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(54) Titre : INHIBITEURS DE DERIVE DE DIFLUOROHALOALLYLAMINE SULFONE DE LYSYL OXYDASES, LEURS PROCEDES DE PREPARATION ET LEURS UTILISATIONS

(54) Title: DIFLUOROHALOALLYLAMINE SULFONE DERIVATIVE INHIBITORS OF LYSYL OXIDASES, METHODS OF PREPARATION, AND USES THEREOF

(57) Abrégé/Abstract:
The present invention relates to methods for preparing a variety of difluorohaloallylamine derivatives. The present invention also relates to novel difluorohaloallylamine derivatives that are capable of inhibiting certain amine oxidase enzymes. These compounds are useful for the treatment of a variety of indications, e.g., fibrosis, cancer and/or scarring in human subjects as well as in pets and livestock. In addition, the present invention relates to pharmaceutical compositions containing these compounds, as well as uses thereof.

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(54) Title: DIFLUOROHALOALLYLAMINE SULFONE DERIVATIVE INHIBITORS OF LYSYL OXIDASES, METHODS OF PREPARATION, AND USES THEREOF

(57) Abstract: The present invention relates to methods for preparing a variety of difluorohaloallylamine derivatives. The present invention also relates to novel difluorohaloallylamine derivatives that are capable of inhibiting certain amine oxidase enzymes. These compounds are useful for the treatment of a variety of indications, *e.g.*, fibrosis, cancer and/or scarring in human subjects as well as in pets and livestock. In addition, the present invention relates to pharmaceutical compositions containing these compounds, as well as uses thereof.

DIFLUOROHALOALLYLAMINE SULFONE DERIVATIVE INHIBITORS OF LYSYL OXIDASES, METHODS OF PREPARATION, AND USES THEREOF

Technical Field

[0001] The present invention relates to methods for preparing a variety of difluorohaloallylamine derivatives. The present invention also relates to novel difluorohaloallylamine derivatives that are capable of inhibiting certain amine oxidase enzymes. These compounds are useful for the treatment of a variety of indications, e.g., fibrosis, cancer and/or scarring in human subjects as well as in pets and livestock. In addition, the present invention relates to pharmaceutical compositions containing these compounds, as well as uses thereof.

Background

[0002] A family of five closely related enzymes have been linked to fibrotic disease and to metastatic cancer. The enzymes are lysyl oxidase (LOX), the first family member to be described and LOX-like1 (LOXL1), LOXL2, LOXL3, and LOXL4 (*J Cell Biochem* 2003; 88: 660 - 672). Lysyl oxidase isoenzymes are copper-dependent amine oxidases which initiate the covalent cross-linking of collagen and elastin. A major function of lysyl oxidase isoenzymes is to facilitate the cross-linking of collagen and elastin by the oxidative deamination of lysine and hydroxylysine amino acid side chains to aldehydes which spontaneously react with neighbouring residues. The resulting cross-linked strands contribute to extracellular matrix (ECM) stability and render it less susceptible to proteolytic degradation by enzymes such as matrix metalloproteases (MMPs). The activity of lysyl oxidase enzymes is crucial for the maintenance of normal tensile and elastic features of connective tissue of many organ systems of the body.

[0003] Lysyl oxidase isoenzymes belong to a larger group of amine oxidases which include flavin-dependent and copper-dependent oxidases which are described by the nature of the catalytic co-factor. Flavin-dependent enzymes including monoamine oxidase-A (MAO-A), monoamine oxidase-B (MAO-B), polyamine oxidase and lysine demethylase (LSD1), and the copper-dependent enzymes include semicarbazide sensitive amine oxidase (vascular adhesion protein-1, SSAO/VAP-1), retinal amine oxidase, diamine oxidase and the lysyl oxidase isoenzymes. The copper-dependent amine oxidases have a second co-factor which varies slightly from enzyme to enzyme. In SSAO/VAP-1 it is an oxidized tyrosine residue (TPQ, oxidized to a quinone), whereas in the lysyl oxidase isoenzymes the TPQ has been further processed by addition of a neighbouring lysine residue (to form LTQ) (*J Cell Biochem* 2003; 88: 660 - 672).

[0004] Lysyl oxidase isoenzymes exhibit different *in vivo* expression patterns, which suggests that specific isoenzymes will have specific biological roles. Catalytically active forms of LOX have been identified in the cytosolic and nuclear compartments and research is in progress to define their roles in these compartments. LOX itself, for example, plays a major role in epithelial-to-mesenchymal transition (EMT), cell migration, adhesion, transformation and gene regulation. Different patterns of LOX expression/activity have been associated with distinct pathological processes including fibrotic diseases, Alzheimer's disease and other neurodegenerative processes, as well as tumour progression and metastasis (*Am J Surg* 2005; 189: 297 - 301).

[0005] Directed replacement of dead or damaged cells with connective tissue after injury represents a survival mechanism that is conserved throughout evolution and appears to be most pronounced in humans, serving a valuable role following traumatic injury, infection or diseases. Progressive scarring can occur following more chronic and/or repeated injuries that causes impaired function to parts or the entire affected organ. A variety of causes, such as chronic infections, chronic exposure to alcohol and other toxins, autoimmune and allergic reactions or surgery, radio- and chemotherapy can all lead to fibrosis. This pathological process, therefore, can occur in almost any organ or tissue of the body and, typically, results from situations persisting for several weeks or months in which inflammation, tissue destruction and repair occur simultaneously. In this setting, fibrosis most frequently affects the lungs, liver, skin, kidneys and cardiovascular system.

[0006] Liver fibrosis, for example, can occur as a complication of haemochromatosis, Wilson's disease, alcoholism, schistosomiasis, viral hepatitis, bile duct obstruction, exposure to toxins and metabolic disorders. Liver fibrosis is characterized by the accumulation of extracellular matrix that can be distinguished qualitatively from that in normal liver. This fibrosis can progress to cirrhosis, liver failure, cancer and eventually death (*Pathology – Research and Practice* 1994; 190: 910 - 919).

[0007] Fibrotic tissues can accumulate in the heart and blood vessels as a result of hypertension, hypertensive heart disease, atherosclerosis and myocardial infarction, where the accumulation of extracellular matrix or fibrotic deposition results in stiffening of the vasculature and stiffening of the cardiac tissue itself (*Am J Physiol Heart Circ Physiol* 2010; 299: H1 - H9).

[0008] Pulmonary arterial hypertension (PAH) is a rare and rapidly lethal condition characterised by elevated pulmonary arterial pressure and caused by increased pulmonary vascular resistance. Although a heterogeneous condition with a wide range of causes, there is increasing recognition that PAH is associated with other diseases such as connective-tissue disease and scleroderma.

Pathological hallmarks of PAH include vascular wall remodelling with excessive extracellular matrix (ECM) deposition and cross-linking. Lysyl oxidases are dysregulated in pulmonary vasculature of patients with idiopathic pulmonary arterial hypertension (IPAH) and contribute to the persistence of ECM components and improper collagen and elastin remodelling through cross-linking (*Arterioscler. Thromb Vasc. Biol.* 2014; 34: 1446 – 1458). Prognosis for patients with PAH is poor. Targeting the lysyl oxidases pharmacologically could provide therapeutic intervention where few or none currently exist.

[0009] A strong association between fibrosis and increased lysyl oxidase activity has been demonstrated. For example, in experimental hepatic fibrosis in rat (*Proc. Natl. Acad. Sci. USA* 1978; 75: 2945 - 2949), in models of lung fibrosis (*J Pharmacol Exp Ther* 1981; 219*:* 675 - 678), in arterial fibrosis (*Arteriosclerosis* 1981; 1: 287 - 291.), in dermal fibrosis (*Br J Dermatol* 1995; 133: 710 - 715) and in adriamycin-induced kidney fibrosis in rat (*Nephron* 1997; 76: 192-200). Of these experimental models of human disease, the most striking increases in enzyme activity were seen in the rat model of CCl_4-induced liver fibrosis. In these studies, the low level of enzyme activity in the healthy liver increased 15- to 30-fold in fibrotic livers.

[0010] In humans, there is also a significant association between lysyl oxidase activity measured in the plasma and liver fibrosis progression. Lysyl oxidase activity level is normally low in the serum of healthy subjects, but significantly increased in chronic active hepatitis and even more in cirrhosis. Therefore, lysyl oxidase might serve as a marker of internal fibrosis.

[0011] Lysyl oxidase isoenzymes are highly regulated by Hypoxia-Inducible Factor 1α (HIF-1α) and TGF-β, the two most prominent growth factors that cause fibrosis (*Cell Biol* 2009; 29: 4467 - 4483). Collagen cross-linking occurs in every type of fibrosis, hence a lysyl oxidase isoenzyme inhibitor could be used in idiopathic pulmonary fibrosis, scleroderma, kidney or liver fibrosis.

[0012] In normal wound healing, granulation tissue formation is a short-lived process, providing a scaffold for re-epithelialisation and repair. Subsequently, the tissue is remodelled and a normotrophic scar is formed. However, after an injury, humans cannot regenerate normal skin. Instead, the repair (or healing) process leads to scar formation (cicatrisation). Scars are both aesthetically and functionally inferior to skin. Scars are a chronic problem and excessive or hypertrophic scarring and its accompanying aesthetic, functional and psychological sequelae remain key challenges for the treatment of deep skin injury and burns. A key factor in the poor appearance and pliability of scars, in particular hypertrophic scars, are the changes to collagen in the dermal layer. In scar tissue the collagen (predominantly Collagen I) is more densely packed and

closely aligned in parallel bundles. In normal skin, collagen is not densely packed and is more of a 'basket-weave' structure. These alterations, both in structure and quantity of collagen, largely underlie the poor appearance of scar and lead to loss of pliability, discomfort and functional problems.

[0013] Dermal fibrosis, or excessive scarring of the skin, is a consequence of exaggerated healing response and is characterized by disproportionate fibroblast proliferation and extracellular matrix (ECM) production in the dermis. Clinically, dermal fibrosis manifests as thickened, tightened and hardened areas of the skin. The spectrum of fibrotic skin disorders is wide, including, but not limited to: hypertrophic scarring, keloids, scleroderma (diffuse and limited subtypes), scleredema (Buschke disease), systemic amyloidosis, lipodermatosclerosis, progeroid disorders, stiff skin syndrome, Dupuytren's contracture, nephrogenic fibrosing dermopathy (NFD), mixed connective tissue disease, scleromyxedema, graft-versus-host disease (GVHD) and eosinophilic fasciitis. Although each of these disorders has its own etiology and clinical characteristics, all involve excessive collagen production, and altered collagen remodelling. One possible mechanism for altered ECM remodelling is through covalent cross-linking. This directly implicates the LOX family of enzymes in the pathogenesis of cutaneous fibrosis (*Laboratory investigation* 2019; 99: 514 – 527). LOX and LOXL1-4 expression is elevated in scar fibroblasts compared to normal skin fibroblasts, with LOX and LOXL1 being the dominant isoforms found in skin tissue.

[0014] Keloid, or keloidal scar, is the formation of a type of scar that results from abnormal deposition of granulation tissue (collagen type 3) at the site of a healed skin injury which is then slowly replaced by collagen type 1. This abnormal deposition of collagen, in turn, results from an imbalance in net collagen synthesis and deposition and collagenolysis. Keloids are firm, rubbery lesions or shiny, fibrous nodules, and can vary from pink to the color of the person's skin or red to dark brown in color.

[0015] Histologically, keloids are fibrotic tumours characterized by a collection of atypical fibroblasts with excessive deposition of extracellular matrix components, especially collagen, fibronectin, elastin, and proteoglycans. In most cases, they contain relatively acellular centers with thick, abundant collagen bundles that form nodules in the deep dermal region of the lesion. Keloids present a therapeutic challenge, as these lesions can cause significant pain, pruritus, and physical disfigurement. Furthermore, they may not improve in appearance over time and can limit mobility if located over a joint.

[0016] Physiologic manipulation of collagen deposition/crosslinking and collagenolysis (through collagenase activity) is, at least theoretically, an opportunity to reduce keloid severity and induce scarring with improved physical properties

[0017] A study on patients with massive, pedunculated keloids has shown that, following excision of the keloid and grafting the defect, treatment by administration of beta aminopropionitrile (BAPN) or penicillamine (non-selective, pan LOX inhibitors) and colchicine (a stimulator of collagenase activity) exerted a measurable beneficial effect on surface scarring (*Ann surg* 1981; 193: 592 -597).

[0018] Studies involving two complimentary, *in-vitro* skin-like models – human skin equivalent (hSEs), and self-assembled stromal tissues identified LOXL4 as the key isoform mediating TGF-β induced fibrotic phenotypes (*Lab. Invest.* 2019; 99: 514 – 527).

[0019] Scarring processes are a considerable problem and challenge in the eye and surrounding structures. Ocular scarring plays a major role in either primary disease (e.g. corneal and conjunctival scarring) or treatment failure (e.g. postoperative trabeculectomy) (*Ocular Surgery News* U. S. Edition, October 1, 2002).

[0020] Glaucoma is a disease in which the optic nerve is being damaged, leading to progressive and irreversible loss of vision. Elevated intraocular pressure (IOP) is one of the major risk factors for the development and progression of glaucoma. Most treatments for glaucoma are targeted at lowering the intraocular pressure, either by decreasing the formation of aqueous fluid in the eye, or, as in the case of glaucoma filtration surgery, by increasing the outflow of fluid from the eye. Trabeculectomy – the current gold standard for the management of IOP - is a filtering surgery where an ostium is created into the anterior chamber from underneath a partial thickness scleral flap to allow for aqueous flow out of the eye. Post-operative scarring is the main cause of treatment failure. The antimetabolites mitomycin-C (MMC) and 5-fluorouracil (5-FU) are used in current clinical practice to help limit post-operative ocular scar tissue formation. While these agents have been shown to improve the IOP outcome of filtration surgery, they do so in a non-selective manner and are associated with significant side effects (*Arch. Ophthalmol.* 2002; 120: 297 – 300). Safer, more targeted, anti-fibrotic agents are needed.

[0021] Gingival fibromatosis is a rare and heterogeneous group of disorders that develop as slow progressive, local or diffuse, fibrous enlargements of keratinized gingiva (gingival overgrowth or enlargement). In severe cases, the excess tissue may cover the crowns of the teeth, thus causing

masticatory, aesthetic, phonetic, functional and periodontal problems. Gingival overgrowth may be inherited, of idiopathic origin, associated with inflammatory diseases of the oral cavity, or associated with other systemic diseases. However, the majority of cases are due to side-effects of systemic medications such as the anti-seizure drug phenytoin, the immunosuppressant cyclosporin A, and certain anti-hypertensive dihydropyridine anti-calcium-channel-blockers, in particular nifedipine (*crit rev oral biol* 2004; 15: 165 – 175). The pathological manifestation of gingival overgrowth comprises excessive accumulation of extracellular matrix proteins, of which Collagen I is the most predominant. One recognized concept of mechanism for drug induced gingival overgrowth is EMT, a process in which interaction of gingival cells and the extracellular matrix are weakened as epithelial cells transdifferentiate into fibrogenic fibroblast-like cells (*AJP* 2010; 177: 208 – 218). The damaged epithelium, basement membrane and underlying stroma result in TGF-β stimulation of lysyl oxidase enzyme activity and contribute to connective tissue fibrosis (*Lab Invest* 1999; 79: 1655 – 1667).

[0022] The rationale for the consistent and strong inhibition of fibrosis by lysyl oxidase isoenzyme blockers is that the lack of cross-linking activity renders the collagen susceptible to degradation by proteolytic enzymes such as MMPs. Hence, any type of fibrosis should be reversed by treatment with lysyl oxidase isoenzyme inhibitors. Given the varied involvement of all lysyl oxidase isoenzymes in fibrosis, an inhibitor that demonstrates sustained, strong inhibition of all lysyl oxidase isoenzymes, *i.e.* a pan LOX inhibitor, should be most efficacious.

[0023] Rheumatoid Arthritis (RA) is a systemic autoimmune disorder characterized by chronic, painful inflammation of the lining of the joints. In some people, however, the condition can progress to involve painful swelling and inflammation of the surrounding tissue, and other body systems, including the skin, eyes, lungs, heart and blood vessels. Rheumatoid arthritis is thus a painful and debilitating disease that can result in substantial loss of function and mobility in the hands, wrists and feet. Active rheumatoid arthritis emanates from a few joints, but can subsequently progress to affect multiple joints. Synovial hyperplasia, involving infiltrated immune cells and resident synovial fibroblasts (SFs), is a typical feature of RA. Rheumatoid arthritis synovial fibroblasts (RASFs) are the most common cell type at sites of invasion and are the main culprit in joint destruction. Activated RASFs are able to transmigrate and, as such, have been implicated in the spread of arthritis between joints. Cytokines from the infiltrated immune cells induce activation and proliferation of synovial fibroblasts. These activated SFs in turn generate the pathogenic stroma to perpetuate chronic inflammation, ultimately leading to cartilage and bone destruction. By implanting RASFs together with human cartilage into severe combined immunodeficient mice, it

has been demonstrated that activated RASFs migrate *in vivo*, spreading the disease to the sites of implanted human cartilage. Furthermore, whilst RASFs actively degrade cartilage, controls implanted with synovial fibroblasts from osteoarthritis (OA) patients and cutaneous fibroblasts from healthy donors did not (*Nat. Med.* 2009; 15: 1414 – 1420). RASFs differ from unactivated, healthy fibroblasts by their morphology and gene expression. RASFs are characterised by the expression of antiapoptotic, proto-oncogenes and lack of expression of tumour suppressor genes. The production of pro-inflammatory cytokines and chemokines by RASFs further enable attraction of immune cells to the synovium. Furthermore, the production of matrix metalloprotease (MMP) enzymes promotes invasion into and destruction of cartilage.

[0024] The type II collagen-induced arthritis (CIA) model is a commonly used animal model for RA as it recapitulates well the signature immunological, pathological and arthritic presentations observed in RA in humans. In CIA rats, high expressions levels of LOX in the synovial membranes, synovial fluid and serum have been demonstrated. Inhibition of LOX with β-aminopropionitrile (BAPN; a pan LOX inhibitor) was found to attenuate inflammation, synovial hyperplasia, angiogenesis and expression of MMP-2 and MMP-9, indicating that LOX promotes synovial hyperplasia and angiogenesis in CIA rats. Furthermore, knockdown of LOXL2 and antibodies against LOXL2 attenuated collagen deposition, proliferation and invasion of RASF (*Mol. Med. Rep.* 2017: 6736 – 6742).

[0025] Whilst there is no cure for RA, there are a number of treatments available that alleviate symptoms and modify disease progression. However, such treatments come with significant side effects associated, in part, with the suppression of the immune system. Selective drugs that target RASF would represent more useful therapy for RA.

[0026] Osteoarthritis (OA) is a disease characterised by degeneration of joint cartilage and underlying bone. Predominantly resulting from "wear and tear', OA causes pain and stiffening of the joint. The most commonly affected joints are those of the fingers, knees, back and hips. Unlike other forms of arthritis (such as RA), osteoarthritis only affects the joints. Often, joints on one side of the body are affected more than those on the other. OA is a progressive and debilitating disease that can have a significant impact on work and normal daily activities.

[0027] Synovial fibrosis is a key contributor to OA, and is a manifestation of fibroblast proliferation and an imbalance in collagen synthesis and collagen degradation. This imbalance leads to excessive deposition of collagen into the extracellular matrix (ECM) and results in thickening and stiffening of the synovial membrane.

[0028] Genes encoding a number of the lysyl oxidase family of enzymes including LOX, LOXL2, LOXL3 and LOXL4 have been shown to be highly expressed in mice with experimental OA, and humans with end-stage OA (*Arthritis and Rheumatology* 2014; 66: 647 – 656).

[0029] Given the varied contribution of many of the members of the lysyl oxidase family of enzymes to the development of both rheumatoid arthritis and osteoarthritis, a pan LOX inhibitor may provide for a potentially more efficacious therapy.

[0030] BAPN is a widely used, nonselective mechanism-based, irreversible lysyl oxidase inhibitor. Since the 1960s BAPN has been used in animal studies (mainly rat, mouse and hamster) and has been efficacious in reducing collagen content in various models (e.g. CCl_4, bleomycin, quartz, cancer) and tissues (e.g. liver, lung and dermis) (*J Cell Biochem* 2003; 88: 660 - 672). However, studies in human patients with scleroderma, found BAPN to be poorly tolerated and highlights the need for safer alternatives (*Clin. Pharmacol. Ther.* 1967: 593 – 602).

[0031] Lysyl oxidase catalysed collagen cross-linking can proceed *via* two pathways: the allysine and hydroxyallysine pathways. In the hydroxyallysine pathway, immature divalent crosslinks are formed first, including dehydro-dihydroxylysinonorleucine (deH-DHLNL) and dehydro-hydroxylysinonorleucine (deH-HLNL), and then further progress (*via* lysyl oxidase independent reactions) to mature trivalent crosslinks, between three collagen molecules to form deoxypyridinoline (DPD) and pyridinoline (PYD). These mature and immature crosslinks can be measured by LC-MS/MS (PLoS One 2014; 9 (11), e112391).

[0032] Lysyl oxidase isoenzymes are not only involved in the cross-linking of elastin and collagen during wound healing and fibrosis, but also regulate cell movement and signal transduction. Its intracellular and intranuclear function is associated with gene regulation and can lead to tumourigenesis and tumour progression (*Inflammapharmacol* 2011; 19: 117-129). Both down and upregulation of lysyl oxidase isoenzymes in tumour tissues and cancer cell lines have been described, suggesting a dual role for lysyl oxidase isoenzymes and LOX pro-peptide as a metastasis promoter gene as well as a tumour suppressor gene.

[0033] In addition to its role in tissue remodelling, the LOX isoenzymes also play a critical role in primary cancer and metastasis. Tumour growth is associated with a reactive stroma, which is predominantly composed of fibroblasts; termed cancer associated fibroblasts (CAFs). Mice subcutaneously inoculated with an equal mixture of tumour and CAFs cells are known to have a faster growth rate and higher incidence of metastases (*Trends Mol Med.* 2013;19(8): 447 - 453).

CAF knockout models have shown to be pro-tumourigenic, however this is quite an abstract scenario when comparing to a patient's tumour microenvironment. CAFs have been shown to have an increased expression of LOXs compared to normal fibroblasts (*Dis Model Mech.* 2018; 11 (4)). Utilising a LOX inhibitor in a cancer setting potentially will affect both the tumour and stromal compartment to assist in decreasing tumour growth and metastasis.

[0034] Emerging evidence suggests an association between idiopathic pulmonary fibrosis and lung cancer, however, more studies are needed. Chemical or irradiation induced fibrosis in both, lung and liver mouse models causes an increase in alpha smooth muscle actin (a marker of fibroblasts), LOX expression and metastatic tumour growth, which is reversed by a LOX antibody (*Cancer Res.* 2013; 73 (6): 1721 - 1732).

[0035] To date, an increase in lysyl oxidase isoenzymes mRNA and/or protein has been observed in breast, CNS cancer cell lines, head and neck squamous cell, esophageal, kidney, lung, prostatic, clear cell renal cell and lung carcinomas, ovarian, uterine, melanoma and osteosarcoma patient samples from The Cancer Genome Atlas (TCGA). Shown in Table 1 is the TCGA patient gene expression data for the LOX family. A plus symbol indicates higher than the average gene expression within this dataset.

Table 1

TCGA patient gene expression data for the LOX family

Cancer	LOX	LOXL1	LOXL2	LOXL3	LOXL4	Number of patient samples
Breast invasive carcinoma	+	+	+	+		1212
Esophageal carcinoma	+	+	+			196
Glioblastoma multiforme			+	+		171
Head & neck squamous cell carcinoma	+	+	+			566
Kidney renal clear carcinoma	+		+		+	606
Kidney renal papillary cell carcinoma		+			+	323
Lung squamous cell carcinoma	+	+	+		+	552
Mesothelioma	+	+	+	+	+	87
Ovarian serous cystadenocarcinoma	+	+		+	+	307
Pancreatic adenocarcinoma	+	+	+	+	+	183
Pheochromocytoma and paraganglioma			+	+		187
Sarcoma	+	+	+	+		265
Skin cutaneous melanoma	+			+	+	473
Uterine carcinoma	+	+	+	+	+	57
Uterine corpus endometrial carcinoma		+				201

[0036] Statistically significant clinical correlations between lysyl oxidase isoenzymes expression and tumour progression have been observed in breast, head and neck squamous cell, myelofibrosis, prostatic, pancreatic, ovarian, and clear cell renal cell carcinomas. The role of lysyl oxidase isoenzymes in tumour progression has been most extensively studied in breast cancer using *in vitro* models of migration/invasion and in *in vivo* tumourigenesis and metastasis mouse models (*Nature*. 2006; 440 (7088): 1222 - 1226). Increased lysyl oxidase isoenzymes expression was found in hypoxic patients, and was associated with negative estrogen receptor status (ER-), decreased overall survival in ER- patients and node-negative patients who did not receive adjuvant systemic treatment, as well as shorter bone metastasis-free survival in ER- patients and node negative patients (*Nature*. 2015; 522 (7554) 106 - 110). *In vivo* models demonstrated that the LOX inhibitors have potential in breast cancer patients with bone metastasis, by modulating bone homeostasis independent of receptor activator of nuclear factor kappa-B ligand (RANKL) (*Nature*. 2015; 522 (7554): 106 - 110). Lysyl oxidase isoenzymes mRNA was demonstrated to be up-regulated in invasive and metastatic cell lines (MDA-MB-231 and Hs578T), as well as in more aggressive breast cancer cell lines and distant metastatic tissues compared with primary cancer tissues (*Cancer Res*. 2002; 62 (15): 4478 - 4483).

[0037] Pathogenic processes in primary myelofibrosis involve a primary megakaryocyte-weighted clonal myeloproliferation and paraneoplastic stromal reaction that includes bone marrow fibrosis, osteosclerosis, angiogenesis, and extramedullary hematopoiesis. The bone marrow reaction includes excess deposition of extracellular matrix proteins such as fibrillary collagen, hypocellularity, activation and recruitment of bone marrow fibroblasts, excessive cytokine and growth factor production, and other changes that result in a reduction in hematopoietic capacity. Secondary myelofibrosis can result from polycythaemia rubra vera or essential thrombocytosis. In myelofibrosis, disease progression correlates with increased numbers of megakaryocytes, which overexpress LOX. In a GATA 1 low mouse model of myelofibrosis, disease progression (including increase in megakaryocytes number, fibrosis and spleen size), were significantly attenuated by a pan LOX inhibitor (*J Biol Chem*. 2011; 286(31): 27630 - 27638).

[0038] In most tumour types, the first line of treatment is surgical resection. A wound healing response is initiated by surgery and may correlate with an increase in metastatic spread. Breast cancer models have shown that abdominal surgery increases lung metastasis. Furthermore, it was shown to be caused by systemic LOX. Injection of plasma, collected from abdominal surgery mice (which contained LOX), into tumour bearing mice resulted in an increase in lung metastasis. The

surgery induced systemic LOX was blocked by BAPN, reducing metastasis and increasing survival (*Cell Rep*. 2017; 19 (4): 774 - 784).

[0039] In colon, breast cancer and melanoma models, tumour associated endothelial cells have been shown to have an increased expression of LOX, which stimulates angiogenesis and tumour growth (*Cancer Res*. 2015; 73(2): 583 - 594).

[0040] In pancreatic, breast, lung, ovarian and colon cancer patients, high collagen content has been correlated with high LOX gene expression, chemotherapy resistance and significantly decreased survival (*Oncogene*. 2018; 37(36) 4921 - 4940, *EMBO Mol Med*. 2015; 7(8) 1063 - 1076, *Oncotarget*. 2016; 7(22) 32100 - 32112). LOX inhibitors (both BAPN and a LOX antibody) and standard of care chemotherapies were combined in desmoplastic tumour mouse models to lower the tumour interstitial pressure causing expansion of vessels (*Oncotarget*. 2016; 7(22) 32100 - 32112). The increased vascular flow increases the concentration of the chemotherapeutic agent at the site of the primary tumour, which leads to a lower metastatic load and increased survival (*Oncotarget*. 2016 May 31; 7(22) 32100-32112).

[0041] In head and neck squamous cell carcinomas, increased lysyl oxidase isoenzyme expression was found in association with CA-IX, a marker of hypoxia, and was associated with decreased cancer specific survival, decreased overall survival and lower metastasis-free survival (*Oncotarget*. 2016; 7(31): 50781 - 50804). In oral squamous cell carcinoma, lysyl oxidase isoenzyme mRNA expression was upregulated compared to normal mucosa.

[0042] Gene expression profiling of gliomas identified over-expressed lysyl oxidase isoenzyme as part of a molecular signature indicative of invasion, and associated with higher-grade tumours that are strongly correlated with poor patient survival (*PloS ONE*. 2015 Mar 19; 10(3) e0119781). Lysyl oxidase isoenzyme protein expression was increased in glioblastoma and astrocytoma tissues, and in invasive U343 and U251 cultured astrocytoma cells.

[0043] In tissues, lysyl oxidase isoenzyme mRNA was upregulated in prostate cancer compared to benign prostatic hypertrophy, correlated with Gleason score, and associated with both high grade and short time to recurrence (*Oncol Rep* 2008; 20: 1561-1567).

[0044] In renal clear cell carcinoma (RCC), smoking was associated with allelic imbalances at chromosome 5q23.1, where the LOX gene is localized, and may involve duplication of the gene (*Cancer Genet Cytogenet*. 2005; 163(1)7: 7 - 11).

[0045] SiHa cervical cancer cells demonstrated increased invasion *in vitro* under hypoxic/anoxic conditions; this was repressed by inhibition of extracellular catalytically active lysyl oxidase activity by treatment with BAPN as well as LOX antisense oligos, LOX antibody, LOX shRNA or an extracellular copper chelator (*Oncol Rep*. 2013; 29 (2), 541 - 548).

[0046] In ovarian cancer genetically engineered mouse models (ApoE knockout) a desmoplastic tumour with increased LOX gene expression is formed. Treatment with BAPN significantly increased survival and decreased lung metastasis (*J Exp Clin Cancer Res*. 2018; 37: 32). Certain tumours from patients with ovarian cancer have a single nucleotide polymorphism of the LOX gene, G473A. Two independent studies have shown that people with the G473A polymorphism expressed have increased chances of developing ovarian cancer (*J Int Med Res*. 2012; 40(3): 917 - 923; *Genet Test Mol Biomarkers*. 2012; 16 (8): 915 - 919).

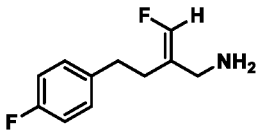
[0047] In primary human oral squamous cell carcinoma (OSCC), levels of lysyl oxidase enzyme (in particular LOX and LOXL2) and lysyl hydroxylase expression are significantly increased, and markedly elevated in late-stage, regional lymph node metastasis (RLNM)-positive tumours. Both reducible, or immature, cross-links (deH-DHLNL and deH-HLNL) and non-reducible, or mature cross-links (DPD and PYD) are significantly elevated in OSCCs compared to normal tissues (*J Dent Res* 2019; 98(5): 517 – 525).

[0048] The findings described herein, provide a strong rationale for combination therapies involving LOX isoenzyme inhibitors and anti-tumour therapy in patients.

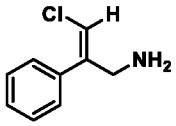
[0049] More recently, CCT365623 a reversible pan LOX inhibitor has been utilised in breast cancer model (MMTV-PyMT) to reduce metastasis and increase survival (*Nat Commun*. 2017; 18 (8): 14909).

[0050] The scientific and patent literature describes small molecule inhibitors of lysyl oxidase isoenzymes and antibodies of LOX and LOXL2 with therapeutic effects in animal models of fibrosis and cancer metastasis. Some known MAO inhibitors also are reported to inhibit lysyl oxidase isoenzyme (e.g., the MAO-B inhibitor Mofegiline illustrated below). This inhibitor is a member of the haloallylamine family of MAO inhibitors; the halogen in Mofegiline is fluorine. Fluoroallylamine inhibitors are described in US Patent No. 4,454,158. There are issued patents claiming fluoroallylamines and chloroallylamines, for example MDL72274 (illustrated below) as inhibitors of lysyl oxidase (US Patents 4,943,593; 4,965,288; 5,021,456; 5,059,714; 5,182,297;

5,252,608). Many of the compounds claimed in these patents are also reported to be potent MAO-B and SSAO/VAP-1 inhibitors.



Mofegiline



MDL72274

[0051] Additional fluoroallylamine inhibitors are described US Patent 4,699,928. Other examples structurally related to Mofegiline can be found in WO 2007/120528.

[0052] WO 2009/066152 discloses a family of 3-substituted 3-haloallylamines that are inhibitors of SSAO/VAP-1 useful as treatment for a variety of indications, including inflammatory disease. None of these documents specifically disclose the fluoroallylamine compounds of formula (I) according to the present invention.

[0053] Antibodies to LOX and LOXL2 have been disclosed in US 2009/0053224 with methods to diagnostic and therapeutic applications. Anti-LOX and anti-LOXL2 antibodies can be used to identify and treat conditions such as a fibrotic condition, angiogenesis, or to prevent a transition from an epithelial cell state to a mesenchymal cell state: US 2011/0044907.

[0054] WO 2017/136871 and WO 2017/136870 disclose haloallylamine indole and azaindole derivative inhibitors of lysyl oxidases and uses thereof.

[0055] WO 2018/157190 discloses haloallylamine pyrazole derivative inhibitors of lysyl oxidases and uses thereof.

[0056] WO 2020/024017 discloses haloallylamine sulfone derivative inhibitors of lysyl oxidases and uses thereof.

[0057] WO 2017/141049 and WO 2019/073251 disclose families of methylamine and bridged homopiperazine derivatives respectively as lysyl oxidase inhibitors and their use in the treatment of cancer and diseases associated with fibrosis.

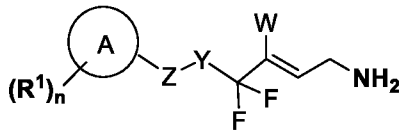
[0058] WO 2003/097612, WO 2006/053555, and US 2008/0293936 disclose another class of lysyl oxidase inhibitors.

[0059] WO 2020/099886, WO 2018/048930, WO 2017/015221, WO 2017/003862, WO 2016/144702 and WO 2016/144703 disclose further LOXL2 inhibitors.

Summary

[0060] The present invention provides substituted difluorohaloallylamine compounds that inhibit lysyl oxidase (LOX), lysyl oxidase-like2 (LOXL2) and other lysyl oxidase isoenzymes. Surprisingly, modification of 3-substituted-3-fluoroallylamine structures described previously has led to the discovery of novel compounds that are potent inhibitors of the human LOX and LOXL isoenzymes. Certain of these novel compounds have been found to have favourable characteristics for topical application. Furthermore, certain of these novel compounds also selectively inhibit certain LOX and LOXL isoenzymes with respect to the other enzymes in the amine oxidase family.

[0061] A first aspect of the invention provides for a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, polymorphic form, solvate, hydrate or tautomeric form thereof; wherein:

W is F or Cl;

Y is $-S(O)_2-$ or -S(O)-;

Z is $-(CH_2)_m-$;

A is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkenyl, or C_{1-6}alkynyl;

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, $-NR^4R^5$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, $-C(O)OR^3$, $-C(O)NR^4R^5$, $-S(O)_2NR^4R^5$, $-S(O)_2R^6$, $-NR^8C(O)R^9$, and $-NR^8S(O)_2R^9$; and wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, -C_{1-4}alkyl, -O-C_{1-4}alkyl, $-CF_3$, - CH_2CF_3 and $-O-CF_3$;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, - SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, O-C_{1-6}alkyl C_{3-7}cycloalkyl, -C(O)OR^3, -C(O)NR^4R^5, -NR^4C(O)R^6, -S(O)$_2$NR^4R^5, -NR^4S(O)$_2R^6$ and -S(O)$_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

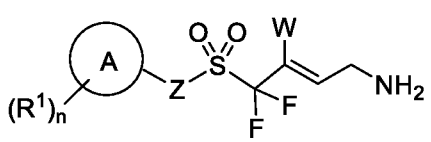
R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

n is 0, 1, 2, 3, 4 or 5; and

m is 0 or 1.

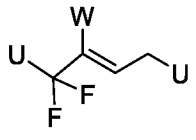
[0062] A second aspect of the invention provides for a process for preparing a compound of Formula Ia:



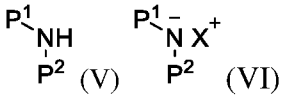
(Ia)

which comprises reaction steps (C), (D), (E) and (F), where:

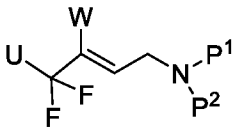
(C) is the reaction of a compound of Formula IV:


(IV)

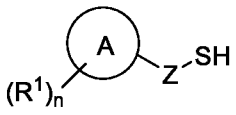
with a compound of Formula V or VI:

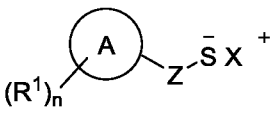

(V) (VI)

to afford a compound of Formula VII:

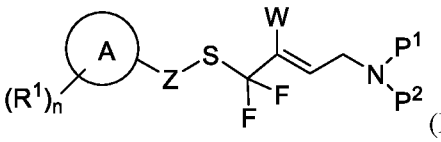

(VII);

(D) is the reaction of a compound of Formula VII with a compound of Formula VIII or IX:

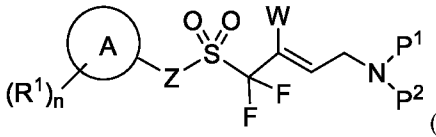

(VIII)


(IX)

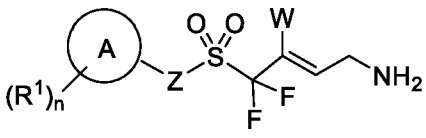
to obtain a compound of Formula X:


(X);

(E) is the oxidation of a compound of Formula X to obtain a compound of Formula XI:


(XI); and

(F) is deprotection of a compound of Formula XI to afford a compound of Formula Ia:


(Ia), or a pharmaceutically acceptable salt thereof

wherein U is Br, Cl or I;

W is F or Cl; and

P^1 is a nitrogen protecting group;

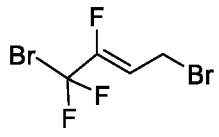
P^2 is hydrogen or a nitrogen protecting group; or

P^1 and P^2 together with the nitrogen to which they are attached form a cyclic nitrogen protecting group;

X^+ is a metal counterion; and

R^1, A, Z and n are as defined in the first aspect of the invention.

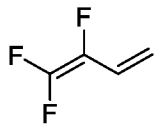
[0063] A third aspect of the invention provides for a process for preparing a single isomer of a compound of Formula IVc:



(IVc)

which comprises:

addition of a compound of Formula IIIc:



(IIIc)

to a solution of Br_2.

[0064] A fourth aspect of the invention provides for a pharmaceutical composition comprising a compound according to the first aspect of the invention, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier or diluent.

[0065] A fifth aspect of the invention provides for a method of inhibiting the amine oxidase activity of any one of LOX, LOXL1, LOXL2, LOXL3 and LOXL4 in a subject in need thereof, comprising administering to the subject an effective amount of a compound according to the first aspect of the invention, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to the fourth aspect of the invention.

[0066] A sixth aspect of the invention provides for a method of treating a condition by inhibiting the activity of any one of the LOX, LOXL1, LOXL2, LOXL3 and LOXL4 proteins, comprising administering to a subject in need thereof a therapeutically effective amount of compound according to the first aspect of the invention, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to the fourth aspect of the invention.

[0067] A seventh aspect of the invention provides for use of a compound according to the first aspect of the invention, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treating a condition by inhibiting the activity of any one of the LOX, LOXL1, LOXL2, LOXL3 and LOXL4 proteins.

[0068] An eighth aspect of the invention provides for a compound according to the first aspect of the invention, or a pharmaceutically acceptable salt or, solvate thereof, for use in treating a condition by inhibiting the activity of any one of the LOX, LOXL1, LOXL2, LOXL3 and LOXL4 proteins.

[0069] In one embodiment of the methods and uses of the present invention the condition is selected from fibrosis, cancer, and arthritis.

[0070] In one embodiment of the methods and uses of the present invention the condition is scarring.

[0071] In one embodiment of the compositions of the present invention, the pharmaceutical composition is a topical composition. In one embodiment of the methods of the present invention the pharmaceutical composition is for topical administration.

[0072] Contemplated herein is combination therapy in which the methods further comprise co-administering additional therapeutic agents that are used for the treatment of cancer, fibrosis, inflammation, immunosuppression, angiogenesis, fungal infections, bacterial infections, metabolic conditions, pain and puritis.

Definitions

[0073] The following are some definitions that may be helpful in understanding the description of the present invention. These are intended as general definitions and should in no way limit the scope of the present invention to those terms alone, but are put forth for a better understanding of the following description.

[0074] Unless the context requires otherwise or specifically states to the contrary, integers, steps, or elements of the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

[0075] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a

stated step or element or integer or group of steps or elements or integers, but not the exclusion of any other step or element or integer or group of elements or integers. Thus, in the context of this specification, the term “comprising” means “including principally, but not necessarily solely”.

[0076] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

[0077] As used herein, the term "alkyl" includes within its meaning monovalent (“alkyl”) and divalent (“alkylene”) straight chain or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms, e.g., 1, 2, 3, 4, 5 or 6 carbon atoms. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. For example, the term alkyl includes, but is not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, 2-butyl, isobutyl, tert-butyl, amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, and the like.

[0078] The term "alkoxy" or “alkyloxy” as used herein refers to straight chain or branched alkyloxy (i.e, O-alkyl) groups, wherein alkyl is as defined above. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, and isopropoxy.

[0079] The term “cycloalkyl” as used herein includes within its meaning monovalent (“cycloalkyl”) and divalent (“cycloalkylene”) saturated, monocyclic, bicyclic, polycyclic or fused analogs. In the context of the present disclosure the cycloalkyl group may have from 3 to 10 carbon atoms. A fused analog of a cycloalkyl means a monocyclic ring fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl and fused analogs thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, adamantyl and the like.

[0080] The term “aryl” or variants such as “arylene” as used herein refers to monovalent (“aryl”) and divalent (“arylene”) single, polynuclear, conjugated and fused analogs of aromatic hydrocarbons having from 6 to 10 carbon atoms. A fused analog of aryl means an aryl group fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is

on the aromatic portion. Examples of aryl and fused analogs thereof include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, tetrahydrobenzopyranyl, 1,4-benzodioxanyl, and the like. A "substituted aryl" is an aryl that is independently substituted, with one or more, preferably 1, 2 or 3 substituents, attached at any available atom to produce a stable compound.

[0081] The term "alkylaryl" as used herein, includes within its meaning monovalent ("aryl") and divalent ("arylene"), single, polynuclear, conjugated and fused aromatic hydrocarbon radicals attached to divalent, saturated, straight or branched chain alkylene radicals. Examples of alkylaryl groups include benzyl.

[0082] The term "heteroaryl" and variants such as "heteroaromatic group" or "heteroarylene" as used herein, includes within its meaning monovalent ("heteroaryl") and divalent ("heteroarylene"), single, polynuclear, conjugated and fused heteroaromatic radicals having from 5 to 10 atoms, wherein 1 to 4 ring atoms, or 1 to 2 ring atoms are heteroatoms independently selected from O, N, NH and S. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. The heteroaromatic group may be C_{1-9} heteroaromatic. A fused analog of heteroaryl means a heteroaryl group fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of heteroaryl groups and fused analogs thereof include pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, triazinyl, thienyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, indolyl, isoquinolyl, imidazopyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyridonyl, phenanthrolinyl, quinolyl, isoquinolinyl, imidazolinyl, thiazolinyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, and the like. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N. A "substituted heteroaryl" is a heteroaryl that is independently substituted, with one or more, preferably 1, 2 or 3 substituents, attached at any available atom to produce a stable compound.

[0083] The term "heterocyclyl" and variants such as "heterocycloalkyl" as used herein, includes within its meaning monovalent ("heterocyclyl") and divalent ("heterocyclylene"), saturated or partially saturated (non-aromatic), monocyclic, bicyclic, polycyclic or fused hydrocarbon radicals having from 3 to 10 ring atoms, wherein from 1 to 4, or from 1 to 2, ring atoms are heteroatoms independently selected from O, N, NH, or S, SO or SO_2, in which the point of attachment may be

carbon or nitrogen. A fused analog of heterocyclyl means a monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. The heterocyclyl group may be C_{3-8} heterocyclyl. The heterocycloalkyl group may be C_{3-6} heterocyclyl. The heterocyclyl group may be C_{3-5} heterocyclyl. Examples of heterocyclyl groups and fused analogs thereof include pyrrolidinyl, thiazolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroindolyl, quinuclidinyl, azetidinyl, morpholinyl, tetrahydrothiophenyl, tetrahydrofuranyl, tetrahydropyranyl, thiomorpholinyl-1,1-dioxide, and the like. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or N-substituted uracils.

[0084] The term "halogen" or variants such as "halide" or "halo" as used herein refers to fluorine, chlorine, bromine and iodine.

[0085] The term "heteroatom" or variants such as "hetero-" or "heterogroup" as used herein refers to O, N, NH and S.

[0086] In general, "substituted" refers to an organic group as defined herein (e.g., an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group will be substituted with one or more substituents, unless otherwise specified. In some embodiments, a substituted group is substituted with 1, 2, 3, 4, 5, or 6 substituents.

[0087] The term "optionally substituted" as used herein means the group to which this term refers may be unsubstituted, or may be substituted with one or more groups independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, thioalkoxy, alkenyloxy, haloalkoxy, NO_2, NH(alkyl), $N(alkyl)_2$, alkylamino, dialkylamino, acyl, alkenoyl, alkynoyl, acylamino, diacylamino, acyloxy, alkylsulfonyl, alkylsulfonyloxy, sulfonamido, heterocycloxy, heterocycloamino, haloheterocycloalkyl, alkylsulfenyl, alkylcarbonyloxy, phosphorus-containing groups such as phosphono and phosphinyl, aryl, heteroaryl, alkylaryl, aralkyl, alkylheteroaryl, cyano, CO_2H, CO_2alkyl, $C(O)NH_2$, -C(O)NH(alkyl), and $-C(O)N(alkyl)_2$. Preferred substituents include halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, hydroxy(C_{1-6})alkyl, C_3-C_6cycloalkyl, C(O)OH, $NHC(O)C_1$-C_4alkyl, $C(O)C_1$-C_4alkyl, NH_2, NHC_1-C_4alkyl, $N(C_1$-$C_4alkyl)_2$, $SO_2(C_1$-C_4alkyl), OH and CN. Particularly

preferred substituents include C_{1-4}alkyl, C_{1-4}alkoxy, $SO_2(C_1$-C_4alkyl), halogen, OH, hydroxy(C_{1-3})alkyl (e.g. $C(CH_3)_2OH$), and C_{1-3}haloalkyl (e.g. CF_3, CH_2CF_3).

[0088] The present invention includes within its scope all diastereomeric isomers, racemates, enantiomers and mixtures thereof. Thus, the present disclosure should be understood to include, for example, (R), (S), (L), (D), (+), and/or (-) forms of the compounds, as appropriate in each case. Where a structure has no specific stereoisomerism indicated, it should be understood that any and all possible optical isomers are encompassed. Compounds of the present invention embrace all conformational isomers. Compounds of the present invention may also exist in one or more tautomeric forms, including both single tautomers and mixtures of tautomers. Also included in the scope of the present invention are all polymorphs and crystal forms of the compounds disclosed herein.

[0089] The present invention includes within its scope isotopes of different atoms. Any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Thus, the present disclosure should be understood to include deuterium and tritium isotopes of hydrogen.

[0090] All references cited in this application are specifically incorporated by cross-reference in their entirety. Reference to any such documents should not be construed as an admission that the document forms part of the common general knowledge or is prior art.

[0091] In the context of this specification the term "administering" and variations of that term including "administer" and "administration", includes contacting, applying, delivering or providing a compound or composition of the invention to an organism, or a surface by any appropriate means. In the context of this specification, the term "treatment", refers to any and all uses which remedy a disease state or symptoms, prevent the establishment of disease, or otherwise prevent, hinder, retard, or reverse the progression of disease or other undesirable symptoms in any way whatsoever.

[0092] In the context of this specification the term "topical administration" or variations on that term including "topical application" includes within its meaning applying, contacting, delivering or providing a compound or composition of the invention to the skin, or localized regions of the body.

[0093] In the context of this specification the term "local administration" or variations on that term including "local application" includes within its meaning applying, contacting, delivering or providing a compound or composition of the invention to the skin, or localized regions of the body.

[0094] In the context of this specification the term "effective amount" includes within its meaning a sufficient but non-toxic amount of a compound or composition of the invention to provide a desired effect. Thus, the term "therapeutically effective amount" includes within its meaning a sufficient but non-toxic amount of a compound or composition of the invention to provide the desired therapeutic effect. The exact amount required will vary from subject to subject depending on factors such as the species being treated, the sex, age and general condition of the subject, the severity of the condition being treated, the particular agent being administered, the mode of administration, and so forth. Thus, it is not possible to specify an exact "effective amount". However, for any given case, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

Brief Description of the Figures

[0095] **Figure 1** A schematic representation of the experimental setup for the preparation of (*Z*)-1,4-dibromo-1,1,2-trifluorobut-2-ene.

[0096] **Figure 2 (a and b)** shows reduction in immature (a) and mature (b) cross-links in mouse scar tissue after injury when treated with topical Compound 1 (cmp 1).

[0097] **Figure 3** shows reduction in LOX activity in the skin of rats after topical application of cream containing Compound 1 versus control.

[0098] **Figure 4 (a-c)** Histological analysis of sclerosis mouse skin model with topical treatment with Compound 1 (cmp 1). (A) Composite skin score; (B) Average collagen score; (C) Average LOX score.

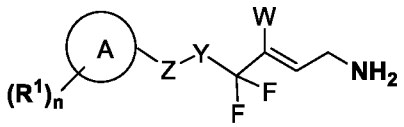
[0099] **Figure 5:** UV spectrum for Compound 1 from 200 nm to 680 nm (Shimadzu LCMS 2020 instrument).

[0100] **Figure 6** shows a dose-dependent improvement in pig scar appearance following topical treatment with **Compound 1** (0, 0.5, 1.5 and 3%).

Detailed Description

[0101] The present invention relates to substituted difluorohaloallylamine derivatives which may inhibit lysyl oxidase (LOX), lysyl oxidase-like2 (LOXL2) and other lysyl oxidase isoenzymes. In particular, the present invention relates to substituted fluoroallylamine derivatives with a sulfone linker.

[0102] In particular, the present invention relates to compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt, polymorphic form, solvate, hydrate or tautomeric form thereof; where

W is F or Cl;

Y is $-S(O)_2-$ or -S(O)-;

Z is $-(CH_2)_m-$

A is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkenyl, or C_{1-6}alkynyl;

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, $-NR^4R^5$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, $-C(O)OR^3$, $-C(O)NR^4R^5$, $-S(O)_2NR^4R^5$, $-S(O)_2R^6$, $-NR^8C(O)R^9$, and $-NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, -C_{1-4}alkyl, -O-C_{1-4}alkyl, $-CF_3$, - CH_2CF_3 and $-O-CF_3$;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, -C_{1-4}alkyl, -O-C_{1-4}alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, -C_{1-4}alkyl, -O-C_{1-4}alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, O-C_{1-6}alkyl C_{3-7}cycloalkyl, -C(O)OR^3, -C(O)NR^4R^5, -NR^4C(O)R^6, -S(O)$_2$NR^4R^5, -NR^4S(O)$_2R^6$ and -S(O)$_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

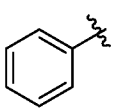
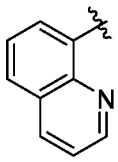
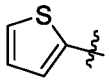
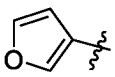
n is 0, 1, 2, 3, 4 or 5; and

m is 0 or 1.

[0103] In one embodiment of compounds of the present invention, W is F. In another embodiment of compounds of the present invention, W is Cl.

[0104] In one embodiment of compounds of the present invention, Y is -S(O)$_2$-. In another embodiment of compounds of the present invention, Y is -S(O)-.

[0105] In one embodiment of the present invention, A is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkenyl, or C_{1-6}alkynyl. In another embodiment of compounds of the present invention, A is selected from aryl and heteroaryl. In another embodiment of compounds of the present invention, A is selected from the group consisting of phenyl, quinolinyl, thiophenyl. furanyl and cyclopentyl. In a further embodiment of compounds of the present invention, A is selected from the group consisting of: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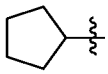

. In another embodiment of compounds of the present invention A is phenyl.

[0106] In one embodiment of compounds of the present invention, each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -C(O)OR^3, -C(O)NR^4R^5, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3 and –O-CF_3. In another embodiment of compounds of the present invention, each R^1 is independently selected from the group consisting of X-R^2, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -C(O)OR^3, -C(O)NR^4R^5, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, - CH_2CF_3 and –O-CF_3. In a further embodiment of compounds of the present invention, each R^1 is independently selected from the group consisting of X-R^2, deuterium, C_{1-6}alkyl, -OH, O-C_{1-6}alkyl, heterocycloalkyl, -NR^4R^5, and -$S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, - CH_2CF_3 and –O-CF_3. In one embodiment of compounds of the present invention, each R^1 is independently selected from the group consisting of X-R^2, deuterium, methyl, OCH_3, -OH, -$NHCH_3$, heterocycloalkyl and SO_2CH_3. In a further embodiment of compounds of the present invention each R^1 is independently selected from the group consisting of X-R^2, deuterium, methyl, OCH_3, -OH, -$NHCH_3$ and SO_2CH_3. In another embodiment of compounds of the present invention each R^1 is independently selected from the group consisting of X-R^2, methyl, OCH_3, -OH, -$NHCH_3$ and SO_2CH_3. In a further embodiment of compounds of the present invention each R^1 is independently selected from the group consisting of methyl, OCH_3, -OH, -$NHCH_3$ and SO_2CH_3.

[0107] In one embodiment of compounds of present invention, X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO. In another embodiment of compounds of the present invention X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, CONH and NHCO. In another embodiment of compounds of the present invention, X is selected from the group consisting of O, OCH_2, CH_2O, and CONH. In a further embodiment of compounds of the present invention, X is selected from the group consisting of O, CH_2 and OCH_2. In another embodiment of compounds of the present invention, X is selected from the group consisting of CONH and NHCO. In another embodiment of compounds of the present invention X is O or OCH_2. In a further embodiment of compounds of the present invention, X is O. In another embodiment of compounds of the present invention, X is OCH_2.

[0108] In one embodiment of compounds of the present invention, R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl where each R^2 is optionally substituted by one or more R^7. In another embodiment of compounds of the present invention, R^2 is selected from the group consisting of aryl and cycloalkyl where each R^2 is optionally substituted by one or more R^7. In a further embodiment of compounds of the present invention, R^2 is cycloalkyl where each R^2 is optionally substituted by one or more R^7. In another embodiment of compounds of the present invention, R^2 is aryl optionally substituted by one or more R^7. In another embodiment of compounds of the present invention, R^2 is phenyl substituted by one R^7. In another embodiment, R^2 is phenyl optionally substituted by $-S(O)_2R^6$. In a further embodiment R^2 is phenyl substituted by $-S(O)_2CH_3$.

[0109] In one embodiment of compounds of the present invention, R^2 is substituted by one R^7. In another embodiment of compounds of the present invention, R^2 is substituted by two R^7. In a further embodiment of compounds of the present invention, R^2 is substituted by three R^7. In another embodiment of compounds of the present invention, R^2 is substituted by four or five R^7.

[0110] In one embodiment of compounds of the present invention, R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, $-CF_3$, $-CH_2CF_3$, and -O-CF_3. In another embodiment of compounds of the present invention, R^3 is hydrogen. In a further embodiment of compounds of the present invention, R^3 is C_{1-6}alkyl or C_{3-7}cycloalkyl. In a still further embodiment of compounds of the present invention, R^3 is hydrogen or C_{1-6}alkyl. In another embodiment of compounds of the present invention, R^3 is C_{1-6}alkyl. In a further embodiment of compounds of the present invention, R^3 is

methyl or ethyl. In another embodiment of compounds of the present invention, R^3 is selected from the group consisting of hydrogen, methyl and ethyl.

[0111] In one embodiment of compounds of the present invention, R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3. In another embodiment of compounds of the present invention, R^4 and R^5 are independently selected from the group consisting of hydrogen and C_{1-6}alkyl. In another embodiment of compounds of the present invention, R^4 and R^5 are hydrogen. In a further embodiment of compounds of the present invention, R^4 and R^5 are C_{1-6}alkyl. In another embodiment of compounds of the present invention, R^4 and R^5 are both methyl. In a further embodiment of compounds of the present invention, R^4 and R^5 are both isopropyl. In one embodiment of compounds of the present invention, R^4 is hydrogen and R^5 is isopropyl. In a further embodiment of compounds of the present invention, R^4 and R^5 are independently selected from the group consisting of hydrogen and C_{3-7}cycloalkyl. In another embodiment of compounds of the present invention, R^4 is hydrogen and R^5 is C_{1-6}alkyl. In one embodiment of compounds of the present invention, R^4 is hydrogen and R^5 is methyl. In a further embodiment of compounds of the present invention, R^4 is hydrogen and R^5 is C_{3-7}cycloalkyl.

[0112] In one embodiment of compounds of the present invention R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members. In a further embodiment, R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having 1 additional heteroatom as ring members. In another embodiment, R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having 0 additional heteroatoms as ring members.

[0113] In one embodiment of compounds of the present invention R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3. In another embodiment, R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl. In another embodiment, R^6 is C_{1-6}alkyl. In a further embodiment, R^6 is C_{3-7}cycloalkyl. In another embodiment R^6 is CH_3.

[0114] In one embodiment of compounds of the present invention, R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, O-C_{1-6}alkyl, C_{3-7}cycloalkyl, -$C(O)OR^3$, -$C(O)NR^4R^5$, -$NR^4C(O)R^6$, -$S(O)_2NR^4R^5$, -$NR^4S(O)_2R^6$ and -$S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally

substituted by one or more substituents selected from the group consisting of halogen and –OH. In another embodiment of compounds of the present invention, R^7 is selected from the group consisting of halogen, C_{1-6}alkyl, $-C(O)NR^4R^5$, $-S(O)_2NR^4R^5$ and $-S(O)_2R^6$. In a further embodiment of compounds of the present invention, R^7 is selected from the group consisting of $-C(O)NR^4R^5$, $-S(O)_2NR^4R^5$ and $-S(O)_2R^6$. In another embodiment of compounds of the present invention, R^7 is $S(O)_2R^6$. In a further embodiment of compounds of the present invention R^7 is $-S(O)_2CH_3$.

[0115] In one embodiment of compounds of the present invention, R^8 is hydrogen or C_{1-6}alkyl. In another embodiment of compounds of the present invention, R^8 is hydrogen. In a further embodiment of compounds of the present invention, R^8 is selected from the group consisting of hydrogen, methyl and ethyl. In another embodiment of compounds of the present invention, R^8 is hydrogen or methyl.

[0116] In one embodiment of compounds of the present invention, R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$. In another embodiment, R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl. In another embodiment, R^9 is C_{1-6}alkyl. In a further embodiment, R^9 is C_{3-7}cycloalkyl.

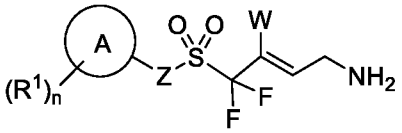
[0117] In one embodiment of compounds of the present invention, R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members. In a further embodiment, R^8 and R^9 are combined to form a 5- to 7-membered ring having 1 additional heteroatom as ring members. In another embodiment, R^8 and R^9 are combined to form a 5- to 7-membered ring having 0 additional heteroatoms as ring members.

[0118] In one of embodiment of compounds of the present invention, n is 0, 1, 2, 3, 4 or 5. In another embodiment of compounds of the present invention, n is 0. In a further embodiment of compounds of the present invention, n is 0, 1 or 2. In another embodiment of compounds of the present invention, n is 1, 2 or 3. In another embodiment of compounds of the present invention, n is 1 or 2. In a further embodiment of compounds of the present invention, n is 1. In another embodiment of compounds of the present invention, n is 2. In a further embodiment of compounds of the present invention, n is 3. In another embodiment of compounds of the present invention, n is 4. In a further embodiment of compounds of the present invention, n is 5. In another embodiment of compounds of the present invention n is 0, 1, 2 or 5. In a further embodiment of compounds of

the present invention n is 0, 1 or 5. In In another embodiment of the compounds of the present invention n is 1 or 5.

[0119] In one of embodiment of compounds of the present invention, m is 0 or 1. In another embodiment of compounds of the present invention, m is 0. In a further embodiment of compounds of the present invention, m is 1.

[0120] In one embodiment, the present invention also relates to compounds of Formula Ia:



Formula Ia

or a pharmaceutically acceptable salt, polymorphic form, solvate, hydrate or tautomeric form thereof; wherein:

W is F or Cl;

Z is $-(CH_2)_m-$;

A is aryl or heteroaryl;

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -C(O)OR^3, -C(O)NR^4R^5, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, - SO_2CH_3, -C_{14}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3 and $-O-CF_3$;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, $O-C_{1-6}$alkyl C_{3-7}cycloalkyl, $-C(O)OR^3$, $-C(O)NR^4R^5$, $-NR^4C(O)R^6$, $-S(O)_2NR^4R^5$, $-NR^4S(O)_2R^6$ and $-S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

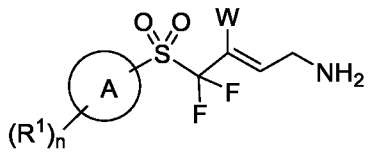
R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

n is 0, 1, 2 or 5; and

m is 0 or 1.

[0121] In another embodiment, the present invention also relates to compounds of Formula Ib:



Formula Ib

or a pharmaceutically acceptable salt, polymorphic form, solvate, hydrate or tautomeric form thereof; wherein:

W is F or Cl;

A is aryl or heteroaryl;

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -C(O)OR^3, -C(O)NR^4R^5, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, - CH_2CF_3 and –O-CF_3;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, O-C_{1-6}alkyl C_{3-7}cycloalkyl, -C(O)OR^3, -C(O)NR^4R^5, -$NR^4C(O)R^6$, -$S(O)_2NR^4R^5$, -$NR^4S(O)_2R^6$ and -$S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

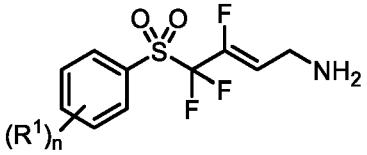
R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

n is 0, 1, 2 or 5; and

m is 0 or 1.

[0122] In one embodiment of compounds of Formula I, Formula Ia, or Formula Ib W is F.

[0123] In one embodiment, the present invention also relates to compounds of Formula Ic:



Formula Ic

or a pharmaceutically acceptable salt, polymorphic form, solvate, hydrate or tautomeric form thereof; wherein:

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -C(O)OR^3, -C(O)NR^4R^5, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3 and –O-CF_3;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more

substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, $O-C_{1-6}$alkyl C_{3-7}cycloalkyl, $-C(O)OR^3$, $-C(O)NR^4R^5$, $-NR^4C(O)R^6$, $-S(O)_2NR^4R^5$, $-NR^4S(O)_2R^6$ and $-S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^8 and R^9 are combined to form a 4- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members; and

n is 0, 1, 2 or 5.

[0124] In one embodiment of compounds of Formula I, Ia, Ib or Ic, n is 0.

[0125] In one embodiment of compounds of Formula I, Ia, Ib or Ic of the invention, each R^1 is independently selected from the group consisting of $X-R^2$, deuterium, C_{1-6}alkyl, -OH, $O-C_{1-6}$alkyl, heterocycloalkyl, $-NR^4R^5$, and $-S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, - CH_2CF_3 and $-O-CF_3$; X is selected from the group consisting of O and OCH_2; R^2 is aryl optionally substituted by one or more R^7; R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; R^7 is $-S(O)_2R^6$ and n is 0, 1, or 5.

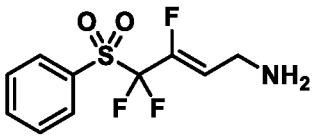
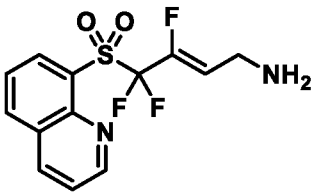
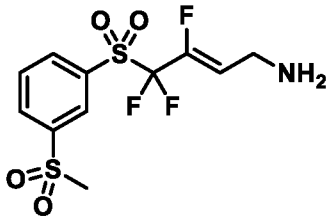
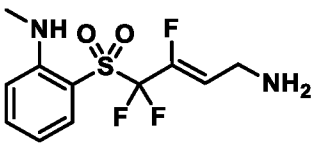
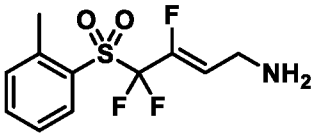
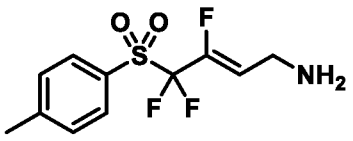
[0126] In another embodiment of compounds of Formula I, Ia, Ib or Ic of the invention, R^1 is independently selected from the group consisting of $X-R_2$, deuterium, methyl, OCH_3, -OH,

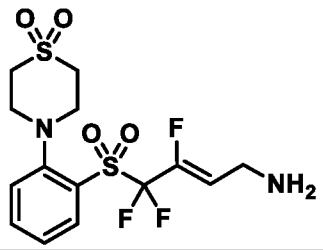
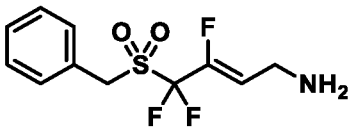
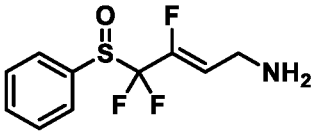
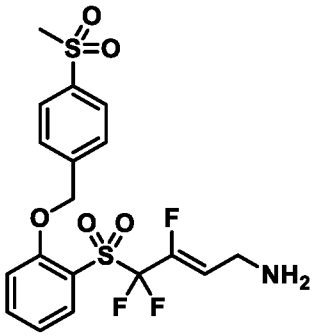
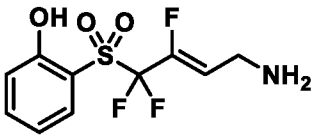
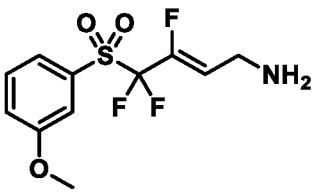
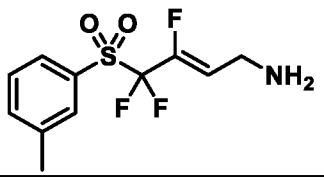
-$NHCH_3$, heterocycloalkyl and SO_2CH_3; X is O or OCH_2; R^2 is phenyl substituted by SO_2CH_3 and n is 0, 1 or 5.

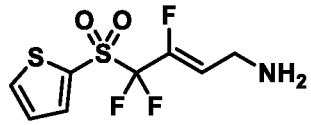
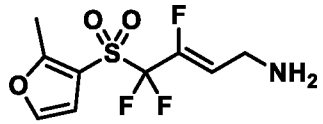
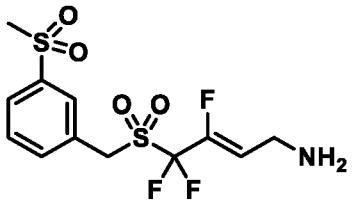
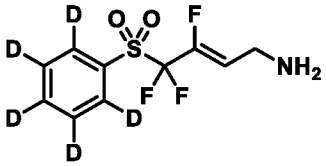
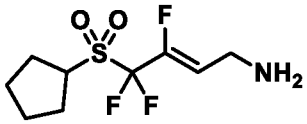
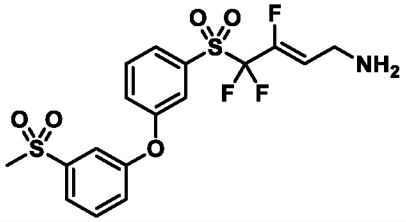
[0127] In the context of the present disclosure, any one or more aspect(s) or embodiment(s) may be combined with any other aspect(s) or embodiment(s).

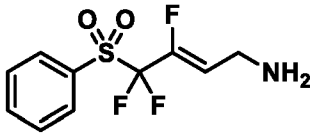
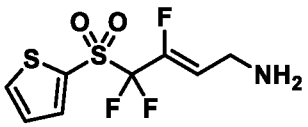
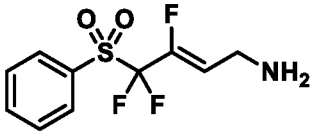
[0128] Exemplary compounds according to the present invention include the compounds set forth in Table 2:

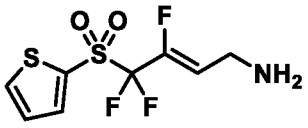
Table 2

1		(*Z*)-3,4,4-trifluoro-4-(phenylsulfonyl)but-2-en-1-amine
2		(*Z*)-3,4,4-trifluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-amine
3		(*Z*)-3,4,4-trifluoro-4-((3-(methylsulfonyl)phenyl)sulfonyl)but-2-en-1-amine
4		(*Z*)-2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)-*N*-methylaniline
5		(*Z*)-3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-amine
6		(*Z*)-3,4,4-trifluoro-4-tosylbut-2-en-1-amine

7		(*Z*)-4-(2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)phenyl)thiomorpholine 1,1-dioxide
8		(*Z*)-4-(benzylsulfonyl)-3,4,4-trifluorobut-2-en-1-amine
9		(*Z*)-3,4,4-trifluoro-4-(phenylsulfinyl)but-2-en-1-amine
10		(*Z*)-3,4,4-trifluoro-4-((2-((4-(methylsulfonyl)benzyl)oxy)phenyl)sulfonyl)but-2-en-1-amine
11		(*Z*)-2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)phenol
12		(*Z*)-3,4,4-trifluoro-4-((3-methoxyphenyl)sulfonyl)but-2-en-1-amine
13		(*Z*)-3,4,4-trifluoro-4-(*m*-tolylsulfonyl)but-2-en-1-amine

14		(Z)-3,4,4-trifluoro-4-(thiophen-2-ylsulfonyl)but-2-en-1-amine
15		(Z)-3,4,4-trifluoro-4-((2-methylfuran-3-yl)sulfonyl)but-2-en-1-amine
17		(Z)-3,4,4-trifluoro-4-((3-(methylsulfonyl)benzyl)sulfonyl)but-2-en-1-amine
18		(Z)-3,4,4-trifluoro-4-((phenyl-d5)sulfonyl)but-2-en-1-amine
19		(Z)-4-(cyclopentylsulfonyl)-3,4,4-trifluorobut-2-en-1-amine
20		(Z)-3,4,4-trifluoro-4-((3-(3-(methylsulfonyl)phenoxy)phenyl)sulfonyl)but-2-en-1-amine

[0129] In one embodiment, the compound of the present invention is selected from the group consisting of  and  , or a pharmaceutically acceptable salt or solvate thereof. In another embodiment the compound of the present invention is  or a pharmaceutically acceptable salt or solvate thereof. In a further

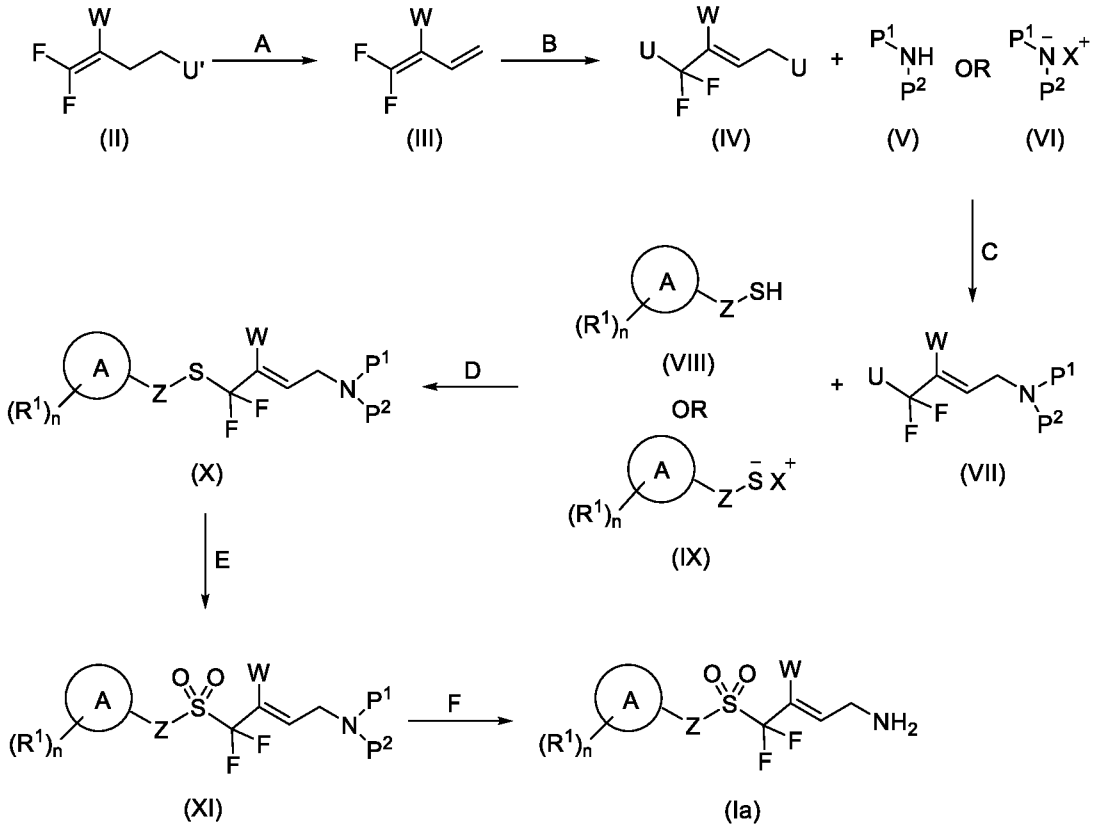
embodiment, the compound of the present invention is  or a pharmaceutically acceptable salt or solvate thereof.

Preparation of Compounds of Formula I

[0130] Compounds of Formula I can be readily prepared by those skilled in the art using methods and materials known in the art and with reference to standard textbooks, such as "Advanced Organic Chemistry" by Jerry March (third edition, 1985, John Wiley and Sons) or "Comprehensive Organic Transformations" by Richard C. Larock (1989, VCH Publishers).

[0131] Compounds of Formula I may be synthesised as described below. The following schemes provide an overview of representative non-limiting embodiments of the invention. Those skilled in the art will recognize that analogues of Formula I, including different isomeric forms, may also be prepared from the analogous starting materials.

[0132] The preparation of compounds described by Formula Ia is described in Scheme 1 below.



Scheme 1

[0133] P^1 is a functional group used to protect a nitrogen functionality. P^2 is hydrogen or a functional group to protect a nitrogen functionality. Examples of P^1 and P^2 are carbamate forming groups such as the *tert*-butyloxycarbonyl (BOC), the 9-fluorenylmethyloxy-carbonyl (FMOC), and the benzyloxycarbonyl (CBZ) groups. Alternatively, P^1 and P^2, together with the nitrogen to which they are attached form a cyclic group to protect a nitrogen functionality. In one embodiment the protecting group is a phthalimide.

[0134] X^+ is a metal counterion such as Li^+, Na^+ and K^+

[0135] In one embodiment of compounds of Formula (II), W is F or Cl. In another embodiment of compounds of Formula (II), W is Cl. In a further embodiment of compounds of Formula (II), W is F.

[0136] In one embodiment of compounds of Formula (II), U' is Br, Cl, I, OMs, OTs. In another embodiment of compounds of Formula (II), U' is Br or I. In a further embodiment of compounds of Formula (II), U' is Br.

[0137] In general Scheme 1 the starting material described by Formula II can be obtained from commercial sources or can be prepared by many methods well known in the art. Whilst there are many ways to achieve the reaction described by Method A, one convenient protocol involves heating a solution a compound of Formula II in the presence of a base, such as potassium hydroxide, in a solvent, such as xylene, to a temperature between 50 and 70 °C, for several hours. In one embodiment, the reaction described by Method A and B is conducted in accordance with the schematic representation of the experimental setup depicted in Figure 1.

[0138] In one embodiment of the process of the present invention, the compound of Formula III is not isolated and is added to a solution of U_2, such as Br_2 in a suitable solvent, such as dichloromethane that has been cooled to a temperature between -10 °C and 10 °C, such as a temperature of 0 °C. The product described by Formula IV can be recovered by standard work up procedures.

[0139] Whilst there are many ways to achieve the reaction described by Method C, one convenient protocol involves reaction of compounds described by Formulae IV and V in the presence of a base in a solvent such as *N,N*-dimethylformamide that has been cooled to a temperature between -10 °C and 10 °C, such as a temperature of 0 °C for 1 hour to several hours. An alternative, convenient protocol involves reaction of compounds described by Formulae IV and

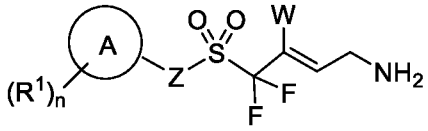
VI in a solvent such as *N*,*N*-dimethylformamide at a temperature between 0 °C and 40 °C for 1 hour to several hours. The product described by Formula VI can be recovered by standard work up procedures.

[0140] Whilst there are many ways to achieve the reaction described by Method D, one convenient protocol involves reaction of compounds described by Formulae VII and VIII in the presence of a base such as cesium carbonate or sodium hydride in a solvent such as *N*,*N*-dimethylformamide at ambient temperature for several hours. An alternative, convenient protocol involves reaction of compounds described by Formulae VII and IX in a solvent such as *N*,*N*-dimethylformamide at a temperature between 0 °C and 40 °C for 1 hour to several hours. Following standard extraction and purification methods the product described by Formula X can be obtained in good yield and purity.

[0141] Whilst there are many ways to achieve the reaction described by Method E, one convenient protocol involves reaction of compounds described by Formula X in a solvent such as acetic acid with an oxidising agent such as hydrogen peroxide at a temperature between 70 °C and 90 °C, such as 80 °C for several hours. Following standard extraction and purification methods the product described by Formula XI can be obtained in good yield and purity. A person skilled in the art would appreciate that through suitable modifcations of the oxidation conditions, sulfoxides can be obtained.

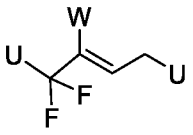
[0142] There are many well established chemical procedures for the deprotection of the compounds described by Formula XI to the compounds described by Formula Ia (Method F). For example if P^1 is a BOC protecting group, compounds described by Formula XI can be treated with an acidic substance such as dry hydrogen chloride in a solvent such as ethyl acetate to furnish the compounds described by Formula Ia as the hydrochloride salts. If P^1 and P^2 together are phthalimide, compounds described by Formula XI can be heated in a solvent, such as methylamine for several hours before being treated with an acidic substance such as dry hydrogen chloride in a solvent such as ethyl acetate to furnish the compounds described by Formula Ia as the hydrochloride salts. In general, the free amino compounds are converted to acid addition salts for ease of handling and for improved chemical stability. Examples of acid addition salts include but are not limited to hydrochloride, hydrobromide, 2,2,2-trifluoroacetate and methanesulfonate salts.

[0143] In one aspect, the present invention provides for a process for preparing a compound of Formula Ia:

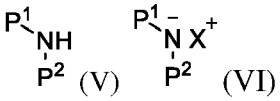


which comprises reaction steps (C), (D), (E) and (F), where:

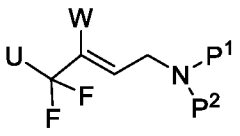
(C) is the reaction of a compound of Formula IV:


(IV)

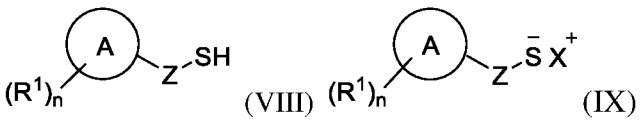
with a compound of Formula V or VI


(V) (VI)

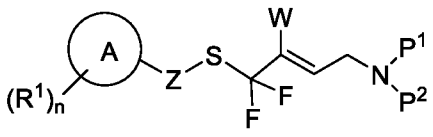
to afford a compound of Formula VII:


(VII);

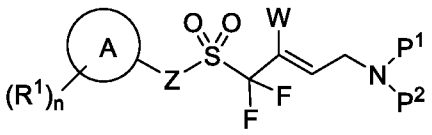
(D) is the reaction of a compound of Formula VII with a compound of Formula VIII or IX:


(VIII) (IX)

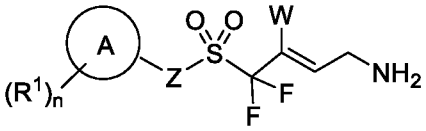
to obtain a compound of Formula X:


(X);

(E) is the oxidation of a compound of Formula X to obtain a compound of Formula XI:


(XI); and

(F) is deprotection of a compound of Formula XI to afford a compound of Formula Ia:


(Ia), or a pharmaceutically acceptable salt thereof

wherein U is Br, Cl or I;

W is F or Cl;

Z is $-(CH_2)_m-$;

P^1 is a nitrogen protecting group;

P^2 is hydrogen or a nitrogen protecting group; or

P^1 and P^2 together with the nitrogen to which they are attached form a cyclic protected nitrogen group;

X^+ is a metal counterion; and

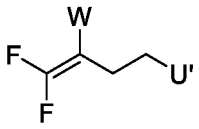
R^1, A and n are as defined above,

n is 0, 1, 2 or 3; and

m is 0 or 1.

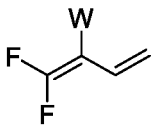
[0144] In one embodiment of the process, reaction step (C) is preceded by reaction steps (A) and (B), wherein:

(A) denotes the reaction of a compound of Formula II:



(II)

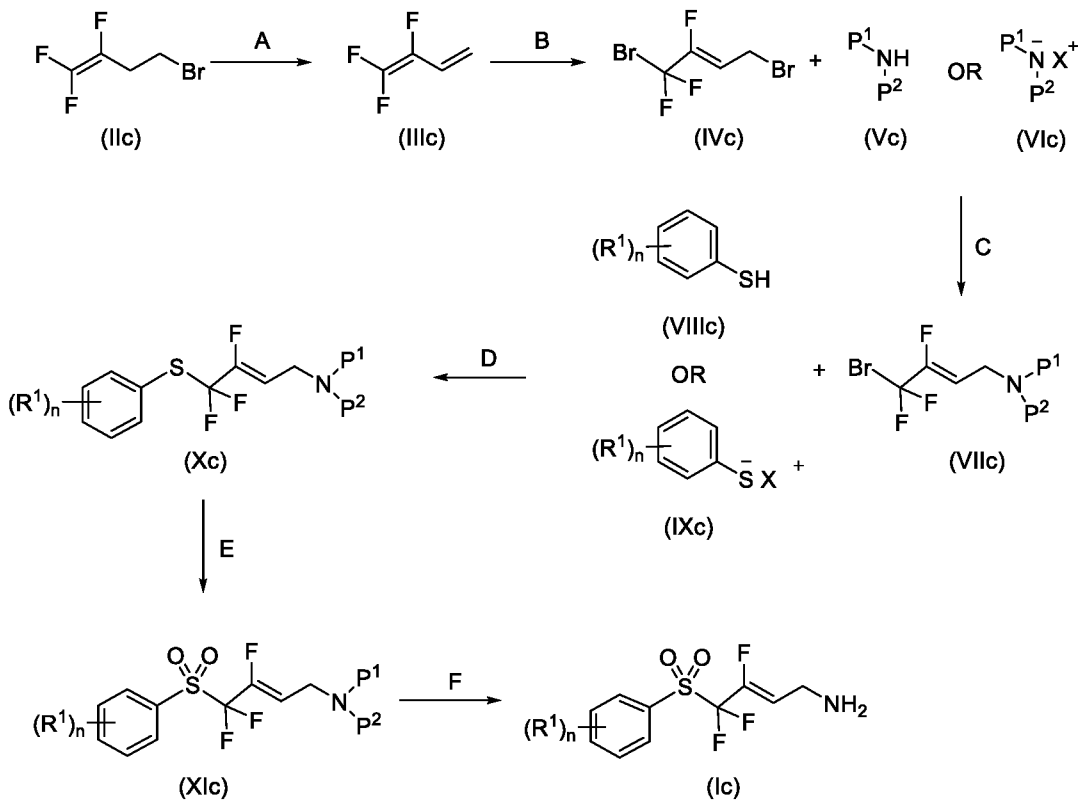
with a base to afford a compound of Formula III:



(III)

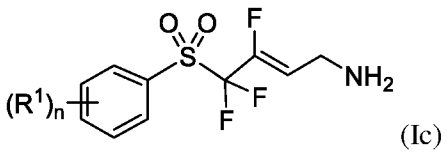
and (B) denotes the reaction of a compound of Formula III with U_2 to afford a compound of Formula IV.

[0145] In one embodiment of the process of the present invention, the process is represented by Scheme 2.



Scheme 2

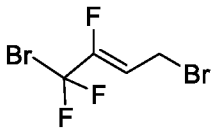
[0146] In one embodiment of the present invention, there is provided a process for preparing a compound of Formula Ic:



(Ic)

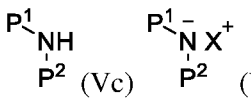
which comprises reaction steps (C), (D), (E) and (F), where:

(C) is the reaction of a compound of Formula IVc:



(IVc)

with a compound of Formula Vc or VIc:

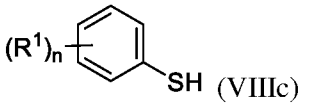
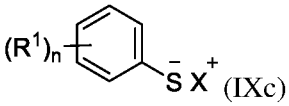


(Vc) (VIc)

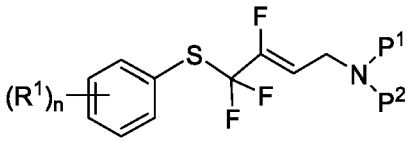
to afford a compound of Formula VIIc:


(VIIc);

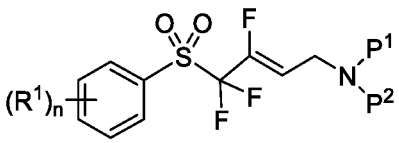
(D) is the reaction of a compound of Formula VIIc with a compound of Formula VIIIc or IXb:


(VIIIc)

(IXc)

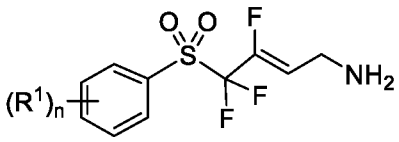
to obtain a compound of Formula Xc:


(Xc);

(E) is the oxidation of a compound of Formula Xc to obtain a compound of Formula XIc:


(XIc); and

(F) is deprotection of a compound of Formula XIc to afford a compound of Formula Ic:


(Ic), or a pharmaceutically acceptable salt thereof

wherein

P^1 is a nitrogen protecting group;

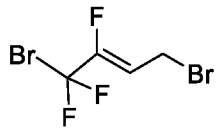
P^2 is hydrogen or a nitrogen protecting group; or

P^1 and P^2 together with the nitrogen to which they are attached form a cyclic nitrogen protecting group

X^+ is a metal counterion, and

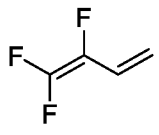
R^1 and n are as defined above.

[0147] A further aspect of the invention provides for a process for preparing a single isomer of a compound of Formula IVc:


(IVc)

which comprises:

addition of a compound of Formula IIIc:

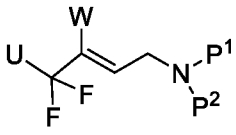

(IIIc)

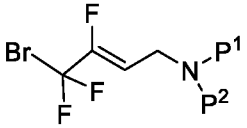
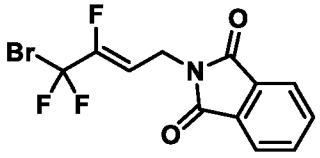
to a solution of Br_2.

[0148] The present invention also provides for compounds of Formula I prepared according to the processes of the invention.

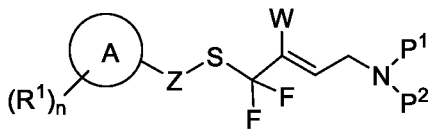
[0149] Further aspects of the invention provide for intermediates of the processes of the invention.

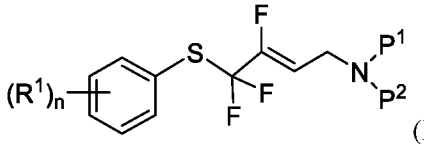
[0150] One aspect of the invention provides for an intermediate of Formula VII,


(VII)

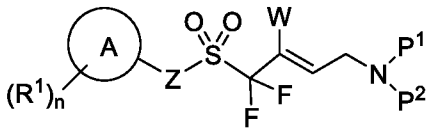
wherein U, W, P^1 and P^2 are as defined above. In one embodiment the present invention provides for an intermediate of Formula VIIc:  (VIIc) wherein P^1 and P^2 are as defined above. A further embodiment of the present invention provides for an intermediate of Formula:  .

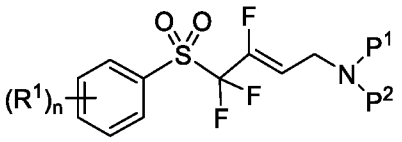
[0151] Another aspect of the invention provides for an intermediate of Formula X,


(X)

wherein W, Z, P^1 and P^2, R^1, A and n are as defined above. In one embodiment the present invention provides for an intermediate of Formula Xc:  (Xc) wherein P^1 and P^2, R^1, and n are as defined above.

[0152] A further aspect of the invention provides for an intermediate of Formula XI,


(XI)

wherein W, Z, P^1 and P^2, R^1, A and n are as defined above. In one embodiment the present invention provides for an intermediate of Formula XIc:  (XIc) wherein P^1 and P^2, R^1, and n are as defined above.

[0153] *Cis/trans* (*E/Z*) isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Therapeutic uses and formulations

[0154] Another aspect of the present invention relates to a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer thereof, together with a pharmaceutically acceptable diluent, excipient or adjuvant.

[0155] The present invention also relates to use of the compounds of Formula I in therapy, in particular to inhibit members of the lysyl oxidase family members, LOX, LOXL1, LOXL2, LOXL3 and LOXL4. In one embodiment, the invention provides for the selective inhibition of specific lysyl oxidase isoenzymes. In another embodiment, the invention provides for the simultaneous inhibition of 2, 3, 4 or 5 LOX isoenzymes. The relative inhibitory potencies of the compounds can be determined by the amount needed to inhibit the amine oxidase activity of LOX, LOXL1, LOXL2, LOXL3 and LOXL4 in a variety of ways, e.g., in an *in vitro* assay with recombinant or purified human protein or with recombinant or purified non-human enzyme, in cellular assays expressing normal rodent enzyme, in cellular assays which have been transfected with human protein, in *in vivo* tests in rodent and other mammalian species, and the like.

[0156] In one embodiment, the compounds of the present invention are long lasting inhibitors of the lysyl oxidase family members LOX, LOXL1, LOXL2, LOXL3 and LOXL4. In one embodiment, the compounds of the present invention are long lasting inhibitors of the LOX or LOXL1-4 enzymes if the inhibition continues to be greater than 50% of the LOX or LOXL1-4 enzymes' activity after the compound concentration has been reduced below the IC50. In one embodiment, the compounds of the present invention show sustained inhibition of the LOX or LOXL1-4 enzymes over a period of 24 hours. In one embodiment, the compounds of the present invention are irreversible inhibitors of the lysyl oxidase family members LOX, LOXL1, LOXL2, LOXL3 and LOXL4.

[0157] Accordingly, a further aspect of the invention is directed to a method of inhibiting the amine oxidase activity of any one of LOX, LOXL1, LOXL2, LOXL3 or LOXL4 in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof.

[0158] In one embodiment, the present invention is directed to a method of inhibiting the amine oxidase activity of LOXL2. In another embodiment, the present invention is directed towards inhibiting the amine oxidase activity of LOX and LOXL2. In a further embodiment, the present invention is directed to a method of inhibiting the amine oxidase activity of LOX.

[0159] As discussed previously, LOX and LOXL1-4 enzymes are members of a large family of flavin-dependent and copper-dependent amine oxidases, which includes SSAO/VAP-1, monoamine oxidase-B (MAO-B) and diamine oxidase (DAO). In one embodiment, compounds of the present invention selectively inhibit members of the lysyl oxidase isoenzyme family with respect to SSAO/VAP-1, MAO-B, DAO and other members of the amine oxidase family.

[0160] The present invention also discloses methods to use the compounds described by Formula I to inhibit one or more lysyl oxidase isoenzymes (LOX, LOXL1, LOXL2, LOXL3 and LOXL4) in patients suffering from a fibrotic disease, and methods to treat fibrotic diseases. Furthermore, the present invention discloses methods to use the compounds described by Formula I to inhibit one or more lysyl oxidase isoenzymes (LOX, LOXL1, LOXL2, LOXL3 and LOXL4) in patients suffering from cancer, including metastatic cancer, and methods to treat cancer and metastatic cancer.

[0161] In a further aspect of the invention, there is provided a method of treating a condition by inhibiting the activity of any one of the LOX, LOXL1, LOXL2, LOXL3 and LOXL4 proteins, comprising administering to a subject in need thereof a therapeutically effective amount of compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof.

[0162] In another aspect, there is a provided a method of treating a condition modulated by any one of LOX, LOXL1, LOXL2, LOXL3 and LOXL4, comprising administering to a subject in need thereof a therapeutically effective amount of compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof.

[0163] In one embodiment of the methods of the present invention, the condition is selected from the group consisting of fibrosis, cancer and arthritis.

[0164] In another aspect, the present invention provides a method for decreasing extracellular matrix formation by treating human subjects, pets and livestock with difluorohaloallylamine inhibitors of lysyl oxidase isoenzyme family of Formula I as described herein.

[0165] The above-described methods are applicable wherein the condition is fibrosis. As employed here "fibrosis" includes such diseases as cystic fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, kidney fibrosis, scleroderma, radiation-induced fibrosis, Peyronie's disease, scarring and other diseases where excessive fibrosis contributes to disease pathology.

[0166] In one embodiment, the fibrosis is selected from the group consisting of mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Crohn's Disease, keloid, scleroderma/systemic sclerosis, arthrofibrosis, Dupuytren's contracture, adhesive capsulitis, fibrosis of the pancreases, fibrosis of the intestine, liver fibrosis, lung fibrosis, kidney fibrosis, cardiac fibrosis, fibrostenosis, cystic fibrosis, idiopathic pulmonary fibrosis, radiation-induced fibrosis, Peyronie's disease and scleroderma or is associated with respiratory disease, abnormal wound healing and repair, scarring, hypertrophic scarring/keloids, scarring post-surgery, cardiac arrest and all conditions where excess or aberrant deposition of fibrous material is associated with disease, injury, implants or surgery. In another embodiment, the fibrosis is selected from the group consisting of liver fibrosis, lung fibrosis, kidney fibrosis, cardiac fibrosis, scarring and scleroderma.

[0167] In one embodiment, kidney fibrosis includes, but is not limited to, diabetic nephropathy, vesicoureteral reflux, tubulointerstitial renal fibrosis; glomerulonephritis or glomerular nephritis, including focal segmental glomerulosclerosis and membranous glomerulonephritis, IgA nephropathy and mesangiocapillary glomerular nephritis. In one embodiment, liver fibrosis results in cirrhosis, and includes associated conditions such as chronic viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic steatohepatitis (ASH), non-alcoholic steatohepatitis (NASH), primary biliary cirrhosis (PBC), biliary cirrhosis, and autoimmune hepatitis.

[0168] In one embodiment, the fibrosis is selected from keloid, scarring, ocular scarring, hypertrophic scarring, scleroderma, Dupuytren's contracture and Peyronie's disease. In one embodiment, the hypertrophic scarring results from a burn. In one embodiment, the hypertrophic scarring is caused by external injuries. In another embodiment, the hypertrophic scarring is caused by surgical procedures. In one embodiment, the keloid is caused by external injuries. In another embodiment, the keloid is caused by surgical procedures. In a further embodiment, the keloid is a result of a skin injury caused by acne, burns, chicken pox, piercing, scratches, surgical cuts or vaccination sites.

[0169] The above-described methods are also applicable wherein the condition is a proliferative disease for example cancer. In one embodiment, the cancer is selected from the group consisting of lung cancer; breast cancer; colorectal cancer; anal cancer; pancreatic cancer; prostate cancer; ovarian carcinoma; liver and bile duct carcinoma; esophageal carcinoma; non-Hodgkin's lymphoma; bladder carcinoma; carcinoma of the uterus; glioma, glioblastoma, medullablastoma, and other tumours of the brain; myelofibrosis, kidney cancer; cancer of the head and neck; cancer of the stomach; multiple myeloma; testicular cancer; germ cell tumour; neuroendocrine tumour; cervical cancer; oral cancer, carcinoids of the gastrointestinal tract, breast, and other organs; signet ring cell carcinoma; mesenchymal tumours including sarcomas, fibrosarcomas, haemangioma, angiomatosis, haemangiopericytoma, pseudoangiomatous stromal hyperplasia, myofibroblastoma, fibromatosis, inflammatory myofibroblastic tumour, lipoma, angiolipoma, granular cell tumour, neurofibroma, schwannoma, angiosarcoma, liposarcoma, rhabdomyosarcoma, osteosarcoma, leiomyoma or a leiomyosarcoma.

[0170] In one embodiment, the cancer is selected from the group consisting of breast cancer, head and neck squamous cell carcinoma, brain cancer, prostate cancer, renal cell carcinoma, liver cancer, lung cancer, oral cancer, cervical cancer and tumour metastasis.

[0171] In one embodiment, lung cancer includes lung adenocarcinoma, squamous cell carcinoma, large cell carcinoma, bronchoalveolar carcinoma, non-small-cell carcinoma, small cell carcinoma and mesothelioma. In one embodiment breast cancer includes ductal carcinoma, lobular carcinoma, inflammatory breast cancer, clear cell carcinoma, and mucinous carcinoma. In one embodiment, colorectal cancer includes colon cancer and rectal cancer. In one embodiment, pancreatic cancer includes pancreatic adenocarcinoma, islet cell carcinoma and neuroendocrine tumours.

[0172] In one embodiment, ovarian carcinoma includes ovarian epithelial carcinoma or surface epithelial-stromal tumour including serous tumour, endometrioid tumour and mucinous cystadenocarcinoma, and sex-cord-stromal tumour. In one embodiment liver and bile duct carcinoma includes hepatocelluar carcinoma, cholangiocarcinoma and hemangioma. In one embodiment, esophageal carcinoma includes esophageal adenocarcinoma and squamous cell carcinoma. In one embodiment, carcinoma of the uterus includes endometrial adenocarcinoma, uterine papillary serous carcinoma, uterine clear-cell carcinoma, uterine sarcomas and leiomyosarcomas and mixed mullerian tumours. In one embodiment, kidney cancer includes renal cell carcinoma, clear cell carcinoma and Wilm's tumour. In one embodiment, cancer of the head and neck includes squamous cell carcinomas. In one embodiment, cancer of the stomach includes stomach adenocarcinoma and gastrointestinal stromal tumour.

[0173] In one embodiment, the cancer is selected from the group consisting of pancreatic cancer, liver cancer, breast cancer, myelofibrosis and mesothelioma.

[0174] In one embodiment, the compounds of the invention may be for use in the treatment of a non-metastatic cancer. In another embodiment, the compounds of the invention may be for use in the treatment of metastatic cancer. In a further embodiment, the compounds of the present invention may be for use in the prevention or treatment of tumour metastasis.

[0175] The above-described methods are applicable wherein the condition is arthritis. As used herein arthritis includes rheumatoid arthritis and osteoarthritis.

[0176] In one embodiment of the methods of the present invention, the subject is selected from the group consisting of humans, pets and livestock. In another embodiment of the methods of the present invention, the subject is a human.

[0177] A further aspect of the invention provides for use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for

treating a condition by inhibiting the activity of any one of the LOX, LOXL1, LOXL2, LOXL3 and LOXL4 proteins.

[0178] Another aspect of the invention provides for use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treating a condition modulated by any one of LOX, LOXL1, LOXL2, LOXL3 and LOXL4.

Pharmaceutical and/or Therapeutic Formulations

[0179] In another embodiment of the present invention, there are provided compositions comprising a compound having Formula I and at least one pharmaceutically acceptable excipient, carrier or diluent thereof. The compound(s) of Formula I may also be present as suitable salts, including pharmaceutically acceptable salts.

[0180] The phrase "pharmaceutically acceptable carrier" refers to any carrier known to those skilled in the art to be suitable for the particular mode of administration. In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

[0181] The phrase "pharmaceutically acceptable salt" refers to any salt preparation that is appropriate for use in a pharmaceutical application. By pharmaceutically acceptable salt it is meant those salts which, within the scope of sound medical judgement, are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art and include acid addition and base salts. Hemisalts of acids and bases may also be formed. Pharmaceutically acceptable salts include amine salts of mineral acids (e.g., hydrochlorides, hydrobromides, sulfates, and the like); and amine salts of organic acids (e.g., formates, acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, maleates, butyrates, valerates, fumarates, sulfonates and the like).

[0182] For compounds of formula (I) having a basic site, suitable pharmaceutically acceptable salts may be acid addition salts. For example, suitable pharmaceutically acceptable salts of such compounds may be prepared by mixing a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, methanesulfonic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, phosphoric acid, acetic acid, oxalic acid, carbonic acid, tartaric acid, or citric acid with the compounds of the invention.

[0183] S. M. Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences,* 1977, *66*:1-19. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, asparate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oleate, palmitate, pamoate, pectinate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, toluenesulfonate, undecanoate, valerate salts, and the like. Suitable base salts are formed from bases that form non-toxic salts. Examples include the arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, dimethylamine, trimethylamine, triethylamine, triethanolamine and the like.

[0184] Pharmaceutically acceptable salts of compounds of formula I may be prepared by methods known to those skilled in the art, including for example:

(i) by reacting the compound of formula I with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

[0185] The above reactions (i)-(iii) are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[0186] Thus, for instance, suitable pharmaceutically acceptable salts of compounds according to the present invention may be prepared by mixing a pharmaceutically acceptable acid such as

hydrochloric acid, sulfuric acid, methanesulfonic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, phosphoric acid, acetic acid, carbonic acid, tartaric acid, or citric acid with the compounds of the invention. Suitable pharmaceutically acceptable salts of the compounds of the present invention therefore include acid addition salts.

[0187] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when the solvent is water.

[0188] In one embodiment, the compounds of Formula I may be administered in the form of a "prodrug". The phrase "prodrug" refers to a compound that, upon *in vivo* administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. Prodrugs can be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to a compound described herein. For example, prodrugs include compounds of the present invention wherein a hydroxy, amino, or carboxylate group is bonded to any group that, when administered to a mammalian subject, can be cleaved to form a free hydroxyl, free amino, or free carboxylic acid group, respectively. Representative prodrugs include, for example, amides, esters, enol ethers, enol esters, acetates, formates, benzoate derivatives, and the like of alcohol and amine functional groups in the compounds of the present invention. The prodrug form can be selected from such functional groups as -C(O)alkyl, -C(O)cycloalkyl, -C(O)aryl, -C(O)-arylalkyl, C(O)heteroaryl, -C(O)-heteroarylalkyl, or the like. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

[0189] Compositions herein comprise one or more compounds provided herein. The compounds are, in one embodiment, formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, creams, gels, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. In one embodiment, the compounds described above are formulated into pharmaceutical compositions

using techniques and procedures well known in the art (see, *e.g.*, Ansel *Introduction to Pharmaceutical Dosage Forms, Fourth Edition* 1985, 126).

[0190] In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives thereof is (are) mixed with a suitable pharmaceutical carrier. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs prior to formulation, as described above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases or disorders to be treated.

[0191] In one embodiment, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected carrier at an effective concentration such that the treated condition is relieved, prevented, or one or more symptoms are ameliorated.

[0192] The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein, and then extrapolated from there for dosages for humans.

[0193] The concentration of active compound in the pharmaceutical composition will depend on absorption, distribution, inactivation and elimination rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

[0194] Dosing may occur at intervals of minutes, hours, days, weeks, months or years or continuously over any one of these periods. Suitable dosages lie within the range of about 0.1 ng per kg of body weight to 0.1 g per kg of body weight per dosage. The dosage is preferably in the range of 1 µg to 0.1 g per kg of body weight per dosage, such as is in the range of 1 mg to 0.1 g per kg of body weight per dosage. Suitably, the dosage is in the range of 1 µg to 50 mg per kg of body weight per dosage, such as 1 µg to 20 mg per kg of body weight per dosage, or 1 µg to 10 mg per kg of body weight per dosage. Other suitable dosages may be in the range of 1 mg to 25 mg per kg of body weight, including 1 mg to 10, 20, 50 or 100 mg per kg of body weight per dosage or 10 µg

to 100 mg per kg of body weight per dosage. In one embodiment, the dosage is in the range of 1 mg to 10 mg per kg of body weight per dosage.

[0195] Alternatively, an effective dosage may be up to about 10 mg/cm^2, or it may be up to about 1 mg/cm^2, about 0.5 mg/cm^2, about 0.2 mg/cm^2, about 0.1 mg/cm^2, about 0.05 mg/cm^2, about 0.02 mg/cm^2, or about 0.01 mg/cm^2. It may be, for example, in the range from about 0.1 µg/cm^2 to about 1 mg/cm^2, or from about 1 µg/cm^2 to about 1 mg/cm^2, about 10 µg/cm^2 to about 1 mg/cm^2, about 10 µg/cm^2 to about 0.1 mg/cm^2, about 10 µg/cm^2 to about 0.01 mg/cm^2, about 10 µg/cm^2 to about 500 µg/cm^2, about 10 µg/cm^2 to about 200 µg/cm^2, about 10 µg/cm^2 to about 100 µg/cm^2, about 10 µg/cm^2 to about 50 µg/cm^2, about 20 µg/cm^2 to about 1 mg/cm^2, about 50 µg/cm^2 to about 1 mg/cm^2, about 100 µg/cm^2 to about 1 mg/cm^2, about 200 µg/cm^2 to about 1 mg/cm^2, about 500 µg/cm^2 to about 1 mg/cm^2, about 50 µg/cm^2 to about 500 µg/cm^2, about 50 µg/cm^2 to about 200 µg/cm^2, about 100 µg/cm^2 to about 500 µg/cm^2, or about 200 µg/cm^2 to about 500 µg/cm^2.

[0196] Suitable dosage amounts and dosing regimens can be determined by the attending physician and may depend on the particular condition being treated, the severity of the condition, as well as the general health, age and weight of the subject.

[0197] In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, dissolution in aqueous sodium bicarbonate, formulating the compounds of interest as nanoparticles, and the like. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

[0198] Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[0199] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof.

[0200] The pharmaceutically therapeutically active compounds and derivatives thereof are, in one embodiment, formulated and administered in unit-dosage forms or multiple-dosage forms. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

[0201] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975.

[0202] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% (wt %) with the balance made up from non-toxic carrier may be prepared. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% (wt %) active ingredient, in one embodiment 0.1-95% (wt %), in another embodiment 75-85% (wt %) and in another embodiment 0.1-25 %. (wt %) active ingredient. The amount of active in such therapeutically useful compositions is such that an effective dosage level can be attained.

Modes of Administration

[0203] Convenient modes of administration include injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application, topical to skin, eyes, ears, oral surfaces, vaginal or rectal administration. Depending on the route of administration, the formulation and/or compound may be coated with a material to protect the compound from the action of enzymes, acids and other natural conditions which may inactivate the therapeutic activity of the compound. The compound may also be administered parenterally or intraperitoneally.

Compositions for oral administration

[0204] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

Solid compositions for oral administration

[0205] In certain embodiments, the formulations are solid dosage forms, in one embodiment, capsules or tablets. The tablets, pills, capsules, troches and the like can contain one or more of the following ingredients, or compounds of a similar nature: a binder; a lubricant; a diluent; a glidant; a disintegrating agent; a coloring agent; a sweetening agent; a flavoring agent; a wetting agent; an emetic coating; and a film coating. Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, molasses, polvinylpyrrolidine, povidone, crospovidones, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0206] The compound, or pharmaceutically acceptable derivative thereof, could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and

releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

[0207] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0208] The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

[0209] In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

Liquid compositions for oral administration

[0210] Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

[0211] Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering

agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents.

[0212] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

[0213] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and ethanol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

[0214] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is in one embodiment encapsulated in a gelatin capsule. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

[0215] Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. RE28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[0216] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

Injectables, Solutions and Emulsions

[0217] Parenteral administration, in one embodiment characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

[0218] Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or

unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[0219] Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[0220] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[0221] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[0222] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, olive oil, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations

must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0223] The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

[0224] The unit-dose parenteral preparations are packaged in an ampule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

[0225] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[0226] Injectables are designed for local and systemic administration. In one embodiment, a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, in certain embodiments more than 1% w/w of the active compound to the treated tissue(s).

[0227] The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

Lyophilized Powders

[0228] Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

[0229] The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to rt.

[0230] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

Topical Administration

A topical composition typically includes an active, a pharmaceutically acceptable carrier and optionally one or more additional ingredients that, for example, aid in the formation of the desired delivery vehicle of the active. Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsion or the like and are formulated as a cream, gel, jelly, wax, ointment, emulsion, solution, elixir, lotion, suspension, tincture, paste, foam, aerosol, irrigation, spray, suppository, bandage, dermal patch, and/or a combination thereof or any other formulations suitable for topical administration.

Carriers

[0231] Active agents can be combined with a pharmaceutically acceptable carrier or diluent to produce a pharmaceutical composition or formulation. In such pharmaceutical formulations, the

active agents or therapeutic composition can be combined with a "carrier" that is physiologically compatible with the skin or mucosal tissue of a human or animal to which it is topically administered. Typically, the carrier is substantially inactive, with the exception of its intrinsic surfactant properties which may aid in the production of a solution or suspension of the active ingredients. The compositions may include other physiologically active constituents that do not interfere with the efficacy of the active agents in the composition. In some embodiments, the carriers can be liquid or gel-based materials for use in liquid or gel formulations. The specific formulations depend, in part, upon the desired routes or modes of administration.

[0232] Suitable carrier materials include any carrier or vehicle commonly used as a base for solutions, dispersions, emulsions, gels, creams, ointment, lotions, pastes, or foams, for topical administration. Examples include emulsifying agents, inert carriers including hydrocarbon bases, emulsifying bases, non-toxic solvents or water-soluble bases.

[0233] Many suitable liquid or gel-based carriers are well known in the art. The carrier should be able to dissolve or disperse an active at an effective level, optionally with the aid of non-toxic surfactants. Examples include water, physiological salt solutions, alcohols (e.g., methanol, ethanol, propanol, or butanol), glycerol, glycols (e.g., ethylene glycol, propylene glycol, or ethoxy diglycol), polyethylene glycol (e.g., MW 400 to 20,000), water-alcohol/glycol blends, and the like. Suitable carriers and diluents for certain embodiments include, for example, water, saline, isotonic saline solutions, for example, phosphate-buffered saline, aqueous dextrose, glycerol, ethoxy diglycol, dimethyl sulfoxide (DMSO), and the like, or combinations thereof.

[0234] Suitable carriers further include aqueous and oleaginous carriers such as, for example, white petrolatum, isopropyl myristate, lanolin or lanolin alcohols, mineral oil, fragrant or essential oil, nasturtium extract oil, sorbitan mono-oleate, cetostearyl alcohol (togetheror in various combinations), and detergents (e.g., polysorbates (Tweens) such as polysorbate 20, 40, 60, or 80; polyoxyl stearate; or sodium lauryl sulfate). One or more carrier materials can be mixed with water to form a lotion, gel, cream, semi-solid composition, or the like. Other suitable carriers include water-in-oil or oil-in-water emulsions and mixtures of emulsifiers and emollients with solvents such as sucrose stearate, sucrose cocoate, sucrose distearate, mineral oil, propylene glycol, 2-ethyl-1,3-hexanediol, polyoxypropylene-15-stearyl ether, water, or combinations thereof. For example, emulsions containing water, glycerol stearate, glycerin, mineral oil, synthetic spermaceti, cetyl alcohol, or combinations thereof, may be used. Preservatives may also be included in the carrier, such as one or more of butylparaben, methylparaben, propylparaben, benzyl alcohol, and

ethylene diamine tetraacetate salts. The composition of the carrier can be varied so long as it does not interfere significantly with the pharmacological activity of the active ingredients of the therapeutic composition.

[0235] Suitable pharmaceutically acceptable carriers include, but are not limited to, creams such as Cetaphil Moisturising Cream (Galderma Laboratories, L.P.), QV Cream (Lision Hong), Sorbolene, or the like. In some embodiments, the pharmaceutically acceptable carrier includes a lotion, such as Alpha Keri Moisturizing Lotion (Mentholatum), DermaVeen Moisturizing Lotion (DermaTech Laboratories), QV Skin Lotion (Lision Hong), Cetaphil Moisturizing Lotion (Galderma Laboratories, L.P.), or the like.

Gelling Agents and Thickening Agents

[0236] The compositions described herein can include one or more gelling agents to increase the viscosity of the composition. Examples of gelling agents and thickening agents, include, but are not limited to, fatty acids, fatty acid salts and esters, fatty alcohols, synthetic polymers, modified celluloses, xanthangum, or combinations thereof. Examples of suitable synthetic polymers include polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), various Pluronics (poloxamers), or carbomers (e.g., Carbomer 940 or Carbomer 934). Examples of suitable modified celluloses include methylcellulose, carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC), hydroxymethyl cellulose (HMC), hydroxypropyl cellulose (HPC), hydroxypropyl-methylcellulose (HPMC), or other cellulose-based gelling agents.

[0237] A variety of gelling agents are commercially available and can be obtained in many suitable molecular weights and ranges. For example, the molecular weights of the gelling agent can be about 1 kDa to about 1,000 kDa, about 10 kDa to about 1,000 kDa, about 100 kDa to about 1,000 kDa, or about 50 kDa to about 500 kDa. Examples of thickening agents include lanolin, hard paraffin, liquid paraffin, white petrolatum, soft yellow paraffin or soft white paraffin, white beeswax, yellow beeswax, propolis (propoleum), cetostearyl alcohol, cetyl alcohol, dimethicones, emulsifying waxes, microcrystalline wax, oleyl alcohol and stearyl alcohol. A gelling agent or thickening agent can be present in a formulation at about 0.05 wt.% to about 20 wt.%, typically about 0.1 wt.% to about 10 wt.%, about 0.1 wt.% to about 5 wt.%, about 0.5 wt.% to about 2 wt.%, about 0.8 wt.% to about 2 wt.%, or about 1-1.5 wt.%. In one embodiment, the composition comprises 0.5 wt.% to 15 wt.%, 1 wt.% to 10 wt.%, or 2 wt.% to 10 wt.%, of one or more thickening agents or gelling agents.

[0238] One or more gelling agents or thickening agents may be included in a single formulation. Such agents can be employed with liquid carriers to form spreadable gels, pastes, ointments, soaps, and the like, for application directly to the skin of the user.

pH Adjusting Agents

[0239] Topical formulations of the present invention can also comprise a pH adjusting agent. In one embodiment, the pH adjusting agent is a base. Suitable pH adjusting bases include bicarbonates, carbonates and hydroxides such as alkali or alkaline earth metal hydroxide as well as transition metal hydroxides. In another embodiment, the pH adjusting agent is an acid, an acid salt, or mixtures thereof. In a further embodiment, the pH adjusting agent is a buffer. Suitable buffers include citrate/citric acid buffers, acetate/acetic acid buffers, phosphate/phosphoric acid buffers, formate/formic acid buffers, propionate/propionic acid buffers, lactate/lactic acid buffers, carbonate/carbonic acid buffers, ammonium/ammonia buffers, and the like.

Solutions and Dispersions

[0240] Solutions of an active or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can be prepared in glycerol, liquid polyethylene glycols, triacetin, or in a pharmaceutically acceptable oil, or mixtures thereof. Under ordinary conditions of storage and use, preparations may contain a preservative to prevent the growth of microorganisms.

[0241] Pharmaceutical dosage forms can include sterile aqueous solutions or dispersions comprising the active ingredient adapted for the extemporaneous preparation of sterile solutions or dispersions, optionally encapsulated in liposomes. The ultimate dosage form should be fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity of the composition can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions, or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thiomersal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers, or sodium chloride. Prolonged

absorption of the compositions can be brought about by agents delaying absorption, for example, aluminum monostearate and/or gelatin.

[0242] Solutions can be prepared by incorporating the active in a desired amount in the appropriate solvent or oil with various other ingredients enumerated herein, as desired, followed by optional filter sterilization. For powders used in the preparation of solutions, methods of preparation can include vacuum drying and freeze drying techniques, which yield a powder of the active plus any additional desired ingredient present in the prepared solutions.

Gels

[0243] Gels are clear, sticky, jelly-like semisolids or solids prepared from high molecular weight polymers in an aqueous or alcoholic base. Alcoholic gels are often drying and cooling. Non-alcoholic gels are more lubricating. Gels or jellies can be produced using a suitable gelling agent including, but not limited to, gelatin, tragacanth, a carbomer, or a cellulose derivative and may include glycerol as a humectant, an emollient, and/or a preservative. In some embodiments, gel formulations will include the same or similar ingredients as a solution or dispersion, with the addition of a gelling agent.

[0244] The gel can include a nonionic copolymer gelling agent. In one embodiment, the gelling agent is a nonionic polyoxyethylene-polyoxypropylene copolymer gel, for example, a Pluronic gel such as Pluronic F-127 (BASF Corp.), to provide a pluronic gel-based formulation. This gel can be advantageous because it is a liquid at low temperatures but rapidly sets at physiological temperatures, which confines the release of the agent to the site of application or immediately adjacent that site. Other formulations can be carboxymethylcellulose (CMC)-based formulations, hydroxymethyl cellulose (HMC)-based formulations, hydroxypropyl cellulose (HPC)-based formulations, or hydroxypropylmethylcellulose (HPMC)-based formulations, and the like.

Creams

[0245] Creams are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and comprise an oil phase, an emulsifier, and an aqueous-phase. Water-in-oil creams may be formulated by using a suitable emulsifying agent with properties similar, but not limited, to those of the fatty alcohols such as cetyl alcohol or cetostearyl alcohol and to emulsifying wax. Oil-in-water creams may be formulated using an emulsifying agent such

as cetomacrogol emulsifying wax. Suitable properties include the ability to modify the viscosity of the emulsion and both physical and chemical stability over a wide range of pH. The water soluble or miscible cream base may contain a preservative system and may also be buffered to maintain an acceptable physiological pH.

[0246] The oil phase, also called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant (a substance, such as glycerin, sorbitol, or urea, that absorbs or helps another substance retain moisture).

[0247] The emulsifier in a cream formulation is generally a nonionic, anionic, cationic, or amphoteric surfactant. Examples of emulsifiers include, but are not limited to, fatty alcohol polyoxyethylene ether (Peregal A-20), stearates such as polyoxylstearate (Softener SG), glyceryl stearate and pegylated forms of glyceryl stearate such as PEG-5 glyceryl stearate, cetyl alcohol, dithranol, or a combination thereof. Oil-phase ingredients can include, but are not limited to, dimethicone, dimethiconol, cyclomethicone, diisopropyl adipate, cetyl alcohol, stearyl alcohol, paraffin, petrolatum, almond oil, stearic acid, or a combination thereof. In particular aspects, aqueous ingredients can include, but are not limited to, purified water, glycerol (glycerin), propylene glycol, ethyl paraben, a humectant, or a combination thereof.

Ointments

[0248] Ointments are semisolid preparations that include the active incorporated into a fatty, waxy, or synthetic base. Ointments are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for suitable drug delivery and other desired characteristics such as emolliency or the like. As with other carriers or vehicles, an ointment base is typically inert, stable, non- irritating and non-sensitizing.

[0249] Ointment bases may be generally grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases can include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and can include, for example, hydroxystearin sulfate, anhydrous lanolin, and hydrophilic

petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and the oil components can include, for example, cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid. Water-soluble ointment bases can be prepared from polyethylene glycols of varying molecular weight.

Lotions

[0250] Lotions are liquid or semiliquid preparations in which solid particles, including the active agent(s), are present in a water or alcohol base. Lotions are usually suspensions of solids, and can include a liquid oily emulsion of the oil-in-water type. Lotions are often desirable formulations because of the ease of applying a more fluid composition. It is generally advantageous for the insoluble matter in a lotion be finely divided. Lotions will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin, e.g., methylcellulose, sodium carboxymethylcellulose, or the like.

Pastes

[0251] Pastes are semisolid dosage forms in which the active agent is suspended in a suitable base. Depending on the nature of the base, pastes are divided between fatty pastes or those made from a single-phase aqueous gel. The base in a fatty paste is generally petrolatum, hydrophilic petrolatum, or the like. The pastes made from single-phase aqueous gels generally incorporate carboxymethylcellulose or the like as a base.

Foams

[0252] Foam preparations may be formulated to be delivered from a pressurized aerosol canister, via a suitable applicator, using inert propellants. Suitable excipients for the formulation of the foam base include, but are not limited to, propylene glycol, emulsifying wax, cetyl alcohol, and glyceryl stearate. Potential preservatives include methylparaben and propylparaben.

[0253] Accordingly, the composition described herein may be formulated for any desired form of topical or transdermal administration, including slow or delayed release preparations. Formulations may include known antioxidants (e.g., vitamin E); buffering agents; lubricants (e.g., synthetic or natural beeswax); sunscreens (e.g., para-aminobenzoic acid); and cosmetic agents (e.g., coloring agents, fragrances, essential oils, moisturizers, or drying agents).

[0254] An auxiliary agent such as casein, gelatin, albumin, or sodium alginate may also be included in various formulations. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. Examples of fragrances include Ylang-Ylang oil, lavender oil, powder scent, jasmine, gardenia oil, or green tea oil. In addition, substances such as wetting or emulsifying agents, stabilizing agents, or pH buffering agents, may also be included. When a water-based carrier is used, the composition is typically near a neutral pH(+/- about 1, or 2, pH units).

[0255] Further examples of dermatological ingredients and compositions for delivering active agents to the skin are known to the art. Such dermatological compositions can be used in combinations with the actives described herein in place of other actives.

[0256] The compositions described above can be prepared using standard compounding techniques. For example, for a composition that includes an active, or a salt of the active it can be triturated to reduce particle size. A second active can then be added with a small amount of carrier such as polysorbate 80 and/or ethoxy diglycol to wet the actives. This mixture can then be incorporated into a desired amount of oil using principles of geometric dilution until a smooth and uniform suspension is formed. This suspension can then be combined with other ingredients, such as a fragrance, to provide a therapeutic composition. The suspension can also be combined with other ingredients to form a variety of formulations, such as a gel, a jelly, a cream, an ointment, a wax, a lotion, a paste, a foam, or an aerosol. The suspension, or a gel, jelly, cream, ointment, wax, lotion, or paste can also be incorporated into a patch, such as an occlusive patch, to further improve transdermal penetration.

Nanoparticles

[0257] Nanoparticles may be composed of materials such as polymers, lipids (e.g., liposomes) or dendrimers, such as PAMAM, PEI, PPI, or polylysine containing dendrimers. For example, the use of a nanoemulsion containing nanoparticles comprising the active, provides for different physical and chemical properties, for instance, nanoparticles may allow for deeper penetration into the skin, delivering treatment to more layers of skin and beyond. The nanoparticles may be coated with and/or embedded with (encapsulate) the composition. The nanoparticles may be formed using techniques such as electrospraying. The nanoparticles may be formed by grinding particles comprising the active to a desired size. The nanoparticles may include a surface coating.

[0258] The nanoparticles may be from about 1 nm to about 100 nm, about 100 nm to about 2,500 nm, or about 2,500 nm to about 10,000 nm in diameter. Nanoparticles may be formed of polymers or surfactants. Polymers and surfactants include but are not limited to non-ionic surfactants, anionic surfactants, e.g., carboxylates such as alkyl carboxylates-fatty acid salts or carboxylate fluoro surfactants; sulfates such as alkyl sulfates (e.g., sodium lauryl sulfate) or alkyl ether sulfates (e.g., sodium laureth sulfate); sulfonates, e.g., docusates (e.g., dioctyl sodium sulfosuccinate) or alkyl benzene sulfonates; and phosphate esters such as alkyl aryl ether phosphates or alkyl ether phosphates; cationic surfactants including fatty amine salts and quaternary ammoniums; zitterionic surfactants such as those with a quaternary amine group and a sulfonic or carboxyl group, natural polymers and synthetic polymers including but not limited to alginate, hyaluronate, chitosan, gelatin, cellulose, e.g., ethylcellulose, PVP, PEG or acylates. In one embodiment, the surfactant includes polyoxyethylene, poloxamer, poloxamine, or polysorbate.

[0259] The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation. These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

[0260] The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye or in the mouth, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for dermal or transdermal delivery and for administration to the eyes or mucosa, including buccal mucosa, or for inhalation therapies. Nasal, buccal, lingual and sublingual formulations of the active compound alone or in combination with other pharmaceutically acceptable excipients enumerated herein can also be administered.

[0261] These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% (vol %) isotonic solutions, pH about 5-7, with appropriate salts.

Compositions for other routes of administration

[0262] Other routes of administration, such as transdermal patches, including iontophoretic and electrophoretic devices, vaginal and rectal administration, are also contemplated herein.

[0263] Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art. For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories as used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by moulding. The weight of a rectal suppository, in one embodiment, is about 2 to 3 gm.

[0264] Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

[0265] Other transdermal delivery methods known in the art or as described herein, including, for example, methods directed to 1) the use of chemical penetration enhancers or skin enhancers; 2) liposome-mediated delivery; 3) electroporation; 5) sonophoresis (ultrasound waves); 6) mechanical (e.g., microporation) devices, and/or 7) air pressure.

[0266] Methods suitable for transdermal delivery of the agents described herein can include, for example, methods directed to enhancing the transport of material across the skin pores by increasing the rate of transport across existing pores or by amplifying the number of available skin pores through the creation of artificial pores.

[0267] Transdermal delivery can be carried out by the use of chemical or penetration enhancers, including for example, a pharmaceutically acceptable oil of vegetable, nut, ethoxylated oil, PEG, linoleic acid, ethanol, methanol, and/or agents which delipidize the stratum comeum. Suitable oils include meadowfoam oil, castor oil, jojoba oil, corn oil, sunflower oil, sesame oil, all of which may be optionally ethoxylated. In addition, transdermal patches can be used for the topical or transdermal delivery of a composition described herein. A patch can also be adapted for delivery of dry or lyophilized forms of the compositions described herein. Other patch technology that can be employed in conjunction with the compositions described herein, e.g., in a reservoir of the patch. Transdermal delivery can also be carried out by liposome-mediated delivery methods (e.g., delivery facilitated by application of lipophilic membrane compositions). Transdermal delivery systems can

also be employed in conjunction with a wide variety of iontophoresis or electrotransport systems. When a sonophoresis technique is used, one ultrasonic frequency can be applied to the skin, or two or more different ultrasonic frequencies can be applied to the skin (e.g., one low and one high ultrasonic frequency). As with the other techniques described above, this technique can be used in combination with other techniques, such as prior to the topical application of a composition described herein, including the application of a transdermal patch.

[0268] Another transdermal drug delivery technique that can be used in conjunction with the compositions described herein includes employing a device to use air pressure to inject a small stream of the composition through the top layers of the skin without the aid of a needle. The air pressure gun can be the same as or similar to the devise used to provide vaccines to children. Small, disposable pen-like devices are also suitable, as for diabetics who take insulin daily.

Targeted Formulations

[0269] The compounds provided herein, or pharmaceutically acceptable derivatives thereof, may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions.

[0270] Liposomal suspensions, including tissue-targeted liposomes, such as tumour-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

Co-administration with other drugs

[0271] In accordance with another aspect of the present invention, it is contemplated that compounds of Formula I as described herein may be administered to a subject in need thereof in combination with medication considered by those of skill in the art to be current standard of care for the condition of interest. Such combinations provide one or more advantages to the subject,

e.g., requiring reduced dosages to achieve similar benefit, obtaining the desired therapeutic effect in less time, and the like.

[0272] Compounds in accordance with the present invention may be administered as part of a therapeutic regimen with other drugs. It may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition. Accordingly, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound of Formula (I) according to the present invention, may be combined in the form of a kit suitable for co-administration of the compositions.

[0273] In one embodiment of the methods of the present inventions a compound of Formula I may be administered with a second therapeutic agent. In one embodiment the second therapeutic agent may be selected from one or more of the following categories:

(i) Anti-cancer agents such as cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, uracil mustard, bendamustin, melphalan, chlorambucil, chlormethine, busulphan, temozolamide, nitrosoureas, ifosamide, melphalan, pipobroman, triethylene-melamine, triethylenethiophoporamine, carmustine, lomustine, stroptozocin and dacarbazine, gemcitabine, 5-fluorouracil, tegafur, raltitrexed, methotrexate, pemetrexed, leucovorin, cytosine arabinoside, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, hydroxyurea, trifluridine, trifluracil, adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, vincristine, vinblastine, vindesine and vinorelbine, taxol, taxotere, eribulin, carfilzomib, bortezomib, etoposide, teniposide, amsacrine, topotecan, irinotecan, mitoxantrone, camptothecin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (Taxol™), nabpaclitaxel, docetaxel, mithramycin, deoxyco-formycin, mitomycin-C, L-asparaginase, IFN-alpha), azacitidine, decitabine, vorinostat, MS-275, panobinostat, romidepsin, valproic acid, mocetinostat (MGCD0103), pracinostat SB939, belinostat, panobinostat, irabectedin, tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene, iodoxyfene, bicalutamide, flutamide, nilutamide, cyproterone acetate, goserelin, leuprorelin, buserelin, progestogens, megestrol acetate, anastrozole, letrozole, vorazole, exemestane, finasteride, navelbene, CPT-II, anastrazole, letrazole, capecitabine, cyclophosphamide, ifosamide, and droloxafine; and abiraterone, Enzalutamide, lanreotide, dasatinib, bosutinib (SKI-606), trastuzumab, pertuzumab, panitumumab, cetuximab, gefitinib, erlotinib, 6- acrylamido-/V-

(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), afatinib, vandetanib, osimertinib, rociletinib, lapatinib, CTLA-4, 4-IBB, PD-I, imatinib, nilotinib (AMN107), sorafenib, tipifarnib and lonafarnib, vemurafenib, dabrafenib, trametinib, cobimetinib, ponatinib, palbociclib, Everolimus, ruxolitinib, Ibrutinib, ceritinib, crizotinib, ectinib, cabozantirsib, vismodegib, soni iegib, BAL3833, regorafenib, vandetanib, vatalanib, sunitinib, axitinib, pazopanib, lenvatinib, talimogene laherparepvec, denosumab, obinuluzumab, biinatomumab, dinutuximab, idarucizumab, daratumumab, necitumumab, e!otuzumab, o!aratumab, alemtuzumab, rituximab, ibritumomab tiuxetan, ofatumumab, peginterferon alpha-2b, aldesleukin, Gardasil, Cervarix, Oncophage, Sipuleucel-T (Provenge) gp100, Ad.p53 DC, Nivolumab, pembrolizumab, atezoiizumab, indoximod, MK-3475, nivolumab, MEDI-4736, RG-7446, ipilumumab, Brentuximab vedotin, irastuzumab emtansine, fludaribine (fludara), cladribine, pentostatin, idelalisib, perifosine, Birinapant, LCL161, AEG40730, SM-164, LBW242, ML101, AT-406, GDC-0917, AEG35156, HGS1029, bortezomib, ixazomib, carfilzomib, marizomib (NPI-0052), MLN9708, Olaparib, rucaparib; antiapoptotic, venetociax, chimeric antigen receptors.

(ii) Anti-inflammatory agents such as meloxicam, feoprofen, oxaprozin, salsalate, etoricoxib, tenoxicam, aspirin, nabumetone, flurbiprofen, mefenamic acid, phenylbutazone, lornoxicam, indomethacin, etodolac, diflunisal, ketoprofen, valdecoxib, tolfenamic acid, piroxicam, sulindac, tolmetin, ketorolac, loxoprofen, acetaminophen, bromfenac, diclofenac, ibuprofen, meclofenamate, nabumetone, naproxen, nepafenac, celecoxib, triamcinolone acetonide, hydrocortisone, hydrocortisone acetate, methylprednisolone, aclomethasone dipropionate, emricasan, BI 1467335, namodenoson.

(iii) Anti-hypertensive agent such as hydrochlorothiazide, chlorthalidone, furosemide, spironolactone, triamterene, amiloride, benazepril, captopril, lisinopril, enalapril, ramipril, fosinopril, moexipril, perindopril, quinapril, trandolapril, losartan, candesartan, valsartan, telmisartan, clonidine, methyldopa, propranolol, nadolol, timolol, pindolol, labetolol, metoprolol, atenolol, esmolol, betaxolol, carvedilol, prazosin, terazosin, doxazosin, phenoxybenzamine, phentolamine, verapamil, diltiazem, nifedipine, felodipine, amlodipine, nimodipine, diazoxide, minoxidil, pinacidil, nicorandil, hydralazine, sodium nitroprusside.

(iv) Anti-fibrotic agent such as pirfenidone, nintedanib, cenicriviroc, selonsertib, lanifibranor, nimacimab, nitrazoxanide, NGM282, apararenone, tipelukast, Actimmune, ponatinib, lenvatinib, dovitinib, lucitanib, danusertinib, brivatinib, erdafitinib, PD173074, PD166866, AZD4547, BGJ398, LY2874455, TAS-120, ARQ087, BLU9931, FGF401, BAY-1163877, ENMD-2076, IMCA1, FGF401, DEBIO1347, FIIN-2, GP-369, PRO-001, H3B-6527, BAY1187982, MFGR1877S, FP-1039, BLU554, PRN1371, S49076, SU6668, SU5416

(v) Anti-angiogenesis agent such as axitinib, bevacizumab, cabozantinib, everolimus, lenalidomide, lenvatinib, pazopanib, ramucirumab, regorafenib, vandetanib, vatalanib, sunitinib, ziv-aflibercept, thalidomide, pomalidomidelenalidomide.

(vi) Anti-diabetic agent such as gliclazide, glimepiride, repaglinide, metformine, pioglitazone, rosiglitazone, acarbose, lingliptine, saxagliptine, sitagliptine, alogliptine, exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide, canaglifozine, dapagliflozine, empagliflozine, ertugliflozine.

(vii) Immunosuppressive agent such as prednisone, budesonide, prednisolone, tofacitinib, cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, leflunomide, mycophenolate, abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, ixekizumab, natalizumab, rituximab, secukinumab, tocilizumab, ustekinumab, vedolizumab, basiliximab, daclizumab.

(viii) Anti-bacterial agent such as daptomycin, delafloxacin, telavancin, ceftaroline, fidaxomicin, amoxicillin, ampicillin, becampicillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, pivampicillin, pivmecillinam, ticarcillin, cefacetrile, cefadroxil, cefalexin, cefaloglycin, cefalonium, cefaloridine, cefalotin, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefradine, cefroxadine, ceftezole, cefaclor, cefamandole, cefmetazole, cefonicid, cefotetan, cefoxitin, cefprozil, cefuroxime, cefuzonam, cefcapene, cefdaloxime, cefdinir, cefditoren, cefetamet, cefixime, cefmenoxime, cefodizime, cefotaxime, cefpimizole, cefpodoxime, cefteram, ceftibuten, ceftiofur, ceftiolene, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime, cefclidine, cefepime, cefluprenam, cefoselis, cefozopran, cefpirome, cefquinome, ceftobiprole, ceftaroline, cefaclomezine, cefaloram, cefaparole, cefcanel, cefedrolor, cefempidone, cefetrzole, cefivitril, cefmatilen, cefmepidium, cefovecin, cefoxazole, cefrotil, cefsumide,

cefuracetime, ceftioxide, ceftazidime, avibactam, ceftolozane, tazobactam, aztreonam, vaborbactam, imipenem, doripenem, ertapenem, meropenem, azithromycin, erythromycin, clarithromycin, dirithromycin, roxithromycin, telithromycin, clindamycin, lincomycin, pristinamycin, quinupristin, dalfopristin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, flumequine, nalidixic acid, oxolinic acid, piromidic acid, pipemidic acid, rosoxacin, ciprofloxacin, enoxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, perfloxacin, rufloxacin, balofloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin, besifloxacin, delafloxacin, clinafloxacin, gemifloxacin, prulifloxacin, sitafloxacin, trovafloxacin, sulfamethizole, sulfamethoxazole, sulfisoxazole, trimethoprim, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, tigecycline, chloramphenicol, metronidazole, tinidazole, nitrofurantoin, vancomycin, teicoplanin, telavancin, linezolid, cycloserine, rifampin, rifabutin, rifapentine, rifalazil, bacitracin, polymixin B, viomycin, capreomycin.

(ix) Anti-fungal agent such as amorolfin, butenafine, naftifine, terbinafine, bifonazole, butoconazole, clotrimazole, econazole, fenticonazole, ketoconazole, isoconazole, luliconazole, miconazole, omoconazole, oxiconazolesertaconazole, sulconazole, tioconazole, terconazole, albaconazole, efinaconazole, fluconazole, isavuconazole, itraconazole, posaconazole, ravuconazole, voriconazole, abafungin, amphotericin B, nystatin, natamycin, trichomycin, anidulafungin, caspofungin, micafungin, tolnaftate, flucytosine, butenafine, griseofulvin, ciclopirox, selenium sulfide, tavaborole.

(x) Anti-pruritic agent such as doxepin, tacrolimus, pimecrolimus, menthol, capsaicin, salicylic acid, pramoxine, lidocaine, polidocanol, N-palmitoylethanolamine, prednisone, prednisolone, mirtazapine, paroxetine, fluvoxamine, sertraline, naltrexone, methylnaltrexone, butorphanol, nalfurafine, gabapentin, pregablin, aprepitant, loratadine, desloratadine, cetirizine, levocetirizine, NGX-4010, TS-022.

(xi) Metabolic agent such as obeticholic acid, elafibranor, aramchol, seladelpar, MGL-3196, tropifexor, MSDC-0602K, BMS-986036, semaglutide, EDP-305, gemcabene, PF-05221304, PF-06865571, PF-06835919, LIK066, LMB763, vitamin E, acarbose, miglitol, pramlintide, alogliptan, linagliptan, saxagliptin, sitagliptin, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, insulin, nateglinide, repaglinide.

Metformin, canagliflozin, dapagliflozin, empagliflozin, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, rosiglitazone, pioglitazone, atorvastatin, amlodipine, simvastatin, ezetimibe, lovastatin, sitagliptin, cholestyramine, colesevelam, colestipol, fenofibrate, gemfibrozil, fenofibric acid, niacin, icosapent, mipomersen, lomitapide, evolocumab, alirocumab, fluvastatin, pravastatin, rosuvastatin, pitavastatin, simvastatin, cerivastatin, allopurinol, lesinurad, pegloticase, febuxostat, rasburicase, ivacaftor, velaglucerase alfa, imiglucerase, alglucosidase alfa, laronidase, cerliponase alfa, alglucerase, idursulfase, taliglucerase alfa, agalsidase beta, sebelipase alfa, vestronidase alfa, galsulfase, elosulfase alfa, eliglustat, burosumab, migalastat, sapropterin, metreleptin, nitisinone, pegvaliase, asfotase alfa, inotersen, miglustat, orlistat, sodium phenylbutyrate, glycerol phenylbutyrate.

[0274] In one embodiment the compounds of the present invention may be administered in combination with other therapeutic treatments. For example, the compounds of the present invention may be administered in combination with radiotherapy or chemotherapy. In one embodiment the compounds of the present invention may be administered in combination with one or more additional anti-tumour agent and/or radiotherapy for the treatment of a cancer. In one embodiment the compounds of the present invention may be administered in combination with wound covers and wound dressings. In one embodiment the compounds of the present invention may be administered in combination with scar covers and scar dressings.

[0275] When two or more active ingredients are co-administered, the active ingredients may be administered simultaneously, sequentially or separately. In one embodiment the compound of Formula I is co-administered simultaneously with a second therapeutic agent. In another embodiment the compound of Formula I and the second therapeutic agent are administered sequentially. In a further embodiment the compound of Formula I and the second therapeutic agent are administered separately.

[0276] The invention will now be described in greater detail, by way of illustration only, with reference to the following non-limiting examples. The examples are intended to serve to illustrate the invention and should not be construed as limiting the generality of the disclosure of the description throughout this specification.

[0277] For purposes of this specification, the following abbreviations have the indicated meanings:

rt = room temperature

min = minute(s)

°C = degrees Celsius

h = hour(s)

aq = aqueous

sat = saturated

NaHMDS = sodium hexamethyldisilazide

THF = tetrahydrofuran

DMF = dimethylformamide

TFA = trifluoroacetic acid

DIBAL = di*iso*butylaluminumhydride

MTBE = methyl *tert*butylether

DIPEA = di*iso*propylethylamine

LC-MS = liquid chromatography-mass spectroscopy

rpm = revolutions per minute

RBF = round bottom flask

NMR = nuclear magnetic resonance

DMSO = dimethylsulfoxide

Boc = *tert*-butyloxycarbonyl

HPLC = high-performance liquid chromatography (also, high pressure liquid chromatography)

TLC = thin-layer chromatography

v = volume(s)

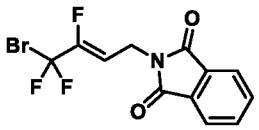
conc = concentrated

Experimental: General methods

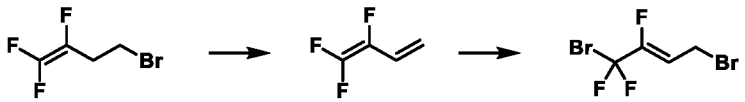
[0278] All commercially available solvents and reagents were used as received. Where appropriate, reactions were carried out under an argon atmosphere. Reactions were monitored by either analytical thin-layer chromatography (TLC) or by analytical liquid chromatography–mass spectrometry (LC-MS) recorded on either a Shimadzu LC-MS 2020 instrument or an Agilent LC/MSD 1200 instrument using reverse-phase conditions. Purification of intermediates and final compounds was conducted, where necessary, using column chromatography or preparative HPLC. Normal-phase column chromatography was conducted under medium pressure either on silica gel or on prepacked silica gel cartridges using a flash chromatography system (CombiFlash Rf200, Teledyne Isco systems, USA). Reverse-phase column chromatography was conducted under low pressure on prepacked C18 cartridges using a flash chromatography system (Reveleris® X2). Eluents were monitored by UV light (λ = 254/280 nm). ^{1}H-NMR and ^{19}F-NMR spectra were recorded using either a Bruker 300 MHz NMR spectrometer, a Bruker Avance III plus 400 MHz NMR spectrometer or a Varian III plus 300 MHz spectrometer. Chemical shifts (δ) are reported as parts per million (ppm) relative to tetramethylsilane (TMS; internal standard). The following abbreviations are used for multiplicities: s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; m = multiplet; and br m = broad multiplet. Low resolution mass spectra (MS) were obtained as electrospray – atmospheric pressure ionization (ES-API) mass spectra, which were recorded on either a Shimadzu LCMS 2020 instrument or an Agilent LC/MSD 1200 instrument using reverse-phase conditions. All animal experiments performed were conducted in compliance with institutional guidelines and approval from local ethics committees.

EXAMPLE 1

[0279] Preparation of (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione



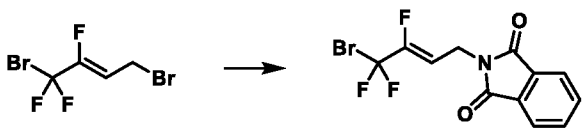
Procedure A: Preparation of (*Z*)-1,4-dibromo-1,1,2-trifluorobut-2-ene



A schematic representation of the experimental set-up is depicted in Figure 1.

[0280] A round bottom flask (RBF1) was charged with a solution of potassium hydroxide (802 g, 14.3 mol) in water (800 mL). Tetra-*n*-butylammonium bromide (TBAB) (30.0 g, 93.1 mmol), 4-bromo-1,1,2-trifluorobut-1-ene (1.00 kg, 5.29 mol) and xylene (2.00 L) were added to RBF1 at rt. A second round bottom flask (RBF2) was charged with Br_2 (635 g, 3.97 mol) in CH_2Cl_2 (4.00 L) and the solution was cooled at 0 °C. The reaction mixture in RBF1 was heated to 60 °C and the volatile 1,1,2-tetrafluorobuta-1,3-diene thus formed was carried over to RBF2 using a fine stream of N_2 gas. Stirring was continued at 60 °C for 4 h. The mixture in RBF1 was then cooled to 20 °C and discarded. The reaction mixture in RBF2 was washed with Na_2SO_3 (5% w/w; 800 mL) and brine (2 x 800 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* at 40 °C to afford (*Z*)-1,4-dibromo-1,1,2-trifluorobut-2-ene (591 g). Procedure A was repeated 2 additional times to obtain 1.70 kg of (*Z*)-1,4-dibromo-1,1,2-trifluorobut-2-ene. The crude material was used in the subsequent step without purification.

Procedure B: Preparation of (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione

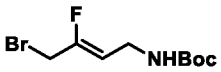


[0281] To a stirring solution of (*Z*)-1,4-dibromo-1,1,2-trifluorobut-2-ene (1.50 kg, 5.60 mol) in DMF (15.0 L) was added potassium phthalimide (1.14 kg, 6.15 mol) at 25 °C. The mixture was stirred at 25 °C for 1 h and then poured into ice water (30 L). The resulting biphasic mixture was stirred for 30 min. The solid was filtered, washed with water (3 x 1.5 L) and then redissolved into CH_2Cl_2 (15 L). The organic phase was washed with brine (3 x 5 L), dried (Na_2SO_4) and concentrated

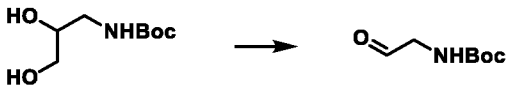
in vacuo to afford (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione (1.59 kg). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.92 – 7.86 (m, 2H), 7.79 – 7.75 (m, 2H), 5.66 (dt,1H), 4.51 (ddt, 2H).

EXAMPLE 2

[0282] Preparation of (*Z*)-*tert*-butyl (4-bromo-3-fluorobut-2-en-1-yl)carbamate

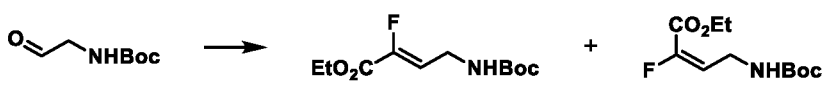


Procedure A2: Preparation of *tert*-butyl 2-oxoethylcarbamate



[0283] To a stirring solution of 3-amino-1,2-propanediol (20.0 g, 0.22 mol) in water (200 mL) at 0-5 °C was added di-*tert*-butyl dicarbonate (55.5 mL, 0.24 mol). After adjusting the alkalinity of the solution to pH~9 by addition of aq. NaOH (6.0 M), the mixture was left to stir at rt for 18 h. The reaction mixture was cooled to 0 - 5 °C and then acidified to pH~6 before the addition of sodium metaperiodate (56.3 g, 0.26 mol). The resulting suspension was stirred at rt for 2 h. The mixture was filtered to remove all solids and the filtrate was transferred to a separatory funnel and extracted with ethyl acetate (200 mL). Sodium chloride was added to the aqueous layer until a saturated solution was obtained. The aqueous layer was then extracted further with ethyl acetate (100 mL). The combined organics were dried over Na_2SO_4 and then concentrated *in vacuo* to give crude *tert*-butyl 2-oxoethylcarbamate (45.7 g). The crude material was used in the subsequent step without purification.

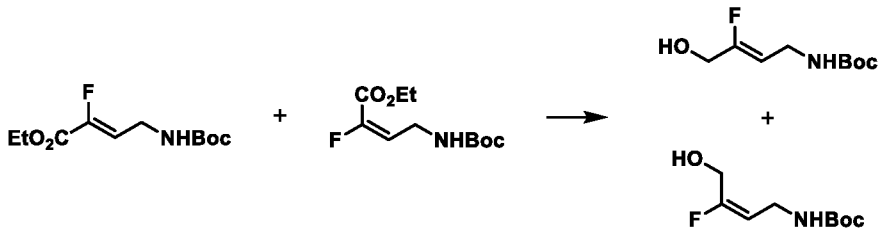
Procedure B2: Preparation of (*E*)-ethyl 4-(*tert*-butoxycarbonylamino)-2-fluorobut-2-enoate and (*Z*)-ethyl 4-(*tert*-butoxycarbonylamino)-2-fluorobut-2-enoate



[0284] To a stirring suspension of crude *tert*-butyl 2-oxoethylcarbamate (43.7 g, 0.22 mol) and magnesium sulfate (32.0 g) in acetonitrile (200 mL) at 0 °C under N_2 was added sequentially ethyl

2-fluorophosphonoacetate (55.7 mL, 0.27 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (32.8 mL, 0.22 mol). The reaction mixture was allowed to warm to rt and stirring was continued for 3 h. After removing the solvent under reduced pressure the residue was taken up in ethyl acetate (200 mL) and then transferred to a separatory funnel. The organics were washed successively with aq. HCl (2 M; 100 mL x 2), aq. NaOH (2 M; 100 mL x 2) and brine (100 mL). After drying over $MgSO_4$, the organics were concentrated *in vacuo* to give the crude, desired product as a mixture of *E*/*Z* isomers (2:3; 57.0 g). This crude material was progressed to the next step without purification.

Procedure C2: Preparation of (*E*)-*tert*-butyl 3-fluoro-4-hydroxybut-2-enylcarbamate and (*Z*)-*tert*-butyl 3-fluoro-4-hydroxybut-2-enylcarbamate



[0285] To a stirring solution of crude *E*/*Z*-ethyl 4-(*tert*-butoxycarbonylamino)-2-fluorobut-2-enoate (18.0 g, 72.8 mmol) in THF (150 mL) at 0 °C under N_2 was added di*iso*butylaluminum hydride (1 M in toluene, 182 mL, 182 mmol) dropwise over 45 min. After complete addition, the mixture was left to stir at 0 °C for 3 h. The reaction mixture was transferred to a separatory funnel and added dropwise to a stirring mixture of ice (100 g) and aq. NaOH (2.0 M; 200 mL). Following addition, the mixture was stirred for 2 h. The quenched reaction mixture was extracted with diethyl ether (100 mL x 2) and the combined organics were washed with brine (100 mL). After drying over $MgSO_4$ the organics were concentrated *in vacuo* to give the crude alcohol as a mixture of *E*/*Z* isomers. The mixture was purified with normal phase chromatography (hexane/ ethyl acetate gradient) to afford (*Z*)-*tert*-butyl 3-fluoro-4-hydroxybut-2-enylcarbamate (6.20 g, 30.2 mmol) and (*E*)-*tert*-butyl 3-fluoro-4-hydroxybut-2-enylcarbamate (1.85 g). (*E*)-*tert*-butyl 3-fluoro-4-hydroxybut-2-enylcarbamate: ^{1}H-NMR (200 MHz; $CDCl_3$) δ ppm: 1.43 (9H, s), 3.72 (2H, dd), 4.25 (2H, d), 4.85 (1H, br. s), 5.18 (1H, dt). (*Z*)-*tert*-butyl 3-fluoro-4-hydroxybut-2-enylcarbamate: ^{1}H-NMR (300 MHz; $CDCl_3$) δ ppm: 1.46 (9H, s), 3.84 (2H, dd,), 4.13 (2H, d,), 4.68 (1H, br. s), 5.03 (1H, dt).

Procedure D2: Preparation of (*Z*)-*tert*-butyl 4-bromo-3-fluorobut-2-enylcarbamate

[0286] To a stirring solution of (*Z*)-*tert*-butyl 3-fluoro-4-hydroxybut-2-enylcarbamate (6.20 g, 30.2 mmol) and triethylamine (6.32 mL, 45.3 mmol) in acetone (100 mL) at 0 °C was added methanesulfonyl chloride (2.81 mL, 36.3 mmol) dropwise. After complete addition the mixture was left to stir at 0 °C for 30 min. After this time, lithium bromide (13.1 g, 0.15 mol) was added portion-wise and the resulting suspension was stirred for a further 2 h. The reaction mixture was filtered to remove all solids and the filtrate was concentrated under reduced pressure. The residue was partitioned between water (50 mL) and CH_2Cl_2 (50 mL) and the aqueous layer was extracted with further CH_2Cl_2 (50 mL x 2). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*.

[0287] The residue was purified with normal phase chromatography (hexane/ ethyl acetate gradient) to afford (*Z*)-*tert*-butyl 4-bromo-3-fluorobut-2-enylcarbamate (7.00 g). ^{1}H-NMR (300 MHz; $CDCl_3$) δ ppm: 1.46 (9H, s), 3.85 (2H, dd), 3.93 (2H, d) 4.66 (1H, br. s), 5.16 (1H, dt).

EXAMPLE 3

[0288] The following compounds were prepared according to the procedures listed in the Table 3 using the appropriately functionalised thiol or thiolate starting material and either (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione or (*Z*)-tert-butyl 4-bromo-3-fluorobut-2-enylcarbamate (synthesis described in procedures B and B2 respectively).

[0289] LC-MS methods are as described below:

Method 1

[0290] Shimadzu LC-MS 2020 instrument; LC-MS column C18 150 mm x 4.6 mm, mobile phase: from 50% water (0.1% formic acid) and 50% methanol (0.1 % formic acid) to 5% water (0.1% formic acid) and 95% methanol (0.1 % formic acid) in 5.6 min.

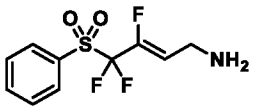
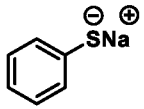
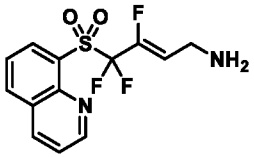
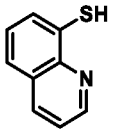
Method 2:

[0291] Agilent LC/MSD 1200 instrument; LC-MS C18 column: 50 mm x 4.6 mm; mobile phase: from 95% water (0.02% NH_4Ac) and 5% CH_3CN to 5% water (0.1% TFA) and 95% CH_3CN in 6.5 min.

Method 3:

[0292] Agilent LC/MSD 1200 Series instrument; LC-MS C18 column: 50 mm x 4.6 mm; mobile phase: from 90% water (0.1% TFA) and 10% CH_3CN to 30% water (0.1% TFA) and 70% CH_3CN in 6.5min,

Table 3: Summary of procedures used to prepare compounds 1 to 20 with corresponding analytical data.

Compound (parent, free-base)	Thiol or thiolate starting material	Procedure used (in order of execution)	Modifications to the procedure	Analytical data for final compound (HCl salt). Compounds 1 to 18
1 		C, D and E	none	^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 8.06 (d, 2H), 7.95 (t, 1H), 7.79 (t, 2H), 6.06 - 5.90 (dt, 1H), 3.88 (d, 2H). LC-MS m/z 266 (MH+), RT 3.23 min (Method 1).
2 		V, W, X and Y	none	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.17 - 9.16 (m, 1H), 8.67 - 8.59 (m, 3H), 8.43 (bs, 3H), 7.97 - 7.93 (t, 1H), 6.32 (bs, 3H) 6.08 - 5.96 (dt, 1H), 3.68 (s, 2H).

				LC-MS m/z 317 (MH+), RT 3.16 min (Method 1).
3		F, G and H	Procedure G was followed until the reaction was cooled to 20 °C. When the solid was not filterable, it was extracted from the aqueous phase with ethyl acetate. The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford (*Z*)-2-(3,4,4-trifluoro-4-((3-(methylsulfonyl)phenyl)sulfonyl)but-2-en-1-yl)isoindoline-1,3-dione.	^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 8.59 – 8.50 (m, 2H), 8.46 – 8.35 (m, 1H), 8.08 (ddd, 1H), 6.03 (dt, 1H), 3.90 (d, 2H), 3.27 (s, 3H). LC-MS m/z 344 (MH+), RT 2.91 min (Method 1).
4		M, N, G, I and J	Procedure G was followed and the reaction was stirred overnight before being cooled to 20 °C. When the solid was not filterable, it was extracted from the aqueous phase with ethyl acetate (3x 20 mL). The combined	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.13 (bs, 2H), 8.44 (bs, 3H), 7.65 (ddd, 1H), 7.59 (dd, 1H), 6.89 (dd, 1H), 6.78 (ddd, 1H), 6.02 (dt,

			Procedure I was followed to remove the protective group. For purification, the free amine was protected as the *tert*-	^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 8.04 (d, 1H), 7.78 (td, 1H),
5		F, G, I and J		

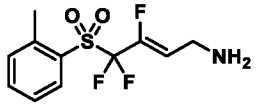
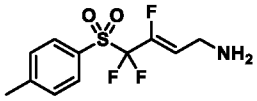
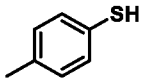
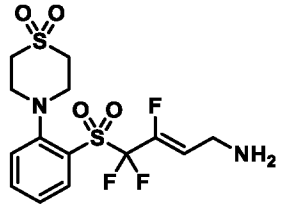
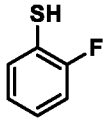
organic phases were washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo* to afford (Z)-2-(3,4, 4-trifluoro-4-((2-fluorophenyl)sulfonyl)but-2-en-1-yl)isoindoline-1,3-dione.

Procedure I was followed to remove the protective group. For purification, the free amine was protected as a carbamate (procedure I) and afforded tert-butyl (Z)-(3,4,4-trifluoro-4-((2-(methylamino)phenyl)sulfonyl)but-2-en-1-yl)carbamate.

After purification the carbamate was cleaved to obtain the product as the hydrochloride salt (procedure J).

1H), 3.79 – 3.62 (m, 2H), 2.86 (s, 3H).

LC-MS m/z 295 (MH+), RT 3.56 min (Method 1).

			butylcarbamate (Procedure I). After purification the *tert*-butylcarbamate was cleaved to obtain the final product as the HCl salt (Procedure J).	7.56 (dddd, 2H), 6.07-5.91(dt, 1H), 3.88 (dd, 2H), 2.74 (s, 3H). LC-MS m/z 280 (MH+), RT 3.50 min (Method 1).
6 		F, G and H	none	^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 7.92 (d, 2H), 7.59 (dq, 2H), 6.04-5.88 (dt, 1H), 3.95 – 3.77 (m, 2H), 2.54 (s, 3H). LC-MS m/z 280 (MH+), RT 3.51 min (Method 1).
7 		M, N, G, O, P and Q	none	^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 8.10 (dd, 1H), 7.91 (ddd, 1H), 7.70 (ddd, 1H), 7.56 (ddd, 1H), 6.09-5.94 (dt,1H), 3.88 (d, 2H), 3.59 – 3.48 (m, 4H), 3.30 – 3.27 (m, 4H).

				LC-MS m/z 399 (MH+), RT 3.17 min (Method 1).
8			F, G and H	Procedure F was followed and when no solid precipitated after dilution with water, the product was extracted with ethyl acetate (3 x 15 mL) . The organics were washed with brine and the solvent was removed *in vacuo* to obtain (Z)-2-(4-(benzylthio)-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione.	^{1}H NMR (300 MHz, Methanol-*d*4) δ ppm: 7.57 – 7.37 (m, 5H), 6.09 - 5.93 (dt, 1H), 4.79 (d, 2H), 3.87 (dd, 2H). LC-MS m/z 280 (MH+), RT 3.21 min (Method 1).
9			C, D and E	Procedure D was followed using 20% H_2O_2 (1.0 V) Water and ethyl acetate were added to the mixture and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried with (Na_2SO_4) and concentrated to dryness. The residue was purified by normal-phase flash chromatography, eluting with a mixture of	^{1}H NMR (300 MHz, Methanol-*d*4) δ ppm: 7.85 – 7.65 (m, 5H), 5.79-5.64 (dtd, 1H), 3.78 (dtd, 2H). LC-MS m/z 249.9 (MH+)

			petroleum ether/ethyl acetate (10:1) to obtain (Z)-2-(3,4,4-trifluoro-4-(phenylsulfinyl)but-2-en-1-yl)isoindoline-1,3-dione.	
10		F, K, G, I and J	Procedure I was followed to remove the protective group. For purification, the free amine was protected as *tert*-butylcarbamate (procedure I). After purification, the *tert*-butylcarbamate was cleaved to obtain the final product as the HCl salt (Procedure J).	^{1}H NMR (300 MHz, Methanol-*d*4) δ ppm: 8.08 – 7.96 (m, 3H), 7.93 – 7.79 (m, 3H), 7.45 (dd, 1H), 7.30 (ddd, 1H), 6.00-5.84 (dt, 1H), 5.46 (s, 2H), 3.78 (dd, 2H), 3.17 (s, 3H). LC-MS m/z 450 (MH+), RT 3.43 min (Method 1).
11		F, G and H	none	^{1}H NMR (300 MHz, Methanol-*d*4) δ ppm: 7.83 (dd, 1H), 7.69 (ddd, 1H), 7.19 – 7.00 (m, 2H), 6.01-5.86 (dt, 1H), 3.91 – 3.81 (m, 2H). LC-MS m/z 282 (MH+), RT 3.10 min (Method 1).

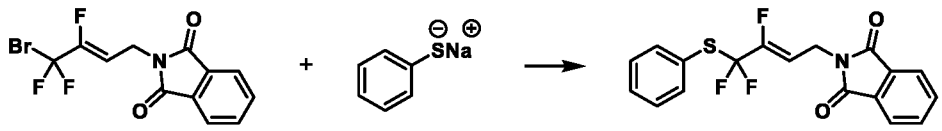
12		L, G and H	Procedure G was followed until reaction completion. The reaction mixture was concentrated *in vacuo* to afford (*Z*)-2-(3,4,4-trifluoro-4-((3-methoxyphenyl)sulfonyl)but-2-en-1-yl)isoindoline-1,3-dione.	^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 7.78 – 7.56 (m, 2H), 7.50 (ddt, 2H), 5.99 (dt,1H), 3.93 (s, 3H), 3.88 (dq, 2H). LC-MS m/z 296 (MH+), RT 3.44 min (Method 1).
13		R, G and T	none	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm: 8.42 (bs, 3H), 7.86 - 7.80 (m, 3H), 7.72 - 7.68 (m, 1H), 6.11 - 5.99 (dt, 1H), 3.75 - 3. 73 (m, 2H), 2.51 - 2.48 (m, 3H). LC-MS m/z 280 (MH+), RT 3.12 min (Method 2).
14		R, G and T	none	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm: 8.55 - 8.53 (m, 1H), 8.39 (bs, 2H), 8.28 (bs, 1H), 8.16 - 8.15 (m, 1H), 7.50 - 7.48 (m, 1H), 6.13 - 6.01 (dt, 1H), 3.75 - 3.74 (m, 2H).

	15		R, S and T	none	LC-MS m/z 272 (MH+), RT 2.41 min (Method 2).
	17		R, G and T	none	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm: 8.43 - 8.36 (bs, 3H), 8.09 (s, 1H), 8.04 - 8.02 (d, 1H), 7.86 -7.84 (d, 1H), 7.78 - 7.74 (t, 1H), 6.21 - 6.11 (dt, 1H), 5.3(s, 1H), 3.75 - 3.74 (d, 2H), 3.24 (s, 3H). LC-MS m/z 358 (MH+), RT 2.76 min (Method 1).
				none	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm: 8.27 (bs, 2H), 7.96 (d, 1H), 6.90 (d, 1H), 6.07-5.97 (dt, 1H), 3.76 (m, 2H), 2.59 (s, 3H). LC-MS m/z 270 (MH+), RT 3.14 min (Method 1).

18		U, F, G and H	Procedure F was followed and reaction was stirred at 0 °C for 1 h. After the work up, the compound was stirred in heptane at 40 °C for 1 h then the solution was allowed to slowly cool to 20 °C. The solid formed was washed with heptane to afford (Z)-2-(3,4,4-trifluoro-4-((phenyl-d_5)thio)but-2-en-1-yl)isoindoline-1,3-dione. Procedure H was followed and the reaction was stirred at 20 °C overnight. After reaction completion, the aqueous phase was extracted with ethyl acetate; the organic phase was washed with water and then brine. The organic layer was transferred into a round bottom flask and then 6.0 M HCl in 1,4-dioxane was added dropwise. It was left to stir at 20 °C for 1 h. The solid was filtered and washed with ethyl acetate to afford (Z)-3,4,4-trifluoro-4-((phenyl-d_5)sulfonyl)but-2-en-1-amine hydrochloride (950 mg).	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.44 (s, 3H), 6.12 – 6.00 (dt, 1H), 3.74 - 3.73 (d, 2H). LC-MS m/z 271 (MH+), RT 3.22 min (Method 1).

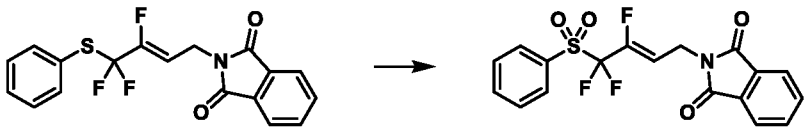
19		F, G, I and J		^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 6.00 (dt, 1H), 3.98 (q, J= 8.1 Hz, 1H), 3.88 (dq, J= 6.8, 2.1 Hz, 2H), 2.26 – 2.08 (m, 4H), 1.92 – 1.65 (m, 4H). LC-MS m/z 258 (MH+), RT 3.16 min (Method 1).
20		Z, AA, R, G and T	none	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm: 7.84-7.82 (bs, 1H), 7.76-7.72 (m, 2H), 7.68-7.64 (m, 2H), 7.60-7.56 (m, 2H), 7.44-7.42 (bs, 1H), 6.02-5.09 (s, 1H), 3.83-3.81 (m, 2H), 3.20 (s, 3H). LC-MS m/z 436 (MH+), RT 3.47 min (Method 3).

Procedure C: Preparation of (*Z*)-2-(3,4,4-trifluoro-4-(phenylthio)but-2-en-1-yl)isoindoline-1,3-dione



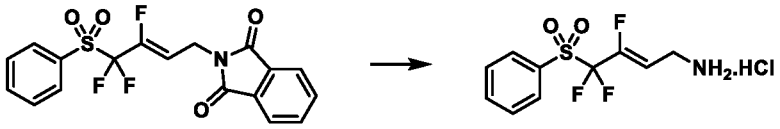
[0293] To a stirring solution of (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione (1.50 kg, 4.49 mol) in DMF (15.0 L) was added PhSNa (1.30 kg, 9.84 mol) at 0 °C. The mixture was left to stir at 0 °C for 1 hr. After completion, the reaction mixture was poured into ice water (30 L) and stirred for 30 min at 0 °C. The solid was filtered, washed with water (3 x 1.5 L) then redissolved into MTBE (10 L) at rt. The organic phase was washed with H_2O (3 x 4.5 L). Activated carbon (150 g, 10 wt%) was added to the organic phase and left to stir at rt for 30 min. The solid was filtered, washed with MTBE (3 x 1.5 L) at rt and the filtrate was concentrated *in vacuo* to give a solid (1.10 kg). The solid material was dissolved into *n*-heptane (22 L) at 60 °C and left to stir at this temperature for 30 min. The mixture was slowly cooled to 20 °C and stirred for 10 hours. The solid was filtered, washed with *n*-heptane (3 x 1.1 L) then left to dry *in vacuo* to afford (*Z*)-2-(3,4,4-trifluoro-4-(phenylthio)but-2-en-1-yl)isoindoline-1,3-dione as a solid (890 g). LC-MS m/z 364 (MH+), RT 6.63 min (Method 1).

Procedure D: Preparation of (*Z*)-2-(3,4,4-trifluoro-4-(phenylsulfonyl)but-2-en-1-yl)isoindoline-1,3-dione



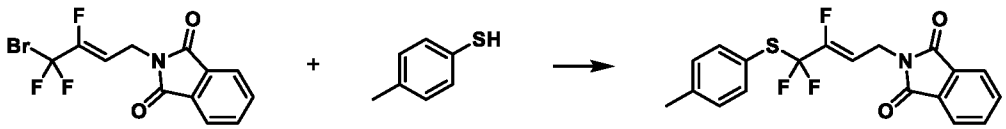
[0294] To a stirring solution of (*Z*)-2-(3,4,4-trifluoro-4-(phenylthio)but-2-en-1-yl)isoindoline-1,3-dione (870 g, 2.45 mol) and AcOH (5.2 L, 6.0 V) was added 30% H_2O_2 (5.20 L, 6.0 V) at rt. The mixture was heated to 80 °C and left to stir for 5 h. After completion, the reaction mixture was slowly cooled to 20 °C over 3 h. The solid was filtered, washed with water (3 x 1.5 L) then left to dry *in vacuo* at 50 °C to afford (*Z*)-2-(3,4,4-trifluoro-4-(phenylsulfonyl)but-2-en-1-yl)isoindoline-1,3-dione as a white solid (693 g). LC-MS m/z 396 (MH+), RT 5.54 min (Method 1).

Procedure E: Preparation of (*Z*)-3,4,4-trifluoro-4-(phenylsulfonyl)but-2-en-1-amine hydrochloride (Compound 1)



[0295] To a stirring solution of methylamine (25 – 40 wt. % in water; 3.45 L) was added (*Z*)-2-(3,4,4-trifluoro-4-(phenylsulfonyl)but-2-en-1-yl)isoindoline-1,3-dione (690 g, 1.75 mol) at rt. The mixture was left to stir at rt for 20 h. After completion, the reaction mixture was extracted with ethyl acetate (3 x 3.45 L). The organic phase was washed with water (4 x 3.45 L). A solution of HCl in ethyl acetate (6.0 M; 320 mL, 1.92 mol) was added dropwise into the organic layer. The mixture was left to stir at rt for 1 hour. The solid was filtered, washed with ethyl acetate (3 x 690 mL) then left to dry in vacuo at 50 °C to afford (*Z*)-3,4,4-trifluoro-4-(phenylsulfonyl)but-2-en-1-amine hydrochloride (Compound 1; 362 g). LC-MS m/z 266 (MH+), RT 3.23 min (Method 1), ^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 8.06 (d, 2H), 7.95 (t, 1H), 7.79 (t, 2H), 6.06 - 5.9 (dt, 1H), 3.88 (d, 2H).

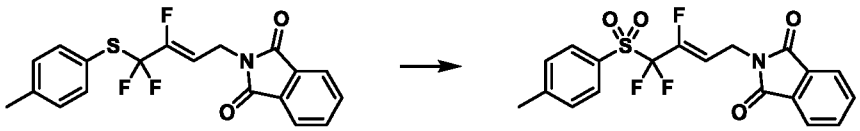
Procedure F: Preparation of (Z)-2-(3,4,4-trifluoro-4-(p-tolylthio)but-2-en-1-yl)isoindoline-1,3-dione



[0296] To a stirring solution of (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione and 4-methylbenzenethiol (0.26 mL, 4.00 mmol) in DMF (4.0 mL) was added cesium carbonate (1.30 g, 4.00 mmol) in one lot at rt. The mixture was left to stir at rt for 2 -5 h. After completion, the reaction mixture was diluted with water (40 mL) and stirred for 10 min at rt. The solid was filtered, washed with water (3 x 10 mL) and dried *in vacuo* to afford (*Z*)-2-(3,4,4-trifluoro-4-(*p*-tolylthio)but-2-en-1-yl)isoindoline-1,3-dione (0.70 g) as a mixture with the thiol starting material (1:1) and also *E*-isomer of the desired product (~10%).

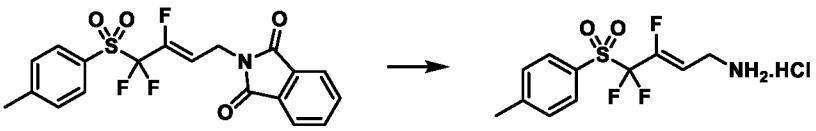
[0297] In the cases where the solid did not form, the reaction mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ ethyl acetate gradient) to obtain the final product.

Procedure G: Preparation of (*Z*)-2-(3,4,4-trifluoro-4-tosylbut-2-en-1-yl)isoindoline-1,3-dione



[0298] To a stirring solution of (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione (700 mg, 1.85 mmol) in AcOH (4.0 mL) was added 30% H_2O_2 (4.0 mL, 35.3 mmol) at rt. The mixture was heated to 80 °C and left to stir for 2 - 5 h. After completion, the reaction mixture was slowly cooled to 20 °C. The solid was filtered, washed with water (3 x 10 mL) then left to dry *in* vacuo at 50 °C to afford ((*Z*)-2-(3,4,4-trifluoro-4-tosylbut-2-en-1-yl)isoindoline-1,3-dione (0.33 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.93 – 7.86 (m, 4H), 7.81 – 7.73 (m, 2H), 7.46 – 7.38 (m, 2H), 5.74 (dt, 1H), 4.54 (m, 2H), 2.46 (s, 3H).

Procedure H: Preparation of (*Z*)-3,4,4-trifluoro-4-tosylbut-2-en-1-amine hydrochloride (Compound 6)

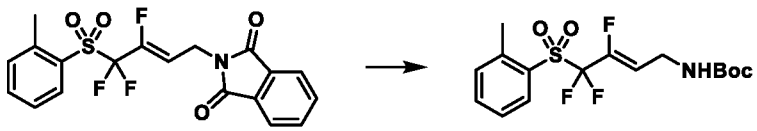


[0299] To a stirring solution methylamine (25 – 40 wt. % in water; 0.70 mL, 20.2 mmol) was added (*Z*)-2-(3,4,4-trifluoro-4-tosylbut-2-en-1-yl)isoindoline-1,3-dione (0.33 g, 0.81 mmol) in ethanol (10.0 mL) at rt. The mixture was stirred at reflux for 2 - 4 hours. After completion, solvents were removed *in vacuo*. Ethanol (10 mL) was used to remove any residual methylamine by co-evaporation.

[0300] Hydrochloric acid (0.5 M; 5.0 mL) was added to the residue and the mixture was extracted with ethyl acetate (3 x 5 mL) and discarded. The aqueous layer pH was adjusted with a 2.0 M NaOH

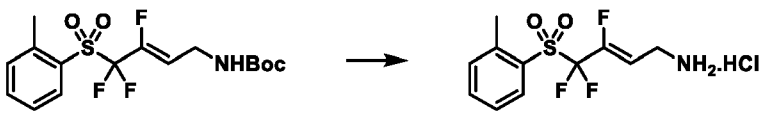
solution until pH~10 and then extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (5 mL) and HCl (2.0 M in diethyl ether; 4.00 mL, 8.00 mmol) was added dropwise into the organic layer. The mixture was left to stir at rt for 1 h. The solid was filtered, washed with ethyl acetate (3 x 5 mL) then left to dry *in vacuo* at 50 °C to afford (*Z*)-3,4,4-trifluoro-4-tosylbut-2-en-1-amine hydrochloride (Compound 6; 85.0 mg). LC-MS m/z 280 (MH+), RT 3.51 min (Method 1), ^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 7.92 (d, 2H), 7.59 (dq, 2H), 6.04 - 5.88 (dt, 1H), 3.95 – 3.77 (m, 2H), 2.54 (s, 3H).

Procedure I: Preparation of *tert*-butyl (*Z*)-(3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-yl)carbamate



[0301] (*Z*)-2-(3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-yl)isoindoline-1,3-dione (189 mg, 0.50 mmol) was treated as per Procedure H until residual methylamine was removed. The residue was then dissolved into dichloromethane (5.0 mL). Triethylamine (0.28 mL, 2.00 mmol) and di-*tert*-butyl dicarbonate (219 mg, 1.00 mmol) were added. The mixture was stirred at rt for 30 min. The solvent was then removed *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ethyl acetate gradient) to obtain *tert*-butyl (*Z*)-(3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-yl)carbamate (75.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.04 (dd, 1H), 7.64 (td, 1H), 7.50 – 7.37 (m, 2H), 5.76 (dt, 1H), 4.79 (bs, 1H), 3.99 (m, 2H), 2.74 (s, 3H), 1.47 (s, 9H).

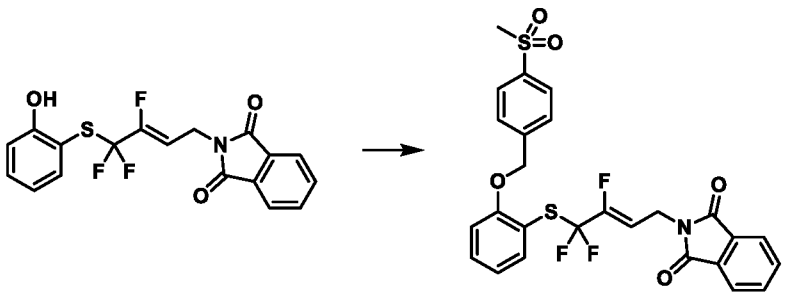
Procedure J: Preparation of (*Z*)-3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-amine hydrochloride Compound 5)



[0302] Hydrogen chloride (2.0 M in diethyl ether; 4.0 mL, 8.0 mmol) was added to a suspension of (*Z*)-(3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-yl)carbamate (70.0 mg, 0.18 mmol) in methanol (1.0 mL). The mixture was stirred at rt for 1.5 h. The reaction mixture was concentrated

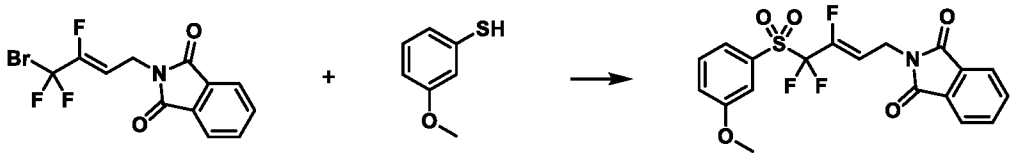
under vacuum and ethyl acetate (4 mL) was added. The suspension was stirred at rt for 15 min and the solid was filtered to afford (*Z*)-3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-amine hydrochloride (Compound 5; 50.0 mg,). LC-MS m/z 280 (MH+), RT 3.50 min (Method 1); ^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 8.04 (d, 1H), 7.78 (td, 1H), 7.56 (dddd, 2H), 6.07 - 5.91(dt, 1H), 3.88 (dd, 2H), 2.74 (s, 3H).

Procedure K: Preparation of (*Z*)-2-(3,4,4-trifluoro-4-((2-((4-(methylsulfonyl)benzyl)oxy)phenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione



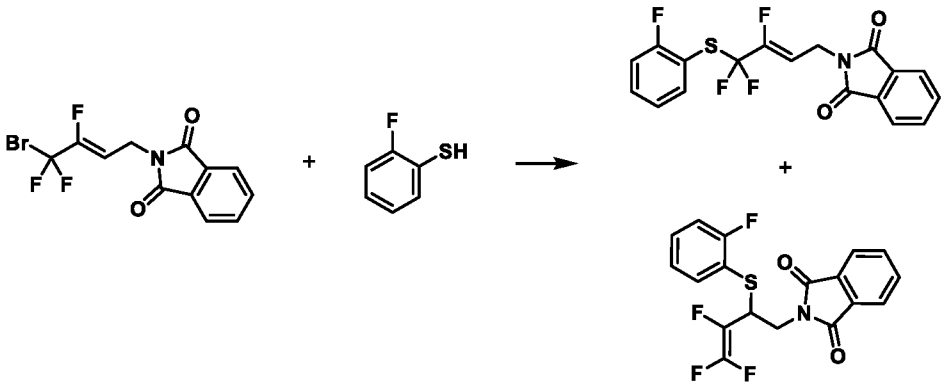
[0303] To a stirred solution of (*Z*)-2-(3,4,4-trifluoro-4-((2-hydroxyphenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione (0.18 g, 0.47 mmol) and 1-(bromomethyl)-4-methanesulfonylbenzene (0.11 mL, 0.52 mmol) in DMF (3.0 mL) was added cesium carbonate (0.23 g, 0.71 mmol) in one lot at rt. The reaction mixture was stirred at this temperature for 2 h. The reaction mixture was diluted with water and the product was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ethyl acetate gradient) to afford (*Z*)-2-(3,4,4-trifluoro-4-((2-((4-(methylsulfonyl)benzyl)oxy)phenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione (0.18 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.05 – 7.97 (m, 2H), 7.91 - 7.82 (m, 2H), 7.81 – 7.70 (m, 4H), 7.59 (dd, 1H), 7.17 (dddd, 1H), 6.94 – 6.82 (m, 2H), 5.45 – 5.27 (m, 1H), 5.24 (s, 2H), 4.40 – 4.29 (m, 2H), 3.10 (s, 3H).

Procedure L: Preparation of (Z)-2-(3,4,4-trifluoro-4-((3-methoxyphenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione



[0304] To a stirred solution of (Z)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione (0.17 g, 0.50 mmol) and 3-methoxybenzenethiol (1.28 mL, 0.99 mmol) in toluene (5.0 mL) and water (5.0 mL) was added cesium carbonate (0.34 g, 1.04 mmol) and TBAB (160 mg, 0.50 mmol) in one lot and the mixture was stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with toluene (5 mL). The combined organic phase was washed with aqueous NaOH (0.5 M; 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ethyl acetate gradient) to obtain (Z)-2-(3,4,4-trifluoro-4-((3-methoxyphenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione (80.0 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.95 – 7.80 (m, 2H), 7.82 – 7.68 (m, 2H), 7.19 – 7.10 (m, 2H), 7.09 (m, 1H), 6.80 – 6.67 (m, 1H), 5.36 (dt, 1H), 4.35 (dq, 2H), 3.78 (s, 3H).

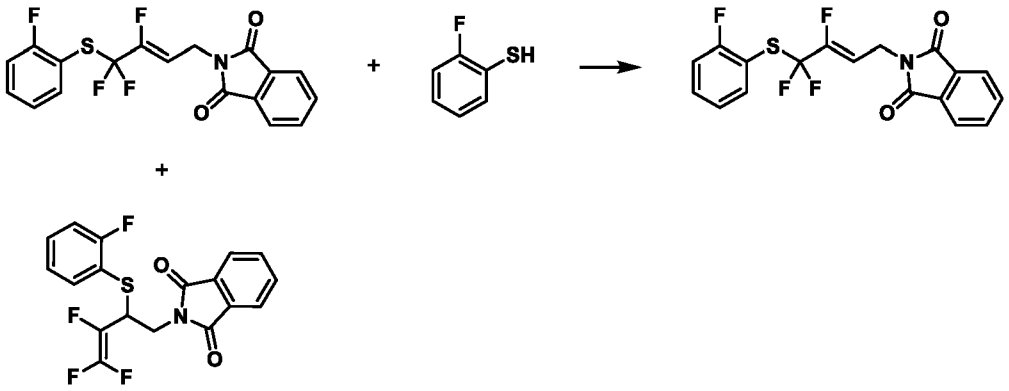
Procedure M: Preparation of (Z)-2-(3,4,4-trifluoro-4-((2-fluorophenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione



[0305] To a stirred solution of (Z)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione (1.67 g, 5.00 mmol) and 2-fluorothiophenol (0.53 mL, 5.00 mmol) in DMSO (9.0 mL) was added cesium carbonate (1.60 g, 5.00 mmol) in one lot at rt. The resulting mixture was stirred at 30 °C for 2 h. The reaction mixture was diluted with water (90 mL) at rt and the product was extracted with ethyl acetate (3 x 45 mL). The combined organics were washed with water (2 x 30 mL) and brine

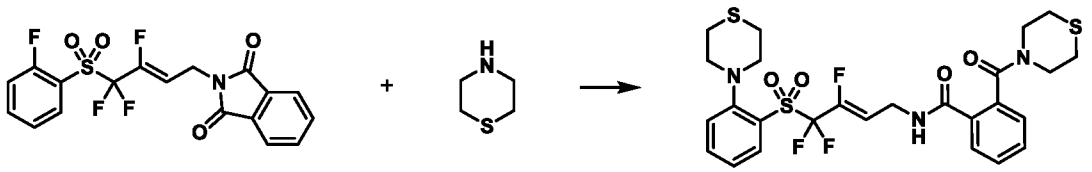
(60 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a mixture of 2-(3,4,4-trifluoro-2-((2-fluorophenyl)thio)but-3-en-1-yl)isoindoline-1,3-dione and (*Z*)-2-(3,4,4-trifluoro-4-((2-fluorophenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione (1.86 g). The mixture was used in the following step. (*Z*)-2-(3,4,4-trifluoro-4-((2-fluorophenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.94 – 7.73 (m, 4H), 7.63 – 7.53 (m, 1H), 7.38 – 7.27 (m, 2H), 7.12 – 7.03 (m, 2H), 5.47 – 5.27 (dt, 1H), 4.38 (dq, 2H).

Procedure N: (Z)-2-(3,4,4-trifluoro-4-((2-fluorophenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione



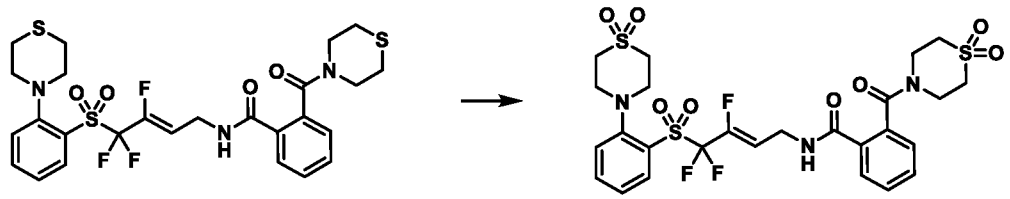
[0306] To a stirred solution of 2-fluorothiophenol (1.11 mL, 10.4 mmol) in DMF (10.0 mL) was added sodium hydride (415 mg, 10.4 mmol) in one lot at 0 °C. The reaction mixture was stirred at this temperature for 5 min, then allowed to warm up to rt. A solution containing a mixture of 2-(3,4,4-trifluoro-2-((2-fluorophenyl)thio)but-3-en-1-yl)isoindoline-1,3-dione and (*Z*)-2-(3,4,4-trifluoro-4-((2-fluorophenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione (1.86 g. 4.80 mmol) in DMF (5.0 mL) was added dropwise. The reaction mixture was stirred at rt for 1 h, then diluted with water (150 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with water (2 x 50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ethyl acetate gradient) to afford (*Z*)-2-(3,4,4-trifluoro-4-((2-fluorophenyl)thio)but-2-en-1-yl)isoindoline-1,3-dione (1.30 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.94 – 7.73 (m, 4H), 7.63 – 7.53 (m, 1H), 7.38 – 7.27 (m, 2H), 7.12 – 7.03 (m, 2H), 5.47 – 5.27 (dt, 1H), 4.38 (dq, 2H).

Procedure O: (*Z*)-2-(thiomorpholine-4-carbonyl)-*N*-(3,4,4-trifluoro-4-((2-thiomorpholinophenyl)sulfonyl)but-2-en-1-yl)benzamide



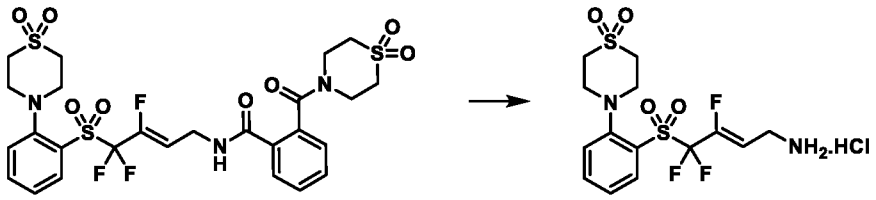
[0307] Neat thiomorpholine (0.50 mL, 4.97 mmol) was added to (*Z*)-2-(3,4,4-trifluoro-4-((2-fluorophenyl)sulfonyl)but-2-en-1-yl)isoindoline-1,3-dione (50.0 mg, 0.12 mmol). The reaction mixture was stirred at rt for 48 h. The reaction mixture was diluted with water (10 mL) when a solid crashed out. The solid was collected by filtration and purified by normal-phase chromatography (hexane/ethyl acetate gradient) to afford (*Z*)-2-(thiomorpholine-4-carbonyl)-*N*-(3,4,4-trifluoro-4-((2-thiomorpholinophenyl)sulfonyl)but-2-en-1-yl)benzamide (10.0 mg), LC-MS m/z 600 (MH+), RT 6.31 min (Method 1).

Procedure P: (*Z*)-2-(1,1-dioxidothiomorpholine-4-carbonyl)-*N*-(4-((2-(1,1-dioxidothiomorpholino)phenyl)sulfonyl)-3,4,4-trifluorobut-2-en-1-yl)benzamide



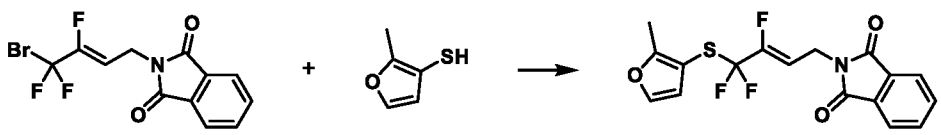
[0308] To a stirring solution of (*Z*)-2-(thiomorpholine-4-carbonyl)-*N*-(3,4,4-trifluoro-4-((2-thiomorpholinophenyl)sulfonyl)but-2-en-1-yl)benzamide (10.0 mg, 0.01 mmol) in AcOH (0.200 mL) was added H_2O_2 (30 wt % in water; 0.379 mL, 3.34 mmol) at rt. The mixture was heated to 80 °C and left to stir for 3 h. After completion, the reaction mixture was slowly cooled to 20 °C. The reaction mixture was diluted with water. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organics were washed with a saturated sodium carbonate solution (20 mL), then dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified with normal phase chromatography (hexane/ ethyl acetate gradient) to afford (*Z*)-2-(1,1-dioxidothiomorpholine-4-carbonyl)-*N*-(4-((2-(1,1-dioxidothiomorpholino)phenyl)sulfonyl)-3,4,4-trifluorobut-2-en-1-yl)benzamide (8.00 mg), LC-MS m/z 664 (MH+), RT 4.38 min (Method 1).

Procedure Q: Preparation of (*Z*)-4-(2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)phenyl)thiomorpholine 1,1-dioxide hydrochloride (Compound 7)



[0309] To a stirring solution of methylamine (25 – 40 wt.% in water; 0.50 mL, 14.4 mmol) was added (*Z*)-2-(1,1-dioxidothiomorpholine-4-carbonyl)-*N*-(4-((2-(1,1-dioxidothiomorpholino)-phenyl)sulfonyl)-3,4,4-trifluorobut-2-en-1-yl)benzamide (8.00 mg, 0.01 mmol) in ethanol (0.5 mL) at rt. The mixture was stirred at reflux for 2 h. After completion, solvents were removed *in vacuo* and ethanol (10 mL) was used to remove any residual methylamine by co-evaporation. The residue was diluted into water (10 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with water (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (1 mL) and HCl (2.0 M in diethyl ether; 0.50 mL, 1.00 mmol) was added to the solution. The mixture was left to stir at rt for 15 min. The solid was filtered, washed with ethyl acetate (3 x 5 mL) then left to dry *in vacuo* at 50 °C to afford (*Z*)-4-(2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)phenyl)thio-morpholine
1,1-dioxide hydrochloride (Compound 7; 5.00 mg). LC-MS m/z 399 (MH+), RT 3.17 min (Method 1); ^{1}H NMR (300 MHz, Methanol-d_4) δ ppm: 8.10 (dd, 1H), 7.91 (ddd, 1H), 7.70 (ddd, 1H), 7.56 (ddd, 1H), 6.09 - 5.94 (dt, 1H), 3.88 (d, 2H), 3.59 – 3.48 (m, 4H), 3.28 (m, 4H).

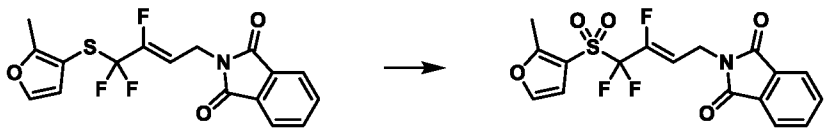
Procedure R: (*Z*)-2-(3,4,4-trifluoro-4-((2-methylfuran-3-yl)thio)but-2-en-1-yl)isoindoline-1,3-dione



[0310] To a stirring solution of 2-methylfuran-3-thiol (2.00 g, 17.5 mmol) in DMF (20.0 mL) at 0 °C was added NaH (60 wt.% in parafin oil, 1.05 g, 26.3 mmol). The reaction mixture was stirred at this temperature for 30 min. The suspension was decanted and the clear solution (10.0 mL, 8.75 mmol) was transferred into another round bottom flask containing DMF (10.0 mL). It was cooled

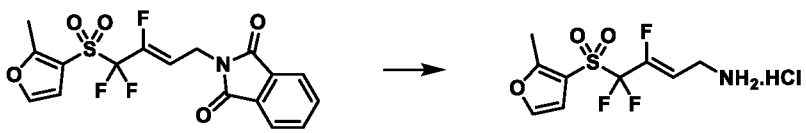
to 0 °C and a solution of (*Z*)-2-(4-bromo-3,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione (1.45 g, 4.37 mmol) in DMF (5.0 mL) was added. The reaction mixture was let to stir for 30 min at 0 °C. After completion, the reaction mixture was diluted with water (50 mL) and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ethyl acetate gradient) to afford (*Z*)-2-(3,4,4-trifluoro-4-((2-methylfuran-3-yl)thio)but-2-en-1-yl)isoindoline-1,3-dione (1.05 g). ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm: 7.93-7.88 (2H, m), 7.81-7.76 (2H, m), 7.12 (1H, d), 6.37 (1H, d), 5.46-5.34 (1H, dt), 4.43-4.41 (2H, m), 2.38 (3H, s).

Procedure S: (*Z*)-2-(3,4,4-trifluoro-4-((2-methylfuran-3-yl)sulfonyl)but-2-en-1-yl)isoindoline-1,3-dione

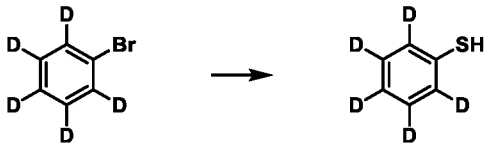


[0311] To a stirring solution of (*Z*)-2-(3,4,4-trifluoro-4-((2-methylfuran-3-yl)thio)but-2-en-1-yl)isoindoline-1,3-dione (1.05 g, 2.86 mmol) in dichloromethane (500 mL) was added *m*-CPBA (4.90 g, 22.9 mmol) at rt. The reaction mixture was stirred for 16 h at 60 °C, under nitrogen. After completion, the reaction mixture was cooled to rt and sat. aq. $NaHCO_3$ was added. The mixture was left to stir for 30 min before the aqueous layer was extracted with dichloromethane (2 x 500 mL). The combined organic phases were wahsed with a 1.0 M solution of sodium hydroxide. The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ethyl acetate gradient) to afford (*Z*)-2-(3,4,4-trifluoro-4-((2-methylfuran-3-yl)sulfonyl)but-2-en-1-yl)isoindoline-1,3-dione (580 mg). ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm: 7.93 - 7.90 (2H, m), 7.81-7.77 (2H, m), 7.40 (1H, d), 6.70 (1H, d), 5.89 - 5.77 (1H, dt), 4.59 - 4.57 (2H, m), 2.64 (3H, s).

Procedure T: (*Z*)-3,4,4-trifluoro-4-((2-methylfuran-3-yl)sulfonyl)but-2-en-1-amine hydrochloride (Compound 15)



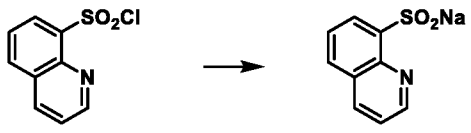
[0312] To a stirring solution of (*Z*)-2-(3,4,4-trifluoro-4-((2-methylfuran-3-yl)sulfonyl)but-2-en-1-yl)isoindoline-1,3-dione (530 mg, 1.33 mmol) in ethanol (10.0 mL) was added $N_2H_4.H_2O$ (133 mg, 2.66 mmol). The resulting mixture was heated to 80 °C and stirred for 3 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by HPLC. To the purified free base was added one drop of conc. HCl and the residue was freeze dried again to afford (*Z*)-3,4,4-trifluoro-4-((2-methylfuran-3-yl)sulfonyl)but-2-en-1-amine hydrochloride (Compound 15; 26.1 mg) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.27 (2H, ds), 7.96 (1H, d), 6.90 (1H, d), 6.07-5.97 (1H, m), 3.76 (2H, d), 2.59 (3H, s). LC-MS m/z 270 (MH+).



Procedure U: Preparation of benzene-d_5-thiol

[0313] To a stirring solution of anhydrous THF (150 mL) was added magnesium (3.38 g, 141 mmol) at rt. The reaction mixture was heated to reflux and a solution of 1-bromobenzene-2,3,4,5,6-d_5 (15.0 g, 92.6 mmol) in THF (18.0 mL) was added dropwise over 20 min. The reaction mixture was let to stir at reflux for 1 h and then cooled to 0 °C under nitrogen. Sulfur (3.18 g, 99.3 mmol) in THF (12.0 mL) was added dropwise to the reaction mixture at 0 °C over 1 h. The resulting reaction mixture was stirred for 1 h. After completion, 6.0 M HCl was added until pH~3 and the solid was filtered. The filtrate was concentrated *in vacuo* to afford benzene-d_5-thiol (8.51 g).

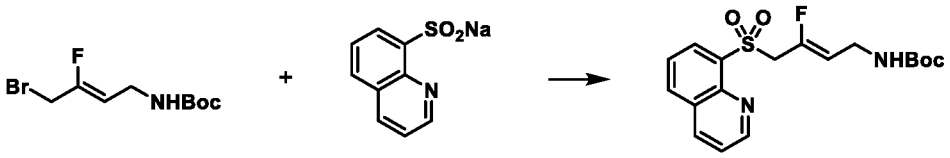
Procedure V: Preparation of sodium quinoline-8-sulfinate



[0314] A vessel charged with Na_2SO_3 (6.70 kg, 53.2 mol) and water (21.0 L) was stirred at rt for 20 min. To the vessel was added Na_2CO_3 (5.50 kg, 51.9 mol) and stirring was continued at rt for 20 min. Quinoline-8-sulfonyl chloride (6.00 kg, 26.4 mol) was then added portion-wise while maintaining the temperature below 40 °C. The resulting mixture was stirred at rt for 3 h. The

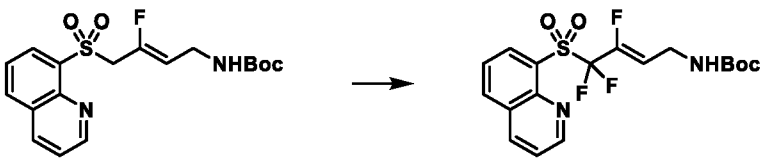
reaction mixture was filtered and the filter "cake" was washed with methanol (7.0 L). The filtrate was concentrated to dryness *in vacuo*, and to the resulting residue was added methanol (7.0 L). After stirring at rt for 1 h, the mixture was filtered and the filtrate concentrated to dryness. In a second, and final, washing cycle the residue was taken up in methanol (10.0 L) and stirring was continued at rt for 1 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford sodium quinoline-8-sulfinate (4.10 kg).

Procedure W: Preparation of *tert*-butyl (*Z*)-(3-fluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-yl)carbamate



[0315] A vessel charged with *tert*-butyl (*Z*)-(4-bromo-3-fluorobut-2-en-1-yl)carbamate (3.50 kg, 13.1 mol), sodium quinoline-8-sulfinate (4.20 kg, 19.5 mol) and DMF (17.5 L) was cooled to 15 – 20 °C. The resulting mixture was stirred at this temperature for 20 h. The mixture was then diluted with ethyl acetate (35.0 L) and water (35.0 L), and stirring was continued for a further 10 min. The organic layer was then separated and washed with water (20.0 L x 2). After concentrating the organic layer to approximately 20 L, *n*-heptane (42.0 L) was added drop-wise. The resulting suspension was stirred at 20 – 30 °C for 20 h. The solid was isolated by filtration, washed with *n*-heptane and then dried under vacuum at 50 – 55 °C for 20 h to afford *tert*-butyl (*Z*)-(3-fluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-yl)carbamate (3.80 Kg). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.13 (dd, 1H), 8.54 (dd, 1H), 8.32 (dd, 1H), 8.17 (dd, 1H), 7.73 (dd, 1H), 7.61 (dd, 1H), 4.93 – 4.77 (dt, 1H), 4.82 (d, 2H), 3.68 (t, 2H), 1.41 (s, 9H).

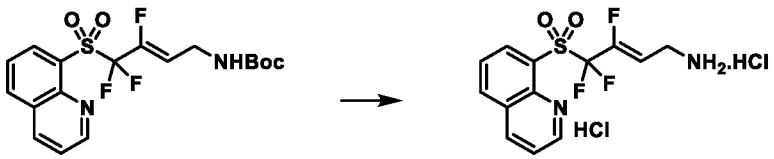
Procedure X: Preparation of *tert*-butyl (*Z*)-(3,4,4-trifluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-yl)carbamate



[0316] To a stirring solution of (*Z*)-(3-fluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-yl)carbamate (5.00 g, 13 mmol) and *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSI) (20.7 g, 65.0

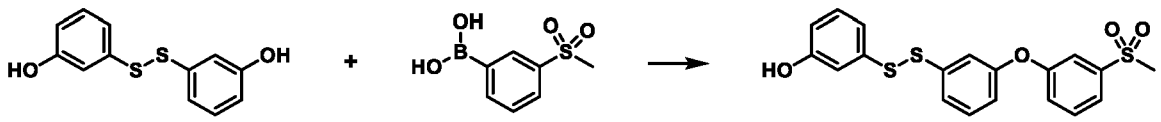
mmol) in anhydrous THF (100 mL) at -65 °C was added dropwise a solution of sodium bis(trimethylsilyl)amide (NaHMDS) (2.00 M in THF; 52.0 mL, 104 mmol). The reaction mixture was left to stir at at -65 °C for 3 h before being diluted with with sat. aq. NH_4Cl (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by normal-phase chromatography (hexane/ethyl acetate gradient) followed by reverse-phase preparative HPLC to afford (*Z*)-(3,4,4-trifluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-yl)carbamate (0.12 g). LC-MS m/z 417 (MH+); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.16 (dd, 1H), 8.62 (dd, 1H), 8.26 (dd, 2H), 7.74 (dd, 1H), 7.58 (dd, 1H), 5.83 - 5.71 (dt, 1H), 4.67 (bs, 1H), 4.12 (t, 2H), 1.45 (s, 9H).

Procedure Y: Preparation of (*Z*)-3,4,4-trifluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-amine dihydrochloride (Compound 2)



[0317] To a stirring solution of *tert*-butyl (*Z*)-(3,4,4-trifluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-yl)carbamate (0.12 g, 0.29 mmol) in anhydrous ethyl acetate (15.0 mL) at 25 °C was added dropwise a solution of HCl (6.0 M in THF; 1.50 mL, 9.00 mmol). The reaction mixture was stirred at at 25 °C for 3 h. After completion, the solid was filtered and washed with ethyl acetate before being stirred for 1 h in ethyl acetate (5 mL). The resulting solid was filtered and dried at 50 °C *in vacuo* to afford (*Z*)-3,4,4-trifluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-amine dihydrochloride (Compound 2; 70.0 mg). LC-MS m/z 317 (MH+), RT 3.16 min (Method 1); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.17 - 9.16 (m, 1H); 8.67 - 8.59 (m, 3H); 8.43 (bs, 3H), 7.97 - 7.93 (t, 1H); 6.32 (bs, 3H) 6.08 - 5.96 (dt,1H), 3.68 (s,2H).

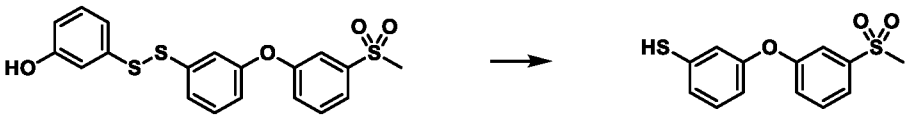
Procedure Z: Preparation of 3-((3-(3-(methylsulfonyl)phenoxy)phenyl)disulfanyl)phenol



[0318] To a stirring solution of 3,3'-disulfanediyldiphenol (2.00 g, 8.00 mmol) and (3-(methylsulfonyl)phenyl)boronic acid (6.40 g, 32.0 mmol) in CH_2Cl_2 (70 mL) was added $Cu(OAc)_2$ (1.90 g, 9.60 mmol) and pyridine (6.54 mL, 80.9 mmol) and the mixture was stirred at rt

for 16 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo, purified by normal-phase chromatography (petroleum ether: ethyl acetate; 10:1) to afford 3-((3-(3-(methylsulfonyl)phenoxy)phenyl)disulfanyl)phenol (2.30 g) as a yellow oil. LC-MS m/z 405 (MH+).

Procedure AA: Preparation of 3-(3-(methylsulfonyl)phenoxy)benzenethiol



[0319] To a stirring solution of 3-((3-(3-(methylsulfonyl)phenoxy)phenyl)disulfanyl)phenol (2.30 g, 5.70 mmol) in AcOH (20.0 mL) was added Zn powder (740 mg, 11.4 mmol). The resulting mixture was stirred at 80 °C for 2 h and then allowed to stand for 1 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by normal-phase chromatography eluting with petroleum ether/ethyl acetate (5:1) to afford 3-(3-(methylsulfonyl)phenoxy)benzenethiol (820 mg) as a yellow oil. LC-MS m/z 281 (MH+).

EXAMPLE 4

[0320] The following examples are intended to serve to illustrate topical formulations and should not be construed as limiting the generality of the disclosure of the description throughout this specification. It should be understood that numerous variations and modifications may be made while remaining within the scope of the invention.

Therapeutic Topical Formulation 1

Material Name	Quantity [g]	Weight %
Cetomacrogol 1000	17.20	1.72
Propylene glycol	393.00	39.30
Petroleum jelly	101.40	10.14

Cetostearyl alcohol	68.30	6.83
Paraffin oil	36.80	3.68
Deionised water	383.00	38.3

Therapeutic Topical Formulation 2

Material Name	**Quantity [g]**	**Weight %**
Cetomacrogol 1000	17.20	1.72
Propylene glycol	393.00	39.30
Petroleum jelly	101.40	10.14
Cetostearyl alcohol	68.30	6.83
Paraffin oil	36.80	3.68
Sodium phosphate buffer	383.00	38.3

Therapeutic Topical Formulation 3

Material Name	**Quantity [g]**	**Weight %**
Pentravan®	100	100

Therapeutic Topical Formulation 4

Material Name	**Quantity [g]**	**Weight %**

Cetomacrogol 1000	2.5	2.17
vaseline	79.5	69.13
Cetostearyl alcohol	3	2.61
Paraffin oil	15	13.04
Propylene glycol	15	13.04

Therapeutic Topical Formulations 5-23

Formulation number	**Therapeutic dose expressed as a percentage of the free base**	**Topical formulation and Quantity (g)**	**Compound 1 HCl salt (g)**	**Additive Name and amount (g)**
5	1.5	Formulation 2 98.3	1.73	
6	3	Formulation 2 241	8.63	
7	16	Formulation 2 40.8	9.2	
8	8	Formulation 2 272.4	27.6	
9	12.5	Formulation 2 356	59.8	
10	25	Formulation 2 296	120	
11	0.5	Formulation 2 38.17	0. 228	0.5 M HCl 1.6
12	1.5	Formulation 2 38.12	0.684	0.5 M HCl 1.2

13	5	Formulation 2 37.32	2.28	0.5 M HCl 0.4
14	3	Formulation 2 279.65	10.35	0.5 M HCl 10
15	6	Formulation 2 275.3	20.7	0.5 M HCl 4
16	0.88	Formulation 1 3	0.03	
17	1.5	Formulation 1 54	0.938	
18	2.64	Formulation 1 3	0.09	
19	0.26	Formulation 3 70	0.21	
20	0.86	Formulation 3 198	2	
21	2.57	Formulation 3 194	6	
22	8.62	Formulation 3 20	2	
23	0.80	Formulation 4 100	1	

Preparation of Topical Formulation 1

[0321] Placed 36.8 g of paraffin oil into a 1 L glass beaker. Added 101.4 g of petroleum jelly and 68.3 g of cetostearyl alcohol. Heated to 70 °C in a heat bath. Stirred well until all ingredients were dissolved to obtain the oil phase. Placed 383.0 g of deionized water in a metal bowl. Heated to 70 °C in a heat bath. Added 393.0 g of propylene glycol. Stirred well until all ingredients were dissolved. Added 17.2 g of cetomacrogol 1000 BPC flakes. Stirred well until all ingredients were dissolved to obtain the aqueous phase. Removed the oil phase and the aqueous phase from the heat bath. Transferred aqueous phase to an aluminum mixer bowl and added oil phase while mixing. Homogenized while gradually cooling down to 25– 30 °C to obtain the cream formulation 1.

Preparation of Topical Formulation 2

[0322] Placed 36.8 g of paraffin oil into a 1 L glass beaker. Added 101.4 g of petroleum jelly and 68.3 g of cetostearyl alcohol. Heated to 70 °C in a heat bath. Stirred well until all ingredients were dissolved to obtain the oil phase. Placed 1.50 g of sodium phosphate dibasic (NaH_2PO_4) and 5.40 g of sodium phosphate monobasic (NaH_2PO_4) into a 1 L glass bottle. Added 1 kg of demineralized water. Stirred well until all solids were dissolved to obtain a sodium phosphate buffer. Placed 383.0 g of sodium phosphate buffer in a 500 mL beaker to adjust the pH of the formulation. Heated to 70 °C in a heat bath. Added 393.0 g of propylene glycol. Stirred well until all ingredients were dissolved. Added 17.2 g of cetomacrogol 1000 BPC flakes. Stirred well until all ingredients were dissolved to obtain the aqueous phase. Removed oil phase and aqueous phase from the heat bath. Transferred aqueous phase to an aluminum mixer bowl and added oil phase while mixing. Homogenized while gradually cooling down to 25 – 30 °C to obtain the cream formulation 2.

Preparation of Topical Formulation 3

[0323] Pentravan® is an oil-in-water emulsion base commercially availaible from Fargon.

Preparation of Topical Formulation 4

[0324] Placed 3.1 g of cetostearyl alcohol, 2.5 g of cetomacrogol, 15.0 g of liquid paraffin and 79.5 g of Vaseline in a vessel. Heated in a water bath to 55 °C. Stirred well until all ingredients were dissolved and the solution is clear. Removed from water bath until temperature reached 25 °C. Added 15 g of propylene glycol. Stirred well to obtain a homogeneous ointment.

Generic procedure for preparing the topical Formulation 5-23

[0325] Weighed the solid active ingredient according the desired percentage for the therapeutic formulation, while taking into account the potency of the active principle. Placed the solid into a mortar. Added the corresponding amount of the topical formulation 1-4, in portions, to obtain 100 g of the desired percentage strength for the therapeutic formulation. 0.5 M HCl added as and where indicated to further adjust the final pH of the therapeutic formulation.

Preparation of Topical Formulation 6

[0326] Weighed 8.63 g of solid active ingredient. Placed the solid into a mortar. Added 241 g of cream formulation 2, in portions, to obtain 250 g of 3% topical formulation, where 3% is the dose expressed as the dose of the free base of the active principle. Mixed well until mixture was homogeneous. pH was measured by diluting 2 g of the mixture with 2 mL of demineralized water. pH reading was 5.7.

Preparation of Topical Formulation 10

[0327] Weighed 120 g of solid active ingredient. Placed the solid into a mortar. Added 296 g of cream formulation 2, in portions, to obtain 416 g of 25% topical formulation, where 25% refers to the free base of the active principle. Mixed well until mixture was homogeneous.

[0328] pH was measured by diluting 1 g of the mixture with 9 mL of demineralized water. pH reading was 5.1.

Preparation of Topical Formulation 15

[0329] Weighed 20.7 g of solid active ingredient. Placed the solid into a mortar. Added 275.3 g of cream formulation 2, in portions, to obtain 300 g of 6% topical formulation, where 6% refers to the free base of the active principle. Added 4 mL of 0.5 M HCl. Mixed well until cream was homogeneous. pH was measured by diluting 1 g of the mixture with 1 mL of demineralized water. pH reading was 4.74.

Preparation of Topical Formulation 23

[0330] Weighed 1 g of solid active ingredient. Placed the solid into a mortar. Weighted 8 g of propylene glycol and added it to the solid in the mortar. Sonicated until fully dissolved. Added 100 g of topical formulation 4. Stirred well until mixture was homogeneous to obtain 109 g of 0.8 % topical formulation, where 0.8% refers to the free base of the active principle.

EXAMPLE 5

Method to determine the ability of compounds of the invention to inhibit LOX and LOXL1-4 from different sources

[0331] LOX and LOXL protein family members can be acquired as recombinant active proteins from commercial sources, or extracted from animal tissues like bovine aorta, tendons, pig skin; or prepared from cell cultures. The inhibitory effects of the compounds of the present invention were tested against the given LOX or LOXL preparation using a method based on the detection of hydrogen peroxide with an Amplex Red oxidation assay (Zhou *et al.* A stable nonfluorescent derivative of resorufin for the fluorometric determination of trace hydrogen peroxide: applications in detecting the activity of phagocyte NADPH oxidase and other oxidases. *Anal. Biochem.* 1997; 253, 162-168). The assay was developed using either 384 or 96 well format. Briefly, in a standard black, clear bottom 384 well plate assay 25 µL of a dilution of any of the isoenzymes and orthologues in 1.2 M urea, 50 mM sodium borate buffer (pH 8.2) were added into each well in the presence of 1 µM mofegiline and 0.5 mM pargyline (to inhibit SSAO and MAO-B and MAO-A, respectively; not necessary if the enzyme is from a recombinant or purified form). Test compounds were dissolved in DMSO and tested in a Concentration Response Curve (CRC) with 11 data points, typically in the micromolar or nanomolar range after incubation with the enzyme for 30 min at 37 °C. 25 µL of a reaction mixture containing twice the K_M concentration of putrescine (Sigma Aldrich, e.g. 20 mM for LOX and LOXL1 or 10 mM for LOXL2 and 4 mM for LOXL3 and LOXL4), 120 µM Amplex Red (Sigma Aldrich) and 1.5 U/mL horseradish peroxidase (Sigma Aldrich) prepared in 1.2 M urea, 50 mM sodium borate buffer (pH 8.2) were then added to the corresponding wells. The above volumes were doubled in the case of 96 wells plate. The fluorescence (RFU) was read every 2.5 min for 30 min at a range of temperatures from 37 °C, excitation 565 nm and emission 590 (Optima; BMG labtech). The slope of the kinetics for each well was calculated using MARS data analysis software (BMG labtech) and this value was used to deduce the IC_{50} value (Dotmatics). The ability of the inventive compounds to inhibit the amine oxidase activity of LOX and other family members is shown in Table 4. Bovine LOX was used as a surrogate of human recombinant LOX due to the poor and unreliable pharmacology often displayed by human recombinant LOX obtained commercially or otherwise.

[0332] Notably, the *E* double bond isomer of Compound 1 (Compound 1(*E*)) displayed significantly reduced inhibitory activity.

Table 4

LOX, LOXL1-4 inhibitory activities of examples of compounds of the invention

Compound	Bovine LOX Activity IC_{50} (μM)	Human recombinant LOXL1 Activity IC_{50} (μM)	Human recombinant LOXL2 Activity IC_{50} (μM)	Human recombinant LOXL3 Activity IC_{50} (μM)	Human recombinant LOXL4 Activity IC_{50} (μM)
BAPN	2.2	2.5	0.4	0.5	0.3
1	3.7	3.4	0.4	1.5	0.3
1(*E*)	23.1		2.1		
2	8.0	13.4	1.8	16.4	0.6
3	11.1		0.7		
4	4.3	4.8	1.0	7.4	0.7
5	3.8		0.5		
6	3.5	5.1	0.5	1.8	0.3
7	22.8		2.0		
8	2.5	3.1	0.3	1.0	0.1
9	6.5	8.7	1.4	5.2	1.1
10	2.7	2.0	0.1	1.5	0.1
11	>30		1.7		
12	5.1	7.4	0.6	2.7	0.3
13	3.9		0.5		
14	4.5	7.0	0.3	1.2	0.2

15	5.9		0.7		
17	3.5	4.6	0.4	0.8	0.2
18	3.6		0.7		
19	2.5	4.3	0.5	1.3	0.5
20	4.4				

EXAMPLE 6

Compounds of the current invention exhibit sustained inhibition of LOXL1 and LOXL2

[0333] For meaningful pharmacological effect in the presence of high substrate concentration, compounds that exert sustained, long lasting inhibition of LOX and LOXL1-4 present an advantage over competitive inhibitors as the pharmacological effect may outlast the presence of the unbound inhibitor. In a preferred embodiment compounds in the current invention exhibit sustained inhibition of LOX and LOXL1-4.

Method of determining sustained inhibition of LOX and LOXL1-4 by compounds of the invention

[0334] Jump Dilution experiment: The assay was developed using a 96 well format and the starting enzyme concentration was set 100 times higher than for the inhibition studies. The enzyme was incubated for 40 minutes at 37 °C in presence of 10x or (where needed to ascertain inhibitor concentration exceeding enzyme concentration) 30 x IC_{50} concentrations of the test inhibitor. After the incubation, the mixture was diluted 50x in assay buffer, followed by a further 2 x dilution in Amplex Red-horseradish peroxidase-putrescine reaction mix (as for Example 5) prior to the fluorescence measurement. Results were expressed in % recovery of the signal after a specified time by comparison with non-inhibited controls. LOXL1 is used as a surrogate for LOX owning to similar pharmacological behaviour.

[0335] A reversible standard, used as a control, showed quasi-complete activity recovery after 30 min, for both LOXL1 and LOXL2 (80.9 % and 96.8% respectively). In contrast, BAPN, a known pan LOX irreversible inhibitor and **Compound 1** exhibit sustained inhibition of LOXL1 and

LOXL2, with the LOXL1/LOXL2 enzyme recovering only 0.3% / 11.2% for BAPN and 8.9% / 12.5% for compound 1, after 30 min.

EXAMPLE 7

Measurement of lysyl oxidase activity in rat skin after topical administration

[0336] Dorsal and ventral skin from rats treated by topical application of compound 1 were semi-defrosted at ice-cold temperature and three 3 mm punches of the skin were taken using a tissue puncher. The core sample was microdissected to leave only the epidermal and dermal layers. All other layers were removed. The microdissected sample was weighed using a fine balance (between 24.5 and 26.7 mg). The tissue punch was placed in a 1.5 mL Eppendorf tube and snap-frozen in liquid nitrogen. A mortar and pestle stored at -80 °C was then used to pulverize skin tissue. The pulverized sample was further washed in 1 mL of ice-cold washing buffer ((0.15 M NaCl, 50 mM sodium borate, pH 8.0, with PMSF: Sigma P7626, 0.25 mM, and Aprotinin: Sigma A6279, 1 µL per mL). The tissue buffer was centrifuged (20000 g for 10 minutes at 4 °C), and the supernatant was discarded. Fresh wash buffer (1 mL) was added and the Eppendorf tube was aggitated for 5 minutes at 4 °C on a vortex shaker. Washing was repeated two more times. After the last wash, the supernatant was completely removed. The rat dorsal skin pellet was re-suspended in 6 M urea 50 mM sodium borate buffer, according to sample weight to achieve final urea concentration of 4.5 M. The extraction buffer contains protease inhibitors; aprotinin and PMSF as above. Each homogenate was well-mixed by continuous vortexing at 4 °C for a 3 hour extraction. After 3 hours, 6 M Urea, 50 mM sodium borate buffer was added to each sample according to sample size to achieve the final urea concentration of 2.4 M. Protease inhibitors - aprotinin and PMSF - are present. The mixture was again centrifuged at (20000 g at 4°C for 10 minutes) and the supernatant was collected in a clean, cold eppendorf. To 50 µl of sample, pargyline (final concentration at 0.5 mM) and mofegiline (final concentration at 1µM) were added. Enzyme mix (25 µL) was transferred to the test plate with or without 600 µM BAPN (0.5 µl 30 mM) and incubated at 37 °C for 30 minutes. Reaction mix (25 µL) is added to each well, plate fluorescence is measured every 2.5' with or without 100 µM BAPN for the low controls (Ex: 544 nm/Em: 590 nm/gain: 1260 at 37 °C).

Sodium borate buffer: 6 M urea, 50 mM sodium borate; pH 8.2

Reaction mix: 120 µM Amplex Red (stock 20 mM at -20 °C; 1:167), 1.5 U/mL HRP (stock 1500 U/mL at 4 °C; 1:1000), 10 mM putrescine (stock 1 M at -20 °C)

Rats treated with cream containing 1% **Compound 1** 400 mg/rat, and cream containing 3% **Compound 1** 200 mg/rat showed significantly lower dorsal skin LOX activity compared to the placebos (Figure 3).

EXAMPLE 8

Method to determine the ability of compounds of Formula I to inhibit human recombinant SSAO/VAP-1

[0337] Human recombinant SSAO/VAP-1 amine oxidase activity was determined using the coupled colorimetric method as described for monoamine oxidase, copper-containing amine oxidases and related enzymes (Holt A. and Palcic M., A peroxidase-coupled continuous absorbance plate-reader assay for flavin monoamine oxidases, copper-containing amine oxidases and related enzymes. *Nat Protoc* 2006; 1: 2498-2505). Briefly, a cloned cDNA template corresponding to residues 34-763 of human SSAO/VAP-1, and incorporating a mouse Ig kappa (κ) signal sequence, N-terminal flag epitope tag and tobacco etch virus (TEV) cleavage site, was assembled in a mammalian expression vector (pLO-CMV) by Geneart AG. This vector containing human SSAO/VAP-1 residues was transfected into CHO-K1 glycosylation mutant cell line, Lec 8. A clone stably expressing human SSAO/VAP-1 was isolated and cultured in large scale. Active human SSAO/VAP-1 was purified and recovered using immunoaffinity chromatography. This was used as the source for SSAO/VAP-1 activity. A high-throughput fluorescent assay was developed using either 96 or 384 well format. Briefly, in a standard 96 well plate assay 50 µL of purified human SSAO/VAP-1 (0.25 µg/mL) in 0.1 M sodium phophate buffer (pH 7.4) was added into each well. Test compounds were dissolved in DMSO and tested in a Concentration Response Curve (CRC) with 4-11 data points, typically in the micromolar or nanomolar range after incubation with human SSAO/VAP-1 for 30 min at 37 °C. After 30 min incubation, 50 µL of the reaction mixture containing 600 µM benzylamine (Sigma Aldrich), 120 µM Amplex Red (Sigma Aldrich) and 1.5 U/mL horseradish peroxidase (Sigma Aldrich) prepared in 0.1 M sodium phosphate buffer (pH 7.4) were added to the corresponding well. The fluorescence unit (RFU) was read every 2.5 min for 30 min at 37 °C excitation 565 nm and emission 590 (Optima; BMG labtech). The slope of the kinetics for each well was calculated using MARS data analysis software (BMG labtech) and this

value was used to deduce the IC_{50} value (Dotmatics). The ability of the compounds of Formula I to inhibit SSAO/VAP-1 is shown in Table 5.

EXAMPLE 9

Method to determine the ability of compounds of Formula I to inhibit human recombinant MAO-B

[0338] The specificity of the compounds of this invention was tested by determining their ability to inhibit MAO-B activity *in vitro* using recombinant human MAO-B (0.02 mg/mL; Sigma Aldrich). The assay was performed in a similar way as for human SSAO/VAP-1 (Example 8) except, the substrate benzylamine was used at 100 µM. The ability of compounds of Formula I to inhibit MAO-B is shown in Table 5.

EXAMPLE 10

Method to determine the ability of compounds of Formula I to inhibit human recombinant MAO-A

[0339] The specificity of the compounds of this invention was tested by determining their ability to inhibit MAO-A activity *in vitro,* using recombinant human MAO-A (0.003 mg/mL; Sigma Aldrich). The assay was performed in a similar way as for human SSAO/VAP-1 (Example 8) except, the incubation with the test compounds was extended to 2 hours, and the substrate tyramine was used at 100 µM in place of benzylamine. The ability of compounds of Formula I to inhibit MAO-A is shown in Table 5.

EXAMPLE 11

Method to determine the ability of compounds of Formula I to inhibit human recombinant DAO

[0340] The specificity of the compounds of this invention was tested by determining their ability to inhibit DAO activity *in vitro,* using recombinant human DAO (100 ng/mL; kindly provided by Prof. Boehm, Department of Clinical Pharmacology, Medical University, Vienna). The assay was performed in a similar way as for human SSAO/VAP-1 (Example 8) except, the incubation with the test compounds was extended to 2 hours, and the substrate tyramine was used at 100 µM in place of benzylamine. The ability of compounds of Formula I to inhibit DAO is shown in Table 5.

[0341] LOX and LOXL1-4 enzymes are members of a large family of flavin-dependent and copper-dependent amine oxidases, which includes SSAO/VAP-1, monoamine oxidase-B (MAO-B), monoamine oxidase-A (MAO-A) and diamine oxydase (DAO). Compounds of the present invention selectively inhibit members of the LOX family of enzymes with respect to SSAO/VAP-1, MAO-B, MAO-A and DAO. Examples of the magnitude of selectivity can be seen in Table 5.

Table 5: SSAO/VAP-1, MAO-B, MAO-A and DAO inhibitory activities of examples of compounds of the invention.

Compound	Human recombinant SSAO/VAP-1 Activity IC50 (uM)	Human MAO-B Activity IC50 (uM)	Human MAO-A Activity IC50 (uM)	Human DAO Activity IC50 (uM)
BAPN	>30	>30	>30	>30
1	>30	>30	>30	>30
4	18.0	30	26.7	>30
5	>30	>30	20.2	
6	>30	>30	>30	
8	>30	>30	>30	
10	14.7	>30	4.7	
14	26.6			

EXAMPLE 12

Compounds of the current invention are permeable when applied topically on the skin

[0342] Skin permeability is essential when considering topical application to treat skin conditions. One way to evaluate skin permeability is to use a Franz diffusion cell system with human skin as a membrane (*Particle Sciences*; *Technical Brief* 2009; Vol. 10). The donor compound, topically formulated, is applied on the top chamber and diffusion through the skin is monitored at

relevant time points by sampling the solution in the receptor chamber via the sampling port. The concentration of **Compound 1** was determined by quantitative HPLC analysis.

[0343] **Compound 1** displays good permeability and diffusion (from a topical formulation containing 3% compound) across the membrane, in a time dependent manner, to reach uM levels in the receptor chamber after 20 hours (Table 6).

Table 6: Concentration of Compound 1 in the receptor chamber at 2, 4, 6 and 20 hour time points.

Time (hr)	Concentration of Compound 1 in the receptor chamber (µM)
0	0
2	0.017
4	0.042
6	0.166
20	1.742

EXAMPLE 13

Ultraviolet (UV) absorbance

[0344] Minimising UV light absorption of drugs may avoid risk of phototoxicity and photoallergy. For induction of phototoxicity and/or photoallergy, a chemical must absorb light within the range of natural sunlight (290 to 700 nm). Therefore, compounds with no absorbance across the natural sunlight spectrum are advantageous.

[0345] The UV spectrum for **Compound 1** exhibits no absorbance from 290 nm to 680 nm as measured on a Shimadzu LCMS 2020 instrument (Figure 5).

EXAMPLE 14

Compounds of the current invention are chemically stable in topical formulation

[0346] The stability of a drug product formulation can have a significant impact on the length and cost of drug development, the nature of the studies required to support regulatory submissions, and, ultimately, safety and approvability. It is important to minimize the amount of impurities or degradation products that form over time due to interactions between the various ingredients in a formulation. This can be particularly important in compositions that are designed to increase skin permeability.

[0347] **Compound 1** exhibits good stability in the topical formulation 2, with the compound peak percentage above 99.5% in all the tested conditions.

[0348] **Table 7: Purity profile in the reference sample and in samples stored at 2 - 8 °C, room temperature (rt) and 40 °C for 161 days.**

	Compound 1 6 % in formulation 2 % Area at 265nm at different temperature				**Compound 1 8 % in formulation 2 % Area at 265nm at different temperature**			
	reference	**2 - 8 °C**	**rt**	**40 °C**	**reference**	**2 - 8 °C**	**rt**	**40 °C**
Compound 1	**100.00**	**100.00**	**100.00**	**99.66**	**100.00**	**99.91**	**99.74**	**99.36**

EXAMPLE 15

Rodent Injury Model

[0349] Mice received injury by excision of full-thickness skin (3 cm^2 on the flank of the mice). In the treatment groups, 0.5% and 1.5% **Compound 1** solution was applied topically, once a day, starting from 24 hours post injury to 1 week, post injury. Wounds were then left to heal for an additional week. Mice were euthanized at 4-6 weeks post injury and the tissue was analyzed for collagen content, hydroxyproline as a surrogate marker of collagen content, extracted cross-link biomarkers: HLNL, DHLNL (reduced forms of deH-HLNL and deH-DHLNL respectively), PYD

and DPD, elastin content, and changes in gross morphology and histology (using polarised light microscopy, immunohistochemistry, standard staining markers and LC-MSMS).

[0350] Immature and mature crosslinks (measured using LC-MS and normalized for protein content) was reduced in treated tissue compared to control (Figure 2a and b).

EXAMPLE 16

Mouse Model of Sclerosis

[0351] Subcutaneous bleomycin (0.1 U/kg) was administered every second day (for 21 days total) to male C57BL/6 to induced skin fibrosis as a model of sclerosis. The lesions were treated, from day 3, with either Vehicle or 1.5% **Compound 1** in a topical formulation. Histology was completed after 21 days. The histological analysis is shown in Figure 4(a-c) and shows significant improvement in the composite skin score, the average collagen score as well as in the average LOX score.

EXAMPLE 17

Excision Injury Model in Pigs

[0352] To confirm the anti-scarring effect of **Compound 1** in a skin model which more closely resembles human physiology, **Compound 1** (0, 0.5, 1.5 and 3%) as an oil in water cream was topically applied onto scars in a porcine excision injury model. Eight full thickness excisions (5 x 2 cm^2) were made on 5 female juvenile pigs (each weighing 18 - 20 kg) for a total of 40 injury sites. The entire epidermis and dermal layers of skin were removed by a plastic surgeon in one operation under anaesthesia leaving excisions approximately 5-8 mm in depth. Wounds were dressed and anti-anxiety jackets (Thundershirt; RSPCA) provided to cover wounds. Analgesia was given - buprenorphine injection and fentanyl patch (50 µg/hr) for 10 days, post-surgery - and animals were allowed to recover. The dressings were changed at regular intervals to protect the wounds and prevent infection. Daily treatment started 14 days post-surgery and continued for 12 weeks.

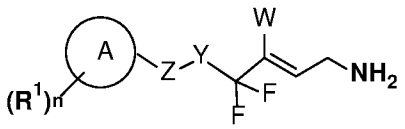
[0353] Photos of each pig scar in set of 4 were shown to plastic surgeons blind to the treatment for scoring. The surgeons ranked scars in each set of 4 from best to worst (0-3) and the scores for each scar were added and analysed.

[0354] Figure 6 shows a substantial, dose-dependent improvement in scar appearance. At 3% **Compound 1,** there was significantly less scar visible than in the control scars. The scoring of the plastic surgeons confirmed that impression.

AMENDED CLAIMS
received by the International Bureau on 25 November 2020 (25.11.2020)

CLAIMS:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, hydrate or tautomeric form thereof; wherein:

W is F or Cl;

Y is $-S(O)_2-$ or -S(O)-;

Z is $-(CH_2)_m-$

A is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkenyl, or C_{1-6}alkynyl;

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, $-NR^4R^5$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, $-C(O)OR^3$, $-C(O)NR^4R^5$, $-S(O)_2NR^4R^5$, $-S(O)_2R^6$, $-NR^8C(O)R^9$, and $-NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, -C_{1-4}alkyl, -O-C_{1-4}alkyl, $-CF_3$, - CH_2CF_3 and $-O-CF_3$;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, -C_{1-4}alkyl, -O-C_{1-4}alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more

substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, $O-C_{1-6}$alkyl C_{3-7}cycloalkyl, $-C(O)OR^3$, $-C(O)NR^4R^5$, $-NR^4C(O)R^6$, $-S(O)_2NR^4R^5$, $-NR^4S(O)_2R^6$ and $-S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

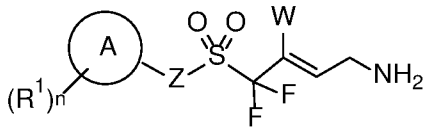
R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

n is 0, 1, 2, 3, 4 or 5; and

m is 0 or 1.

2. A compound according to claim 1 of Formula Ia:



Formula Ia

or a pharmaceutically acceptable salt, solvate, hydrate or tautomeric form thereof; wherein:

W is F or Cl;

Z is $-(CH_2)_m-$;

A is aryl or heteroaryl;

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -C(O)OR^3, -C(O)NR^4R^5, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3 and –O-CF_3;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, O-C_{1-6}alkyl C_{3-7}cycloalkyl, -C(O)OR^3, -C(O)NR^4R^5, -$NR^4C(O)R^6$, -$S(O)_2NR^4R^5$, -$NR^4S(O)_2R^6$ and -$S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

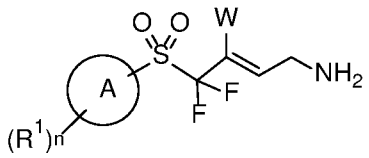
R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

n is 0, 1, 2 or 5; and

m is 0 or 1.

3. The compound according to claim 1 or 2 of Formula Ib:



Formula Ib

or a pharmaceutically acceptable salt, solvate, hydrate or tautomeric form thereof; wherein:

W is F or Cl;

A is aryl or heteroaryl;

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -$C(O)OR^3$, -$C(O)NR^4R^5$, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3 and –O-CF_3;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the

group consisting of halogen, -OH, $-SO_2CH_3$, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-SO_2CH_3$, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, $O-C_{1-6}$alkyl C_{3-7}cycloalkyl, $-C(O)OR^3$, $-C(O)NR^4R^5$, $-NR^4C(O)R^6$, $-S(O)_2NR^4R^5$, $-NR^4S(O)_2R^6$ and $-S(O)_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, $-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-CF_3$, $-CH_2CF_3$, and $-O-CF_3$; or

R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

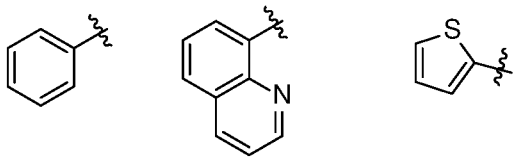
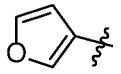
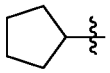
n is 0, 1, 2 or 5; and

m is 0 or 1.

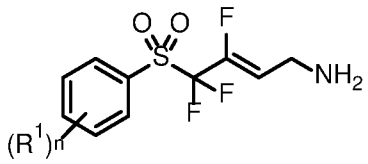
4. The compound according to any one of claims 1 to 3, wherein W is F.

5. A compound according to any one of claims 1 to 4, wherein A is selected from the group consisting of phenyl, quinolinyl, thiophenyl, furanyl and cyclopentyl.

6. A compound according to any one of claims 1 to 5, wherein A is selected from the group consisting of:



and


7. A compound according to claim 1, of Formula Ic:



Formula Ic

or a pharmaceutically acceptable salt, solvate, hydrate or tautomeric form thereof; wherein:

each R^1 is independently selected from the group consisting of X-R^2, deuterium, halogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl, -NR^4R^5, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -CN, -C(O)OR^3, -C(O)NR^4R^5, -$S(O)_2NR^4R^5$, -$S(O)_2R^6$, -$NR^8C(O)R^9$, and -$NR^8S(O)_2R^9$; wherein each C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3 and –O-CF_3;

X is selected from the group consisting of O, CH_2, OCH_2, CH_2O, $CH_2S(O)_2$, CONH and NHCO;

R^2 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein each R^2 is optionally substituted by one or more R^7;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^4 and R^5 when attached to the same nitrogen atom are combined to form a 4- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3;

R^7 is selected from the group consisting of halogen, -OH, C_{1-6}alkyl, O-C_{1-6}alkyl C_{3-7}cycloalkyl, -C(O)OR^3, -C(O)NR^4R^5, -NR^4C(O)R^6, -S(O)$_2$NR^4R^5, -NR^4S(O)$_2R^6$ and -S(O)$_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen and –OH;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl; wherein each C_{1-6}alkyl and C_{3-7}cycloalkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, -CH_2CF_3, and -O-CF_3; or

R^8 and R^9 are combined to form a 5- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members; and

n is 0, 1, 2 or 5.

8. A compound according to any one of claims 1 to 7, wherein n is 0.

9. A compound according to any one of claims 1 to 8, wherein

each R^1 is independently selected from the group consisting of X-R^2, deuterium, C_{1-6}alkyl, -OH, O-C_{1-6}alkyl, heterocycloalkyl, -NR^4R^5, and -S(O)$_2R^6$; wherein each C_{1-6}alkyl is optionally substituted by one or more substituents selected from the group consisting of halogen, -OH, -SO_2CH_3, -C_{1-4}alkyl, -O-C_{1-4}alkyl, -CF_3, - CH_2CF_3 and –O-CF_3;

X is selected from the group consisting of O and OCH_2;

R^2 is aryl optionally substituted by one or more R^7;

R^4 and R^5 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl;

R^6 is selected from the group consisting of C_{1-6}alkyl and C_{3-7}cycloalkyl;

R^7 is -S(O)$_2R^6$;

and

n is 0, 1, or 5.

10. A compound according to any one of claims 1 to 9, wherein

each R^1 is independently selected from the group consisting of X-R_2, deuterium, methyl, OCH_3, -OH, -$NHCH_3$, heterocycloalkyl and SO_2CH_3;

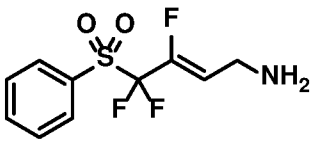
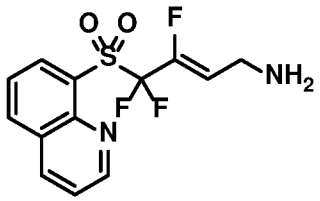
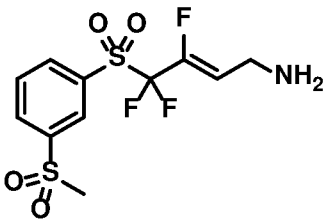
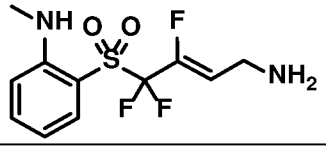
X is O or OCH_2;

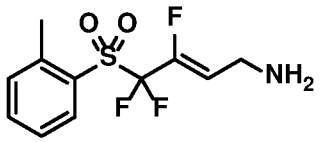
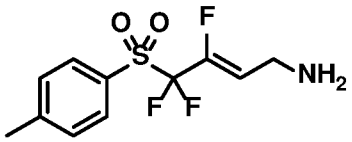
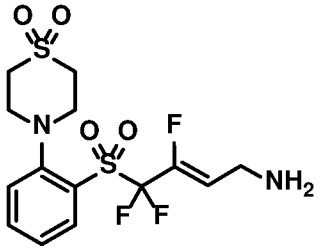
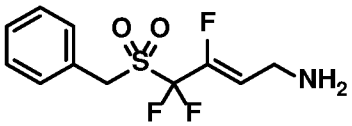
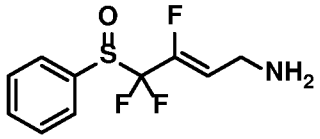
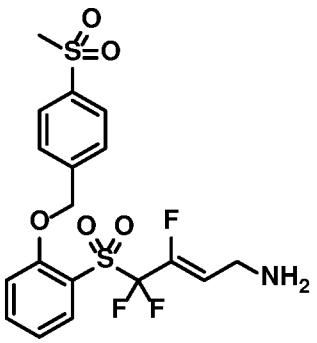
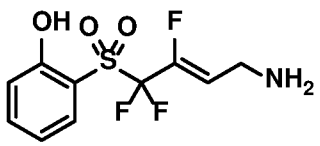
R^2 is phenyl substituted by SO_2CH_3

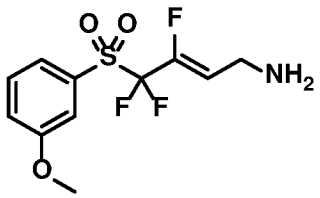
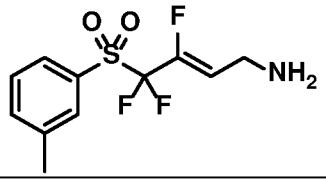
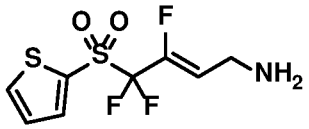
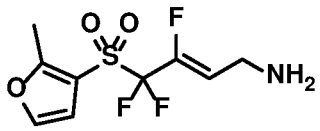
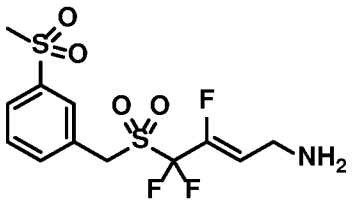
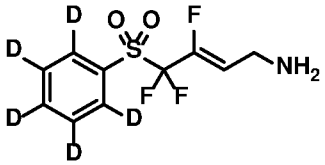
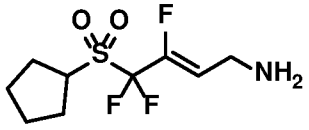
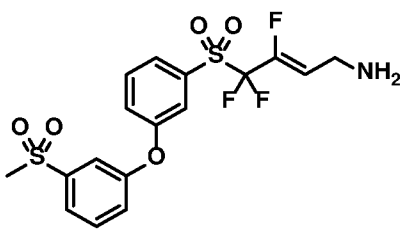
and

n is 0, 1 or 5.

11. A compound according to claim 1 selected from the group consisting of

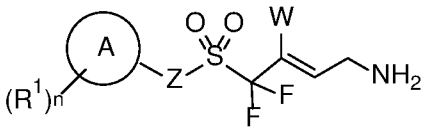
1		(Z)-3,4,4-trifluoro-4-(phenylsulfonyl)but-2-en-1-amine
2		(Z)-3,4,4-trifluoro-4-(quinolin-8-ylsulfonyl)but-2-en-1-amine
3		(Z)-3,4,4-trifluoro-4-((3-(methylsulfonyl)phenyl)sulfonyl)but-2-en-1-amine
4		(Z)-2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)-*N*-methylaniline

5		(*Z*)-3,4,4-trifluoro-4-(*o*-tolylsulfonyl)but-2-en-1-amine
6		(*Z*)-3,4,4-trifluoro-4-tosylbut-2-en-1-amine
7		(*Z*)-4-(2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)phenyl)thiomorpholine 1,1-dioxide
8		(*Z*)-4-(benzylsulfonyl)-3,4,4-trifluorobut-2-en-1-amine
9		(*Z*)-3,4,4-trifluoro-4-(phenylsulfinyl)but-2-en-1-amine
10		(*Z*)-3,4,4-trifluoro-4-((2-((4-(methylsulfonyl)benzyl)oxy)phenyl)sulfonyl)but-2-en-1-amine
11		(*Z*)-2-((4-amino-1,1,2-trifluorobut-2-en-1-yl)sulfonyl)phenol

12		(Z)-3,4,4-trifluoro-4-((3-methoxyphenyl)sulfonyl)but-2-en-1-amine
13		(Z)-3,4,4-trifluoro-4-(*m*-tolylsulfonyl)but-2-en-1-amine
14		(Z)-3,4,4-trifluoro-4-(thiophen-2-ylsulfonyl)but-2-en-1-amine
15		(Z)-3,4,4-trifluoro-4-((2-methylfuran-3-yl)sulfonyl)but-2-en-1-amine
17		(Z)-3,4,4-trifluoro-4-((3-(methylsulfonyl)benzyl)sulfonyl)but-2-en-1-amine
18		(Z)-3,4,4-trifluoro-4-((phenyl-d5)sulfonyl)but-2-en-1-amine
19		(Z)-4-(cyclopentylsulfonyl)-3,4,4-trifluorobut-2-en-1-amine
20		(Z)-3,4,4-trifluoro-4-((3-(3-(methylsulfonyl)phenoxy)phenyl)sulfonyl)but-2-en-1-amine

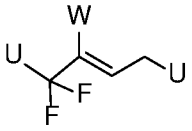
or a pharmaceutically acceptable salt or solvate thereof.

12. A process for preparing a compound of Formula Ia:



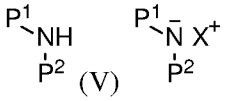
which comprises reaction steps (C), (D), (E) and (F), where:

(C) is the reaction of a compound of Formula IV:



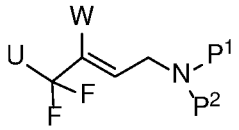
(IV)

with a compound of Formula V or VI:



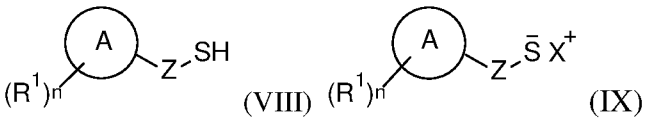
(V) (VI)

to afford a compound of Formula VII:



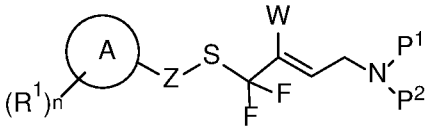
(VII);

(D) is the reaction of a compound of Formula VII with a compound of Formula VIII or IX:



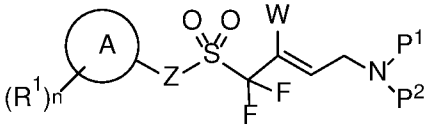
(VIII) (IX)

to obtain a compound of Formula X:



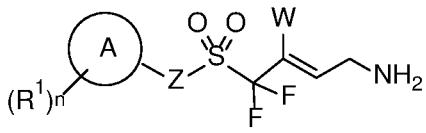
(X);

(E) is the oxidation of a compound of Formula X to obtain a compound of Formula XI:



(XI); and

(F) is deprotection of a compound of Formula XI to afford a compound of Formula Ia:



(Ia), or a pharmaceutically acceptable salt thereof

wherein U is Br, Cl or I;

W is F or Cl;

Z is $-(CH_2)_m-$;

P^1 is a nitrogen protecting group;

P^2 is hydrogen or a nitrogen protecting group; or

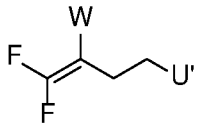
P^1 and P^2 together with the nitrogen to which they are attached form a cyclic nitrogen protecting group

X^+ is a metal counterion, and

R^1, A, m and n are as defined in claim 1.

13. The process according to claim 12, wherein reaction step (C) is preceded by reaction steps (A) and (B), wherein:

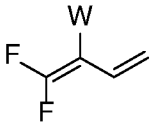
(A) denotes the reaction of a compound of Formula II:



(II)

wherein U' is Br, Cl, I, OMs, OTs;

with a base to afford a compound of Formula III:

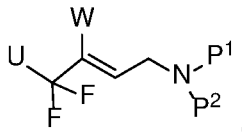


(III)

and

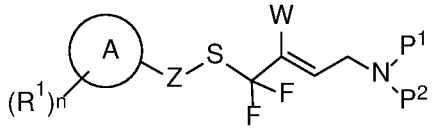
(B) denotes the reaction of a compound of Formula III with U_2 to afford a compound of Formula IV.

14. An intermediate compound of Formula VII,


(VII)

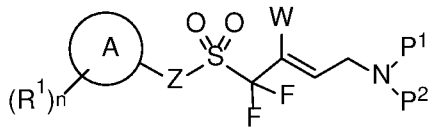
wherein U, W, P^1 and P^2 are as defined in claim 12.

15. An intermediate compound of Formula X,


(X)

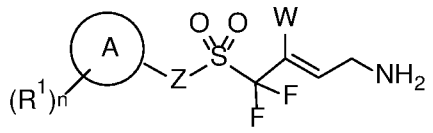
wherein W, P^1 and P^2 are as defined in claim 12 and R^1, A, Z and n are as defined in claim 1.

16. An intermediate compound of Formula XI,


(XI)

wherein W, P^1 and P^2 are as defined in claim 12 and R^1, A, Z and n are as defined in claim 1.

17. A compound of Formula Ia:


(Ia)

prepared according to the process of claim 12, wherein W, R^1, Z, A and n are as defined in claim 1.

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier or diluent.

19. A method of inhibiting the amine oxidase activity of any one of LOX, LOXL1, LOXL2, LOXL3 or LOXL4 in a subject in need thereof, comprising administering to the subject an effective amount of a compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 18.

20. A method of treating a condition by inhibiting the activity of any one of the LOX, LOXL1, LOXL2, LOXL3 and LOXL4 proteins, comprising administering to a subject in need thereof a therapeutically effective amount of compound according to any one of claims 1 to 11, or a

pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 18.

21. The method of claim 20, wherein the condition is selected from the group consisting of fibrosis, cancer and arthritis.

22. The method of claim 21, wherein in a case that the condition is fibrosis, the fibrosis is selected from the group consisting of mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Crohn's Disease, keloid, scleroderma/systemic sclerosis, arthrofibrosis, Dupuytren's contracture, adhesive capsulitis, fibrosis of the pancreases, fibrosis of the intestine, liver fibrosis, lung fibrosis, kidney fibrosis, cardiac fibrosis, fibrostenosis, cystic fibrosis, idiopathic pulmonary fibrosis, radiation-induced fibrosis, Peyronie's disease and scleroderma or is associated with respiratory disease, abnormal wound healing and repair, scarring, hypertrophic scarring/keloids, scarring post-surgery, cardiac arrest and all conditions where excess or aberrant deposition of fibrous material is associated with disease, injury, implants or surgery; preferably the fibrosis is selected from the group consisting of keloid, scarring, hypertrophic scarring, scleroderma, Dupuytren's contracture and Peyronie's disease;

wherein in a case that the condition is cancer, the cancer is selected from the group consisting of lung cancer; breast cancer; colorectal cancer; anal cancer; pancreatic cancer; prostate cancer; ovarian carcinoma; liver and bile duct carcinoma; esophageal carcinoma; mesothelioma, non-Hodgkin's lymphoma; bladder carcinoma; carcinoma of the uterus; glioma, glioblastoma, medullablastoma, and other tumours of the brain; myelofibrosis, kidney cancer; cancer of the head and neck; cancer of the stomach; multiple myeloma; testicular cancer; germ cell tumour; neuroendocrine tumour; cervical cancer; oral cancer, carcinoids of the gastrointestinal tract, breast, and other organs; signet ring cell carcinoma; mesenchymal tumours including sarcomas, fibrosarcomas, haemangioma, angiomatosis, haemangiopericytoma, pseudoangiomatous stromal hyperplasia, myofibroblastoma, fibromatosis, inflammatory myofibroblastic tumour, lipoma, angiolipoma, granular cell tumour, neurofibroma, schwannoma, angiosarcoma, liposarcoma, rhabdomyosarcoma, osteosarcoma, leiomyoma or a leiomysarcoma; and

wherein in a case the condition is arthritis, the arthritis is rheumatoid arthritis or osteoarthritis.

23. The method according to any one of claims 19 to 22 further comprising administering a second therapeutic agent.

24. The method according to claim 23, wherein the second therapeutic agent is selected from the group consisting of anti-cancer agent, an anti-inflammatory agent, an anti-hypertensive agent, an anti-fibrotic agent, an anti-angiogenic agent, an immunosuppressive agent, a metabolic agent, an anti-pruritic agent, an anti-fungal agent and an anti-bacterial agent.

25. Use of a compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treating a condition by inhibiting the activity of any one of the LOX, LOXL1, LOXL2, LOXL3 and LOXL4 proteins.

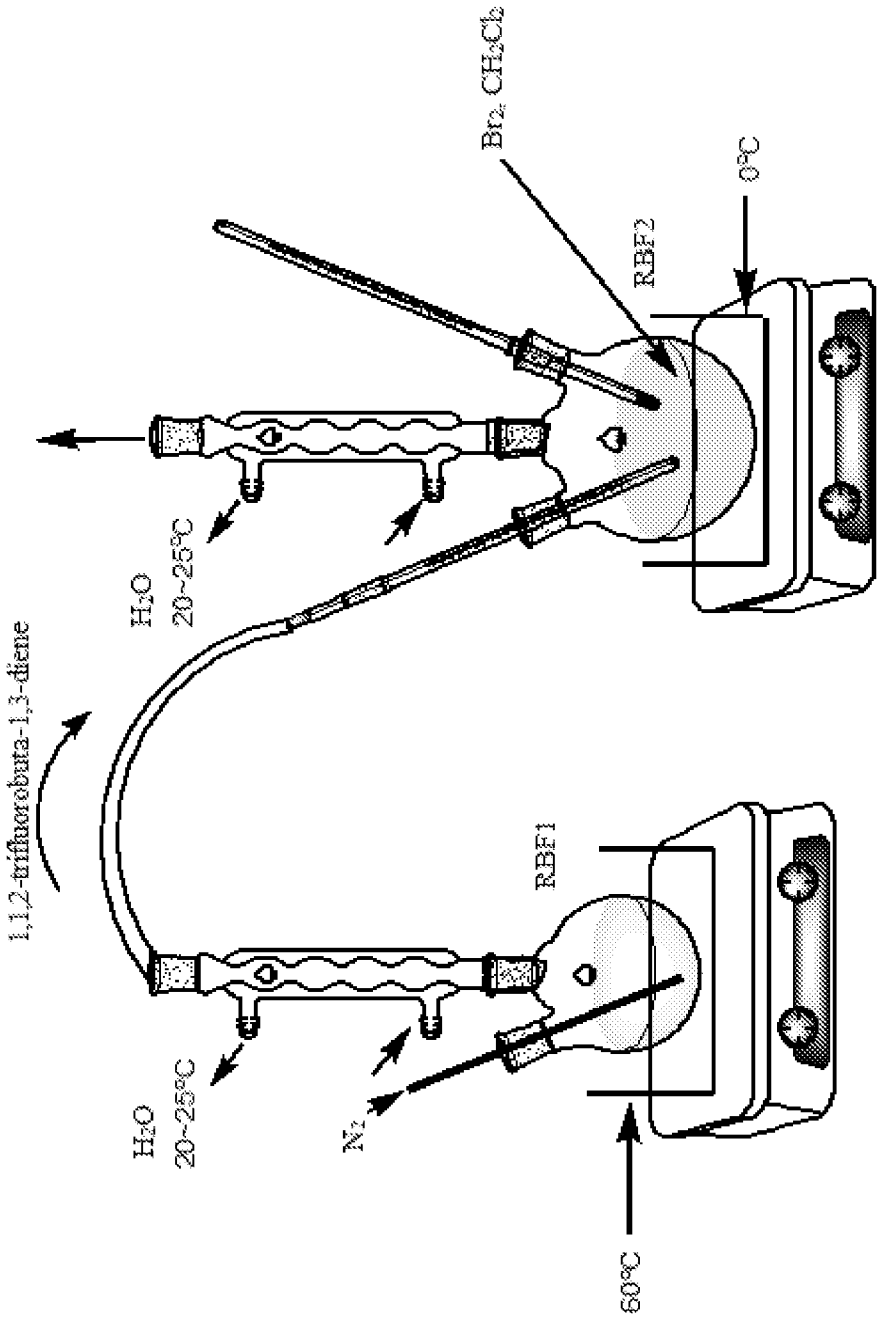

Br2, CH2Cl2
RBF2
0°C
H2O
20~25°C
1,1,2-trifluorobuta-1,3-diene
RBF1
H2O
20~25°C
N2
60°C

Figure 1

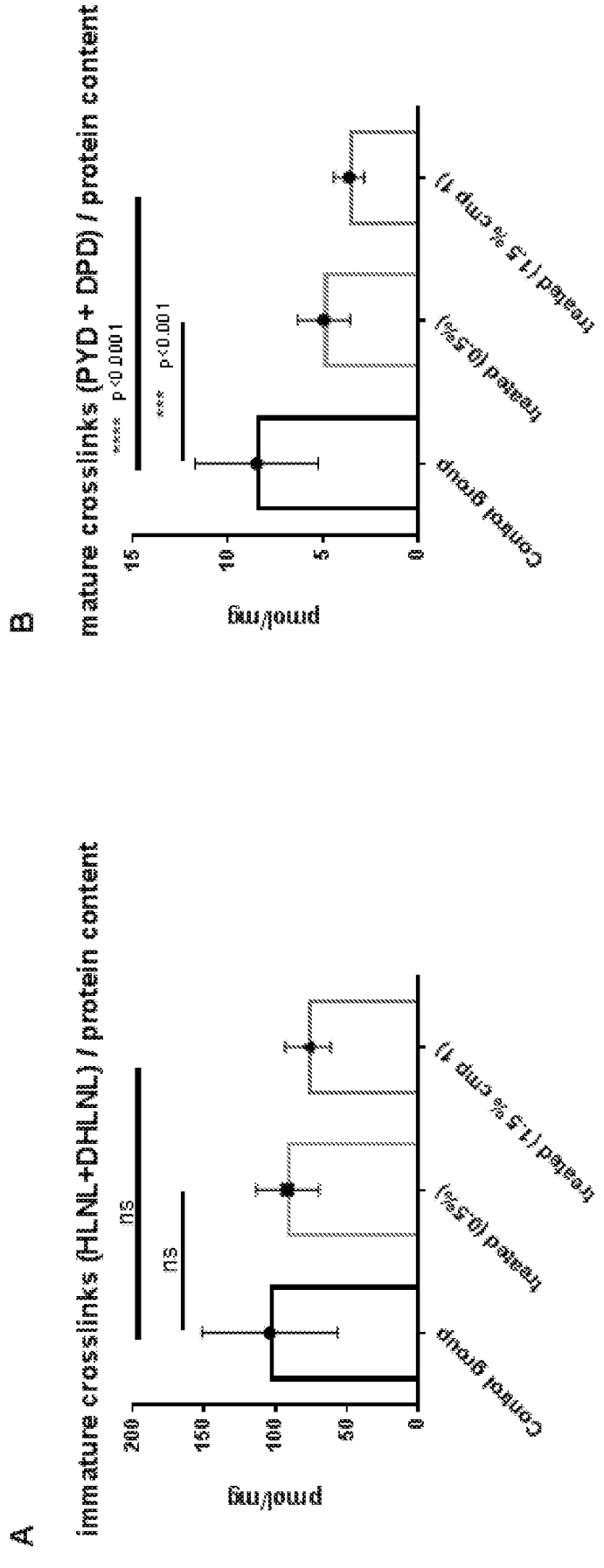


Figure 2a and 2b

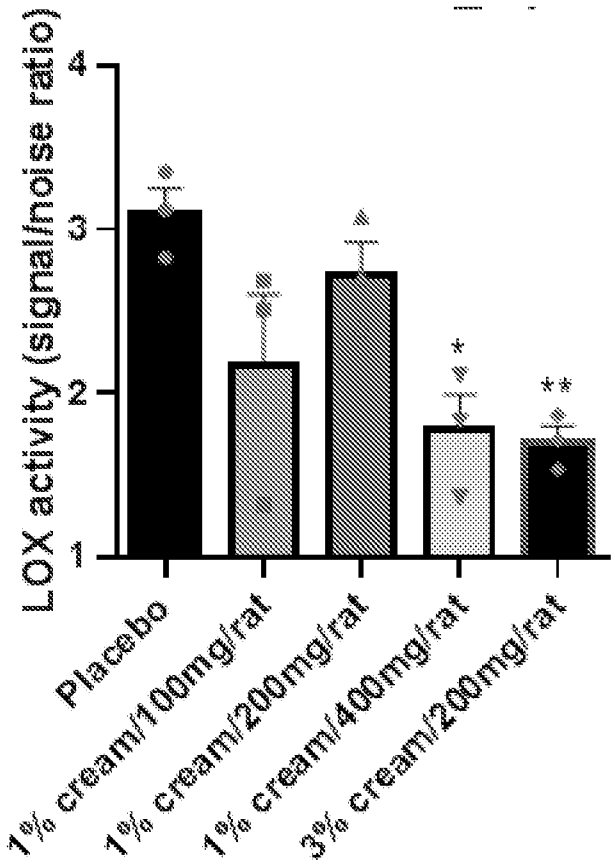

LOX activity (signal/noise ratio)
1
2
3
4
*
**
Placebo
1% cream/100mg/rat
1% cream/200mg/rat
1% cream/400mg/rat
3% cream/200mg/rat

Figure 3

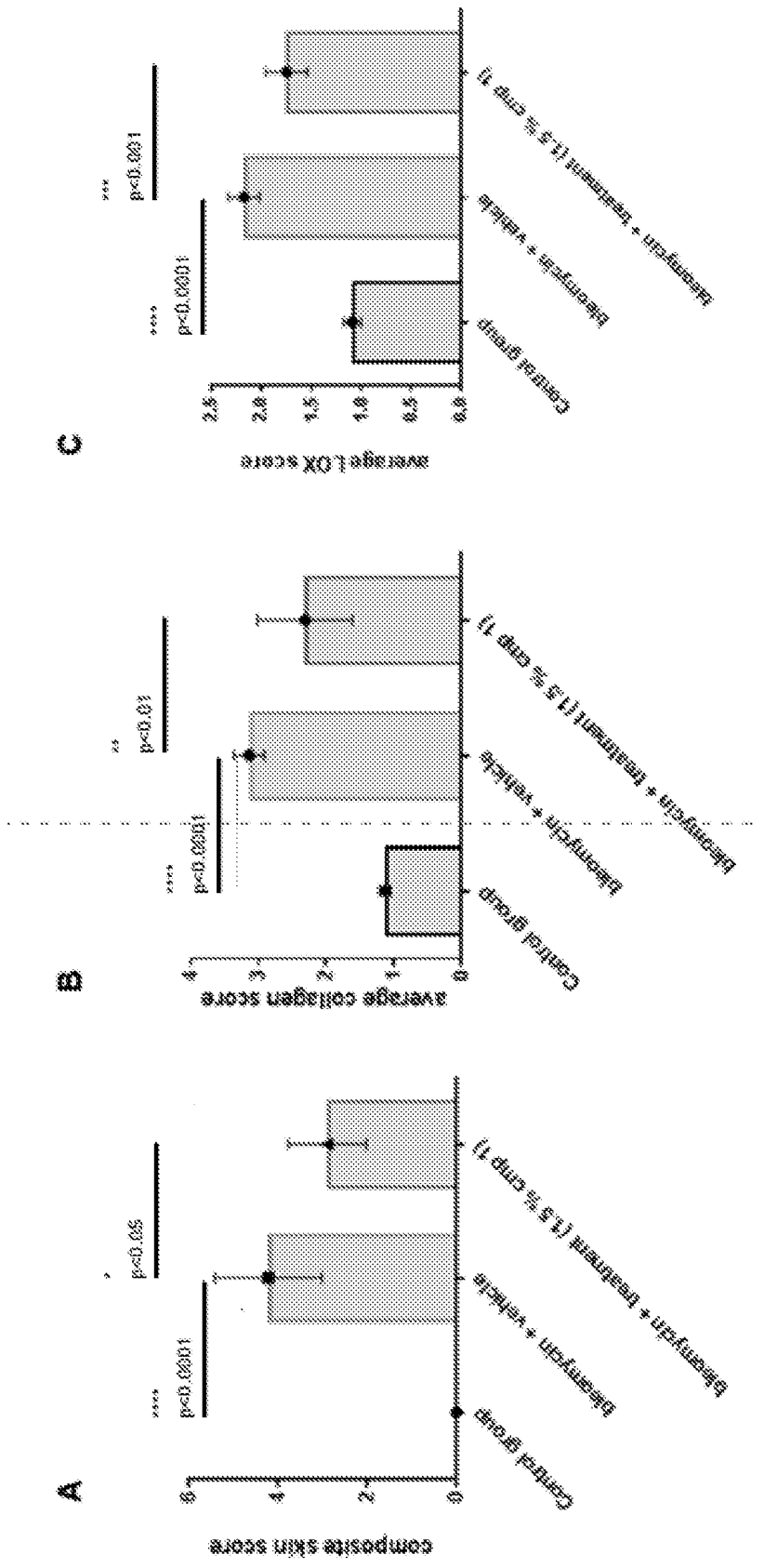

A
composite skin score
p<0.0001
p<0.05
Control group
Bepanthen + Vehicle
Bepanthen + Treatment (1.5 % comp 1)
B
average collagen score
p<0.0001
p<0.01
Control group
Bepanthen + Vehicle
Bepanthen + Treatment (1.5 % comp 1)
C
average LOX score
p<0.0001
p<0.0001
Control group
Bepanthen + Vehicle
Bepanthen + Treatment (1.5 % comp 1)

Figure 4 (a-c)

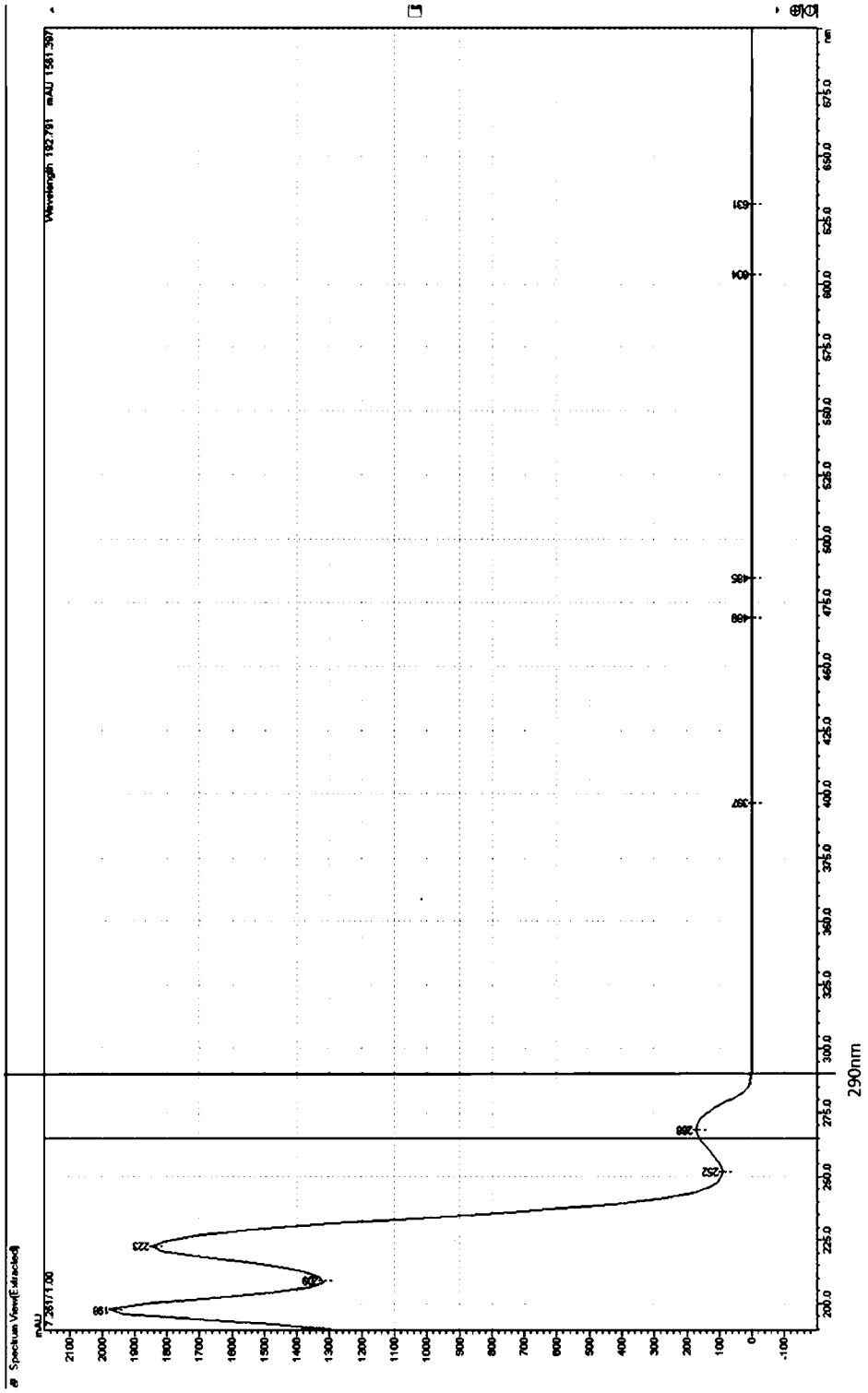


Figure 5

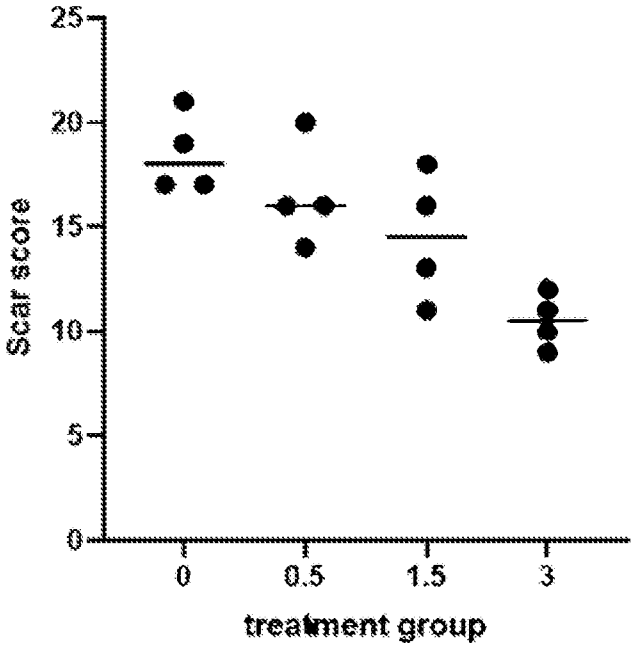


Figure 6