Human CYP450 inhibition					
Compound	IC ₅₀ (μM)				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
ABD899	>25	3.9	7.3	45.3	21.6
HMC-C-01-A	25	21	>25	16.6	>25
HMC-C-08-A	27	6.7	30	19	29
HMC-C-09-A	23	34	>50	>50	33
HMC-C-10-B	>16	2.4	8.5	>16	9.2
HMC-C-11-A	11	2.7	5.1	9.3	12
HMC-N-05-A	36	27	>50	>50	>50
NASMP-01	>50	>50	>50	>50	>50
NASMP-05	>50	>50	>50	>50	>50
NASMP-06	>50	42.7	>50	>50	>50
NASMP-07	>50	19.6	36.4	>50	>50
NASMP-09	>50	>50	17.8	>50	44.5
NASMP-12	>50	15.4	>50	45.4	>50
NASMP-15	>50	21.5	>50	>50	>50

The data demonstrate that the NASMP compounds described herein show reduced drug-drug interaction liability as compared with the reference compounds, with compounds NASMP-01 and NASMP-05 showing a particularly good profile.

5

Biological Study 7

Rodent Pharmacokinetics Studies

Absorption and metabolic stability were studied using an *in vivo* pharmacokinetics assay.

10

Male Han Wistar rats, 196-329 g, were dosed with test compounds administered either orally or intravenously (dose level of 0.25 mg/kg body weight intravenous or 1.25 mg/kg body weight orally). Test compounds were formulated in 0.5% carboxymethylcellulose (CMC) / 0.1% Tween-80 for administration via the oral route, or in 5% DMSO / 10% solutol in saline for administration via the intravenous route. For compound HMC-C-01-A the oral administration was formulated in 2% dimethylacetamide / 20% hydroxypropyl-β-cyclodextrin in water. Animals were given free access to food throughout the study except for fasting overnight and until 2 hours post dose on the day of dosing.

15

20 Blood samples were taken from the retro-orbital plexus at the following time points and placed in microtubes containing 20% K₂EDTA solution:

Oral Dosing: predose; 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post dose.

- 160 -

Intravenous Dosing: predose; 0.033, 0.1, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post dose.

- 5 Blood samples were centrifuged to obtain plasma, which was transferred to a separate container and frozen at -20°C.

- For analysis, samples were thawed at room temperature and prepared by protein precipitation with acetonitrile spiked with internal standard (500 ng/mL glipizide) in the ratio 1 : 4 with plasma. The concentration of test compound in rat plasma samples was
10 determined using LC-MS/MS, with the conditions shown in the following table.

Table 10 LC-MS/MS Conditions			
Compound	References	NASMP-01	NASMP-06, -12, -15
HPLC/UHPLC:	Schimadzu Agilent	Vanquish Flex	Vanquish
MS/MS:	API 4000	Q-Exactive	TSQ Quantiva
Ionisation mode:	Turbo spray, negative mode	Positive	Positive
Scan mode:	Multiple reaction monitoring (MRM)		
Column	Waters, Xterra, MS-C18 (2) 5 µm 50 x 3.0 mm; Discovery Grace Smart RP183µ, 150 x 2.1, 3 µM; Waters Symmetry Shelf C18 75 x 4.6, 3.5 µM; Agilent Zorbax XDB, 150 x 4.6, 5 µM	Luna Omega Polar C18, 50 x 2.1mm, 1.6µm.	Phenomenex Luna Omega 1.6µm, C18 100Å, 50 x 2.1mm
Column Temperature (°C):	40	65	65
Phase A:	Acetonitrile + 0.1% formic acid	MilliQ water + 0.1% formic acid	MilliQ water + 0.1% formic acid
Phase B:	0.1% formic acid	Methanol + 0.1% formic acid	Methanol + 0.1% formic acid
Flow Rate (mL/min):	0.8-1.2	0.8	0.8

- The pharmacokinetic parameters for the test compounds were calculated by Phoenix WinNonlin version 8.0 (Certara, CA) using standard non-compartmental methods. Peak
15 plasma concentrations (C_{max}) and time of the peak plasma concentration (T_{max}) were the

- observed values. The area under the plasma concentration-time curve (AUC) was determined by use of the linear trapezoidal rule up to the last measurable concentration (AUC_{last}) and thereafter by extrapolation of the terminal elimination phase to infinity (AUC_{inf}). The elimination phase half-life ($t_{1/2}$) was calculated as $0.693 / k_{el}$. The tentative oral bioavailability (F) was calculated by dividing the AUC (0-24 hours) after oral administration by the adjusted AUC (0-8 hours) after intravenous administration (i.e., $F = AUC(p.o.) \times Dose(i.v.) / AUC(i.v.) \times Dose(p.o.)$) and reported as a percentage (%).
- 10 The pharmacokinetic data are summarised in the following table.

Table 11 Pharmacokinetic data				
Compound	Bioavail, F (%)	i.v. AUC (ng/mL/min)	p.o. AUC (ng/mL/min)	$T_{1/2}$ (h)
ABD899	50	2133	10740 ⁽⁴⁾	10.8
REF001	50	963	4766 ⁽⁴⁾	7.2
HMC-C-07-B ^{(1) (2)}	100	24072	146299 ⁽⁵⁾	9.7
HMC-C-07-B ⁽³⁾	86	11627	39463	9.0
HMC-N-05-A ⁽¹⁾	88	891	3937	0.8
NASMP-01-A	56	816	2299	6.6
NASMP-06-A	24	349	3030	3.3
NASMP-12-A	>69	581	3160	5.1
NASMP-15-A	>62	282	1750	4.9

⁽¹⁾ Compound was dosed in 5% DMSO / 10% solutol in saline for administration via both the oral and intravenous routes.

- 15 ⁽²⁾ Samples were collected at: pre-dose, 0.08, 0.25, 0.5, 1, 2, 4, 8, 23, and 24 hours post intravenous dosing, and at pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 23, and 24 hours post oral dosing.

⁽³⁾ Samples were collected at: pre-dose, 0.03, 0.1, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours post intravenous dosing.

- 20 ⁽⁴⁾ Dosed at 5 mg/kg orally.

⁽⁵⁾ Dosed at 10 mg/kg orally.

These data demonstrate that the NASMP compounds described herein have excellent oral pharmacokinetic properties comparable to those of the reference compounds. This indicates that these compounds are likely to be suitable for use as oral drugs.

5

Biological Study 8

Mouse Collagen-Induced Arthritis

Seven- to eight-week-old male DBA/1j mice were used for all procedures. Animals were housed in groups of 10, and were maintained at $21^{\circ}\text{C} \pm 2^{\circ}\text{C}$ on a 12-hour light/dark cycle with food and water ad libitum. Complete Freund's adjuvant (CFA) was prepared by emulsifying bovine type II collagen at 4 mg/mL with a 4 mg/mL suspension of Mycobacterium tuberculosis H37Ra in Incomplete Freund's Adjuvant (IFA) (0.85 mL paraffin oil and 0.15 mL mannide monooleate) in a 1 : 1 (v/v) ratio. All mice were immunised subcutaneously with 200 μg of bovine type II collagen in CFA. 21 days later, all mice were immunised subcutaneously with 100 μg of bovine type II collagen in IFA. The mice started to develop signs and symptoms of arthritis following the 'booster' immunisation.

For macroscopic assessment of arthritis, the following signs were monitored in each paw of each mouse three times per week and summed to generate the Arthritic Index (AI) (the maximum AI for one animal is 16):

- 0 = no visible effects of arthritis.
- 1 = oedema and/or erythema of 1 digit.
- 2 = oedema and/or erythema of 2 digits.
- 3 = oedema and/or erythema of more than 2 digits.
- 4 = severe arthritis of entire paw and digits.

Animals were sorted into treatment groups with a mean arthritic index of 2.5 and then dosed once daily for 14 days with compound: by oral gavage for test compounds, or by subcutaneous injection at a dose of 10 mg/kg for the positive control, etanercept. After completion of the experiment, the mice were sacrificed.

The data were analysed by generating an average of the arthritic index across each treatment group. The mean arthritic index was then compared to the arthritic index of control (untreated) animals using the following formula to generate a percentage inhibition of disease.

% inhibition of disease = 100 - $\left[\frac{\text{average arthritic index: treated animals}}{\text{average arthritic index: untreated animals}} * 100 \right]$

The data are summarised in the following table.

Table 12 Inhibition of Arthritis		
Compound	Dose (mg / kg / day)	% inhibition of disease
ABD899	10	77
HMC-C-01-A	10	40
HMC-N-01-A	10	45
HMC-C-01-B	10	26
HMC-N-01-B	10→1 (*)	38
CHMSA-01-A	10	63
CHMSA-03-A	10	62
NASMP-01-A	10	64

5

These data indicate that the NASMP compounds described herein show excellent oral *in vivo* activity in preventing the progression of established, severe arthritis.

* * *

10

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive. It should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention.

15

REFERENCES

A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these
5 publications are provided below.

Each of these publications is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

10

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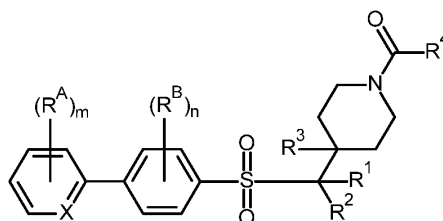
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CLAIMS

1. A compound of the following formula:



- 5 or a pharmaceutically acceptable salt or solvate thereof;
wherein:
- X= is independently -CH= or -N=;
- 10 “m” is independently 0, 1, 2, or 3;
each -R^A is independently -F, -Cl, -R^{AC}, -R^{AF}, or -CN;
-R^{AC} is independently saturated linear or branched C₁₋₃alkyl;
-R^{AF} is independently saturated linear or branched C₁₋₃fluoroalkyl;
- 15 “n” is independently 0, 1, or 2;
each -R^B is independently -F, -Cl, -R^{BC}, -R^{BF}, or -CN;
-R^{BC} is independently saturated linear or branched C₁₋₃alkyl;
-R^{BF} is independently saturated linear or branched C₁₋₃fluoroalkyl;
- 20 -R¹ is independently -H or -R^{1X};
-R^{1X} is independently -F, -R^{1C}, or -R^{1F};
-R^{1C} is independently saturated linear or branched C₁₋₃alkyl;
-R^{1F} is independently saturated linear or branched C₁₋₃fluoroalkyl;
- 25 -R² is independently -H or -R^{2X};
-R^{2X} is independently -F, -R^{2C}, or -R^{2F};
-R^{2C} is independently saturated linear or branched C₁₋₃alkyl;
-R^{2F} is independently saturated linear or branched C₁₋₃fluoroalkyl;
- 30 or -R¹ and -R², taken together with the carbon atom to which they are attached,
form saturated C₃₋₆cycloalkyl;
- R³ is independently -H or -R^{3X};
-R^{3X} is independently -R^{3C} or -R^{3F};
- 35 -R^{3C} is independently saturated linear or branched C₁₋₃alkyl;
-R^{3F} is independently saturated linear or branched C₁₋₃fluoroalkyl;

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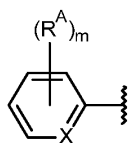
- R⁴ is independently -R^{4C}, -R^{4CC}, or -N(R^{4N1})(R^{4N2});
-R^{4C} is independently saturated linear or branched C₁₋₆alkyl;
-R^{4CC} is independently saturated C₃₋₆cycloalkyl;
5 -R^{4N1} is independently -H or -R^{4N1C};
-R^{4N1C} is independently saturated linear or branched C₁₋₄alkyl;
-R^{4N2} is independently -H or -R^{4N2C}; and
-R^{4N2C} is independently saturated linear or branched C₁₋₄alkyl.
- 10 or -N(R^{4N1})(R^{4N2}) is independently azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is optionally substituted with one or more saturated linear or branched C₁₋₄alkyl groups.
2. A compound according to claim 1, wherein -X= is -CH=.
- 15 3. A compound according to claim 1, wherein -X= is -N=.
4. A compound according to any one of claims 1 to 3, wherein "m" is independently 0, 1, or 2.
- 20 5. A compound according to any one of claims 1 to 3, wherein "m" is 1 or 2.
6. A compound according to any one of claims 1 to 5, wherein each -R^A, if present, is independently -F, -Cl, or -CN.
- 25 7. A compound according to any one of claims 1 to 5, wherein each -R^A, if present, is -F.
8. A compound according to any one of claims 1 to 5, wherein each -R^A, if present,
- 30 is -Cl.
9. A compound according to any one of claims 1 to 8, wherein each -R^{AC}, if present, is -CH₃.
- 35 10. A compound according to any one of claims 1 to 9, wherein each -R^{AF}, if present, is -CF₃.
11. A compound according to any one of claims 1 to 10, wherein "n" is independently 1 or 2.
- 40 12. A compound according to any one of claims 1 to 10, wherein "n" is 0.

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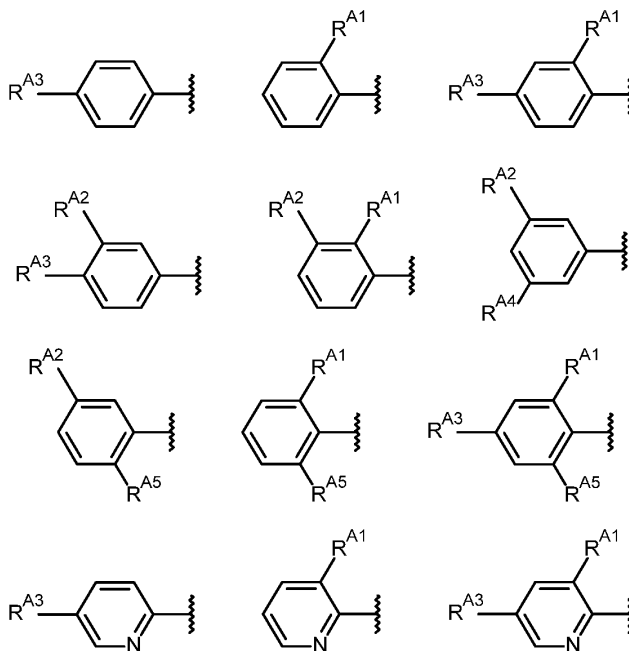
13. A compound according to any one of claims 1 to 12, wherein each $-R^B$, if present, is independently -F, -Cl, or -CN.
- 5 14. A compound according to any one of claims 1 to 12, wherein each $-R^B$, if present, is -F.
15. A compound according to any one of claims 1 to 12, wherein each $-R^B$, if present, is -Cl.
- 10 16. A compound according to any one of claims 1 to 15, wherein each $-R^{BC}$, if present, is $-CH_3$.
- 15 17. A compound according to any one of claims 1 to 16, wherein each $-R^{BF}$, if present, is $-CF_3$.

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18 A compound according to claim 1, wherein the group:



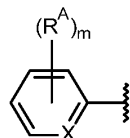
is independently selected from:



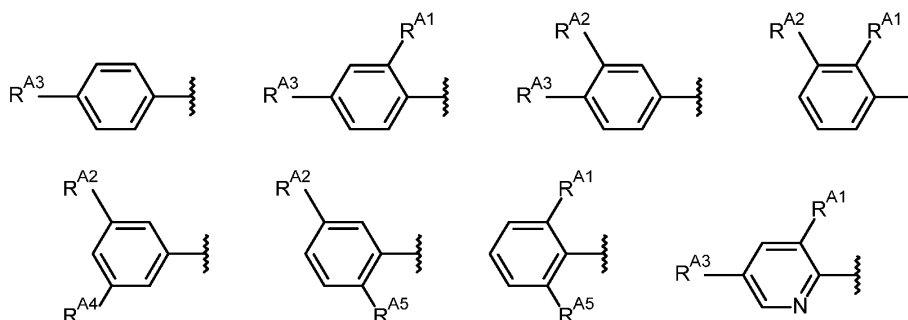
wherein each of $-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, and $-R^{A5}$ is independently as defined for $-R^A$.

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19. A compound according to claim 1, wherein the group:

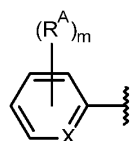


is independently selected from:

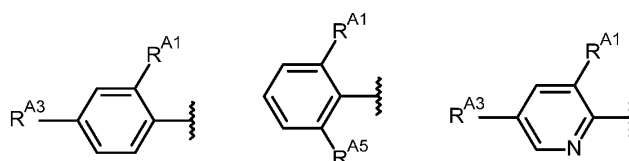


wherein each of $-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, and $-R^{A5}$ is independently as defined for $-R^A$.

10 20. A compound according to claim 1, wherein the group:



is independently selected from:

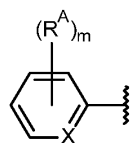


wherein each of $-R^{A1}$, $-R^{A3}$, and $-R^{A5}$ is independently as defined for $-R^A$.

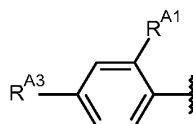
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21. A compound according to claim 1, wherein the group:

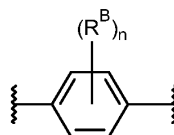


is:

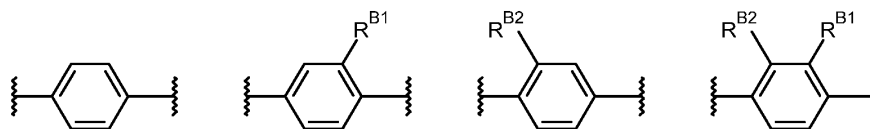


5 wherein each of $-R^{A1}$ and $-R^{A3}$ is independently as defined for $-R^A$.

22. A compound according to any one of claims 1 and 18 to 21, wherein the group:



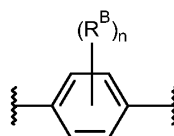
is independently selected from:



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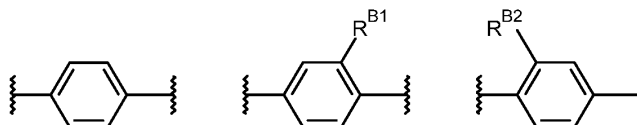
wherein each of $-R^{B1}$ and $-R^{B2}$ is independently as defined for $-R^B$.

23. A compound according to any one of claims 1 and 18 to 21, wherein the group:



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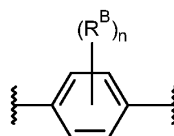
is independently selected from:



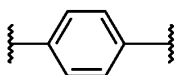
wherein each of $-R^{B1}$ and $-R^{B2}$ is independently as defined for $-R^B$.

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24. A compound according to any one of claims 1 and 18 to 21, wherein the group:

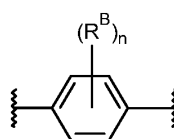


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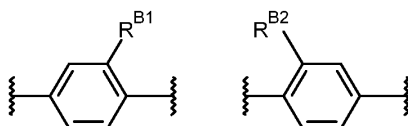


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25. A compound according to any one of claims 1 and 18 to 21, wherein the group:



is independently selected from:



10

wherein each of $-R^{B1}$ and $-R^{B2}$ is independently as defined for $-R^B$.

26. A compound according to any one of claims 1 to 25, wherein $-R^1$ is $-R^{1X}$.

27. A compound according to any one of claims 1 to 25, wherein $-R^1$ is $-H$.

15

28. A compound according to any one of claims 1 to 27, wherein $-R^{1X}$, if present, is independently $-F$, $-R^{1C}$, or $-R^{1F}$.

29. A compound according to any one of claims 1 to 27, wherein $-R^{1X}$, if present, is $-F$.

20

30. A compound according to any one of claims 1 to 27, wherein $-R^{1X}$, if present, is $-R^{1C}$.

31. A compound according to any one of claims 1 to 30, wherein $-R^{1C}$, if present, is $-CH_3$.

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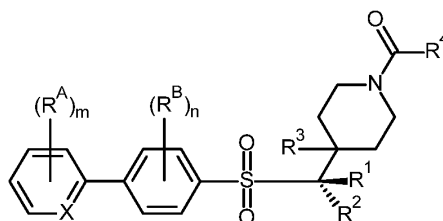
32. A compound according to any one of claims 1 to 31, wherein $-R^2$ is $-R^{2X}$.

33. A compound according to any one of claims 1 to 31, wherein $-R^2$ is $-H$.

34. A compound according to any one of claims 1 to 33, wherein $-R^{2X}$, if present, is independently $-F$, $-R^{2C}$, or $-R^{2F}$.
- 5 35. A compound according to any one of claims 1 to 33, wherein $-R^{2X}$, if present, is $-F$.
36. A compound according to any one of claims 1 to 33, wherein $-R^{2X}$, if present, is $-R^{2C}$.
- 10 37. A compound according to any one of claims 1 to 36, wherein $-R^{2C}$, if present, is $-CH_3$.
38. A compound according to any one of claims 1 to 25, wherein $-R^1$ and $-R^2$, taken together with the carbon atom to which they are attached, form saturated
15 C_{3-6} cycloalkyl.
39. A compound according to any one of claims 1 to 38, wherein $-R^3$ is $-R^{3X}$.
40. A compound according to any one of claims 1 to 38, wherein $-R^3$ is $-H$.
- 20 41. A compound according to any one of claims 1 to 40, wherein $-R^{3X}$, if present, is $-R^{3C}$.
42. A compound according to any one of claims 1 to 41, wherein $-R^{3C}$, if present,
25 is $-CH_3$.
43. A compound according to any one of claims 1 to 42, wherein $-R^4$ is $-R^{4C}$.
44. A compound according to any one of claims 1 to 42, wherein $-R^4$ is $-R^{4CC}$.
- 30 45. A compound according to any one of claims 1 to 42, wherein $-R^4$ is $-N(R^{4N1})(R^{4N2})$.
46. A compound according to any one of claims 1 to 45, wherein $-R^{4C}$, if present, is saturated linear or branched C_{1-4} alkyl.
- 35 47. A compound according to any one of claims 1 to 45, wherein $-R^{4C}$, if present, is $-CH_3$ or $-CH_2CH_3$.
- 40 48. A compound according to any one of claims 1 to 47, wherein $-R^{4N1}$, if present, is $-R^{4N1C}$.

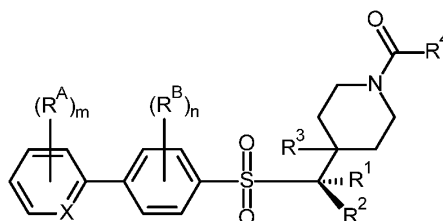
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49. A compound according to any one of claims 1 to 47, wherein $-R^{4N1}$, if present, is -H.
50. A compound according to any one of claims 1 to 49, wherein $-R^{4N1C}$, if present, is saturated linear or branched C_{1-3} alkyl.
51. A compound according to any one of claims 1 to 49, wherein $-R^{4N1C}$, if present, is $-CH_3$ or $-CH_2CH_3$.
52. A compound according to any one of claims 1 to 51, wherein $-R^{4N2}$, if present, is $-R^{4N2C}$.
53. A compound according to any one of claims 1 to 51, wherein $-R^{4N2}$, if present, is -H.
54. A compound according to any one of claims 1 to 53, wherein $-R^{4N2C}$, if present, is saturated linear or branched C_{1-3} alkyl.
55. A compound according to any one of claims 1 to 53, wherein $-R^{4N2C}$, if present, is $-CH_3$ or $-CH_2CH_3$.
56. A compound according to any one of claims 1 to 45, wherein $-N(R^{4N1})(R^{4N2})$, if present, is independently pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl; and is optionally substituted with one or more saturated linear or branched C_{1-4} alkyl groups.
57. A compound according to any one of claims 1 to 56, wherein $-R^1$ and $-R^2$ are different, and the compound is a compound of the following formula, or a pharmaceutically acceptable salt or solvate thereof:



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58. A compound according to any one of claims 1 to 56, wherein -R¹ and -R² are different, and the compound is a compound of the following formula, or a pharmaceutically acceptable salt or solvate thereof:



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59. A compound according to claim 1, which is a compound of one of following formulae, or a pharmaceutically acceptable salt or solvate thereof:
NASMP-01 through NASMP-21.

- 10 60. A composition comprising a compound according to any one of claims 1 to 59, and a carrier, diluent, or excipient.
61. A method of preparing a composition comprising the step of mixing a compound according to any one of claims 1 to 59 and a carrier or diluent.
- 15 62. A compound according to any one of claims 1 to 59 for use in a method of treatment of the human or animal body by therapy.
63. A compound according to any one of claims 1 to 59 for use in a method of treatment of a disorder.
- 20 64. Use of a compound according to any one of claims 1 to 59 in the manufacture of a medicament for treatment of a disorder.
- 25 65. A method of treatment of a disorder comprising administering to a patient in need of treatment a therapeutically effective amount of a compound according to claim 1.
- 30 66. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
a disorder associated with changes in cellular metabolism.
- 35 67. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
an autoimmune/inflammatory disorder; cancer; or a disorder mediated by osteoclasts.

68. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
multiple myeloma, diffuse large B-cell lymphoma, acute myeloid leukemia,
eosinophilic leukemia, glioblastoma, melanoma, ovarian cancer, chemotherapy
resistant cancer, radiation resistant cancer, inflammatory arthritis, rheumatoid
arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic
lupus erythematosus (SLE), lupus nephritis, asthma, chronic obstructive
pulmonary disease (COPD).
69. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
an autoimmune/inflammatory disorder.
70. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
inflammatory arthritis (including, e.g., rheumatoid arthritis; psoriatic
arthritis; ankylosing spondylitis; spondyloarthritis; reactive arthritis; infectious
arthritis; systemic lupus erythematosus; scleroderma; gout; adult-onset Still's
disease; juvenile idiopathic arthritis); psoriasis; systemic lupus erythematosus;
lupus nephritis; systemic sclerosis; scleroderma; hepatitis; endometriosis;
adenomyosis; Sjogren's syndrome; inflammatory bowel disease; ulcerative colitis;
Crohn's disease; multiple sclerosis; asthma; atherosclerosis; chronic obstructive
pulmonary disease (COPD); uveitis; Hidradenitis suppurativa; autoimmune
hepatitis; pulmonary fibrosis; allergic disease (including, e.g., atopy, allergic
rhinitis, atopic dermatitis, anaphylaxis, allergic bronchopulmonary aspergillosis,
allergic gastroenteritis, hypersensitivity pneumonitis); an allergy; type I diabetes;
rheumatic fever; celiac disease; encephalitis; oophoritis; primary biliary cirrhosis;
insulin-resistant diabetes; autoimmune adrenal insufficiency (Addison's disease);
acne; acne conglobate; acne fulminans; autoimmune oophoritis; autoimmune
orchitis; autoimmune haemolytic anaemia; paroxysmal cold hemoglobinuria;
Behçet's disease; autoimmune thrombocytopenia; autoimmune neutropenia;
pernicious anaemia; pure red cell anaemia; autoimmune coagulopathy;
myasthenia gravis; autoimmune polyneuritis; pemphigus; rheumatic carditis;
Goodpasture's syndrome; postcardiotomy syndrome; polymyositis;
dermatomyositis; irritable bowel syndrome; pancreatitis; gastritis, lichen planus;
delayed type hypersensitivity; chronic pulmonary inflammation; pulmonary
alveolitis; pulmonary granuloma; gingival inflammation; endodontic disease;
periodontal disease; hypersensitivity pneumonitis; hay fever; anaphylaxis; skin
allergy; hives; gout; polycystic kidney disease; cryopyrin-associated
periodic syndrome (CAPS); Muckle-Wells Syndrome; Guillain-Barre syndrome;

- chronic inflammatory demyelinating polyneuropathy; organ or transplant rejection; chronic allograft rejection; acute or chronic graft versus-host disease; dermatitis; atopic dermatomyositis; Graves' disease; autoimmune (Hashimoto's) thyroiditis; blistering disorder; vasculitis syndrome; immune-complex mediated vasculitis;
- 5 bronchitis; cystic fibrosis; pneumonia; pulmonary oedema; pulmonary embolism; sarcoidosis; hypertension; emphysema; respiratory failure; acute respiratory distress syndrome; BENTA disease; or polymyositis.
71. A compound for use according to claim 63, use according to claim 64, or a
10 method according to claim 65, wherein the treatment is treatment of:
 inflammatory arthritis (including, e.g., rheumatoid arthritis; psoriatic arthritis; systemic lupus erythematosus; juvenile idiopathic arthritis); psoriasis; lupus nephritis; systemic sclerosis; inflammatory bowel disease; ulcerative colitis; Crohn's disease; Hidradenitis suppurativa; or multiple sclerosis.
- 15 72. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
 cancer.
- 20 73. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
 multiple myeloma; lymphoma; leukaemia; carcinoma; or sarcoma.
- 25 74. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
 Hodgkin's lymphoma; non-Hodgkin's lymphoma; lymphocytic lymphoma; granulocytic lymphoma; monocytic lymphoma; diffuse large B-cell lymphoma (DLBCL); mantle cell lymphoma (MCL); follicular cell lymphoma (FL); mucosa-associated lymphoid tissue (MALT) lymphoma; marginal zone lymphoma; T-cell
30 lymphoma; marginal zone lymphoma; or Burkitt's lymphoma.
75. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
 chronic lymphocytic leukemia (CLL); acute myeloid leukemia (AML); acute
35 lymphocytic leukemia (ALL); lymphoblastic T-cell leukemia; chronic myelogenous leukemia (CML); hairy-cell leukemia; acute lymphoblastic T-cell leukemia; acute eosinophilic leukemia; immunoblastic large-cell leukemia; megakaryoblastic leukemia; acute megakaryocytic leukemia; promyelocytic leukemia;
 erythroleukemia; or plasmacytoma.
- 40

76. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
- colon cancer; breast cancer; ovarian cancer; lung cancer (including, e.g., small cell lung carcinoma and non-small cell lung carcinoma); prostate cancer; cancer of the oral cavity or pharynx (including, e.g., cancer of the lip, tongue, mouth, larynx, pharynx, salivary gland, buccal mucosa); esophageal cancer; stomach cancer; small intestine cancer; large intestine cancer; rectal cancer; liver passage cancer; biliary passage cancer; pancreatic cancer; bone cancer; connective tissue cancer; skin cancer; cervical cancer; uterine cancer; corpus cancer; endometrial cancer; vulval cancer; vaginal cancer; testicular cancer; bladder cancer; kidney cancer; ureter cancer; urethral cancer; urachus cancer; eye cancer; glioma; spinal cord cancer; central nervous system cancer; peripheral nervous system cancer; meningeal cancer; thyroid cancer; adrenocarcinoma; astrocytoma; acoustic neuroma; anaplastic astrocytoma; basal cell carcinoma; blastoglioma; choriocarcinoma; chordoma; craniopharyngioma; cutaneous melanoma; cystadenocarcinoma; embryonal carcinoma; ependymoma; epithelial carcinoma; gastric cancer; genitourinary tract cancer; glioblastoma multiforme; head and neck cancer; hemangioblastoma; hepatocellular carcinoma; renal cell carcinoma (RCC); hepatoma; large cell carcinoma; medullary thyroid carcinoma; medulloblastoma; meningioma mesothelioma; myeloma; neuroblastoma; oligodendroglioma; epithelial ovarian cancer; papillary carcinoma; papillary adenocarcinoma; paraganglioma; parathyroid tumour; pheochromocytoma; pinealoma; plasmacytoma; retinoblastoma; sebaceous gland carcinoma; seminoma; melanoma; squamous cell carcinoma; sweat gland carcinoma; synovioma; thyroid cancer; uveal melanoma; or Wilm's tumour.
77. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
- colon cancer; breast cancer; ovarian cancer; lung cancer (including, e.g., small cell lung carcinoma and non-small cell lung carcinoma); prostate cancer; stomach cancer; pancreatic cancer; bone cancer; skin cancer; cervical cancer; uterine cancer; endometrial cancer; testicular cancer; bladder cancer; kidney cancer; eye cancer; liver cancer; glioma; thyroid cancer; adrenocarcinoma; astrocytoma; acoustic neuroma; anaplastic astrocytoma; cutaneous melanoma; gastric cancer; glioblastoma multiforme; head and neck cancer; hepatocellular carcinoma; renal cell carcinoma (RCC); melanoma; or squamous cell carcinoma.

78. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
colon cancer; breast cancer; ovarian cancer; lung cancer (including, e.g., small cell lung carcinoma and non-small cell lung carcinoma); prostate cancer;
5 pancreatic cancer; bone cancer; liver cancer; glioblastoma multiforme; head and neck cancer; or melanoma.
79. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
10 Askin's tumour; sarcoma botryoides; chondrosarcoma; endotheliosarcoma; Ewing's sarcoma; Malignant hemagioendothelioma; malignant Schwannoma; osteosarcoma; gastrointestinal stromal tumour (GIST); myxosarcoma; alveolar soft part sarcoma; angiosarcoma; cystosarcoma phyllodes; dermatofibrosarcoma; desmoid tumour; desmoplastic small round cell tumour; extraskeletal
15 chondrosarcoma; osteosarcoma; fibrosarcoma; hemagiopericytoma; hemangiosarcoma; Kaposi's sarcoma; leiomyosarcoma; liposarcoma; lymphangiosarcoma; lymphangioendotheliosarcoma; lymphosarcoma; malignant peripheral nerve sheath tumour; neurofibrosarcoma; plexiform fibrohistiocytic tumour; rhabdomyosarcoma; or synovial sarcoma.
- 20 80. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
treatment refractory cancer (including, e.g., chemotherapy resistant cancer and radiotherapy resistant cancer); metastatic cancer; metastases; or recurrent
25 cancer.
81. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
30 a disorder mediated by osteoclasts.

82. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
rheumatoid arthritis; osteoporosis; Paget's disease; osteopetrosis;
osteoarthritis; ectopic bone formation; bone loss associated with endometriosis;
5 adenomyosis; neoplasia of bones (including, e.g., as a primary tumour or as metastases and including, e.g., bone cancer; osteosarcoma; or osteoma);
cancer-associated bone disease (including, e.g., metastatic bone disease associated with, e.g., breast cancer, lung cancer, prostate cancer, or multiple myeloma; changes in bone mineralisation and density associated with cancer,
10 including, e.g., hypercalcaemia associated with cancer); bone metastases (including, e.g., osteolytic bone metastases); hypercalcaemia (including, e.g., hypercalcaemia associated with cancer; hypercalcaemia caused by conditions associated with increased bone resorption (including, e.g., hypercalcaemia caused by vitamin D intoxication, primary or tertiary hyperparathyroidism,
15 immobilisation, or sarcoidosis); or aseptic loosening of prosthetic implants (e.g., artificial joints, e.g., knees, hips, etc.).
83. A compound for use according to claim 63, use according to claim 64, or a method according to claim 65, wherein the treatment is treatment of:
20 rheumatoid arthritis; osteoporosis; neoplasia of bones (including, e.g., as a primary tumour or as metastases and including, e.g., bone cancer; osteosarcoma; or osteoma); cancer-associated bone disease (including, e.g., metastatic bone disease associated with, e.g., breast cancer, lung cancer, prostate cancer, or multiple myeloma; changes in bone mineralisation and density associated with
25 cancer, including, e.g., hypercalcaemia associated with cancer); or bone metastases (including, e.g., osteolytic bone metastases).