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(54) Title: INDANES AS NRF2 ACTIVATORS

(57) Abstract: The present invention relates indane compounds, methods of making them, pharmaceutical compositions containing them and their use as NRF2 activators. In particular, the invention relates to compounds of Formula (I) or Formula (II), and pharmaceutically acceptable salts thereof.

WO 2019/224667 A1

INDANES AS NRF2 ACTIVATORS

FIELD OF THE INVENTION

The present invention relates to indane compounds, methods of making them, pharmaceutical compositions containing them and their use as NRF2 activators.

BACKGROUND OF THE INVENTION

NRF2 (NF-E2 related factor 2) is a member of the cap-n-collar family of transcription factors containing a characteristic basic-leucine zipper motif. Under basal conditions, NRF2 levels are tightly controlled by the cytosolic actin-bound repressor, KEAP1 (Kelch-like ECH associating protein 1), which binds to NRF2 and targets it for ubiquitylation and proteasomal degradation via the Cul3-based E3-ubiquitin ligase complex. Under conditions of oxidative stress, DJ1 (PARK7) is activated and stabilizes NRF2 protein by preventing NRF2 from interacting with KEAP1. Also, modification of reactive cysteines on KEAP1 can cause a conformational change in KEAP1 that alters NRF2 binding and promotes NRF2 stabilization. Thus, the levels of NRF2 in the cell are usually kept low in normal conditions but the system is designed to respond quickly to environmental stress by increasing NRF2 levels and thus downstream NRF2 activity.

Inappropriately low NRF2 activity in the face of on-going oxidative stress appears to be a pathological mechanism underlying chronic obstructive pulmonary disease (COPD). Yamada, K., et al. *BMC Pulmonary Medicine*, 2016, 16: 27. This may be a result of an altered equilibrium between NRF2 activators with both inappropriate lack of positive activators such as DJ1, and overabundance of negative activators such as Keap1 and Bach1. Therefore, restoration of NRF2 activity in the lungs of COPD patients should result in repair of the imbalance and mitigation of deleterious processes such as apoptosis of structural cells (including alveolar epithelial and endothelial cells) and inflammation. The results of these effects would be enhanced cytoprotection, preservation of lung structure, and structural repair in the COPD lung, thus slowing disease progression. Therefore, NRF2 activators may treat COPD (Boutten, A., et al. 2011. *Trends Mol. Med.* 17:363-371) and other respiratory diseases, including asthma, Acute Lung Injury (ALI) (Cho, H.Y., and Kleeberger, S.R., 2015, *Arch Toxicol*. 89:1931-1957; Zhao, H. et al., 2017, *Am J Physiol Lung Clee Mol Physiol* 312:L155-L162, first published November 18, 2016; doi:10.1152/ajplung.00449.2016), Acute Respiratory Distress Syndrome (ARDS) and pulmonary fibrosis (Cho, H.Y., and Kleeberger, S.R. 2010. *Toxicol. Appl. Pharmacol.* 244:43-56).

The therapeutic potential of an NRF2 activator is exemplified in pulmonary macrophages from COPD patients where NRF2 pathway appears maladaptive. These cells have impaired bacterial phagocytosis compared with similar cells from control patients, and this effect is reversed by the addition of NRF2 activators in vitro. Therefore, in addition to the effects mentioned above, restoration of appropriate NRF2 activity could also rescue COPD exacerbations by reducing lung infection.

This is demonstrated by the NRF2 activator, Sulforaphane, which increases the expression of Macrophage Receptor with Collagenous structure (MARCO) by COPD macrophages and alveolar macrophages from cigarette smoke-exposed mice, thereby improving in these cells bacterial phagocytosis (*Pseudomonas aeruginosa*, non-typable *Haemophilus influenzae*) and bacterial clearance both *ex vivo* and *in vivo. (*Harvey, C. J., et al. 2011. *Sci. Transl. Med.* 3:78ra32*).*

The therapeutic potential of targeting NRF2 in the lung is not limited to COPD. Rather, targeting the NRF2 pathway could provide treatments for other human lung and respiratory diseases that exhibit oxidative stress components such as chronic asthma and acute asthma, lung disease secondary to environmental exposures including but not limited to ozone, diesel exhaust and occupational exposures, fibrosis, acute lung infection (e.g., viral (Noah, T.L. et al. 2014. PLoS ONE 9(6): e98671), bacterial or fungal), chronic lung infection, α1 antitrypsin disease, ALI, ARDS and cystic fibrosis (CF, Chen, J. et al. 2008. PLoS One. 2008;3(10):e3367).

A therapy that targets the NRF2 pathway also has many potential uses outside the lung and respiratory system. Many of the diseases for which an NRF2 activator may be useful are autoimmune diseases (psoriasis, IBD, MS), suggesting that an NRF2 activator may be useful in autoimmune diseases in general.

In the clinic, a drug targeting the NRF2 pathway (bardoxolone methyl) has shown efficacy in diabetic patients with diabetic nephropathy/chronic kidney disease (CKD) (Aleksunes, L.M., et al. 2010. *J. Pharmacol. Exp. Ther.* 335:2-12), though phase III trials with this drug in patients with the most severe stage of CKD were terminated. Furthermore, there is evidence to suspect that such a therapy would be effective in sepsis-induced acute kidney injury, other acute kidney injury (AKI) (Shelton, L.M., et al. 2013. *Kidney International.* Jun 19. doi: 10.1038/ki.2013.248.), and kidney disease or malfunction seen during kidney transplantation.

In the cardiac area, bardoxolone methyl is currently under investigation in patients with Pulmonary Arterial Hypertension and so a drug targeting NRF2 by other mechanisms may also be useful in this disease area. Oxidative stress is increased in the diseased myocardium, resulting in accumulation of reactive oxygen species (ROS) which impairs cardiac function [*Circ* (1987) **76**(2); 458-468] and increases susceptibility to arrhythmia [*J of Mol & Cell Cardio* (1991) **23**(8); 899-918] by a direct toxic effect of increased necrosis and apoptosis [*Circ Res* (2000) **87**(12); 1172-1179]. In a mouse model of pressure overload (TAC), NRF2 gene and protein expression is increased during the early stage of cardiac adaptive hypertrophy, but decreased in the later stage of maladaptive cardiac remodeling associated with systolic dysfunction [*Arterioscler Thromb Vasc Biol* (2009) **29(11)**; 1843- 5 1850; *PLOS ONE* (2012) **7**(9); e44899]. In addition, NRF2 activation has been shown to suppress myocardial oxidative stress as well as cardiac apoptosis, fibrosis, hypertrophy, and dysfunction in mouse models of pressure overload [*Arterioscler Thromb Vasc Biol* (2009) **29(11)**; *J of Mol & Cell Cardio* (2014) **72**; 305-315; and 1843-1850; *PLOS ONE* (2012) **7**(9); e44899]. NRF2 activation has also been shown to protect against cardiac I/R injury in mice 10 [*Circ Res* (2009) **105**(4); 365-374; *J of Mol & Cell Cardio* (2010) **49**(4); 576-586] and reduce myocardial oxidative damage following cardiac I/R injury in rat. Therefore, a drug targeting NRF2 by other mechanisms may be useful in a variety of cardiovascular diseases including but not limited to atherosclerosis, hypertension, and heart failure (Oxidative Medicine and Cellular Longevity Volume 2013 (2013), Article ID 104308, 10 pages), acute coronary 15 syndrome, myocardial infarction, myocardial repair, cardiac remodeling, cardiac arrhythmias, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction and diabetic cardiomyopathy.

A drug activating the NRF2 pathway could also be useful for treatment of several neurodegenerative diseases including Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) (Brain Res. 2012 Mar 29;1446:109-18. 2011.12.064. Epub 2012 Jan 12.), Huntington's disesase (HD), multiple sclerosis (MS), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, and cognitive impairment (FEBS 201 8, doi: 10.1111/febs.14379, Pharmacology & Therapeutics 2016, 157, 84-104). Multiple *in vivo* models have shown that NRF2 KO mice are more sensitive to neurotoxic insults than their wild-type counterparts. Treatment of rats with the NRF2 activator tert-

butylhydroquinone (tBHQ) reduced cortical damage in rats in a cerebral ischemia-reperfusion model, and cortical glutathione levels were increased in NRF2 wild-type but not KO mice after administration of tBHQ (Shih, A.Y.,et al. 2005. *J. Neurosci.* 25: 10321–10335). Tecfidera™ (dimethyl fumarate), which activates NRF2 among other targets, is approved in the U.S. to treat relapsing-remitting multiple sclerosis (MS). Activation of NRF2 may also help treat cases of Friedreich's Ataxia, where increased sensitivity to oxidative stress and impaired NRF2 activation has been reported (Paupe V., et al, 2009. PLoS One; 4(1):e4253. Omaveloxolone (RTA-408) is also in clinical trials for Friedreich's Ataxia.

There is preclinical evidence of the specific protective role of the NRF2 pathway in models of inflammatory bowel disease (IBD, Crohn's Disease and Ulcerative Colitis) and/or colon cancer (Khor, T.O., et al 2008. *Cancer Prev. Res. (Phila)* 1:187-191).

Age-related macular degeneration (AMD) is a common cause of vision loss in people over the age of 50. Cigarette smoking is a major risk factor for the development of non-neovascular (dry) AMD and perhaps also neovascular (wet) AMD. Findings *in vitro* and in preclinical species support the notion that the NRF2 pathway is involved in the anti-oxidant response of retinal epithelial cells and modulation of inflammation in pre-clinical models of eye injury (Schimel, et al. 2011. *Am. J. Pathol.* 178:2032-2043). Fuchs Endothelial Corneal Dystrophy (FECD) is a progressive, blinding disease characterized by corneal endothelial cells apoptosis. It is a disease of aging and increased oxidative stress related to low levels of NRF2 expression and/or function (Bitar, M.S., et al. 2012. *Invest Ophthalmol. Vis. Sci.* August 24, 2012 vol. 53 no. 9 5806-5813). In addition, an NRF2 activator may be useful in uveitis or other inflammatory eye condtions.

Non-alcoholic steatohepatitis (NASH) is a disease of fat deposition, inflammation, and damage in the liver that occurs in patients who drink little or no alcohol. In pre-clinical models, development of NASH is greatly accelerated in KO mice lacking NRF2 when challenged with a methionine- and choline-deficient diet (Chowdhry S., et al. 2010. *Free Rad. Biol. & Med.* 48:357-371). Administration of the NRF2 activators oltipraz and NK-252 in rats on a choline-deficient L-amino acid-defined diet significantly attenuated progression of histologic abnormalities, especially hepatic fibrosis (Shimozono R. et al. 2012. *Molecular Pharmacology*. 84:62-70). Other liver diseases that may be amenable to NRF2 modulation are toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, and cirrhosis (Oxidative Medicine and Cellular Longevity Volume 2013 (2013), Article ID 763257, 9 page).

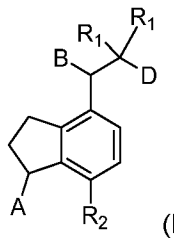
Recent studies have also begun to elucidate the role of ROS in skin diseases such as psoriasis. A study in psoriasis patients showed an increase in serum malondialdehyde and nitric oxide end products and a decrease in erythrocyte-superoxide dismutase activity, catalase activity, and total antioxidant status that correlated in each case with disease severity index (Dipali P.K., et al. Indian J Clin Biochem. 2010 October; 25(4): 388–392). Also, an NRF2 activator may be useful in treating the dermatitis/topical effects of radiation (Schäfer, M. et al. 2010. *Genes & Devl.* 24:1045-1058), and the immunosuppression due to radiation exposure (Kim, J.H. et al., J. Clin. Invest. 2014 Feb 3; 124(2):730-41).

There are also data suggesting that an NRF2 activator may be beneficial in preeclampsia, a disease that occurs in 2-5% of pregnancies and involves hypertension and proteinuria (Annals of Anatomy - Anatomischer Anzeiger Volume 196, Issue 5, September 2014, Pages 268–277).

Preclinical data has shown that compounds with NRF2 activating activity are better at reversing high altitude-induced damage than compounds without NRF2 activity, using animal and cellular models of Acute Mountain Sickness (Lisk C. et al, 2013, Free Radic Biol Med. Oct 2013; 63: 264–273.)

SUMMARY OF THE INVENTION

In one aspect, this invention provides for indane analogs, or a salt, particularly a pharmaceutically acceptable salt thereof, and pharmaceutical compositions containing them. In particular, the compounds of this invention include a compound of Formula (I):



(I)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C_{1-3}alkyl, -O-C_{1-3}alkyl,
-CN, -$(CH_2)_2$–O–$(CH_2)_2$-OR_3 and halo;

D is –C(O)OH, -C(O)NR_3R_4, -C(O)$NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -$(CH_2)_n$-O-$(CH_2)_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –C(O) or one –$S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-7}heterocycloalkyl, -(CH_2)phenyl, halogen, -NR_3R_5, -CHF_2, -CF_3, and -$(CH_2)_n$-O-$(CH_2)_m$-CH_3;

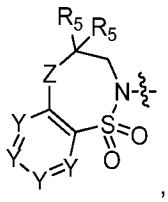
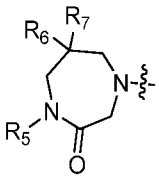
A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl,

tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from -C_{1-3}alkyl, -C_{3-6}spirocycloalkyl, halo, -CN, -O-C_{1-3}alkyl, -CH_2-O-CH_3, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from -C_{1-3}alkyl and –C_{3-7}cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from -C_{1-3} alkyl and -O-C_{1-3} alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

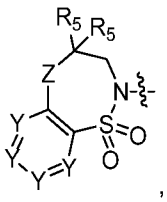
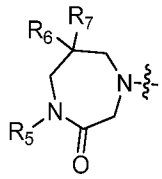
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -OMe,
-$C(O)NH_2$, -OCF_3 and -C_{1-4}alkylNR_7R_8;

R_8 is -C_{1-3}alkyl, aryl, heteroaryl, -C(O)C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl,
-C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl, wherein each of -C_{1-3}alkyl, aryl, heteroaryl, -C(O)C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl, -C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, -CF_3, -OCF_3,
-OCH_3, -C_{1-3}alkyl, -OC_{1-3}alkyl, -OC_{3-7}cycloalkyl, -OC_{3-7}hetercycloalkyl, -O-aryl and –O-heteroaryl;

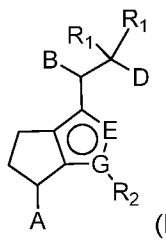
R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, C(O)R_6;

m is 0, 1 or 2; and

n is 1 or 2; or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides for indane analogs, or a salt, particularly a pharmaceutically acceptable salt thereof, and pharmaceutical compositions containing them. In particular, the compounds of this invention include a compound of Formula (II):



(II)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C_{1-3}alkyl, -O-C_{1-3}alkyl,
-CN, -$(CH_2)_2$–O–$(CH_2)_2$-OR_3 and halo;

D is –C(O)OH, -C(O)NR_3R_4, -C(O)$NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -$(CH_2)_n$-O-$(CH_2)_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –C(O) or one –$S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-7}heterocycloalkyl, -(CH_2)phenyl, halogen, -NR_3R_5, -CHF_2, -CF_3, and -$(CH_2)_n$-O-$(CH_2)_m$-CH_3;

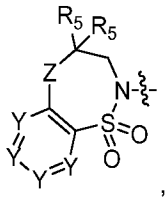
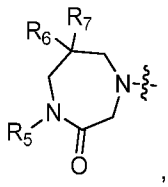
A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1,

2, or 3 substituents independently selected from -C_{1-3}alkyl, -C_{3-6}spirocycloalkyl, halo, -CN, -O-C_{1-3}alkyl, -CH_2-O-CH_3, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from -C_{1-3}alkyl and –C_{3-7}cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from -C_{1-3} alkyl and -O-C_{1-3} alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

E is independently S, O, N;

G is independently C, N;

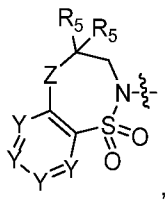
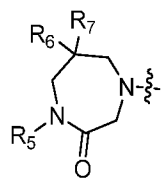
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -

OMe,
$-C(O)NH_2$, $-OCF_3$ and $-C_{1-4}alkylNR_7R_8$;

R_8 is $-C_{1-3}alkyl$, aryl, heteroaryl, $-C(O)C_{1-3}alkyl$, $-SO_2C_{1-3}alkyl$, -C(O)aryl, -C(O)heteroaryl, $-SO_2$aryl, $-SO_2$heteroaryl, $-C_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}heterocycloalkyl$,
$-C_{1-3}alkyl$-heteroaryl or $-C_{1-3}alkyl$-aryl, wherein each of $-C_{1-3}alkyl$, aryl, heteroaryl, $-C(O)C_{1-3}alkyl$, $-SO_2C_{1-3}alkyl$, -C(O)aryl, -C(O)heteroaryl, $-SO_2$aryl, $-SO_2$heteroaryl, $-C_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}heterocycloalkyl$, $-C_{1-3}alkyl$-heteroaryl or $-C_{1-3}alkyl$-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, $-CF_3$, $-OCF_3$,
$-OCH_3$, $-C_{1-3}alkyl$, $-OC_{1-3}alkyl$, $-OC_{3-7}cycloalkyl$, $-OC_{3-7}hetercycloalkyl$, -O-aryl and –O-heteroaryl;

R_9 is hydrogen, $-C_{1-5}alkyl$ or $–(CH_2)_m$-$C_{3-5}cycloalkyl$;

R_{10} is H, SO_2R_6, $C(O)R_6$;

m is 0, 1 or 2; and

n is 1 or 2; or a pharmaceutically acceptable salt thereof.

In a third aspect, this invention provides for the use of a compound of Formula (I) or Formula (II) as an NRF2 activator.

Accordingly, the present invention is also directed to a method of regulating NRF2 which method comprises contacting a cell with a compound according to Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt, thereof.

In another aspect, this invention provides for the use of the compounds of Formula (I) or Formula (II) for treating and/or preventing conditions associated with NRF2 imbalance.

In one aspect, the invention is provides a pharmaceutical composition comprising a compound of the invention according to Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Particularly, this invention is directed to a pharmaceutical composition for the treatment of an NRF2 regulated disease or disorder, wherein the composition comprises a compound according to Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In a further aspect, this invention provides for a method of treating a respiratory or non-respiratory disorder, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disesase (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness, which comprises administering to a human in need thereof, a compound of Formula (I) or Formula (II).

In one aspect, this invention relates to a method of treating COPD, which comprises administering to a human in need thereof, a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof.

In one aspect, this invention relates to a method of treating heart failure, which comprises administering to a human in need thereof, a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof.

In yet another aspect, this invention provides for the use of a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, for the treatment of a respiratory or non-respiratory disorder, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute

kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disesase (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

In one aspect, this invention relates to the use of a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, for the treatment of COPD.

In one aspect, this invention relates to the use of a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, for the treatment of heart failure.

In a further aspect, this invention relates to use of a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a respiratory or non-respiratory disorder, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disesase (HD), spinal cord injury, traumatic brain injury,

ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

In one aspect, this invention relates to use of a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of COPD.

In one aspect, this invention relates to use of a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of heart failure.

In a further aspect, this invention relates to a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, for use in medical therapy.This invention relates to a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, for use in therapy, specifically for use in the treatment of a respiratory or non-respiratory disorder, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disesase (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis,

cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

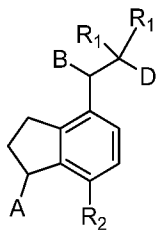
In one aspect, this invention relates to a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, for use in the treatment of COPD.

In one aspect, this invention relates to a compound of Formula (I) or Formula (II), or a salt, particularly a pharmaceutically acceptable salt thereof, for use in the treatment of heart failure.

Other aspects and advantages of the present invention are described further in the following detailed description of the embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



(I)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C_{1-3}alkyl, -O-C_{1-3}alkyl,
-CN, -$(CH_2)_2$–O–$(CH_2)_2$-OR_3 and halo;

D is –C(O)OH, -$C(O)NR_3R_4$, -$C(O)NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -$(CH_2)_n$-O-$(CH_2)_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –C(O) or one –$S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-7}heterocycloalkyl, -(CH_2)phenyl, halogen, -NR_3R_5, -CHF_2, -CF_3, and -$(CH_2)_n$-O-$(CH_2)_m$-CH_3;

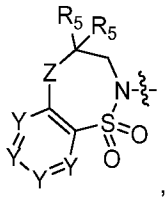
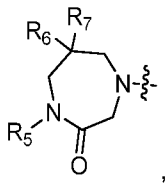
A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1,

2, or 3 substituents independently selected from -C_{1-3}alkyl, -C_{3-6}spirocycloalkyl, halo, -CN, -O-C_{1-3}alkyl, -CH_2-O-CH_3, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from -C_{1-3}alkyl and –C_{3-7}cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from -C_{1-3} alkyl and -O-C_{1-3} alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

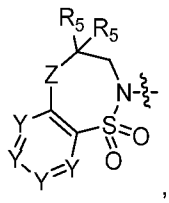
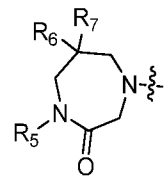
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -OMe,

-$C(O)NH_2$, -OCF_3 and -C_{1-4}alkylNR_7R_8;

R_8 is -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-}

$_7$heterocycloalkyl,

-C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl, wherein each of -C_{1-3}alkyl, aryl, heteroaryl, -C(O)C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl, -C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, -CF_3, -OCF_3,

-OCH_3, -C_{1-3}alkyl, -OC_{1-3}alkyl, -OC_{3-7}cycloalkyl, -OC_{3-7}hetercycloalkyl, -O-aryl and –O-heteroaryl;

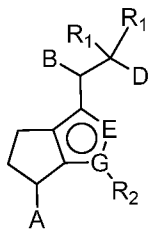
R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, C(O)R_6;

m is 0, 1 or 2; and

n is 1 or 2; or a pharmaceutically acceptable salt thereof.

The present invention provides for compounds of Formula (II):



(II)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C $_{1-3}$alkyl, -O-C_{1-3}alkyl,

-CN, -$(CH_2)_2$–O–$(CH_2)_2$-OR_3 and halo;

D is –C(O)OH, -C(O)NR_3R_4, -C(O)$NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -$(CH_2)_n$-O-$(CH_2)_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

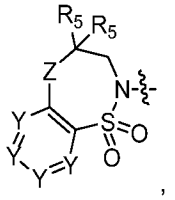
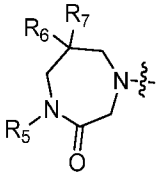
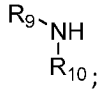
or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –C(O) or one –$S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-7}heterocycloalkyl, -(CH_2)phenyl, halogen, -NR_3R_5, -CHF_2, -CF_3, and -$(CH_2)_n$-O-$(CH_2)_m$-CH_3;

A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from -C_{1-3}alkyl, -C_{3-6}spirocycloalkyl, halo, -CN, -O-C_{1-3}alkyl, -CH_2-O-CH_3, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from -C_{1-3}alkyl and –C_{3-7}cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from -C_{1-3} alkyl and -O-C_{1-3} alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

E is independently S, O, N

G is independently C, N

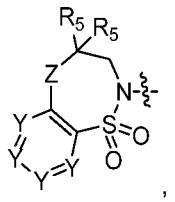
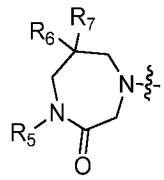
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -OMe,
-$C(O)NH_2$, -OCF_3 and -C_{1-4}alkylNR_7R_8;

R_8 is -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl,
-C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl, wherein each of -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-}$

$_3$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl, -C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, -CF_3, -OCF_3,
-OCH_3, -C_{1-3}alkyl, -OC_{1-3}alkyl, -OC_{3-7}cycloalkyl, -OC_{3-7}hetercycloalkyl, -O-aryl and –O-heteroaryl;

R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, C(O)R_6;

m is 0, 1 or 2; and

n is 1 or 2; or a pharmaceutically acceptable salt thereof.

"Alkyl" refers to a monovalent saturated hydrocarbon chain having the specified number of carbon member atoms. For example, C_{1-4} alkyl refers to an alkyl group having from 1 to 4 carbon member atoms. Alkyl groups may be straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl includes methyl, ethyl, propyl, (*n*-propyl and isopropyl), butyl (*n*-butyl, isobutyl, s-butyl, and t-butyl), pentyl (n-pentyl, tert-pentyl, iso-pentyl), and hexyl (n-hexyl, isohexyl, ter-hexyl).

"Cycloalkyl" refers to a monovalent saturated or unsaturated hydrocarbon ring having the specified number of carbon member atoms. For example, C_{3-7}cycloalkyl refers to a cycloalkyl group having from 3- to 7-carbon member atoms, unless otherwise limited. Unsaturated cycloalkyl groups have one or more carbon-carbon double bonds within the ring. Cycloalkyl groups are not aromatic. Cycloalkyl includes cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, and cyclohexenyl.

"C_{3-8}heterocycloalkyl" refers to a 3- to 8-membered ring, unless otherwise limited, containing from 1 to 4 heteroatoms, generally 1 or 2 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Examples are azetidine, thietane, thietane 1-oxide, thietane 1,1-dioxide, tetrahydrofuran, pyrrolidine, tetrahydrothiophene, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1, 2-dioxide, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran 1-oxide, tetrahydrothiopyran 1-1 dioxide, piperidine-2-one, azepan-2-one, pyrrolidin-2-one, azepane, oxepane, oxazepane, thiepane, thiepane 1-oxide, thiepane 1,1-dioxide, and thiazepane.

A heterocyclic group is a cyclic group having, as ring members, atoms of at least two different elements, which cyclic group may be saturated, partially unsaturated (non-aromatic) or fully unsaturated (aromatic). The terms "heterocyclic" or “heterocyclyl” includes heterocycloalkyl and heteroaryl groups. It is to be understood that the terms heterocyclic, heterocyclyl, heteroaryl, and heterocycloalkyl, are intended to encompass stable groups where a ring nitrogen heteroatom is optionally oxidized (e.g., heteroaryl groups containing an N-oxide, such as oxo-pyridyl (pyridyl-N-oxide) and oxo-oxadiazolyl (oxo-4,5-dihydro-1,3,4-oxadiazolyl) or where a ring sulfur heteroatom is optionally oxidized (e.g., heterocycloalkyl groups containing sulfones or sulfoxide moieties, such as tetrahydrothienyl-1-oxide (tetrahydrothienyl sulfoxide, tetrahydrothiophenyl sulfoxide) and tetrahydrothienyl-1,1-dioxide (tetrahydrothienyl sulfone)).

"Aryl" refers to a group or moiety comprising an aromatic, monocyclic or bicyclic hydrocarbon radical containing from 6- to 10-carbon ring atoms and having at least one aromatic ring. Examples of "aryl" groups are phenyl, naphthyl, indenyl, and dihydroindenyl (indanyl). Generally, in the compounds of this invention, aryl is phenyl.

"Heteroaryl" represents a group or moiety comprising an aromatic monocyclic or bicyclic radical, containing 5- to 10-ring atoms, including 1- to 4-heteroatoms independently selected from nitrogen, oxygen and sulfur. This term also encompasses bicyclic heterocyclic-aryl groups containing either an aryl ring moiety fused to a heterocycloalkyl ring moiety or a heteroaryl ring moiety fused to a cycloalkyl ring moiety.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine, and fluoro, chloro, bromo, and iodo, respectively.

"Substituted" in reference to a group indicates that one or more hydrogen atom attached to a member atom within the group is replaced with a substituent selected from the group of defined substituents. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with the permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound (i.e., one that does not spontaneously undergo transformation such as by rearrangement, cyclization, or elimination and that is sufficiently robust to survive isolation from a reaction mixture). When it is stated that a group may contain one or more substituents, one or more (as appropriate) member atoms within the group may be substituted. In addition, a single member atom within the group may be substituted with more than one substituent as long as such substitution is in accordance with the permitted

valence of the atom. Suitable substituents are defined herein for each substituted or optionally substituted group.

The term "independently" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different. That is, each substituent is separately selected from the entire group of recited possible substituents.

The invention also includes various isomers of the compounds of Formula (I) and mixtures thereof. "Isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers). The compounds according to Formula (I) contain one or more asymmetric centers, also referred to as chiral centers, and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. All such isomeric forms are included within the present invention, including mixtures thereof.

Chiral centers may also be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral center present in Formula (I), or in any chemical structure illustrated herein, is not specified the structure is intended to encompass any stereoisomer and all mixtures thereof. Thus, compounds according to Formula (I) containing one or more chiral centers may be used as racemic mixtures, enantiomerically enriched mixtures, or as enantiomerically pure individual stereoisomers.

Individual stereoisomers of a compound according to Formula (I) which contain one or more asymmetric centers may be resolved by methods known to those skilled in the art. For example, such resolution may be carried out (1) by formation of diastereoisomeric salts, complexes or other derivatives; (2) by selective reaction with a stereoisomer-specific reagent, for example by enzymatic oxidation or reduction; or (3) by gas-liquid or liquid chromatography in a chiral environment, for example, on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. The skilled artisan will appreciate that where the desired stereoisomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired form. Alternatively, specific stereoisomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

For compounds falling within the scope of the invention, the structural conventions used in the Examples are as follows: (a) absolute stereochemistry is defined by the structure; (b) when annotated by "or", then stereochemistry is unknown but resolved; and (c) when annotated by "&" or "and", then stereochemistry is relative, but racemic.

It is to be understood that the references herein to a compound of Formula (I) or Formula (II) or a salt thereof includes a compound of Formula (I) or Formula (II) as a free base [or acid, as appropriate], or as a salt thereof, for example as a pharmaceutically acceptable salt thereof. Thus, in one embodiment, the invention is directed to a compound of Formula (I) or Formula (II). In another embodiment, the invention is directed to a salt of a compound of Formula (I) or Formula (II). In a further embodiment, the invention is directed to a pharmaceutically acceptable salt of a compound of Formula (I) or Formula (II). In another embodiment, the invention is directed to a compound of Formula (I) or Formula (II) or a salt thereof. In a further embodiment, the invention is directed to a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof.

If a compound of Formula (I) or Formula (II) has both a basic amine group and a carboxylic acid group and can consequently be in the form of a zwitterion, also known as an inner salt. Therefore, in an embodiment the compound of Formula (I) or Formula (II) is in a zwitterion form.

As used herein, "pharmaceutically acceptable" refers to those compounds (including salts), materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts include, amongst others, those described in Berge, J. Pharm. Sci., 1977, 66, 1-19, or those listed in P H Stahl and C G Wermuth, editors, *Handbook of Pharmaceutical Salts; Properties, Selection and Use, Second Edition* Stahl/Wermuth: Wiley- VCH/VHCA, 2011 (see http://www.wiley.com/WileyCDA/WileyTitle/productCd-3906390519.html).

The skilled artisan will appreciate that pharmaceutically acceptable salts of the compounds according to Formula (I) or Formula (II) may be prepared. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately treating the purified compound in its free acid or free base form with a suitable base or acid, respectively.

It will be understood that if a compound of Formula (I) or Formula (II) contains two or more basic moieties, the stoichiometry of salt formation may include 1, 2 or more equivalents of acid. Such salts would contain 1, 2 or more acid counterions, for example, a dihydrochloride salt.

Stoichiometric and non-stoichiometric forms of a pharmaceutically acceptable salt of a compound of Formula (I) or Formula (II) are included within the scope of the invention, including sub-stoichiometric salts, for example where a counterion contains more than one acidic proton.

Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate), caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate, glycerophosphorate, glycolate, hexylresorcinate, hippurate, hydrabamine (*N*,*N*′-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, *p*-aminobenzenesulfonate, *p*-aminosalicyclate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N*,*N*'-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chloroprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolildine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron,

isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

As used herein, the term “a compound of Formula (I) or Formula (II)” or “the compound of Formula (I) or Formula (II)” refers to one or more compounds according to Formula (I) or Formula (II). The compound of Formula (I) or Formula (II) may exist in solid or liquid form. In the solid state, it may exist in crystalline or noncrystalline form, or as a mixture thereof. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed from crystalline compounds wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve non-aqueous solvents such as, but not limited to, ethanol, isopropanol, DMSO, acetic acid, ethanolamine, or ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

The skilled artisan will further appreciate that certain compounds of the invention that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e., the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." The invention includes all such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

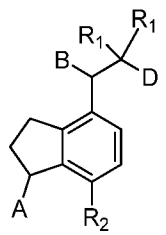
The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula (I) or Formula (II) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that

can be incorporated into compounds of the invention and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I.

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of Formula (I) or Formula (II) and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Representative Embodiments

In one embodiment, the compound of Formula (I) is:



(I)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl is

unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C_{1-3}alkyl, -O-C_{1-3}alkyl, -CN, -$(CH_2)_2$–O–$(CH_2)_2$-OR_3 and halo;

D is –C(O)OH, -C(O)NR_3R_4, -C(O)$NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -$(CH_2)_n$-O-$(CH_2)_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

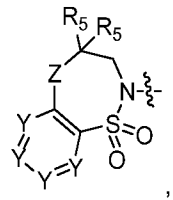
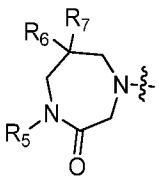
or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –C(O) or one –$S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-7}heterocycloalkyl, -(CH_2)phenyl, halogen, -NR_3R_5, -CHF_2, -CF_3, and -$(CH_2)_n$-O-$(CH_2)_m$-CH_3;

A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from -C_{1-3}alkyl, -C_{3-6}spirocycloalkyl, halo, -CN, -O-C_{1-3}alkyl, -CH_2-O-CH_3, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from -C_{1-3}alkyl and –C_{3-7}cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from -C_{1-3} alkyl and -O-C_{1-3} alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

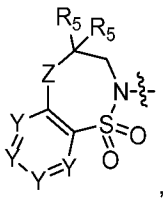
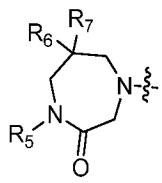
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -

OMe,
$-C(O)NH_2$, $-OCF_3$ and $-C_{1-4}alkylNR_7R_8$;

R_8 is $-C_{1-3}alkyl$, aryl, heteroaryl, $-C(O)C_{1-3}alkyl$, $-SO_2C_{1-3}alkyl$, -C(O)aryl, -C(O)heteroaryl, $-SO_2$aryl, $-SO_2$heteroaryl, $-C_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}heterocycloalkyl$,
$-C_{1-3}alkyl$-heteroaryl or $-C_{1-3}alkyl$-aryl, wherein each of $-C_{1-3}alkyl$, aryl, heteroaryl, $-C(O)C_{1-3}alkyl$, $-SO_2C_{1-3}alkyl$, -C(O)aryl, -C(O)heteroaryl, $-SO_2$aryl, $-SO_2$heteroaryl, $-C_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}cycloalkyl$, $-C_{1-3}alkylC_{3-7}heterocycloalkyl$, $-C_{1-3}alkyl$-heteroaryl or $-C_{1-3}alkyl$-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, $-CF_3$, $-OCF_3$,
$-OCH_3$, $-C_{1-3}alkyl$, $-OC_{1-3}alkyl$, $-OC_{3-7}cycloalkyl$, $-OC_{3-7}hetercycloalkyl$, -O-aryl and –O-heteroaryl;

R_9 is hydrogen, $-C_{1-5}alkyl$ or $–(CH_2)_m-C_{3-5}cycloalkyl$;

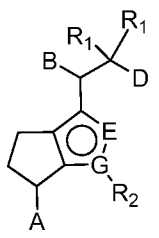
R_{10} is H, SO_2R_6, $C(O)R_6$;

m is 0, 1 or 2; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound of Formula (II) is:



(II)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, $-O-(CH_2)$-triazolyl, or $-(CH_2)_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, $-O-(CH_2)$-triazolyl, or $-(CH_2)_2$-triazolyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from $–C_{1-3}alkyl$, $-O-C_{1-3}alkyl$,
-CN, $-(CH_2)_2–O–(CH_2)_2-OR_3$ and halo;

D is –C(O)OH, -C(O)NR_3R_4, -C(O)$NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -$(CH_2)_n$-O-$(CH_2)_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –C(O) or one –$S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-7}heterocycloalkyl, -(CH_2)phenyl, halogen, -NR_3R_5, -CHF_2, -CF_3, and -$(CH_2)_n$-O-$(CH_2)_m$-CH_3;

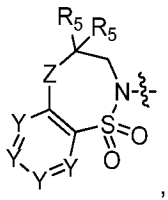
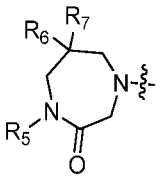
A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl,

tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from -C_{1-3}alkyl, -C_{3-6}spirocycloalkyl, halo, -CN, -O-C_{1-3}alkyl, -CH_2-O-CH_3, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from -C_{1-3}alkyl and –C_{3-7}cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from -C_{1-3} alkyl and -O-C_{1-3} alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

E is independently S, O, N;

G is independently C, N;

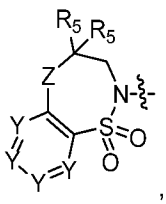
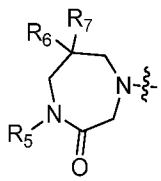
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -

OMe,
-C(O)NH_2, -OCF_3 and -C_{1-4}alkylNR_7R_8;

R_8 is -C_{1-3}alkyl, aryl, heteroaryl, -C(O)C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl,
-C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl, wherein each of -C_{1-3}alkyl, aryl, heteroaryl, -C(O)C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl, -C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, -CF_3, -OCF_3,
-OCH_3, -C_{1-3}alkyl, -OC_{1-3}alkyl, -OC_{3-7}cycloalkyl, -OC_{3-7}hetercycloalkyl, -O-aryl and –O-heteroaryl;

R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, C(O)R_6;

m is 0, 1 or 2; and

n is 1 or 2; or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound of Formula (I) is substituted as follows:

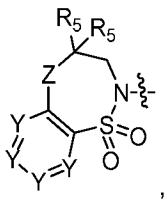
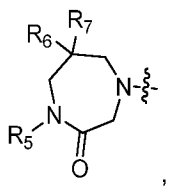
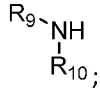
B is benzotriazolyl which is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C $_{1-3}$alkyl, -O-C_{1-3}alkyl, -CN, -$(CH_2)_2$–O–$(CH_2)_2$-OR_3 and halo;

D is –C(O)OH;

R_1 is independently hydrogen or -C_{1-3}alkyl;

R_2 is hydrogen or methyl;

R_3 is hydrogen or -C_{1-3}alkyl;

A is  , or  , or  ;

Y is independently selected from N or CH;

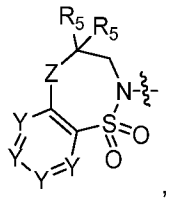
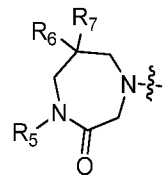
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -OMe,
-$C(O)NH_2$, -OCF_3 and -C_{1-4}alkylNR_7R_8;

R_8 is -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl,
-C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl, wherein each of -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl, -C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, -CF_3, -OCF_3,
-OCH_3, -C_{1-3}alkyl, -OC_{1-3}alkyl, -OC_{3-7}cycloalkyl, -OC_{3-7}hetercycloalkyl, -O-aryl and
–O-heteroaryl;

R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, $C(O)R_6$; and

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

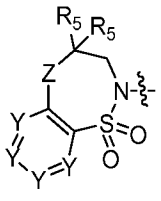
In yet another embodiment, the compound of Formula (I) is substituted as follows:

B is benzotriazolyl which is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C $_{1\text{-}3}$alkyl and -O-$C_{1\text{-}3}$alkyl;

D is –C(O)OH;

R_1 is independently hydrogen or -$C_{1\text{-}3}$alkyl;

R_2 is hydrogen or methyl;

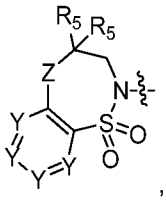
A is  , or  ;

Y is independently selected from N or CH;

Z is CH_2;

R_5 is hydrogen;

R_6 is hydrogen, -$C_{1\text{-}5}$alkyl or –$(CH_2)_m$-$C_{3\text{-}5}$cycloalkyl;

and, wherein when A is  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3 and -$C_{1\text{-}4}$alkyl;

R_9 is hydrogen, -$C_{1\text{-}5}$alkyl or –$(CH_2)_m$-$C_{3\text{-}5}$cycloalkyl;

R_{10} is H, SO_2R_6, $C(O)R_6$; and

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

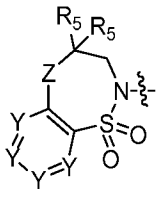
In still a further embodiment, the compound of Formula (I) is substituted as follows:

B is benzotriazolyl which is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from methyl and -O-CH_3;

D is –C(O)OH;

R_1 is independently hydrogen;

R_2 is methyl;

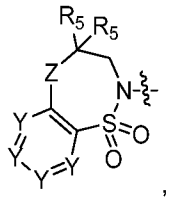
A is  , or  ;

Y is independently selected from N or CH;

Z is CH_2;

R_5 is hydrogen;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

and, wherein when A is  , it is unsubstituted or substituted with one, two or three substituents independently selected from fluoro, -CF_3 and methyl;

R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, $C(O)R_6$; and

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

It is to be understood that the present invention covers all combinations of the embodiments and particular groups described hereinabove.

Specific examples of compounds of the present invention include the following:

3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid – Stereoisomer 1;

3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid – Stereoisomer 2;

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)propanoic acid;

3-(1-(N-(cyclohexylmethyl)methylsulfonamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid;

3-(1-(N-(cyclohexylmethyl)acetamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid, ethyl acetate solvate;

3-(1-((cyclohexylmethyl)amino)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid;

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylmethylsulfonamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid; and

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylcyclohexanecarboxamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid;

or a pharmaceutically acceptable salt thereof.

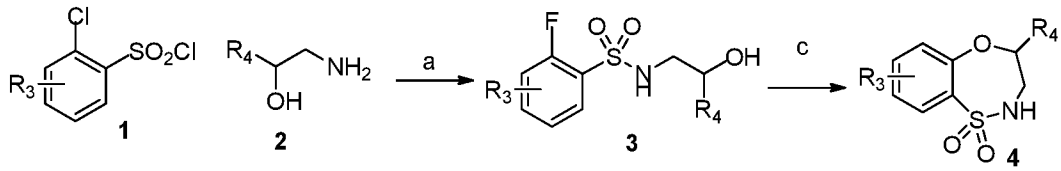
Compound Preparation

The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999). In some

instances, a substituent may be specifically selected to be reactive under the reaction conditions used. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound or is a desired substituent in a target compound.

The synthesis of the compounds of the general Formula (I) and Formula (II) and pharmaceutically acceptable derivatives and salts thereof may be accomplished as outlined below in Schemes 1-47. In the following description, the groups are as defined above for compounds of Formula (I) and Formula (II) unless otherwise indicated. Abbreviations are as defined in the Examples section. Starting materials are commercially available or are made from commercially available starting materials using methods known to those skilled in the art.

Scheme 1



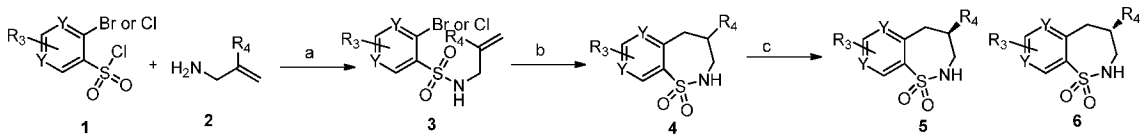
R4 = (R) ethyl, or di-methyl

Conditions: a) K_2CO_3, THF/H_2O; b) t-BuOK, DMSO

Scheme **1** represents a general scheme for the preparation of sulfonamide **4**. In this, amino alcohol **2** and substituted 2-cholorobenzene-1-sulfonyl chloride depicted as starting material are commercially available or may be synthesized from readily available materials. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Sulfonamide formation under basic condition with appropriate amino alcohol and commercially available 2-chloro-pyridine-3-sulfonyl chloride to give intermediate **3**, followed by displacement of choloride with potassium tert-butoxide provides the required intermediate **4**.

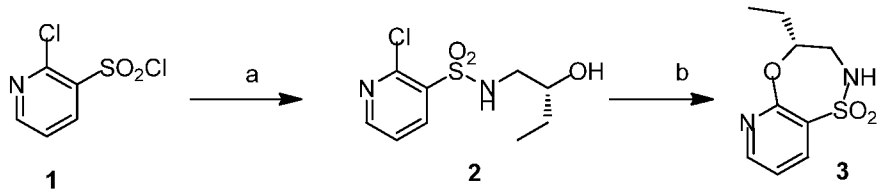
Scheme 2



Conditions: a) Et_3N, DCM; b) AIBN, Bu_3SnH, toluene; c) Chiral SFC

Scheme **2** represents a general scheme for the preparation of compounds according to Formula (I). Substituted 2-bromo or chloro benzene-sulfonyl chloride **1** is either commercially available or may be synthesized from readily available materials. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Sulfonamides formation with appropriate amine **2** and sulfonyl chloride **1** to give compound **3**, followed by radical cyclization with AIBN to yield compound **4**. Compound **4** is then resolved by Chiral SFC to give single isomer **5** and **6**.

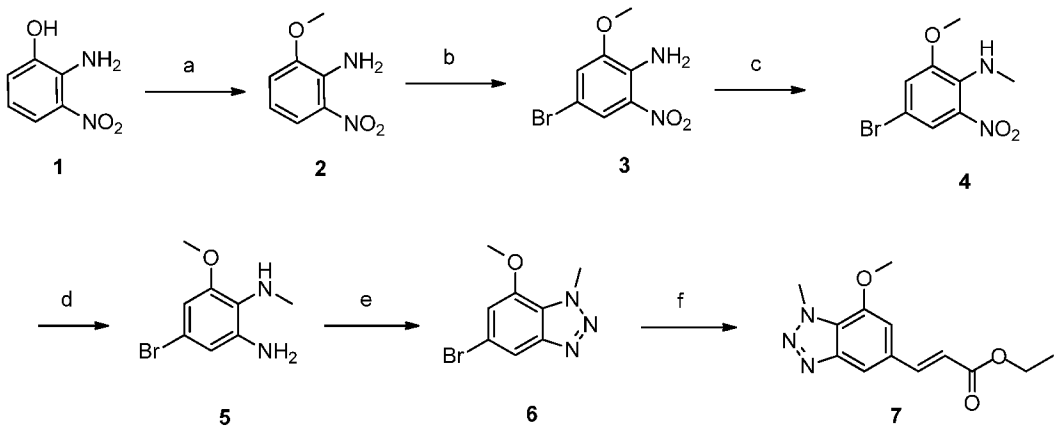
Scheme 3



Conditions: a) (R)-$H_2NCH_2CH(Et)OH$, K_2CO_3, THF/H_2O; b) t-BuOK, DMSO

Scheme **3** represents a general scheme for the preparation of (R)-4-ethyl-3,4-dihydro-2H-pyrido[2,3-b][1,4,5]oxathiazepine 1,1-dioxide, used in the invention. In this, the 2-chloropyridine-3-sulfonyl chloride depicted as starting material is commercially available. Reaction with the appropriate amino alcohol followed by displacement of the chloride with a base provides the required intermediate **3**.

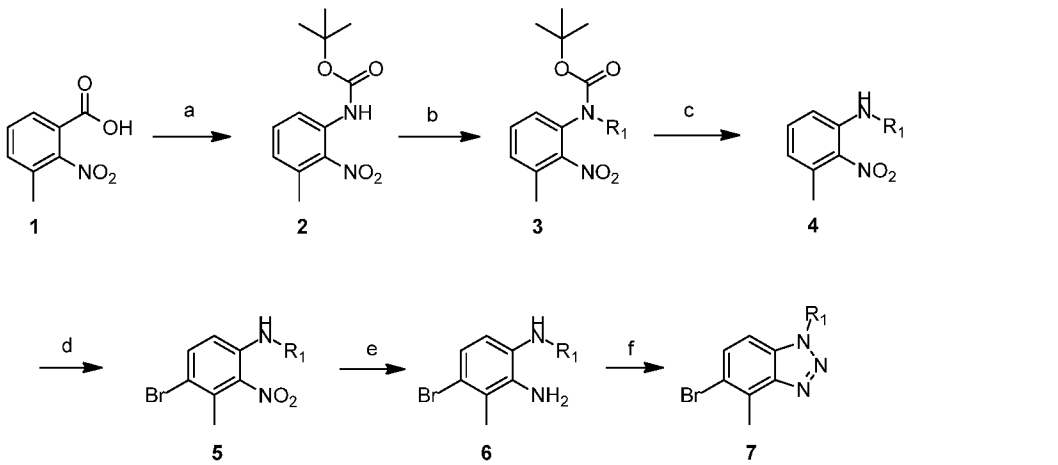
Scheme 4



Conditions: a) K_2CO_3, MeI, DMF; b) Br_2, acetic acid; c) NaH, MeI, DMF; d) Zinc, acetic acid; e) $NaNO_2$, H_2SO_4; f) Ethyl acrylate, $Pd(OAc)_2$, DIEA, DMF.

Scheme **4** shows a general scheme for the preparation of 5-bromo-7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazole. Starting with commercially available 2-amino-3-nitrophenol, methylation of the phenol using K_2CO_3 and MeI (step a) provides intermediate **2** which can be brominated with NBS (step c). Methylation of the aniline (step d) followed by reduction of the nitro group (step d) and diazotization and cyclization (step e) provide the required triazole **6**. This can be further elaborated to the requisite acrylate **7** via reaction with ethyl acrylate in the presence of palladium.

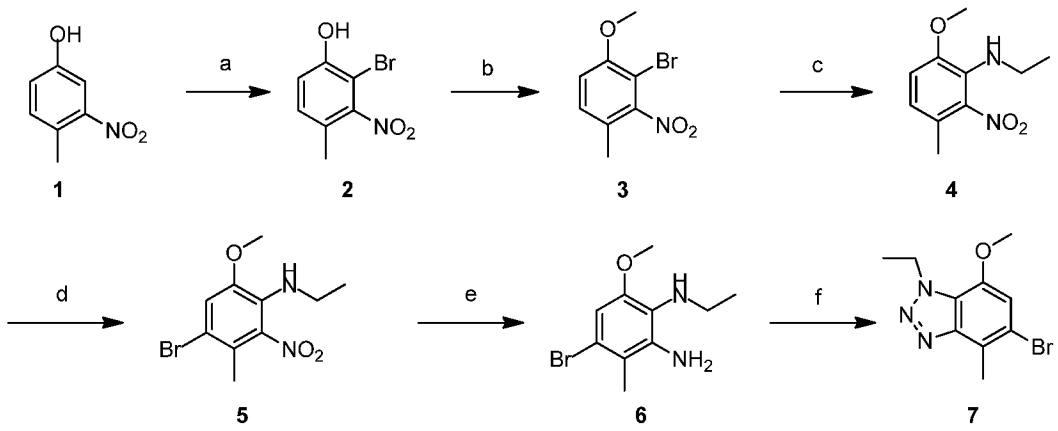
Scheme 5



Conditions: a) DPPA, TEA, t-BuOH; b) NaH, R_1I, DMF; c) TFA, DCM; d) NBS, DMF; e) $SnCl_2$-$2H_2O$, EtOH; f) $NaNO_2$, H_2SO_4

Scheme **5** shows an alternate general scheme for the preparation of 5-bromo-4-methyl-1-methyl-1H-benzo[d][1,2,3]triazole. In scheme **2**, R_1 is $C_{1\text{-}3}$alkyl or -$(CH_2)_2$–O–$(CH_2)_2$-OR_4. Starting with commercially available 3-methyl-2-nitrobenzoic acid, a Curtius rearrangement with DPPA provides intermediate **2**. A skilled artisan will appreciate that compound **2** could be prepared from the appropriate aniline compound. Alkylation of the carbamate with an alkyl iodide provides intermediate **3**. Deprotection of the amine with TFA and bromination with NBS provides intermediate **5.** Reduction of the nitro to the aniline and diazotization and cyclization provides the required triazole **7**.

Scheme 6

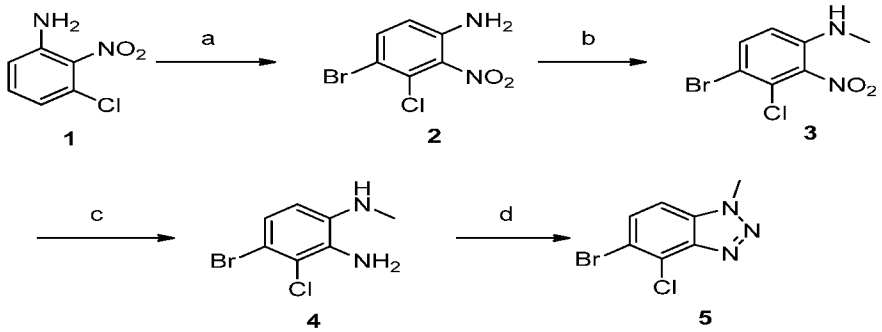


Conditions: a) Br_2, chloroform; b) K_2CO_3, MeI, acetone; c) Cu, ethanamine, DMSO; d) NBS, DMF; e) Ni, hydrazine, H_2O, EtOH/DCE; f) $NaNO_2$, H_2SO_4

Scheme **6** shows an general scheme for the preparation of 5-Bromo-1-ethyl-7-methoxy-4-methyl-1H-benzo[d][1,2,3]triazole. The triazole depicted as starting material is either commercially available or may be synthesized from readily available materials. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Bromination at C2 of the commercially available 4-methyl-3-nitrophenol **1** provides intermediate **2**. Methylation of the corresponding phenol **2** with MeI under basic condition to give intermediate **3**. It is then converted to ethyl amine under copper conditions to give intermediate **4**. Bromination at C5 with NBS to give intermediate **5**. Reductions with hydrazine hydrate catalyzed by Raney Nickel of **5** to yield aniline **6**. Diazotization and cyclization provides the required triazole **7**.

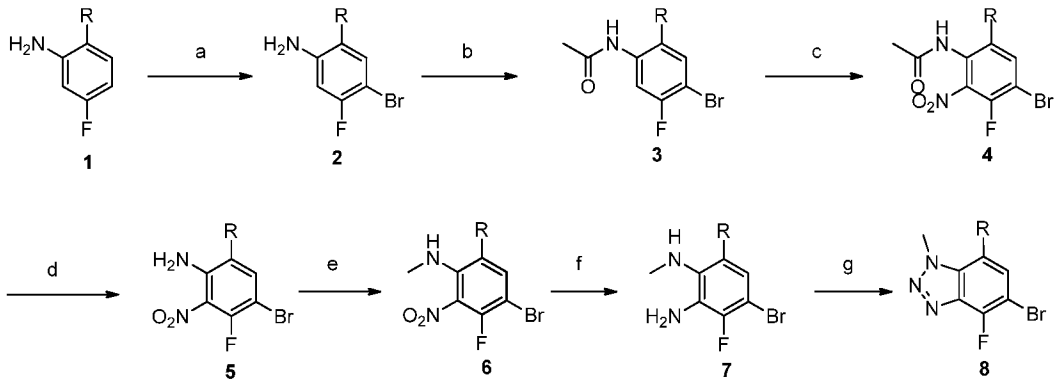
Scheme 7



Conditions: a) NBS, acetic acid; b) NaH, MeI, DMF; c) Zinc, acetic acid; d) $NaNO_2$, H_2SO_4

Scheme **7** shows a general scheme for the preparation of 5-bromo-4-chloro-1-methyl-1H-benzo[d][1,2,3]triazole. Starting with commercially available 3-chloro-2-nitroaniline, bromination with NBS provides intermediate **2**. Methylation of the aniline (step b) followed by reduction of the nitro group (step c) and diazotization and cyclization (step d) provides the required triazole **5**.

Scheme 8

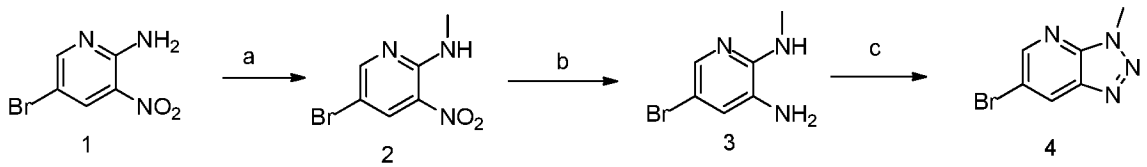


Conditions: a) NBS, DMF; b) acetic anhydride; c) HNO_3, H_2SO_4; d) HCl; e) NaH, MeI, DMF; f) Zinc, acetic acid; g) $NaNO_2$, H_2SO_4;

Scheme **8** represents a general scheme for the preparation of analogs containing 4-fluoro-1-methyl-1*H*-benzo[d][1,2,3]triazole or 4-fluoro-1,7-dimethyl-1*H*-benzo[d][1,2,3]triazole where R is hydrogen or methyl. Starting with commercially available 3-fluoroaniline or 5-fluoro-2-methylaniline, bromination can be accomplished via treatment with NBS. Protection of the aniline as the acetamide, nitration and removal of the acetyl group provides

intermediate **5**. Conversion to the requisite triazole **8** is achieved via methylation, reduction of the nitro group followed by diazotization and cyclization.

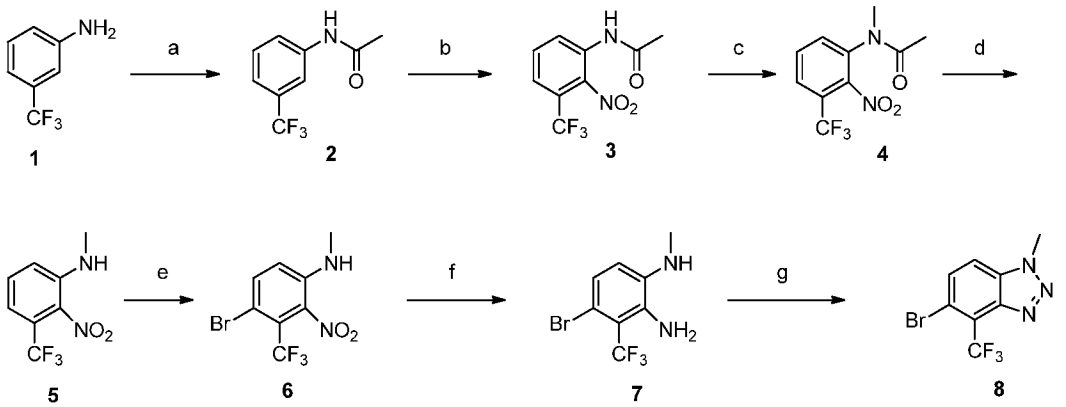
Scheme 9



Conditions: a) NaH, MeI, DMF; b) $TiCl_2$, EtOH; c) $NaNO_2$, H_2SO_4;

Scheme **9** represents a general scheme for the preparation of 3-methyl-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine. 5-bromo-3-nitropyridin-2-amine, which is commercially available, is methylated by deprotonation with sodium hydride followed by reaction with methyl iodide to afford intermediate **2**. The nitro group can be reduced using $TiCl_2$ and triazole formation accomplished via diazotization and cyclization to provide intermediate **4**.

Scheme 10

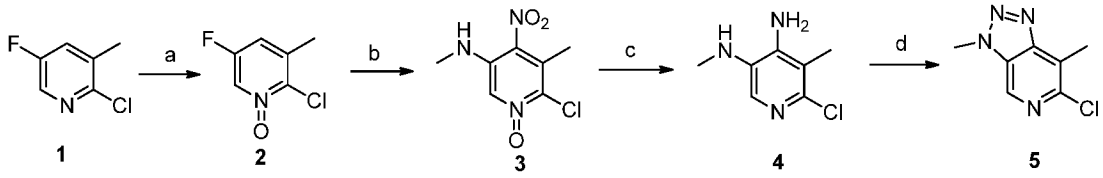


Conditions: a) acetic anhydride; b) HNO_3; c) NaH, MeI, DMF; d) NaOH, EtOH; e) NBS, DMF; f) Zinc, acetic acid; g) $NaNO_2$, H_2SO_4;

Scheme **10** represents a general scheme for the preparation of 5-bromo-1-methyl-4-(trifluoromethyl)-1H-benzo[d][1,2,3]triazole starting material. Starting with 3-(trifluoromethyl)aniline which is commercially available, acetylation of the aniline nitrogen provides acetamide **2**. A three step sequence involving nitration, methylation of the acetamide and deprotection provides intermediate **5**. This intermediate can be brominated

using NBS to provide **6**. Reduction of the nitro to the aniline followed by diazotization and cyclization gives the requisite triazole.

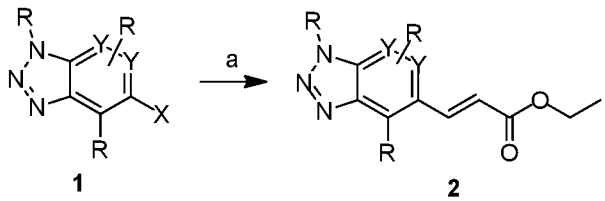
Scheme 11



Conditions: a) H_2O_2, TFA; b) (ii) KNO_3, H_2SO_4; (ii) CH_3NH_2; c) Ni, EtOH, 40 psi; d) $NaNO_2$, H_2SO_4

Scheme **11** shows a general scheme for the preparation of 6-chloro-3,7-dimethyl-3H-[1,2,3]triazolo[4,5-c]pyridine. Starting with commercially available 2-chloro-5-fluoro-3-methylpyridine, oxidation provides intermediate **2**. This is subsequently converted to nitro intermediate **3**. Displacement of the fluoride using an appropriate amine followed by nickl metal reduction of the nitro to the aniline yield **4**. Diazotization and cyclization provides the required triazole **5**.

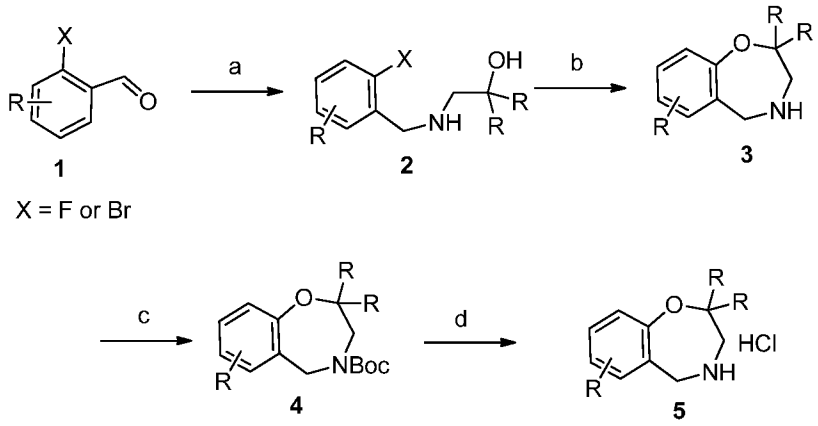
Scheme 12



Conditions: a) Ethyl acrylate, $Pd(OAc)_2$, DIEA, DMF

Scheme **12** represents a scheme for the preparation of the intermediate acrylate used in the preparation of compounds of Formula I. In this scheme, the starting material is prepared as described in other schemes. In this scheme, the R groups are the defined substituents for A in Formula I and II. Conversion to the acrylate can be accomplished via a Heck reaction using ethyl acrylate and $Pd(OAc)_2$. It will be appreciated by those skilled in the art that other reaction conditions may be employed to complete the preparation of **2**.

Scheme 13

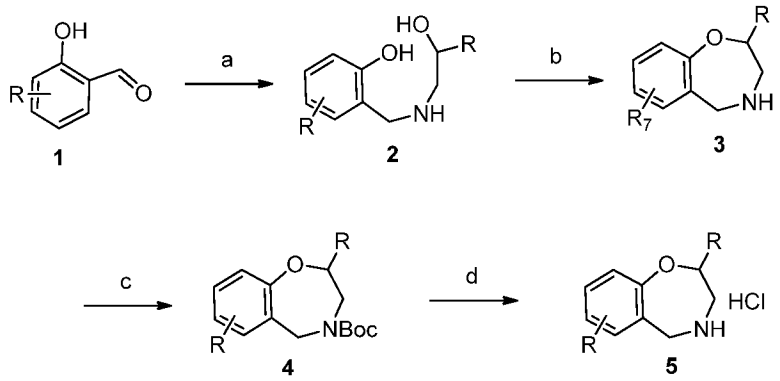


Conditions: a) $H_2NCH_2C(R_8)(R_9)OH$, $NaBH_4$, NaOH, MeOH; b) Cs_2CO_3, CuI, IPA; or KO_tBu, DMSO; c) Boc anhydride, Et_3N, THF; d) HCl, dioxane

Scheme **13** represents a general scheme for the preparation of 2-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines, and 2,2-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines used in the invention. In this scheme, the R group is the defined substituents for A in Formula I and II. Substituted 2-bromobenzaldehyde or substituted 2-fluorobenzaldehyde depicted as starting material are commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reductive amination of the starting aldehyde with the appropriate aminoalcohol followed by displacement of the bromide or fluoro provides the required intermediate **3**. This is then protected as the Boc carbamate to facilitate purification. It will be appreciated by the skilled artisan that alternative protecting groups may be used. Deprotection yields the requisite amine **5**.

Scheme 14

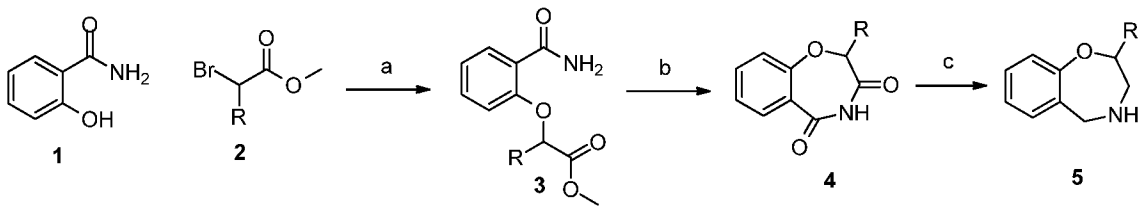


Conditions: a) $H_2NCH_2CH(R_8)OH$, $NaBH_4$, NaOH, MeOH; b) PPh_3, DEAD, THF; c) Boc anhydride, Et_3N, THF; d) HCl, dioxane

Scheme **14** represents a general scheme for the preparation of (R)-2-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines, and 2,2-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines used in the invention. In this scheme, the R groups are the defined substituents for Formula I and II. Substituted 2-hydroxybenzaldehyde depicted as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reductive amination of aldehyde with the appropriate aminoalcohol followed by Mitsunobo reaction provides the required intermediate **3**. This was then protected as the Boc carbamate to facilitate purification. It will be appreciated by the skilled artisan that alternative protecting groups may be used. Deprotection yields the requisite amine **5**.

Scheme 15

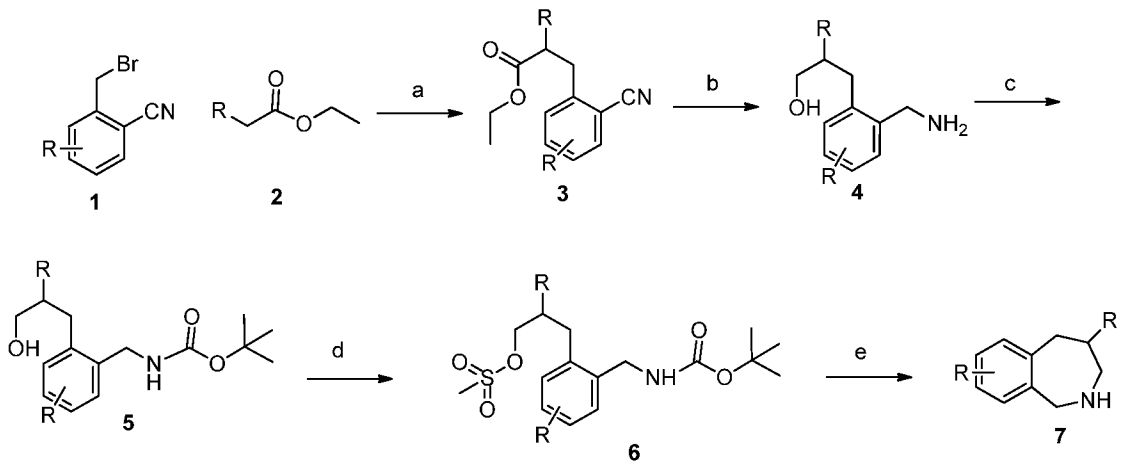


Conditions: a) K_2CO_3, THF; b) NaOMe, DMF; c) LAH, THF

Scheme **15** represents a general scheme for the preparation of substituted-tetrahydrobenzo[f][1,4]oxazepines used in the invention. In this, 2-hydroxybenzamide depicted as starting material is commercially available. In this scheme, the R groups are the defined substituents for A in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reaction of 2-hydroxybenzamide with the appropriate bromoacetate yields the intermediate **3**. Cyclization under basic conditions followed by reduction of the resulting imide with LAH yields the required amine **5**.

Scheme 16

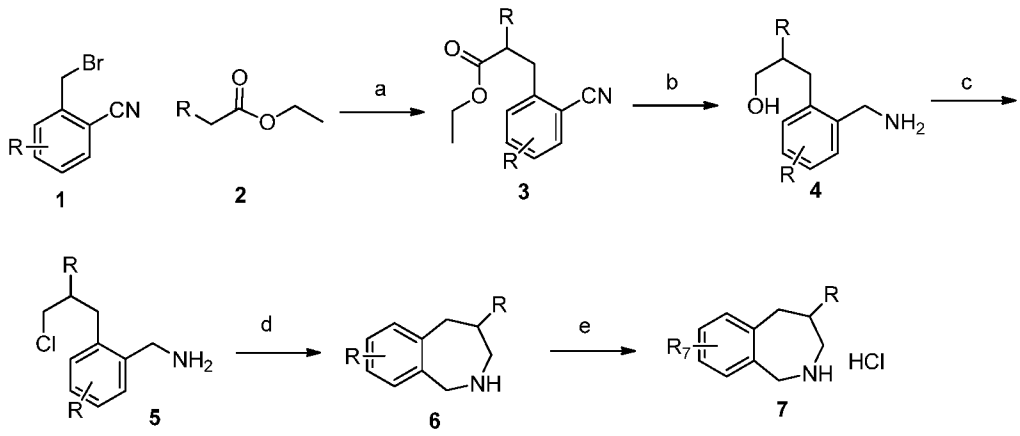


Conditions: a) LDA, THF; b) LAH, THF; c) Boc anhydride, DCM; d) $MeSO_2Cl$, Et_3N, DCM; (e) Cs_2CO_3, CuI, IPA

Scheme **16** represents a general scheme for the preparation of 2,3,4,5-tetrahydro-1H-benzo[c]azepines used in the invention. The substituted 2-(bromomethyl)benzonitrile depicted as starting material is commercially available. In this scheme, the R groups are the defined substituents for A in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reaction of starting 2-(bromomethyl)benzonitrile with the enolated generated from the appropriate ester **2** yields nitrile **3**. Reduction of the nitrile and ester functions with LAH followed by protection of the amine group and conversion of the alcohol to the mesylate leaving group affords intermediate **6**. Completion of the desired **7** is accomplished by cyclization under basic condition with CuI.

Scheme 17

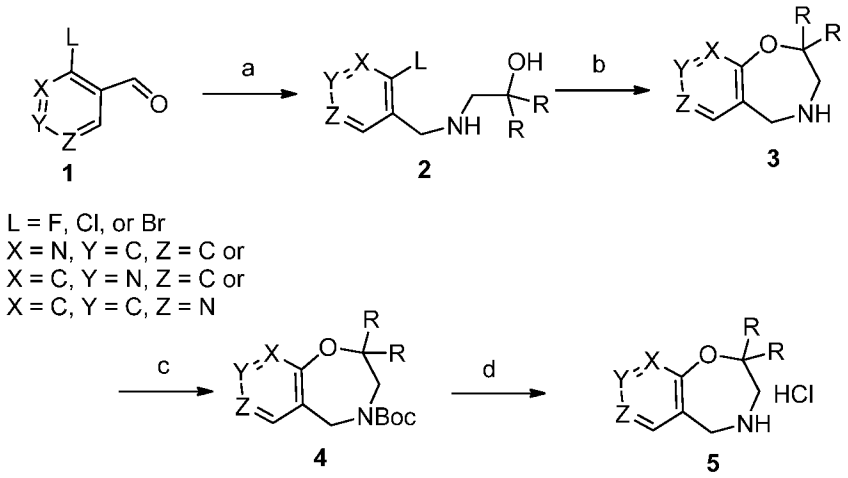


Conditions: a) LDA, THF; b) LAH, THF; c) $SOCl_2$, DCE; d) DIPEA, CH_3CN; (e) (i) $(Boc)_2O$, TEA, DCM; (ii) HCl in dioxane, THF

Scheme **17** represents a general scheme for the preparation of 2,3,4,5-tetrahydro-1H-benzo[c]azepines used in the invention. The substituted 2-(bromomethyl)benzonitrile depicted as starting material is commercially available. In this scheme, the R groups are the defined substituents for A in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reaction of starting 2-(bromomethyl)benzonitrile with the enolate generated from the appropriate ester **2** yields nitrile **3**. Reduction of the nitrile and ester functions with LAH. Alcohol was then converted intermediate **5** with thionyl chloride. Displacement of the chloride provides the intermediate **6** It was then protected with Boc group and then deprotection to give desired **7** as hydrochloride salt.

Scheme 18

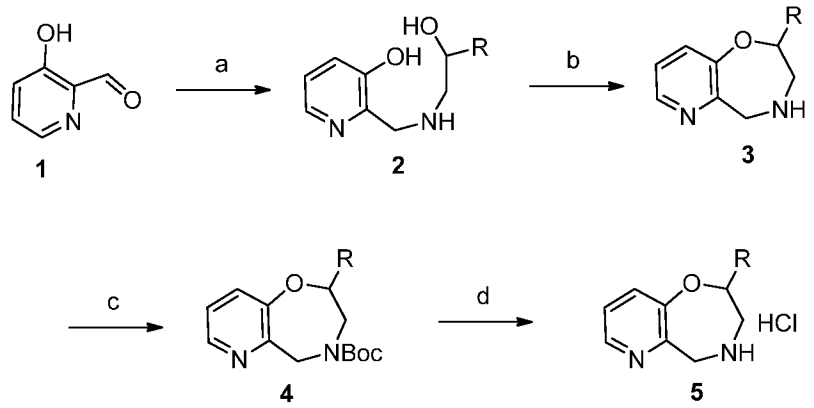


Conditions: a) $H_2NCH_2C(R_6)(R_7)OH$, $NaBH_4$, NaOH, MeOH; b) Cs_2CO_3, CuI, IPA; or KO_tBu, DMSO; c) Boc anhydride, Et_3N, THF; d) HCl, dioxane

Scheme **18** represents a general scheme for the preparation of tetrahydropyrido[1,4]oxazepine hydrochloride used in the invention. The fluoronicotinaldehyde, chloronicotinaldehyde or bromonicotinaldehyde depicted as starting material are commercially available. In this scheme, the R groups are the defined substituents for A in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reductive amination of the starting aldehyde with the appropriate aminoalcohol followed by displacement of the bromide or fluoro provides the required intermediate **3**. This was then protected as the Boc carbamate to facilitate purification. It will be appreciated by the skilled artisan that alternative protecting groups may be used. Deprotection yields the requisite amine **5** as hydrochloride salt.

Scheme 19

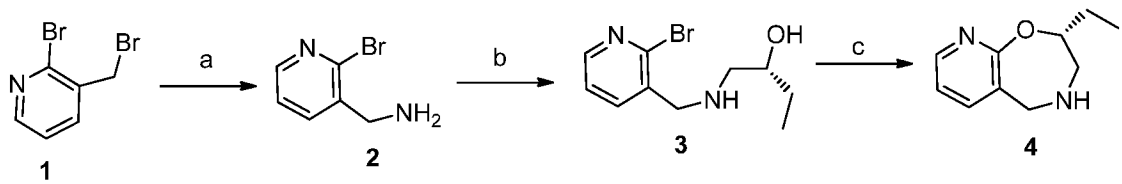


Conditions: a) $H_2NCH_2CH(R_8)OH$, $NaBH_4$, NaOH, MeOH; b) PPh_3, DEAD, THF; c) Boc anhydride, Et_3N, THF; d) HCl, dioxane

Scheme **19** represents a general scheme for the preparation of (R)-2-ethyl-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine hydrochloride, and 2,2-dimethyl-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine hydrochloride used in the invention. The 3-hydroxypicolinaldehyde depicted as starting material is commercially available. In this scheme, the R groups are the defined substituents for A in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reductive amination of the commercially available aldehyde with the appropriate aminoalcohol followed by Mitsunobo reaction provides the required intermediate **3**. This was then protected as the Boc carbamate to facilitate purification. It will be appreciated by the skilled artisan that alternative protecting groups may be used. Deprotection yields the requisite amine **5**.

Scheme 20

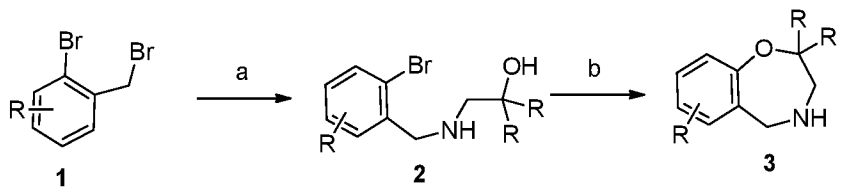


Conditions: a) NH_4OH; b) (R)-(2)-ethyloxirane, EtOH; c) KO_tBu, DMF

Scheme **20** represents a general scheme for the preparation of (R)-2-ethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine used in the invention. In this, 2-bromo-3-(bromomethyl)pyridine depicted as starting material are commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of commercially avialable 2-bromo-3-(bromomethyl)pyridine with ammonium hydroxide yields primary amine **2**. Alkylation via epoxide opening followed by displacement of the bromide provides intermediate **4**.

Scheme 21

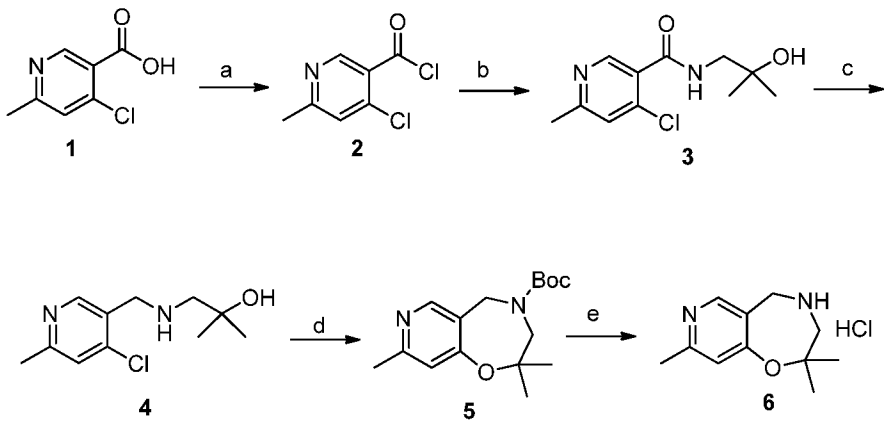


Conditions: a) amine, K_2CO_3, THF, water; b) Cs_2CO_3, CuI, IPA

Scheme **21** represents a general scheme for the preparation of 2-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine hydrochloride, and 2,2-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine hydrochloride used in the invention. The substituted 1-bromo-2-(bromomethyl)benzene depicted as starting material is commercially available. In this scheme, the R groups are the defined substituents for A in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Alkylation with the appropriate aminoalcohol followed by displacement of the bromide provides the required intermediate **3**.

Scheme 22

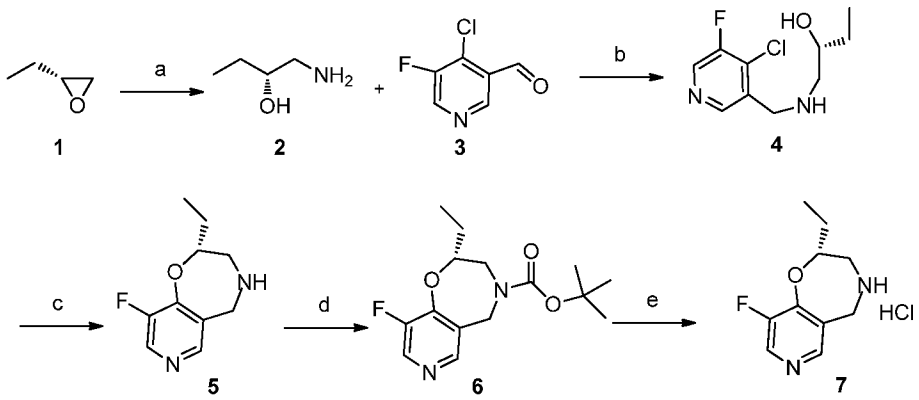


Conditions: a) $POCl_3$; b) NaOH, DCM; c) borane dimethyl sulfide, THF; d) (i) KO_tBu, DMSO; (ii) Boc anhydride, Et_3N, THF; d) HCl, dioxane

Scheme **22** represents a general scheme for the preparation of 2,2,8-trimethyl-2,3,4,5-tetrahydropyrido[3,4-f][1,4]oxazepine hydrochloride used in the invention. In this, 4-hydroxy-6-methylnicotinic acid depicted as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Commercially available acid **1** was converted to the acid chloride with $POCl_3$, followed by amide formation to give intermediate **3**. Reduction of the amide with borane dimethyl sulfide produces amine **4**. Cyclization with potassium *tert*-butoxide as base followed by amine protection as the *tert*-butylcarbamate group yields compound **5**. Deprotection under acidic condtion yields the requisite amine **6**.

Scheme 23

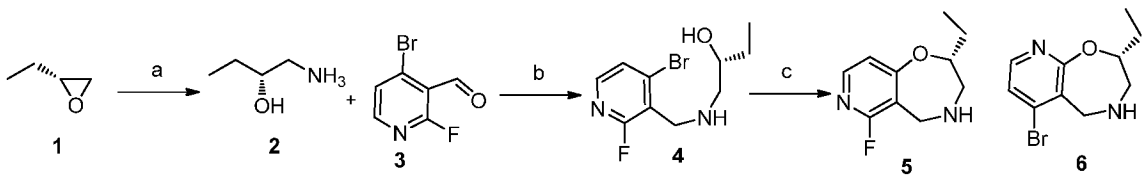


Conditions: a) NH_4OH; b) $NaBH_4$, NaOH, MeOH c) KO_tBu, DMSO, 90 °C; d) Boc anhydride, Et_3N, THF; d) HCl, dioxane

Scheme **23** represents a general scheme for the preparation of (R)-2-Ethyl-9-fluoro-2,3,4,5-tetrahydropyrido[3,4-f][1,4]oxazepine, hydrochloride used in the invention. The 4-chloro-5-fluoronicotinaldehyde as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Commercially available (R)-2-ethyloxirane **1** is opened with ammonium hydroxide to obtain (R)-1-aminobutan-2-ol **2**. Reductive amination of the commercially available aldehyde **3** with (R)-1-aminobutan-2-ol **2** followed by displacement of the chloride provides the required intermediate **5**. This is then protected as the Boc carbamate to facilitate purification. It will be appreciated by the skilled artisan that alternative protecting groups may be used. Deprotection yields the requisite amine **7**.

Scheme 24

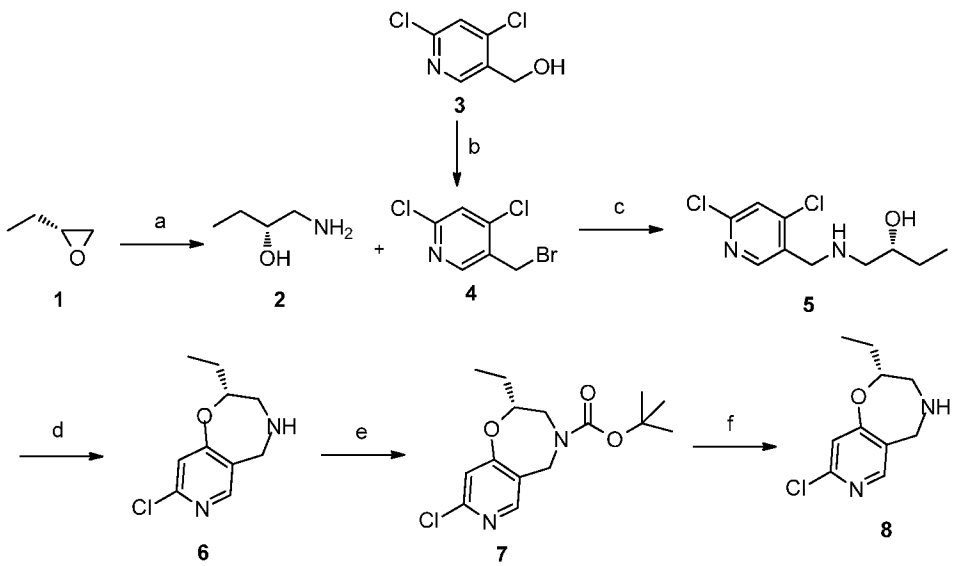


Conditions: a) NH_4OH; b) $NaBH_4$, NaOH, MeOH c) Cs_2CO_3, CuI, IPA

Scheme **24** represents a general scheme for the preparation of (R)-2-Ethyl-6-fluoro-2,3,4,5-tetrahydropyrido[3,4-f][1,4]oxazepine and (R)-6-Bromo-2-ethyl-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine used in the invention. The 4-bromo-2-fluoronicotinaldehyde as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Commercially available (R)-2-ethyloxirane **1** is opened with ammonium hydroxide to obtain enantiomerically pure (R)-1-aminobutan-2-ol **2**. Reductive amination of the commercially available aldehyde **3** with (R)-1-aminobutan-2-ol **2** followed by displacement of the halogen gives amine **5** and amine **6**.

Scheme 25

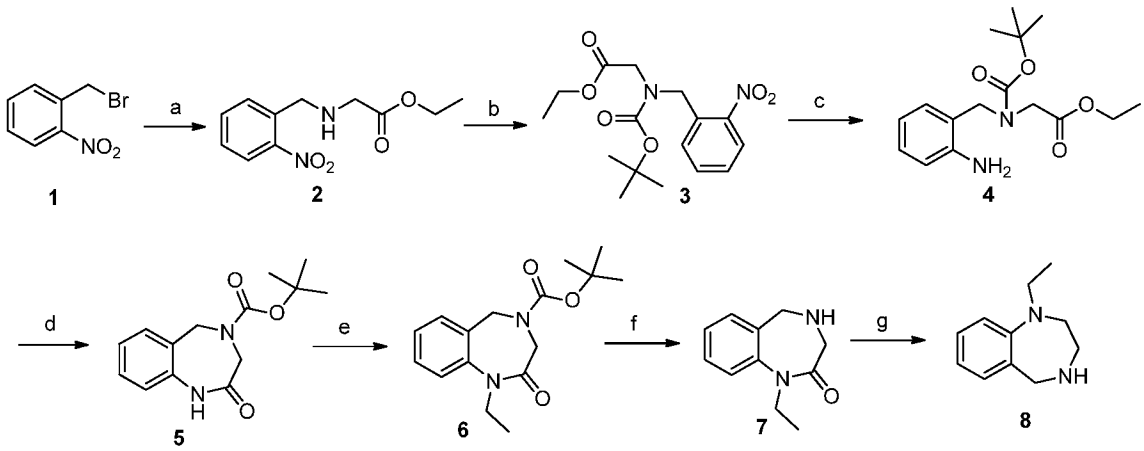


Conditions: a) NH_4OH; b) PBr_3, DCM; c) Et_3N, DCM c) KO_tBu, DMSO, 65 °C; d) Boc anhydride, Et_3N, THF; e) HCl, dioxane

Scheme **25** represents a general scheme for the preparation of (R)-8-Chloro-2-ethyl-2,3,4,5-tetrahydropyrido[3,4-f][1,4]oxazepine hydrochloride used in the invention. The (4,6-dichloropyridin-3-yl)methanol as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Commercially available (R)-2-ethyloxirane **1** is opened with ammonium hydroxide to obtain (R)-1-aminobutan-2-ol **2**. Bromination of alcohol **3** with PBr_3 in DCM produces intermediate **4**. Alkylation of **4** with (R)-1-aminobutan-2-ol **2** followed by displacement of the chloride provides the required intermediate **6**. This is then protected as the Boc carbamate to facilitate purification. It will be appreciated by the skilled artisan that alternative protecting groups may be used. Deprotection yields the requisite amine **8**.

Scheme 26

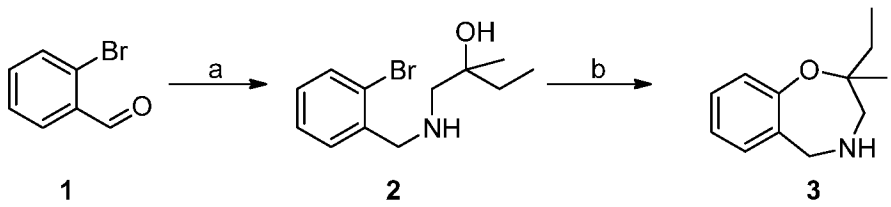


Conditions: a) 2-aminoacetate, DIPEA, DMF; b) Boc_2O, DMAP, TEA, DCM; c) Pd/C, H_2, EtOH; d) HOBt, Toluene; (e) NaH, CH_3CH_2I, DMF; (f) TFA, DCM; (g) LAH, THF

Scheme **26** represents a general scheme for the preparation of 1-ethyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine used in the invention. In this, the 1-(bromomethyl)-2-nitrobenzene depicted as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reaction of starting 1-(bromomethyl)-2-nitrobenzene with 2-aminoacetate provides intermediate **2**. Boc protected the amine, followed by reduction of nitro to anilines to yield intermediate **4**. Cyclization with HOBt to yield intermediate **5**, followed by alkylation. Deprotection under acidic condition followed by reduction with LAH to provide desired intermediate **8**.

Scheme 27

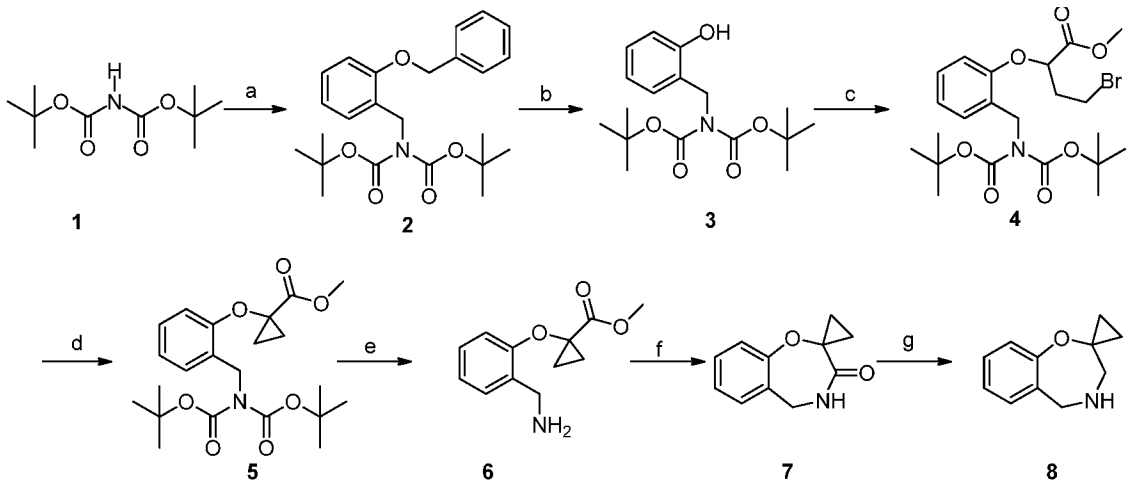


Conditions: a) 1-amino-2-methylbutan-2-ol, $NaBH_4$, NaOH, MeOH; b) Cs_2CO_3, CuI, isopropanol

Scheme **27** represents a general scheme for the preparation of 2-ethyl-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine used in the invention. In Scheme **27**, substituted 2-bromobenzaldehyde depicted as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reductive amination of aldehyde **1** with the appropriate aminoalcohol followed by alkylation reaction provides the required intermediate **3**.

Scheme 28

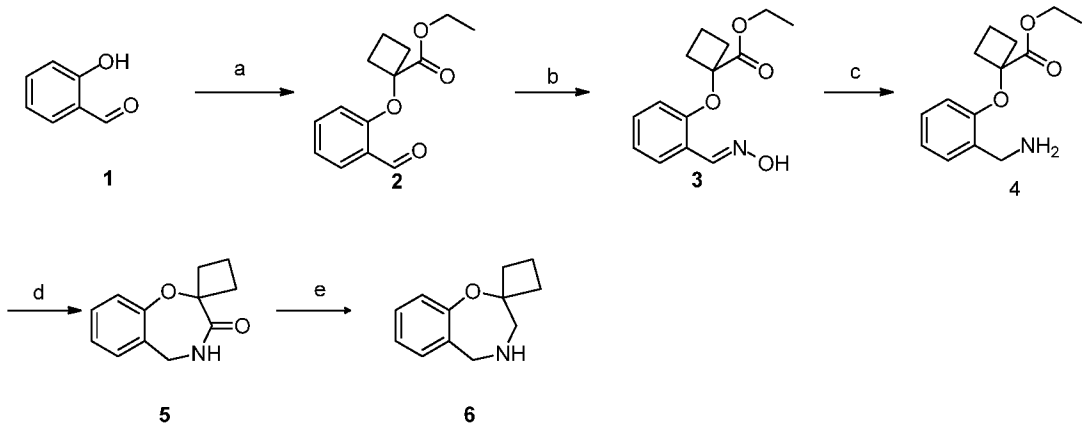


Conditions: a) 1-(benzyloxy)-2-(chloromethyl)benzene, Cs_2CO_3, NaI, DMF; b) Pd/C, H_2, MeOH/THF; c) 2,4-dibromobutanoate, Cs_2CO_3, CH3CN; d) potassium tert-butoxide, THF; (e) HCl; (f) DIPEA, 1,4-dioxane; (g) LAH, THF

Scheme **28** represents a general scheme for the preparation of 4,5-dihydro-3H-spiro[benzo[f][1,4]oxazepine-2,1'-cyclopropane] used in the invention. In this, the (bis-tert-butoxycarbonyl)amine depicted as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reaction of starting (bis-tert-butoxycarbonyl)amine with 1-(benzyloxy)-2-(chloromethyl)benzene provides intermediate **2**. Deprotection of the phenol by hydrogenation, followed by reacting with 2,4-dibromobutanoate under basic condition to yield intermediate **4.** Then it is treated with potassium tert-butoxide to yield intermediate **5**. Deprotection under acidic condition followed by cyclization and reduction with LAH to provide desired intermediate **8.**

Scheme 29

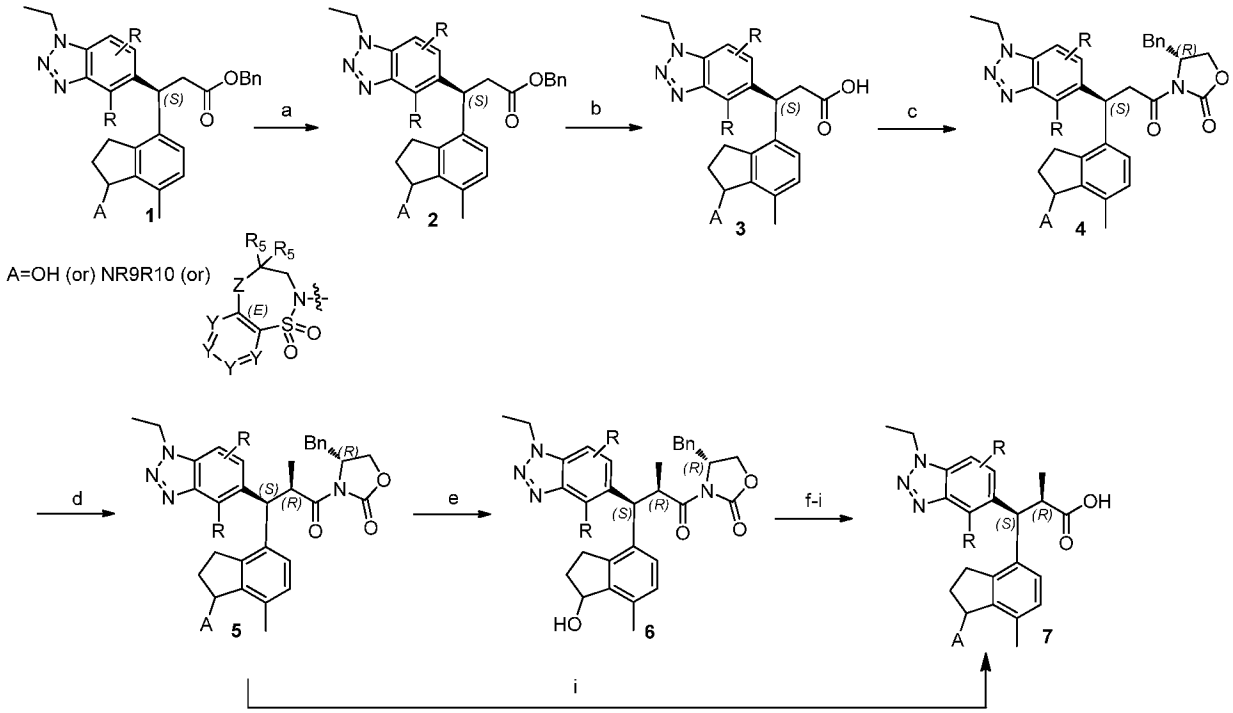


Conditions: a) 1-bromocyclobutanecarboxylate, NaH, KI, DMF; b) hydroxylamine hydrochloride, ammonium acetate, ethanol/water; c) platinum(IV)oxide, H_2, acetic acid; d) DIPEA, 1,4-dioxane; (e) LAH, THF

Scheme **29** represents a general scheme for the preparation of 4,5-dihydro-3H-spiro[benzo[f][1,4]oxazepine-2,1'-cyclobutane] used in the invention. In this, the 2-hydroxybenzaldehyde depicted as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Reaction of starting 2-hydroxybenzaldehyde **1** with 1-bromocyclobutanecarboxylate provides intermediate **2**, followed by reduction of aldehyde to hydroxy amine to yield intermediate **4**. Cyclization with DIPEA to yield intermediate **5**, followed by reduction with LAH to provide desired intermediate **6**.

Scheme 30



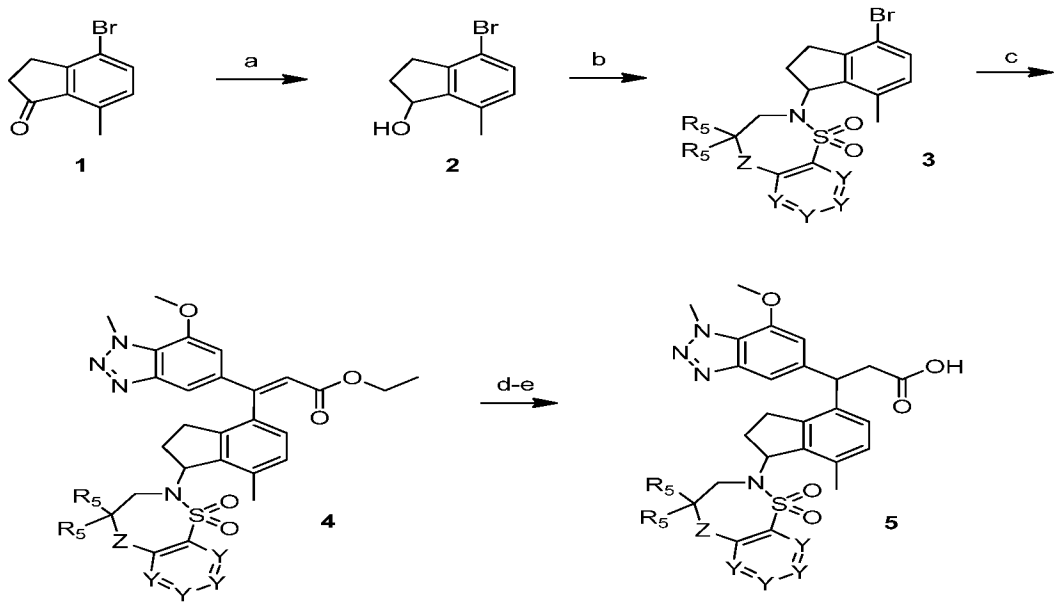
Conditions: a) TBSCl, imidazole, DCM; b) H_2 10% Pd-C, EtOAc; c) CDI, DBU, (R)-4-benzyloxazolidin-2-one, THF, MeCN; d) NaHMDS, MeI, THF; e) HCl, MeOH; f) $SOCl_2$, DCM g) R_1NH_2, NaI, K_2CO_3; h) R_2Cl, TEA, DCM; i) LiOH, H_2O_2 (or) 6N HCl, Dioxane, 95 C.

Scheme **30** represents a general scheme for the preparation of compounds according to Formula (I). The starting material **1** can be synthesized from readily available materials. In this scheme, the R groups are the defined substituents for B in Formula I and II.

Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents

used are possible. In the scheme, one enantiomer is shown as starting material for illustrative purposes. In the scheme, **A** represents either an alcohol or a sulphonamide or amine used in the invention. In the case when **A** is an alcohol, this may be protected as the TBS ether. The skilled artisan will appreciate that different protecting groups are possible. Installing the alpha-methyl group is accomplished via removal of the of benzyl protecting group, incorporating the chiral auxiliary followed by deprotonation and methylation. Removing the TBS protecting group reveals an alcohol **6**. Alcohol **6** can be transformed to the final compound in a four step sequence involving conversion to the chloride using thionyl chloride, displacement of chloride with an appropriate amine, reaction of the amine with the appropriate acid or sulfonyl chloride followed by hydrolysis to produce **7**. Alternatively, when A is a sulphonamide or amine, hydrolysis to the acid can provide **7**.

Scheme 31

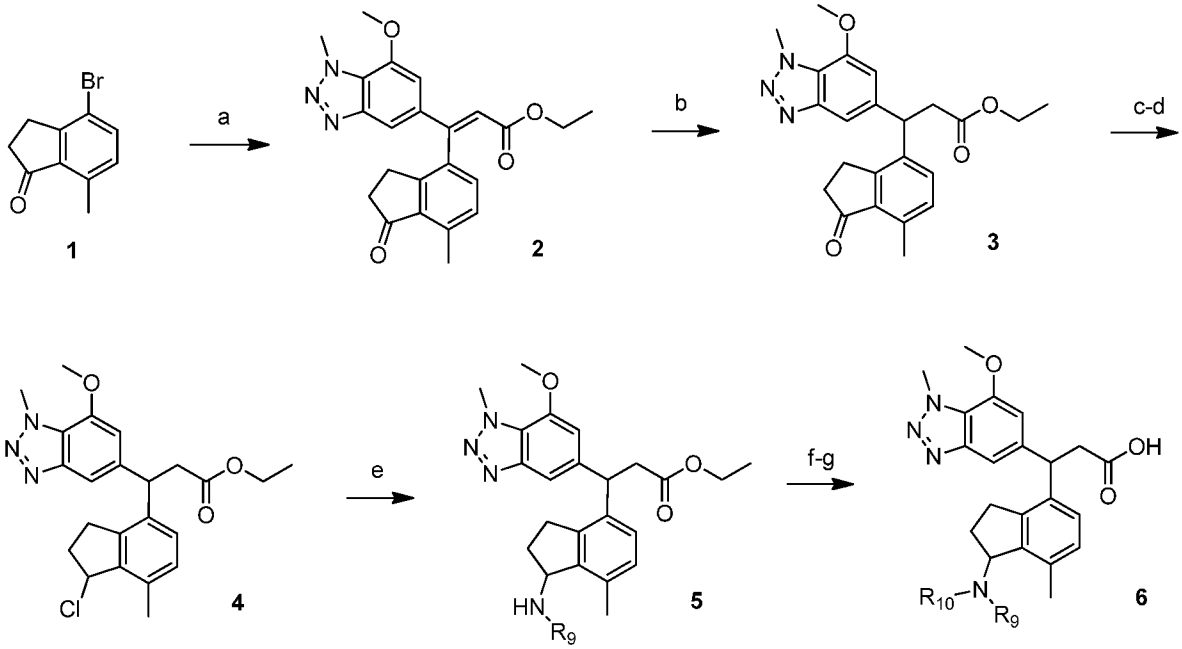


Conditions: a) $NaBH_4$, EtOH; b) Bu_3P, ADDP, sulfonamide; c) bis(tri-t-butylphosphine)palladium(0), ethyl acrylate, N-cyclohexyl-N-methylcyclohexanamine; d) $Pd(OH)_2$, H_2; e) LiOH, THF, MeOH

Scheme **31** shows a general scheme for the preparation of compounds of Formula I. Starting with commercially available 4-bromo-7-methyl-2,3-dihydro-1H-inden-1-one, reduction of the ketone to the alcohol provides intermediate **2** which can be reacted further under Mitsunobu conditions to afford bromide **3**. Further elaboration via a Heck coupling to

the requisite acrylate followed by reduction of the intermediate olefin and hydrolysis of the ester to the acid provides the desired analogs **5**.

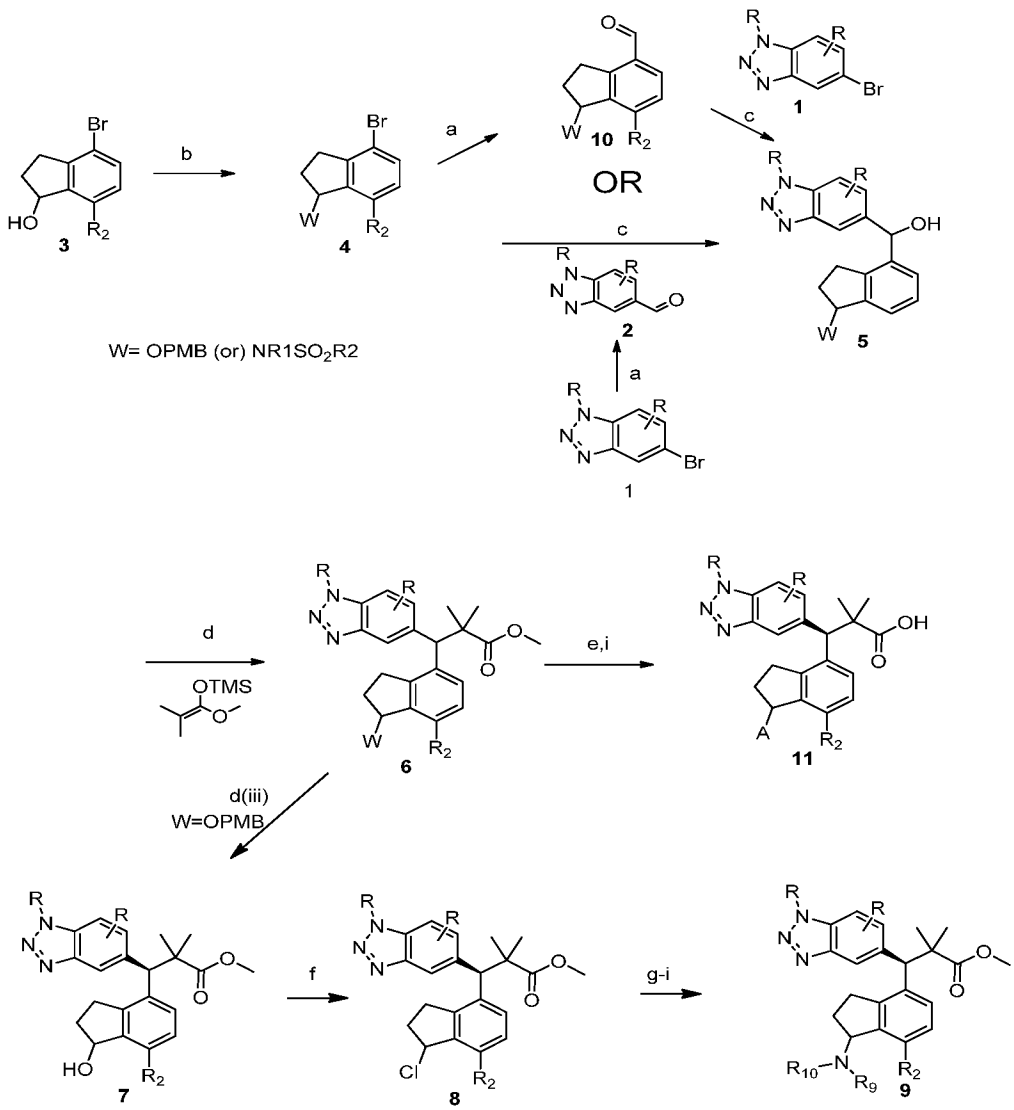
Scheme 32



Conditions: a) bis(tri-t-butylphosphine)palladium(0), ethyl acrylate, N-cyclohexyl-N-methylcyclohexanamine; b) $Pd(OH)_2$, H_2; c) $NaBH_4$, EtOH; d) $SOCl_2$, DCM; e) R_1NH_2, NaI, K_2CO_3; f) R_2Cl, TEA, DCM; g) LiOH, THF, MeOH

Scheme **32** shows a general scheme for the preparation of compounds of Formula I. Starting with commercially available 4-bromo-7-methyl-2,3-dihydro-1H-inden-1-one Heck coupling to the requisite acrylate followed by reduction of the intermediate olefin and ketone to the alcohol and transformation to the chloride provides intermediate **4**. Reaction of the chloride with the appropriate amine followed by reaction with either an acid chloride or sulfonyl chloride and subsequent hydrolysis provides desired analogs **6**.

Scheme 33



Conditions: a) n-BuLi, DMF, THF b) NaH, PMBCl, DMF (or) Bu_3P, ADDP, sulfonamide; c) t-BuLi or n-BuLi, THF d) $TiCl_4$, DCM (or) (i) DBU, Cl_3CCN, CH_3CN; ii) Tf_2NH, iii) DDQ, DCM/H_2O e) Chiral SFC; f) $SOCl_2$, DCM; g) R_1NH_2, NaI, K_2CO_3; h) R_2Cl, TEA, DCM; i) LiOH, THF, MeOH

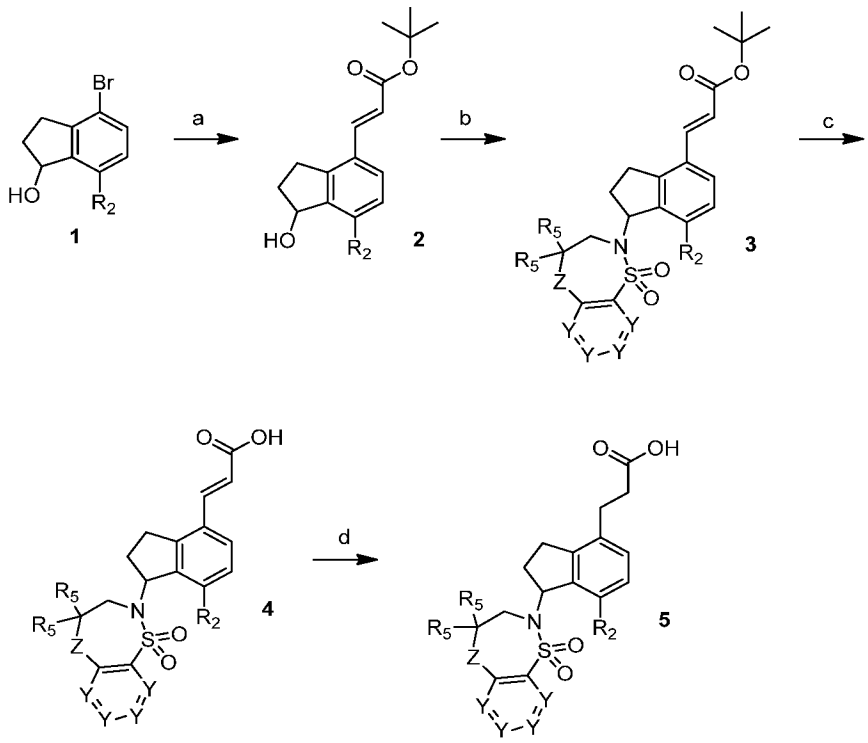
Scheme **33** represents a general scheme for the preparation of compounds according to Formula (I). In this scheme, the R groups are the defined substituents for B in Formula I and II. R_2 is as defined for Formula I and II. Triazole **1** is either commercially available or may be synthesized from readily available materials. Reaction conditions are as

described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of triazole **1** with n-butyl lithium and DMF in presence of a suitable solvent produces the desired aldehyde product **2**. The coupling partner for aldehyde **2** is obtained by first protecting the benzylic alcohol **3** as its para-methoxybenzylether. It will be appreciated that alternative protecting groups are possible. Coupling of the aldehyde **2** and bromide **4** can be accomplished via treatment of the bromide first with t-butyl lithium or n-butyl lithium followed by addition of the aldehyde. However, the skilled artisan will appreciate that other aldehydes, such as substituted phenyl aldehyde may also be applied. Intermediate benzyl alcohol **6**, arises from treatment of alcohol **5** with the appropriate silylketene acetal in the presence of a Lewis acid or via one-pot Brϕnsted base / Brϕnsted acid system, followed by deprotection with DDQ. Benzylic alcohol **6** may be separated by Chiral SFC to give a single enantiomerically pure product **7**. Alternatively, the scheme may be started with a single enantiomer of benzylic alcohol **3**. Alcohol **7** can be transformed to the requisite chloride **8** using thionyl chloride. Completion of the synthesis can be accomplished by displacement of chloride, reaction with the appropriated acid or sulfonyl chloride following by hydrolysis of the ester to produce **9**. Alternatively, when A is a sulphonamide chiral SFC followed by hydrolysis of the ester to the acid provides **11**.

It will be also be appreciated by the skilled artisan that intermediate **5** may be prepared by coupling bromide **1** with aldehyde **10**.

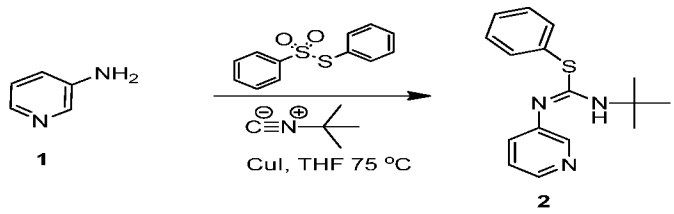
Scheme 34



Conditions: a) bis(tri-t-butylphosphine)palladium(0), ethyl acrylate, N-cyclohexyl-N-methylcyclohexanamine; b) Bu_3P, ADDP, sulfonamide; c) TFA; d) $Pd(OH)_2$, H_2

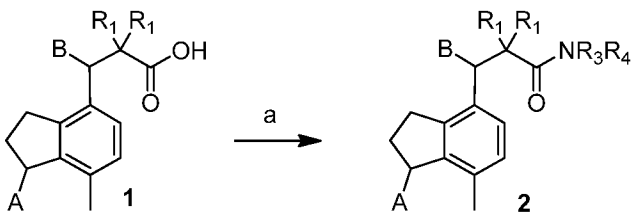
Scheme **34** shows a general scheme for the preparation of compounds of Formula I. Starting with 4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol, Heck coupling to the requisite acrylate followed by coupling of the required sulfonamide under Mitsunobu conditions and removal of the ester protecting group yields the intermediate acrylate **4**. Reduction of the olefin provides desired analogs **5**.

Scheme 35



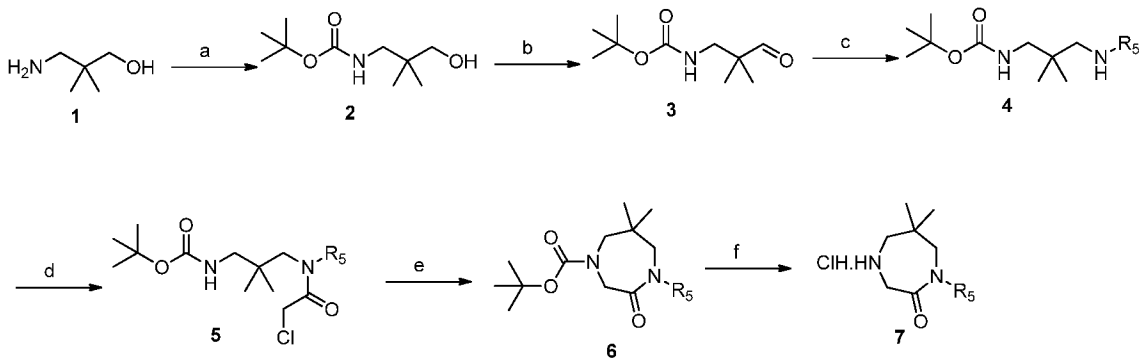
Scheme **35** represents a general scheme for the preparation of phenyl (E)-N-(tert-butyl)-N'-(pyridin-3-yl)carbamimidothioate, used in the invention. In this, pyridin-3-amine depicted as starting material is commercially available. The reaction with 2-isocyano-2-methylpropane and S-phenyl benzenesulfonothioate in 2-methyltetrahydrofuran is heated with copper(I) iodide and provides the required intermediate **2**. While the scheme shows pyridin-3-amine as starting material, it will be appreciated by the skilled artisan that other starting amines may be used.

Scheme 36



Scheme **36** represents a general scheme for the preparation of compounds according to Formula (I). Carboxylic acids **1** are activated by typical amidation activation methods including, but not limited to, thionyl chloride, amide coupling reagents such as HATU, 1-(fluoro(pyrrolidin-1-yl)methylene)pyrrolidin-1-ium hexafluorophosphate(V) (BTFFH) or phenyl (E)-N-(tert-butyl)-N'-(pyridin-3-yl)carbamimidothioate. Amines $R_3R_4NH_2$ are either combined during the activation process or after a period of time, to provide the desired amides.

Scheme 37

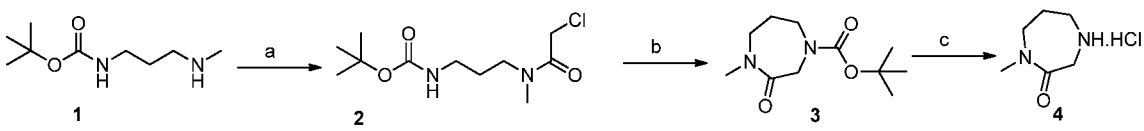


Conditions: a) $(Boc)_2O$, DCM b) TEMPO, KBr, $NaHCO_3$, NaOCl, DCM C) amine, $NaCNBH_3$, ACOH, MeOH d) Et_3N, 2-chloroacetyl chloride, DCM e) NaH, DMF f) HCl, dioxane, DCM

Scheme **37** represents a general scheme for the preparation of compounds according to Formula (I). 3-Amino-2,2-dimethylpropan-1-ol **1** is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Protection of amine **1** as its Boc carbamate followed by oxidation of the alcohol to the aldehyde with TEMPO gives intermediate **3**. Reductive amination with an appropriate amine yields compound **4**. Compound **4** was reacted with 2-chloroacetyl chloride in the presence of triethylamine to give compound **5**. Cyclization with NaH gives lactam **6**. Removing the Boc group with HCl gives lactam **7** as the hydrochloride salt.

Scheme 38

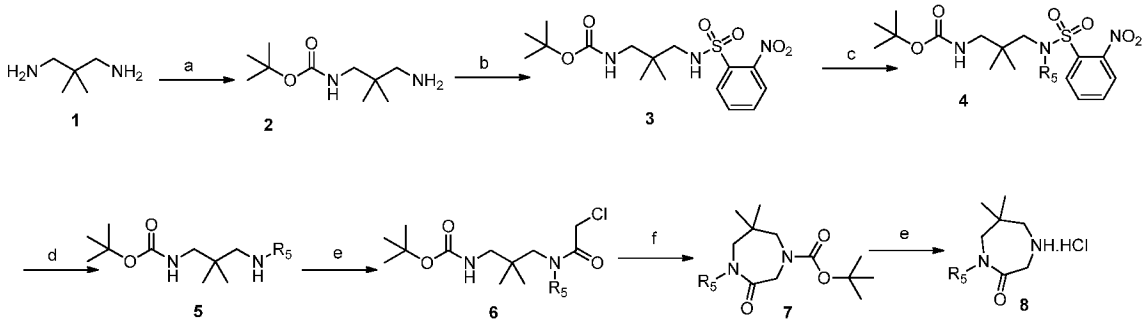


Conditions: a) Et_3N, 2-chloroacetyl chloride, THF b) NaH, DMF c) HCl, dioxane, DCM

Scheme **38** represents a general scheme for the preparation of compounds 1-methyl-1,4-diazepan-2-one hydrochloride. tert-Butyl (3-(methylamino)propyl)carbamate **1** is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Alkylation of commercially available starting

material **1** with 2-chloroacetyl chloride in the presence of triethylamine produces compound **2**. Cyclization using NaH as base gives lactam **3**. Deprotection the Boc group with HCl furnishes lactam **4** as the hydrochloride salt.

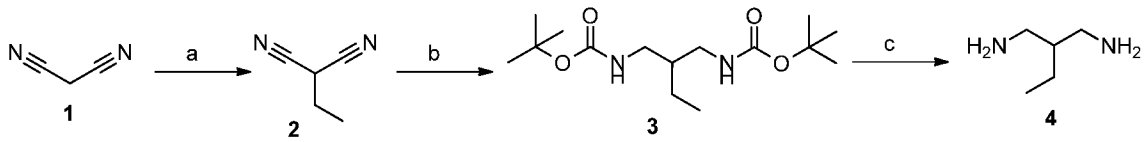
Scheme 39



Conditions: a) $(Boc)_2O$, DCM; b) K_2CO_3, 2-nitrobenzene-1-sulfonyl chloride, DCM; c) R_5I, K_2CO_3, DMF, 90 °C; d) PhSH, K_2CO_3, DMF; e) Et_3N, 2-chloroacetyl chloride, DCM; f) NaH, DMF; g) HCl, dioxane, DCM

Scheme **39** represents a general scheme for the preparation of compounds according to Formula (I). 2,2-Dimethylpropane-1,3-diamine **1** is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Protection of mono-amine **1** as its Boc carbamate followed by sulfonamide formation with 2-nitrobenzene-1-sulfonyl chloride under basic conditions provides compound **3**. Treatment of compound **3** with an appropriate available alkyl iodide at high temperature provides compound **4**, followed by deprotection to give amine **5**. Compound **5** was reacted with 2-chloroacetyl chloride in the presence of triethylamine to furnish compound **6**. Cyclization was successful with NaH to give lactam **7** which can be subsequently deprotected HCl to give lactam **8** as the hydrochloride salt.

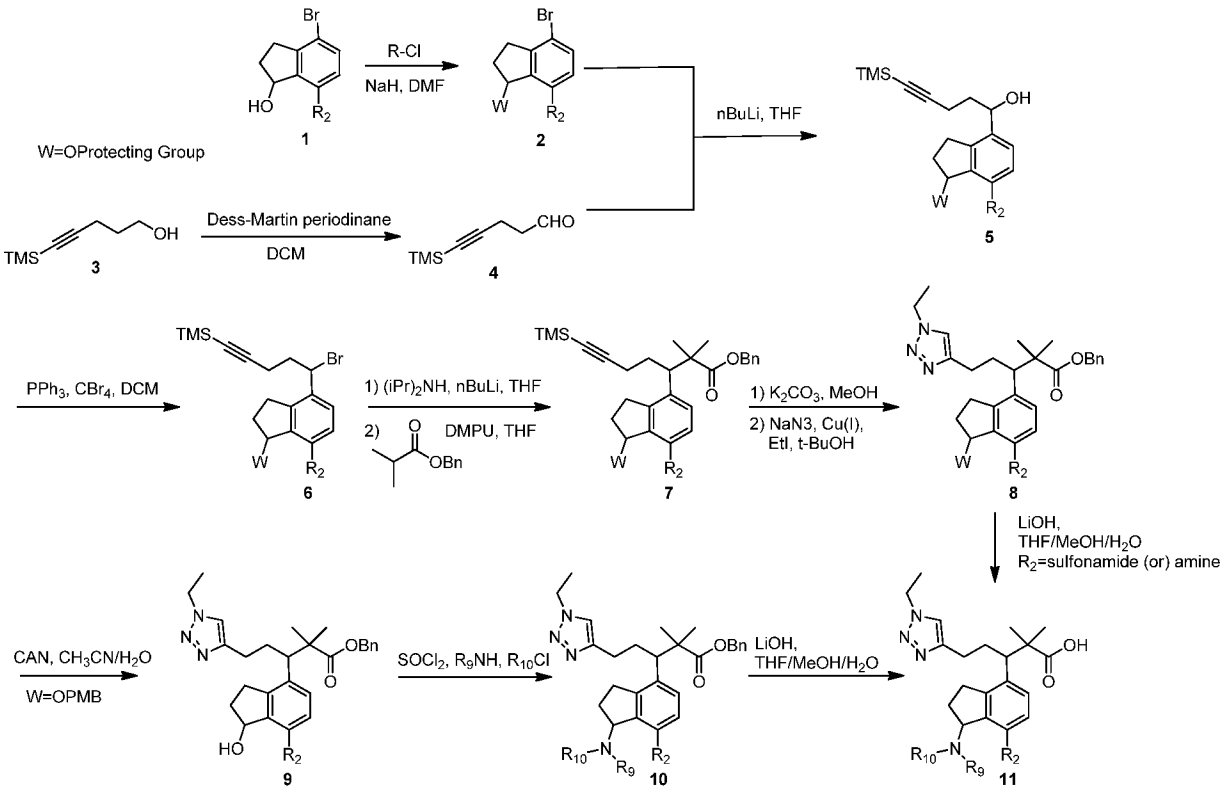
Scheme 40



Conditions: a) iodoethane, tetrabutylammonium bromide, K_2CO_3; b) Raney-Ni, Boc anhydride, MeOH; c) HCl, dioxane, DCM

Scheme **40** represents a general scheme for the preparation of 6-Ethyl-1-methyl-1,4-diazepan-2-one hydrochloride. Malononitrile **1** is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Treatment of malononitrile with iodoethane under basic conditions gives compound **2**. Hydrogenation followed by Boc protection to aid in purification produces compound **3**. Removal of the Boc groups with HCl provides diamine **4** as hydrochloride salt. Following the same sequence as Scheme **39** above the lactam 6-ethyl-1-methyl-1,4-diazepan-2-one hydrochloride can be produced.

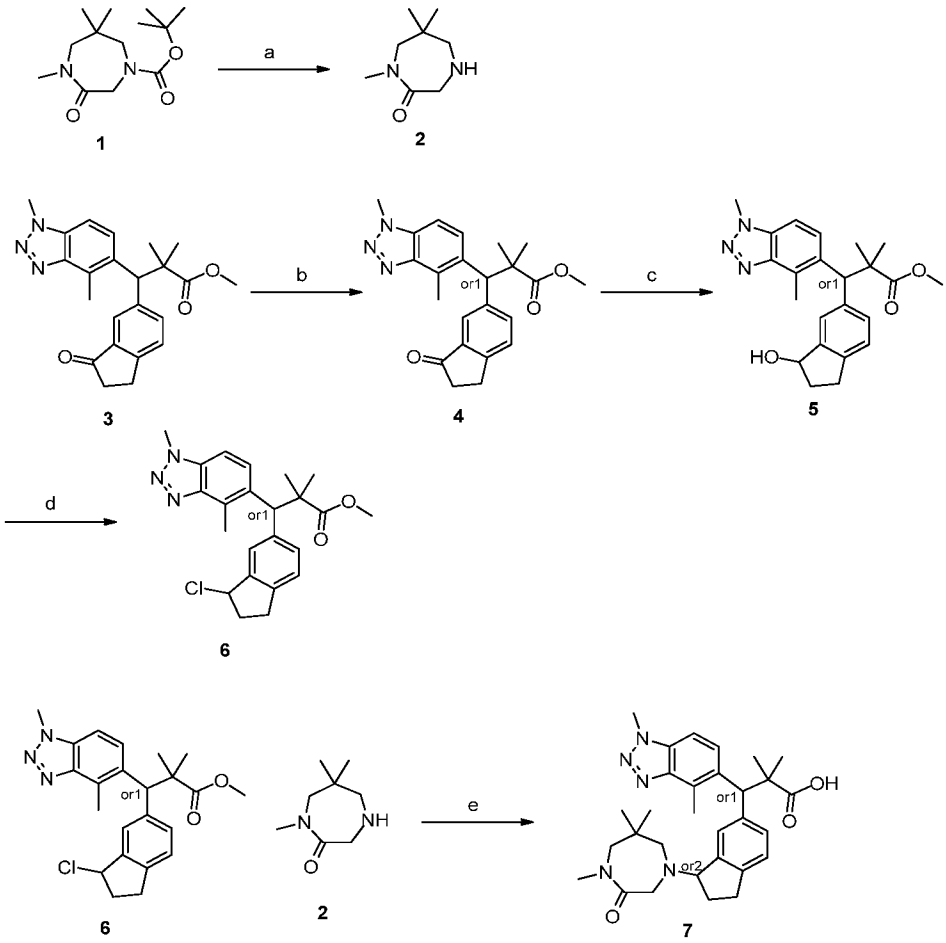
Scheme 41



Scheme **41** represents a general scheme for the preparation of compounds according to Formula (I). The starting alcohol can be prepared via reduction of the corresponding ketone. Intermediate **2** is prepared by alkylation of **1** using a strong base and a suitable protecting group as defined for W. An example of a suitable protecting group is

the para-methoxybenzyl (PMB) protecting group. Alternatively, W as a sulfonamide may be installed via Mitsunobu reaction and W as an amine via alkylation of the chloride formed from the alcohol and sulfonyl chloride. Intermediate **4** is prepared by the oxidation of the acetylenic alcohol with Dess-Martin periodinane in DCM. One skilled in the art could also envisage using other suitable alcohol oxidation methods to perform this conversion. A metal halogen exchange reaction is then performed on **2**, after which, aldehyde **4** is added to provide the secondary benzylic alcohol **5**. Conversion of the benzylic alcohol **5** to bromide **6** is achieved using triphenylphosphine and a bromide source such as carbon tetrabromide. The reaction of **6** with enolates such as that derived from iso-butyates affords the esters **7**. The use of an additive such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) may improve the effectiveness of this reaction. The dialkylated ester **7** containing the TMS protected acetylene can be de-silylated with aqueous potassium carbonate and subjected to a click reaction using sodium azide and ethyl iodide with a copper catalyst to afford the triazoles such as **8**. The protected benzyl alcohol can be deprotected and in the case where the protecting group is a PMB ether deprotection with ceric ammonium nitrate provides **9**. One skilled in the art could also envisage using other suitable oxidative or acidic methods to perform this reaction when W is OPMB. Alcohol **9** can be transformed to the final compound in a four step sequence involving conversion to the chloride using thionyl chloride, displacement of chloride with an appropriate amine, reaction of the amine with the appropriate acid or sulfonyl chloride followed by hydrolysis to produce **7**. Alternatively, when W in **8** is a sulphonamide or amine (i.e. when W = A), hydrolysis to the acid can provide **7**.

Scheme 42

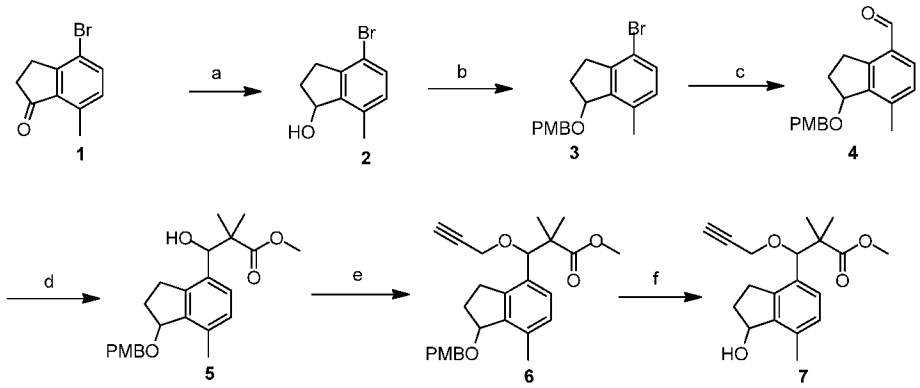


Conditions: a) 4 M HCl in p-dioxane; b) Chiral SFC; c) $NaBH_4$, MeOH d) $SOCl_2$, DCM; e) (i) K_2CO_3, NaI, MeCN/THF; (ii) NaOH, MeOH/H_2O; (iii) Chiral SFC

Scheme **42** represents a general scheme for the preparation of compounds according to Forumula I. Starting material **1** and **3** are synthesized as described above. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Treatment of Boc protected lactam amine **1** with 4 M HCl in p-dioxane gives the corresponding amine HCl salt **2**. The racemic bisaryl indanone **3** is chirally separated with chiral SFC gives both enantiomers **4**. Each enantiomer **4** is treated with $NaBH_4$ to give hydroxyindane **5** which is further treated with $SOCl_2$ to give corresponding chloride **6**. This bisaryl indane chloride **6** reacted with the above lactam amine **2** and K_2CO_3, NaI in MeCN/THF gives corresponding lactam amine substituted bisaryl indane ester. Further

hydrolysis of the ester with NaOH in MeOH/H_2O followed by chiral SFC separation gives desired product **7**.

Scheme 43

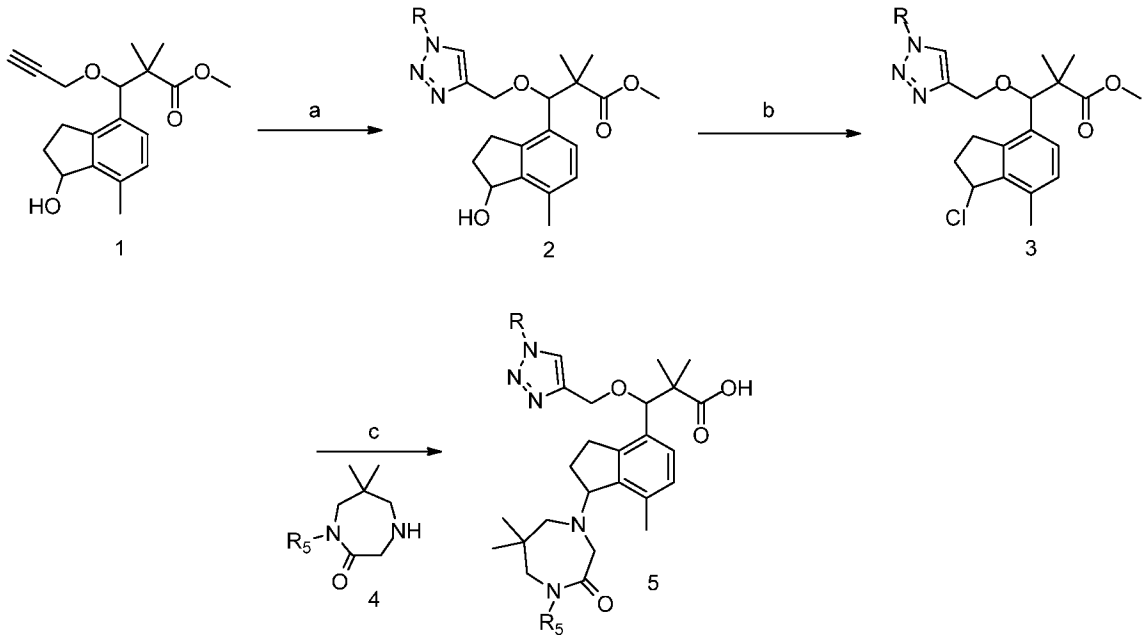


Conditions: a) $NaBH_4$, EtOH; b) NaH, DMF, PMB-Cl; c) nBuLi, THF, DMF; d) (i) 1-methylimidazole, ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane, LiCl, DMF, (ii) NaOH, KHF_2, H_2O, HCl; e) 3-bromoprop-1-yne, NaH, DMF; f) DDQ, DCM/H_2O

Scheme **43** represents a general scheme for the preparation of compounds according to Formula I. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Ketone **1** can be reduced to the benzyl alcohol using sodium borohydride to provide **2**. This alcohol can be resolved via chiral preparative methods if a single stereoisomer is desired. Alkylation of the alcohol using a strong base and a suitable protecting group provides intermediate **3**. Formylation of the bromide using n-butyl lithium and DMF affords **4**. Intermediate **5**, arises from treatment of aldehyde **4** with the appropriate silylketene acetal in the presence of lithium chloride. Intermediate **6** can be prepared by treatement of the alcohol with an strong base, like sodium hydride, followed by addition of 3-bromoprop-1-yne. Deprotection of the benzyl alcohol can be achieved using an oxidative reagent such as DDQ to provide **7**.

Alternatively, alcohol **2** may be converted to the corresponding sulfonamide via a Mitsunobu reaction with the appropriate sulfonamide. This could be carried forward through analogous steps as described in the scheme.

Scheme 44

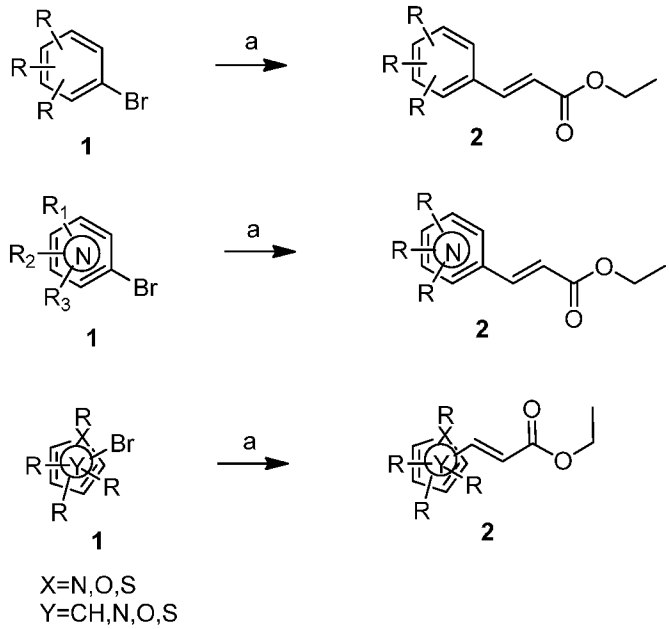


Conditions: a) RI, NaN_3, CuI, i-PrOH/THF/H_2O; b) $SOCl_2$, DCM; c) (i) DIEA, DMF; (ii) NaOH, MeOH/H_2O

Scheme **44** represents a general scheme for the preparation of compounds according to Formula I. Starting material **1** and **4** are synthesized as described in schemes previously presented. In this scheme, R is the defined substituents for B in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Application of click chemistry on starting material ether linked alkyne **1** with an alkyl iodoide RI, NaN_3, CuI, DIEA in i-PrOH/THF/H_2O gives the corresponding ether linked triazole **2**. This ether linked triazole benzyl alcohol **2** is treated with $SOCl_2$ to give corresponding benzyl chloride **3**. The benzyl chloride **3** reacted with the lactam amine **4** and DIEA in DMF gives corresponding lactam amine substituted ether linked bisaryl ester. Further hydrolysis of this ester with NaOH in MeOH/H_2O gives desired product **5**.

Alternatively, alcohol **2** may be converted to additional compounds of the invention as previously described via a four step sequence involving conversion to the chloride using thionyl chloride, displacement of chloride with an appropriate amine, reaction of the amine with the appropriate acid or sulfonyl chloride followed by hydrolysis to produce **7**. Alternatively, when R_2 in **8** is a sulphonamide or amine, hydrolysis to the acid can provide **7**.

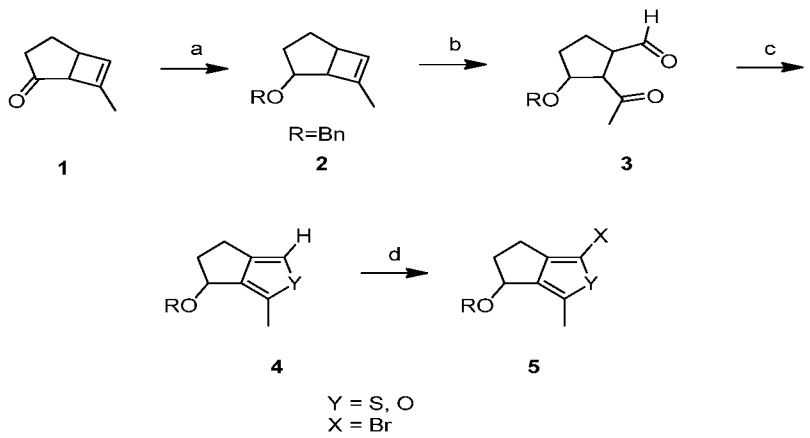
Scheme 45



Conditions: bis(tri-t-butylphosphine)palladium(0), ethyl acrylate, N-cyclohexyl-N-methylcyclohexanamine

Scheme **45** represents a general scheme for the preparation of compounds according to Formula I or II. In this scheme, the R groups are the defined substituents for B in Formula I and II. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Reaction of the appropriate aryl halide under Heck conditions produces the desired acrylate **2**. This may be carried forward to compounds of the invention as described previously via Heck coupling and further elaboration.

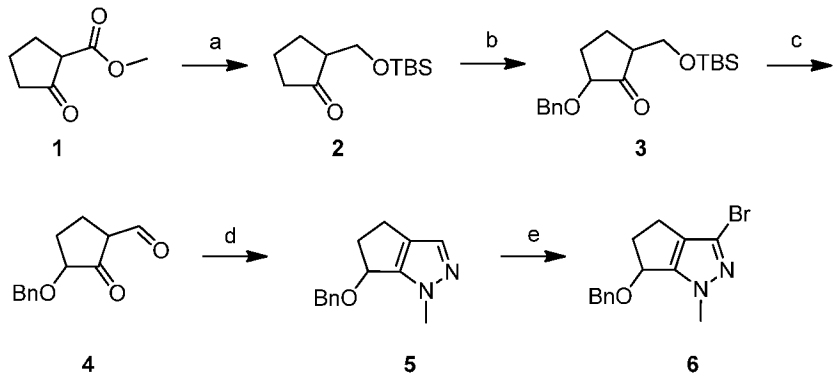
Scheme 46



Conditions: a) i) $NaBH_4$, EtOH, ii) Base, RCl; b) O3; c) P_2S_5 (or) P_2O_5; d) NBS

Scheme **46** represents a general scheme for the preparation of compounds according to Formula II. Starting material **1** is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Reduction of the ketone to the alcohol followed by introduction of a protecting group provides **2**. Subsequent ozonolysis and cyclization to either the furan or thiophene provides the intermediate heterocycle 4. Conversion to the required bromide is accomplished with NBS. The resulting bromide can be used to couple under Heck conditions with the appropriate acrylate as outlined above.

Scheme 47



Conditions: a) i) Ethylene glycol, H+; ii) LAH; iii) H+ ; iv) TBSCl, Imidazole, DMF; b) i) TEA, DCM, TMSCl, mCPBA; ii) BnBr, NaH; c) i) TBAF; ii) Dess-Martin periodinane, DCM; d) Methyl hydrazine; e) NBS

Scheme **47** represents a general scheme for the preparation of intermediates used in preparing compounds according to Formula II. Starting material **1** is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible. Protection of the ketone of **1** as the ethylene glycol ketal followed by reduction of the ester to the alcohol and subsequent deprotection of the ketal and protection of the alcohol as the TBS ether provides intermediate **2**. Oxidation of the alpha position of the ketone via a Rubottom oxidation followed by protecting the alcohol as the benzyl ether provides **3**. Further transformation to keto-aldehyde **4** may be accomplished via removal of the TBS protecting group followed by oxidation of the primary alcohol. Completion of the required intermediate **6** may be accomplished via reaction with methyl hydrazine to provide the pyrazole followed by bromination using NBS. This intermediate may be progressed compounds of the invention as previously described.

Biological Activity

As stated above, the compounds according to Formula I are NRF2 activators, and are useful in the treatment or prevention of human diseases that exhibit oxidative stress components such as respiratory and non-respiratory disorders, including COPD, asthma, ALI, ARDS, fibrosis, chronic and acute asthma, lung disease secondary to environmental

exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disesase (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Nonalcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

The biological activity of the compounds according to Formula I can be determined using any suitable assay for determining the activity of a candidate compound as a Nrf2 activator, as well as tissue and in vivo models.

The biological activity of the compounds of Formula (I) or Formula (II) are demonstrated by the following tests.

BEAS-2B NQO1 MTT Assay

NAD(P)H:quinone oxidoreductase 1 (NQO1), also called DT diaphorase, is a homodimeric FAD-containing enzyme that catalyzes obligatory NAD(P)H-dependent two-electron reductions of quinones and protects cells against the toxic and neoplastic effects of free radicals and reactive oxygen species arising from one-electron reductions. The transcription of NQO1 is finely regulated by NRF2, and thus NQO1 activity is a good marker for NRF2 activation. On day one, frozen BEAS-2B cells (ATCC) were thawed in a water bath, counted, and re-suspended at a concentration of 250,000 cells/mL. Fifty microliters of cells were plated in 384 well black clear-bottomed plates. Plates were incubated at 37°C, 5% CO_2 overnight. On day two, plates were centrifuged and 50nL of compound or controls were added to the cells. Plates were then incubated at 37°C, 5% CO_2 for 48 hours. On day

four, medium was aspirated from the plate and crude cell lysates were made by adding 13uL of 1X Cell Signaling Technologies lysis buffer with 1 Complete, Mini, EDTA-free Protease Inhibitor Tablet (Roche) for each 10mL of lysis buffer. After lysis plates were incubated for 20 minutes at room temperature. Two microliters of lysate were removed for use in Cell Titer Glo assay (Promega) and MTT cocktail was prepared (Prochaska et. al. 1998) for measurement of NQO1 activity. Fifty microliters of MTT cocktail was added to each well, plate was centrifuged, and analyzed on an Envision plate reader (Perkin Elmer) using Absorbance 570nm label for 30 minutes. Product formation was measured kinetically and the pEC_{50} of NQO1 specific activity induction was calculated by plotting the change in absorbance (Delta OD/min) versus the log of compound concentration followed by 3-parameter fitting.

All examples described herein possessed activity in the BEAS-2B cell assay unless otherwise noted (see table below). EC_{50}s <1nM (+++++), EC_{50}s 1nM-10nM (++++), EC_{50}s 10nM-100nM (+++), EC_{50}s 100nM-1uM (++), EC_{50}s 1uM-10uM (+).

Ex	EC50
1	+++++
2	+++++
3	+++++
4	+++
5	++
6	++
7	+
8	+
9	+

Methods of Use

The compounds of the invention are NRF2 activators, and are useful in the treatment or prevention of respiratory and non-respiratory disorders, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD),

Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disesase (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

Accordingly, in another aspect the invention is directed to methods of treating such conditions.

The methods of treatment of the invention comprise administering a safe and effective amount of a compound according to Formula I or a pharmaceutically-acceptable salt thereof to a patient in need thereof.

As used herein, "treat" in reference to a condition means: (1) to ameliorate or prevent the condition or one or more of the biological manifestations of the condition, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the condition or (b) one or more of the biological manifestations of the condition, (3) to alleviate one or more of the symptoms or effects associated with the condition, or (4) to slow the progression of the condition or one or more of the biological manifestations of the condition.

The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological manifestation thereof.

As used herein, "safe and effective amount" in reference to a compound of the invention or other pharmaceutically-active agent means an amount of the compound sufficient to treat the patient's condition but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the

condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be routinely determined by the skilled artisan.

As used herein, "patient" refers to a human or other animal.

The compounds of the invention may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration, rectal administration, and administration by inhalation. Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. Topical administration includes application to the skin as well as intraocular, otic, intravaginal, and intranasal administration.

The compounds of the invention may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

Typical daily dosages may vary depending upon the particular route of administration chosen. Typical dosages for oral administration range from 1 mg to 1000 mg per person per day. Preferred dosages are 1 – 500 mg once daily, more preferred is 1 – 100 mg per

person per day. IV dosages range form 0.1-000mg/day, preferred is 0.1-500mg/day, and more preferred is 0.1-100mg/day. Inhaled daily dosages range from 10ug-10mg/day, with preferred 10ug-2mg/day, and more preferred 50ug-500ug/day.

Additionally, the compounds of the invention may be administered as prodrugs. As used herein, a "prodrug" of a compound of the invention is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of the invention in vivo. Administration of a compound of the invention as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of the compound in vivo; (b) modify the duration of action of the compound in vivo; (c) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome a side effect or other difficulty encountered with the compound. Typical functional derivatives used to prepare prodrugs include modifications of the compound that are chemically or enzymatically cleaved in vivo. Such modifications, which include the preparation of phosphates, amides, ethers, esters, thioesters, carbonates, and carbamates, are well known to those skilled in the art.

Compositions

The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. Accordingly, in another aspect the invention is directed to pharmaceutical compositions comprising a compound of the invention and one or more pharmaceutically-acceptable excipient.

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of the invention can be extracted and then given to the patient such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a safe and effective amount of a compound of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically contain from 1 mg to 1000 mg.

The pharmaceutical compositions of the invention typically contain one compound of the invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. For example, in certain embodiments the pharmaceutical compositions of the invention contain two compounds of the invention. In addition, the pharmaceutical compositions of the invention may optionally further comprise one or more additional pharmaceutically active compounds.

As used herein, "pharmaceutically-acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must of course be of sufficiently high purity to render it pharmaceutically-acceptable.

The compound of the invention and the pharmaceutically-acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as dry powders, aerosols, suspensions, and solutions; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants,

preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a safe and effective amount of a compound of the invention and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

In another aspect, the invention is directed to a dosage form adapted for administration to a patient parenterally including subcutaneous, intramuscular, intravenous or intradermal. Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include

suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

In another aspect, the invention is directed to a dosage form adapted for administration to a patient by inhalation. For example, the compound of the invention may be inhaled into the lungs as a dry powder, an aerosol, a suspension, or a solution.

Dry powder compositions for delivery to the lung by inhalation typically comprise a compound of the invention as a finely divided powder together with one or more pharmaceutically acceptable excipients as finely divided powders. Pharmaceutically acceptable excipients particularly suited for use in dry powders are known to those skilled in the art and include lactose, starch, mannitol, magnesium stearate and mono-, di-, and polysaccharides.

The dry powder compositions for use in accordance with the present invention are administered via inhalation devices. As an example, such devices can encompass capsules and cartridges of for example gelatin, or blisters of, for example, laminated aluminum foil. In various embodiments, each capsule, cartridge or blister may contain doses of composition according to the teachings presented herein. Examples of inhalation devices can include those intended for unit dose or multi-dose delivery of composition, including all of the devices set forth herein. As an example, in the case of multi-dose delivery, the formulation can be pre-metered (e.g., as in Diskus®, see GB2242134, U.S. Patent Nos. 6,032,666, 5,860,419, 5,873,360, 5,590,645, 6,378,519 and 6,536,427 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Pat. Nos. 4,778,054, 4,811,731, 5,035,237) or metered in use (e.g., as in Turbuhaler, see EP 69715, or in the devices described in U.S. Patent No 6,321,747). An example of a unit-dose device is Rotahaler (see GB 2064336). In one embodiment, the Diskus® inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing the compound optionally with other excipients and additive taught herein. The peelable seal is an engineered seal, and in one embodiment the engineered seal is a hermetic seal. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the leading end portions is constructed to be attached to a

winding means. Also, preferably the engineered seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the base sheet.

A dry powder composition may also be presented in an inhalation device which permits separate containment of two different components of the composition. Thus, for example, these components are administrable simultaneously but are stored separately, e.g., in separate pharmaceutical compositions, for example as described in WO 03/061743 A1 WO 2007/012871 A1 and/or WO2007/068896, as well as U.S. Patent Nos. 8,113,199, 8,161,968, 8,511,304, 8,534,281, 8,746,242 and 9,333,310.

In one embodiment an inhalation device permitting separate containment of components is an inhaler device having two peelable blister strips, each strip containing pre-metered doses in blister pockets arranged along its length, e.g., multiple containers within each blister strip, e.g., as found in ELLIPTA®. Said device has an internal indexing mechanism which, each time the device is actuated, peels opens a pocket of each strip and positions the blisters so that each newly exposed dose of each strip is adjacent to the manifold which communicates with the mouthpiece of the device. When the patient inhales at the mouthpiece, each dose is simultaneously drawn out of its associated pocket into the manifold and entrained via the mouthpiece into the patient's respiratory tract. A further device that permits separate containment of different components is DUOHALER™ of Innovata. In addition, various structures of inhalation devices provide for the sequential or separate delivery of the pharmaceutical composition(s) from the device, in addition to simultaneous delivery.

Aerosols may be formed by suspending or dissolving a compound of the invention in a liquefied propellant. Suitable propellants include halocarbons, hydrocarbons, and other liquefied gases. Representative propellants include: trichlorofluoromethane (propellant 11), dichlorofluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), tetrafluoroethane (HFA-134a), 1,1-difluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-12), heptafluoropropane (HFA- 227a), perfluoropropane, perfluorobutane, perfluoropentane, butane, isobutane, and pentane. Aerosols comprising a compound of the invention will typically be administered to a patient *via* a metered dose inhaler (MDI). Such devices are known to those skilled in the art.

The aerosol may contain additional pharmaceutically acceptable excipients typically used with multiple dose inhalers such as surfactants, lubricants, cosolvents and other

excipients to improve the physical stability of the formulation, to improve valve performance, to improve solubility, or to improve taste.

Suspensions and solutions comprising a compound of the invention may also be administered to a patient *via* a nebulizer. The solvent or suspension agent utilized for nebulization may be any pharmaceutically acceptable liquid such as water, aqueous saline, alcohols or glycols, e.g., ethanol, isopropyl alcohol, glycerol, propylene glycol, polyethylene glycol, etc. or mixtures thereof. Saline solutions utilize salts which display little or no pharmacological activity after administration. Both organic salts, such as alkali metal or ammonium halogen salts, e.g., sodium chloride, potassium chloride or organic salts, such as potassium, sodium and ammonium salts or organic acids, e.g., ascorbic acid, citric acid, acetic acid, tartaric acid, etc. may be used for this purpose.

Other pharmaceutically acceptable excipients may be added to the suspension or solution. The compound of the invention may be stabilized by the addition of an inorganic acid, e.g., hydrochloric acid, nitric acid, sulfuric acid and/or phosphoric acid; an organic acid, e.g., ascorbic acid, citric acid, acetic acid, and tartaric acid, etc., a complexing agent such as EDTA or citric acid and salts thereof; or an antioxidant such as antioxidant such as vitamin E or ascorbic acid. These may be used alone or together to stabilize the compound of the invention. Preservatives may be added such as benzalkonium chloride or benzoic acid and salts thereof. Surfactant may be added particularly to improve the physical stability of suspensions. These include lecithin, disodium dioctylsulphosuccinate, oleic acid and sorbitan esters.

The compounds of Formula (I) or Formula (II) and pharmaceutically acceptable salts thereof may be used in combination with one or more other agents which may be useful in the prevention or treatment of allergic disease, inflammatory disease, autoimmune disease, for example; antigen immunotherapy, anti-histamines, corticosteroids, (e.g., fluticasone propionate, fluticasone furoate, beclomethasone dipropionate, budesonide, ciclesonide, mometasone furoate, triamcinolone, flunisolide), NSAIDs, leukotriene modulators (e.g., montelukast, zafirlukast, pranlukast), iNOS inhibitors, tryptase inhibitors, IKK2 inhibitors, p38 inhibitors, Syk inhibitors, protease inhibitors such as elastase inhibitors, integrin antagonists (e.g., beta-2 integrin antagonists), adenosine A2a agonists, mediator release inhibitors such as sodium chromoglycate, 5-lipoxygenase inhibitors (zyflo), DP1 antagonists, DP2 antagonists, PI3K delta inhibitors, ITK inhibitors, LP (lysophosphatidic) inhibitors or FLAP (5-lipoxygenase activating protein) inhibitors (e.g., sodium 3-(3-(tert-butylthio)-1-(4-(6-ethoxypyridin-3-yl)benzyl)-5-((5-methylpyridin-2-yl)methoxy)-1H-indol-2-yl)-2,2-

dimethylpropanoate), bronchodilators (e.g., muscarinic antagonists, beta-2 agonists), methotrexate, and similar agents; monoclonal antibody therapy such as anti-IgE, anti-TNF, anti-IL-5, anti-IL-6, anti-IL-12, anti-IL-1 and similar agents; cytokine receptor therapies e.g. etanercept and similar agents; antigen non-specific immunotherapies (e.g. interferon or other cytokines/chemokines, chemokine receptor modulators such as CCR3, CCR4 or CXCR2 antagonists, other cytokine/chemokine agonists or antagonists, TLR agonists and similar agents).

A compound of the invention that enhances NRF2 target gene expression may offer additional benefits when combined with a therapy that inhibits cell stress responses. The unfolded protein response (UPR) and integrated stress response (ISR) are critical protective pathways that can become maladaptive under conditions of chronic stress and aging (Martinez et al, 2017. Aging Cell, 1-9.; Pakos-Zebrucka et al, 2016. EMBO Reports. DOI 10.15252/embr.201642195;). Both the UPR and ISR pathways repress global protein translation through the phosphorylation of the alpha subunit of eukaryotic initiation factor-2 (eIF2α), effected by a family of four eIF2α kinases (PERK, PKR, HRI, and GCN2). Increased eIF2α phosphorylation and a corresponding decrease in protein synthesis is observed broadly in neurodegenerative diseases, which can significantly impact synaptic plasticity and contribute to cognitive decline (Moon et al. 2018. Trends Mol. Med. https://doi.org/10.1016/j.molmed.2018.04.001; Trinh and Klann, 2013. Neurobio Learning Memory, 105, 93-99). Moreover, pathological hallmarks of UPR and ISR activation found in brain specimens are frequently associated with oxidative stress and in diseases of aging and neurodegeneration (Hoozemans et al, 2005. Acta Neuropathol 110, 165-172; Scheper and Hoozemans, 2016. Acta Neuropath, DOI 10.1007/s00401-015-1462-8; Stutzbach et al. 2013. Acta Neuropathol Comm, 1, 31, http://www.actaneurocomms.org/content/1/1/31). Hence, compounds that block stress response signaling and translational repression, such as UPR inhibitors, eIF2α kinase inhibitors, or enhancers of eIF2B activity have emerged as potential therapies for neurodegenerative diseases and cognitive disorders.(Smith and Mallucci, 2016. Brain, doi:10.1093/brain/aww101; Freeman and Mallucci, 2016. Brain Res. http://dx.doi.org/10.1016/j.brainres.2016.03.029; Sidrauski et al., 2013. eLIFE, 2:e00498, DOI: 10.7554/eLife.00498).

NRF2 is a protective stress-responsive protein activated during the UPR with reported dependence on PERK kinase activity (Cullinan et al., 2003. Mol Cell Biol, 23, 7198-7209). However, in disease relevant situations of chronic stress and maladaptive UPR signaling, NRF2 function can be exhausted or compromised by defective nuclear trafficking. For example, evidence of NRF2 localization defects have been reported in Alzheimer's

disease, Lewy body dementia, and progeria (Ramsey et al., 2007. J Neuropathol Exp Neurol, 66, 75-85; Kubben et al., 2016. Cell, 165, 1361-1374). The loss of NRF2 target gene transcription during chronic UPR and ISR activation when protein synthesis is repressed may further enhance or accelerate disease pathogenesis, making cells and neurons more vulnerable to apoptosis. Thus, an activator of NRF2 activity in combination with a stress response inhibitor could provide significant therapeutic benefit by increasing both the protective antioxidant response and sustaining synaptic plasticity through restoration of global translation.

Suitably, for the treatment of asthma, compounds or pharmaceutical formulations of the invention may be administered together with an anti-inflammatory agent such as, for example, a corticosteroid, or a pharmaceutical formulation thereof. For example, a compound of the invention may be formulated together with an anti-inflammatory agent, such as a corticosteroid, in a single formulation, such as a dry powder formulation for inhalation. Alternatively, a pharmaceutical formulation comprising a compound of the invention may be administered in conjunction with a pharmaceutical formulation comprising an anti-inflammatory agent, such as a corticosteroid, either simultaneously or sequentially. In one embodiment, a pharmaceutical formulation comprising a compound of the invention and a pharmaceutical formulation comprising an anti-inflammatory agent, such as a corticosteroid, may each be held in device suitable for the simultaneous administration of both formulations via inhalation.

Suitable corticosteroids for administration together with a compound of the invention include, but are not limited to, fluticasone furoate, fluticasone propionate, beclomethasone diproprionate, budesonide, ciclesonide, mometasone furoate, triamcinolone, flunisolide and prednisilone. In one embodiment of the invention a corticosteroids for administration together with a compound of the invention via inhalation includes fluticasone furoate, fluticasone propionate, beclomethasone diproprionate, budesonide, ciclesonide, mometasone furoate, and, flunisolide.

Suitably, for the treatment of COPD, compounds or pharmaceutical formulations of the invention may be administered together with one or more bronchodilators, or pharmaceutical formulations thereof. For example, a compound of the invention may be formulated together with one or more bronchodilators in a single formulation, such as a dry powder formulation for inhalation. Alternatively, a pharmaceutical formulation comprising a compound of the invention may be administered in conjunction with a pharmaceutical formulation comprising one or more bronchodilators, either simultaneously or sequentially.

In a further alternative, a formulation comprising a compound of the invention and a bronchodilator may be administered in conjunction with a pharmaceutical formulation comprising a further bronchodilator. In one embodiment, a pharmaceutical formulation comprising a compound of the invention and a pharmaceutical formulation comprising one or more bronchodilators may each be held in device suitable for the simultaneous administration of both formulations via inhalation. In a further embodiment, a pharmaceutical formulation comprising a compound of the invention together with a bronchodilator and a pharmaceutical formulation comprising a further bronchodilator may each be held in one or more devices suitable for the simultaneous administration of both formulations via inhalation.

Suitable bronchodilators for administration together with a compound of the invention include, but are not limited to, β_2-adrenoreceptor agonists and anticholinergic agents. Examples of β_2-adrenoreceptor agonists, include, for example, vilanterol, salmeterol, salbutamol, formoterol, salmefamol, fenoterol carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerbuterol, reproterol, bambuterol, indacaterol, terbutaline and salts thereof, for example the xinafoate (1-hydroxy-2-naphthalenecarboxylate) salt of salmeterol, the sulphate salt of salbutamol or the fumarate salt of formoterol. Suitable anticholinergic agents include umeclidinium (for example, as the bromide), ipratropium (for example, as the bromide), oxitropium (for example, as the bromide) and tiotropium (for example, as the bromide). In one embodiment of the invention, a compound of the invention may be administered together with a β_2-adrenoreceptor agonist, such as vilanterol, and an anticholinergic agent, such as, umeclidinium.

The compounds may also be used in combination with agents for aiding transplantation including Cyclosporines, Tacrolimus, Mycophenolate mofetil, Prednisone, Azathioprine , Sirolimus, Daclizumab, Basiliximab and OKT3.

They may also be used in combination with agents for Diabetes: metformin (biguanides), meglitinides, sulfonylureas, DPP-4 inhibitors, Thiazolidinediones, Alpha-glucosidase inhibitors, Amylin mimetics, Incretin mimetics and insulin.

The compounds may be used in combination with antihypertensives such as diuretics, ACE inhibitors, ARBS, calcium channel blockers, and beta blockers.

One embodiment of the invention encompasses combinations comprising one or two other therapeutic agents. It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower

alkyl esters, or as solvates, for example hydrates to optimize the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. In one embodiment, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents will readily be appreciated by those skilled in the art.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of the invention together with another therapeutically active agent.

EXAMPLES

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

All temperatures are given in degrees Celsius, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon (Ar) or nitrogen (N_2) atmosphere where necessary.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. The CombiFlash® system used for purification in this application was purchased from Isco, Inc. CombiFlash® purification was carried out using prepacked silica gel columns, a detector with UV wavelength at 254 nm and a variety of solvents or solvent combinations.

Preparative HPLC was performed using a Gilson Preparative System with variable wavelength UV detection or an Agilent Mass Directed AutoPrep (MDAP) system with both mass and variable wavelength UV detection or Waters Preparative System with UV/PDA detection or an Shimadzu PREP LC 20AP. A variety of reverse phase columns, e.g., Luna 5m C18(2) 100A, SunFire C18, XBridge C18, Atlantics T3, Kromasil C18, Xbridge Phenyl-Hexyl, were used in the purification with the choice of column support dependent upon the conditions used in the purification. The compounds are eluted using a gradient of CH_3CN and water. Neutral conditions used an CH_3CN and water gradient with no additional modifier, acidic conditions used an acid modifier, 0.1% TFA (added to both the CH_3CN and water) or 0.1 % formic acid, and basic conditions used a basic modifier, usually 0.1% NH_4OH (added to the water) or 10 mM ammonium bicarbonate (added to the water), or 0.05 % NH_4HCO_3 (added to water).

Analytical HPLC was run using an Agilent system, Shimadzu/Sciex LCMS with variable wavelength UV detection using reverse phase chromatography with a CH_3CN and water gradient with a 0.02 or 0.1% TFA modifier (added to each solvent). LC-MS was determined using either a PE Sciex Single Quadrupole 150EX LC-MS, or Waters ZQ Single Quadrupole LC-MS or Agilent 1200 series SL (dectectors: Agilent 6140 single quadrupole and Agilent 1200 MWD SL) instruments. The compound is analyzed using a reverse phase column, e.g., Thermo Hypersil Gold C18, eluted using a gradient of CH_3CN and water with a low percentage of an acid modifier such as 0.02% TFA or 0.1 % formic acid or a base modifier such as 5mM ammonium bicarbonate (adjusted to pH 10 with aqueous ammonia). When specified “acid method” refers to 0.1 % formic acid in water and CH_3CN gradient (1.8 min. 0.9 mL/min flow) with a Waters Acquity UPLC HSS C18; 1.8μ; 2.1x50mm at 50 °C; “basic method” refers to 95:5 H_2O+0.1% NH_4OH:CH_3CN (pH = 9.4) and water gradient (1.8 min. 0.9 mL/min flow) with a Waters Acquity UPLC BEH C18; 1.7μ; 2.1x50mm at 50 °C and “overnight basic method” refers to 95:5 H_2O+0.1% NH_4OH:CH_3CN (pH = 9.4) and water gradient (16 min. 0.8 mL/min flow) with a Waters Acquity UPLC BEH C18; 1.7μ; 2.1x50mm at 50 °C.

Preparative Chiral SFC was performed using a Thar/Waters Preparative SFC System with single wavelength UV detection system or PDA detector. A variety of chiral SFC columns, e.g. Chiralpak IA, IC, AY, AD. OD, OJ, C2 were used in the purification. The compounds are eluted using supercritical fluid CO_2 and co-solvents, such as MeOH, EtOH, IPA, and combination of these solvent in different ratio based on the compound selectivity. Modifiers (0.1% of TFA, NH_4OH, DEA) would be used as needed.

Analytical Chiral SFC was run using a Thar/Waters SFC system with variable wavelength UV detection or PDA detector. A variety of chiral SFC columns, e.g. Chiralpak IA, IB, IC, ID, AY, AD, AS, CCL4 were used in the purification. The compounds are eluted using supercritical fluid CO_2 and co-solvents, such as MeOH, EtOH, IPA, and combination of these solvent in different ratio based on the compound selectivity. Modifiers (0.1% of TFA, NH_4OH, DEA) would be used as needed.

Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado. Isolute® is a functionalized silica gel based sorbent, and is a registered trademark of Biotage AB Corp., Sweden.

Nuclear magnetic resonance spectra were recorded at 400 MHz using a Bruker AVANCE 400 or Brucker DPX400 or Varian MR400 400 MHz spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-D_6 is hexadeuteriodimethylsulfoxide, and MeOD is tetradeuteriomethanol, CD_2Cl_2 is deuteriodichloromethane. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS) or calibrated to the residual proton signal in the NMR solvent (e.g., $CHCl_3$ in $CDCl_3$). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. *J* indicates the NMR coupling constant measured in Hertz.

Heating of reaction mixtures with microwave irradiations was carried out on a Biotage Initiator® or CEM microwave reactor, typically employing the high absorbance setting.

Cartridges or columns containing polymer based functional groups (acid, base, metal chelators, etc) can be used as part of compound workup. The "amine" columns or cartridges are used to neutralize or basify acidic reaction mixtures or products. These include NH_2 Aminopropyl SPE-ed SPE Cartridges available from Applied Separations and diethylamino SPE cartridges available from United Chemical Technologies, Inc.

Table of Abbreviations

$[Rh(cod)Cl]_2$ or $[RhCl(cod)]_2$: di-μ-chlorido-bis[η^2,η^2-(cycloocta-1,5-diene)rhodium
®T3P: 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide
ºC: degree Celsius
AcOH: acetic acid
ADDP: (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone)

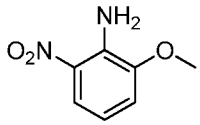
aq = aqueous
BINAP: 2,2'-bis(diphenylphosphino)-1,1'- binaphthalene
CDI: Carbonyl dimidazole
CH_2Cl_2: dichloromethane
CH_3CN: acetonitrile
$CHCl_3$: chloroform
Cs_2CO_3: cesium carbonate
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE: dichloromethane
DCM: dichloromethane
DIPEA or DIEA: diisopropylethyl amine
DME: dimethyl ether
DMF: *N,N*-dimethylformamide
DMF-DMA or DMF-dimethyl acetal: N,N-dimethylformaide-dimethyl acetal
DMSO: dimethyl sulfoxide
EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et_2O: diethyl ether
Et_3N: triethylamine
EtOAc: ethyl acetate
EtOH: ethanol
g: gram(s)
h: hour(s)
HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU: N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate
HCl: hydrochloric acid
HOAt: 1-hydroxy-7-azabenzotriazole
HPLC: high performance liquid chromatography
IPA: isopropyl alcohol
K_2CO_3: potassium carbonate
KOAc: potassium acetate
LAH: lithium aluminum hydride
LC: liquid chromatography

LC-MS: liquid chromatography-mass spectroscopy
$LiBH_4$: lithium borohydride
LiHMDS: lithium hexamethyldisilazane
LiOH: lithium hydroxide
M: molar
MeCN: acetonitrile
MeI: methyl iodide
MeOH: methanol
mg: milligram(s)
$MgCl_2$: magnesium chloride
$MgSO_4$: magnesium sulfate
MHz: megahertz
min: minute(s)
mL: milliliter(s)
mmol: millimole(s)
MS: mass spectroscopy
N_2: nitrogen gas
Na_2CO_3: sodium carbonate
Na_2SO_4: sodium sulfate
$NaBH_3CN$ or $NaCNBH_3$: sodium cyanoborohydride
NaCl: sodium chloride
NaH: sodium hydride
$NaHCO_3$: sodium bicarbonate
NaHMDS: sodium hexamethyldisilazane
$NaHSO_4$: sodium bisulfate
NaOAc: sodium acetate
NaOH: sodium hydroxide
NBS: N-bromosuccinimide
nBuLi: n-butyl lithium
NH_4Cl: ammonium chloride
NMR: nuclear magnetic resonance
$P(tBu)_3$: tri-t-butyl phosphine
$Pd(PhP_3)_4$: tetrakistriphenylphosphine palladium
Pd/C: pallidium on carbon

$Pd_2(dba)_3$: *tris*(dibenzylideneacetone)-dipalladium(0)
$PdCl_2(dppf)$ or $Pd(dppf)Cl_2$: [1,1'-*bis*(diphenylphosphino)-ferrocene] dichloropalladium(II)
Petrol: petroleum ether
PS-PPh_3: polymer supported triphenylphosphine
PtO_2: platinum(IV) oxide
RT: room temperature
T3P: 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide solution
TEA: triethylamine
TFA: trifluoroacetic acid
TFFH: tetrafluoroformamidinium hexafluorophosphate
THF: tetrahydrofuran
triflic anhydride: trifluoromethanesulfonic anhydride
TsOH: p-toluenesulfonic acid
wt%: weight percent

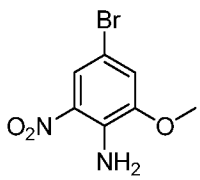
Intermediates

Intermediate 1: 2-Methoxy-6-nitroaniline



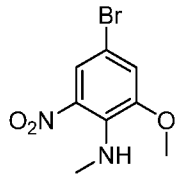
To a solution of 2-amino-3-nitrophenol (35 g, 227 mmol) in DMF (400 mL), K_2CO_3 (37.7 g, 273 mmol) and MeI (17.04 mL, 273 mmol) were added at ambient temperature. The reaction mixture was stirred at ambient temperature for 16 h. Then it was poured into water. The resulting precipitate was collected by filtration and the solid was washed with water to give 35 g (89%) of the title compound. LC-MS *m/z* 168.9 $(M+H)^+$, 1.71 (ret. time).

Intermediate 2: 4-Bromo-2-methoxy-6-nitroaniline



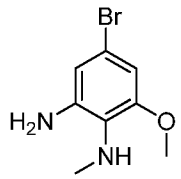
To a solution of 2-methoxy-6-nitroaniline (35 g, 208 mmol) in Acetic Acid (500 mL), NaOAc (27.3 g, 333 mmol) and bromine (11.80 mL, 229 mmol) were added. Then the reaction mixture was stirred at ambient temperature for 20 min. The resulting precipitate was filtered and washed with water and dried in-vacuum pump to give 50 g (95%) of the title compound. LC-MS *m/z* 248.9 $(M+H)^+$, 1.78 (ret. time).

Intermediate 3: 4-Bromo-2-methoxy-N-methyl-6-nitroaniline



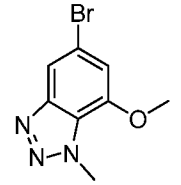
To a solution of 4-bromo-2-methoxy-6-nitroaniline (50 g, 202 mmol) in DMF (400 mL) at 0 °C, NaH (5.83 g, 243 mmol) was added. After 30 min, MeI (13.92 mL, 223 mmol) was added and the reaction mixture was stirred 30 min further. Water (1000 mL) was added. The red precipitate was collected by filtration and washed with water, dried to give 50 g (71.8%) of the title compound. LC-MS *m/z* 263.0 $(M+H)^+$, 1.86 (ret. time).

Intermediate 4: 4-Bromo-6-methoxy-N1-methylbenzene-1,2-diamine



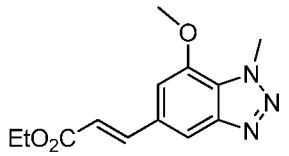
To 4-bromo-2-methoxy-N-methyl-6-nitroaniline (25 g, 96 mmol) in acetic acid (300 mL), zinc (18.78 g, 287 mmol) was added in small portions. Then the reaction mixture was stirred at ambient temperature for 10 h. The reaction mixture was filtered through celite and the solid was washed copiously with EtOAc. The combined solutions were concentrated to give 20 g (27.6%) of the title compound. LC-MS *m/z* 233.0 $(M+H)^+$, 1.25 (ret. time).

Intermediate 5: 5-Bromo-7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazole



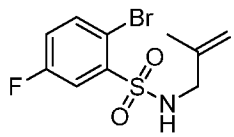
To 4-bromo-6-methoxy-N1-methylbenzene-1,2-diamine (40 g, 173 mmol) in 100 mL of 10% H_2SO_4 at 0 °C, $NaNO_2$ (16.72 g, 242 mmol) was added in small portions over a 20 minute period. After the reaction mixture was stirred for 30 min further, 200 mL of water was added. The resulting precipitate was collected by filtration, washed with water and dried. The mother liquid was left to stand 16 h and a second batch of precipitate formed, which was collected as before. The combined solids were columned in EtOAc to remove inorganic salts, to give 15 g (35.8%) of the title compound. LC-MS *m/z* 244.0 $(M+H)^+$, 1.68 (ret. time).

Intermediate 6: (E)-Ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate



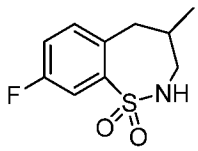
To a solution of 5-bromo-7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazole (10 g, 41.3 mmol) in dry DMF (10 mL), ethyl acrylate (20.68 g, 207 mmol), DIPEA (18.04 mL, 103 mmol), and tri-o-tolylphosphine (2.51 g, 8.26 mmol) were added, followed by $Pd(OAc)_2$ (0.927 g, 4.13 mmol). The reaction was heated to 95 °C under a nitrogen atmosphere for 4 h. The reaction mixture was diluted with water and extracted with EtOAc (x3). Combined organic fractions were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (10-50% EtOAc/Petrol) to give 9.2 g (83%) of the title compound. LC-MS *m/z* 262.1 $(M+H)^+$, 1.70 (ret. time).

Intermediate 7: 2-Bromo-5-fluoro-N-(2-methylallyl)benzenesulfonamide



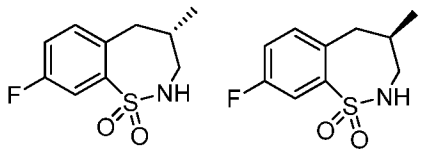
To a solution of 2,5-dibromobenzene-1-sulfonyl chloride (25 g, 74.8 mmol) in dichloromethane (250 mL) 2-methylprop-2-en-1-amine (5.32 g, 74.8 mmol) and TEA (10.42mL, 74.8 mmol) was added at 0°C and stirred for 10 min. The reaction was then stirred at ambient temperature for 16h. The reaction mixture was quenched with ice cold water (50 mL) and extracted with DCM (2 X 100mL). The combined organic layers were washed with ice cold water (2 X 50mL), washed with brine (50mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the title compound (20 g,44.3 mmol, 59.3% yield), LCMS *m/z* 308 $(M+H)^+$, 2.23 min (ret. time).

Intermediate 8: 8-Fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide



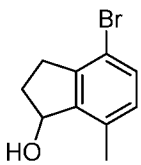
To a solution of 2-bromo-5-fluoro-N-(2-methylallyl)benzenesulfonamide (6.5 g, 20.04 mmol) in toluene (50 mL) was added AIBN (0.617 g, 3.75 mmol) at ambient temperature. The reaction mixture was heated to 75°C and tri-n-butyltin hydride (7.52 mL, 28.2 mmol) was added and stirred at 110°C for 18h. The reaction mixture was quenched with ice cold water (40 mL) and extracted with ethyl acetete (2 X 50mL). The combined organic layers were washed with ice cold water (2 X 50mL), brine (50mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash chromatography eluting with 12% EtOAc / petroleum ether to provide the title compound. (1.5 g, 33% yield) LC/MS *m/z* = 228 $(M+H)^+$, 1.97 min (ret time).

Intermediate 9: (S)-8-Fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide and (R)-8-fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide



8-fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (14 g, 59.8 mmol) was purified with chiral SFC (Column: Lux Amylose-2(250 X30)mm,5µ; Co-Solvent: 10% EtOH; Total flow rate: 100 g/min; Pressure: 100 Bar, 90% CO2) to give (S)-8-fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (5.7 g, 40% yield). LC-MS *m/z* 228 $(M+H)^+$, 2.42 min (ret. time), and (R)-8-fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (5.2 g, 36% yield). LCMS *m/z* 228 $(M+H)^+$, 2.42 min (ret. time).

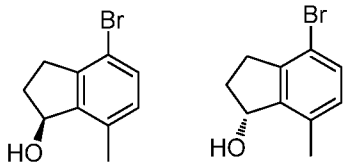
Intermediate 10: 4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol



Ethanol (20 mL) was added to a mixture of 4-bromo-7-methyl-2,3-dihydro-1H-inden-1-one (0.450 g, 1.999 mmol) and sodium borohydride (0.081 g, 2.141 mmol) at ambient temperature. The bromide appeared to dissolve slowly. After 3hr 15min the reaction was quenched via slow addition of 1N HCl until no further gas evolution was evident then diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organics extracted with brine, dried over magnesium sulfate, filtered and concentrated to give 0.445 g of a clear, light yellow oil which solidified slowly.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 2.00 - 2.17 (m, 1 H) 2.35 - 2.57 (m, 4 H) 2.77 - 2.99 (m, 1 H) 3.13 (dt, J=16.50, 7.94 Hz, 1 H) 5.39 (d, J=6.53 Hz, 1 H) 6.92 (d, J=7.78 Hz, 1 H) 7.33 (d, J=7.78 Hz, 1 H)

Intermediate 11: (S)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol and **(R)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol**



Ethanol (200 mL) was added to a mixture of 4-bromo-7-methyl-2,3-dihydro-1H-inden-1-one (4.481 g, 19.91 mmol) and sodium borohydride (0.818 g, 21.62 mmol) at ambient temperature. The bromide appeared to dissolve slowly. After 16hr 30min the reaction was quenched via slow addition of 1N HCl until no further gas evolution was evident then diluted with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (1x) and the combined organics extracted with water (1x), brine, dried over magnesium sulfate, filtered and concentrated to give 4.57 g of a light yellow solid. This was purified by chiral SFC. The first eluting fraction gave 1.885 g of a light yellow solid and was identified via vibrational circular dichroism to be (R)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol. The second eluting fraction gave 1.945 g of a light yellow solid and was identified via vibrational circular dichroism to be (S)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol.

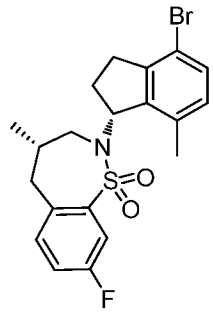
(R)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol:

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 1.99 - 2.17 (m, 1 H) 2.33 - 2.52 (m, 4 H) 2.78 - 2.95 (m, 1 H) 3.04 - 3.27 (m, 1 H) 5.40 (br. s., 1 H) 6.92 (d, *J*=7.78 Hz, 1 H) 7.34 (d, *J*=8.03 Hz, 1 H)

(S)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol:

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 1.99 - 2.18 (m, 1 H) 2.32 - 2.51 (m, 4 H) 2.86 (ddd, *J*=16.63, 9.10, 2.89 Hz, 1 H) 3.13 (dt, *J*=16.50, 7.94 Hz, 1 H) 5.39 (d, *J*=6.53 Hz, 1 H) 6.92 (d, *J*=7.78 Hz, 1 H) 7.33 (d, *J*=8.03 Hz, 1 H)

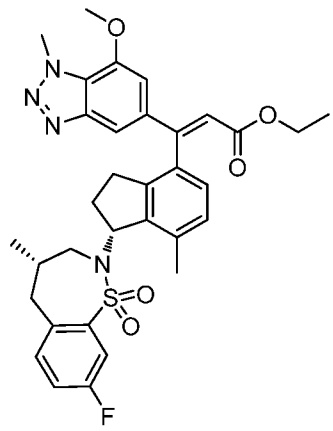
Intermediate 12: (S)-2-((R)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-yl)-8-fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide



To a solution of (S)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-ol (0.340 g, 1.497 mmol), (S)-8-fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (0.345 g, 1.505 mmol), and 1,1'-(Azodicarbonyl)dipiperidine (0.401 g, 1.589 mmol) in tetrahydrofuran (THF) (15 mL) at 0 °C was added tri-n-butyl phosphine (0.490 mL, 1.986 mmol). After 23 hr 20 mins additional 1,1'-(Azodicarbonyl)dipiperidine (0.200 g, 0.793 mmol) and tri-n-butyl phosphine (0.250 mL, 1.013 mmol) were added. After 30 hrs the reaction suspension was adsorbed onto isolute and diluted with ethyl acetate and concentrated and dried overnight under vacuum and purified via silica gel chromatography to give 0.294 g of a white solid.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.88 (br. s., 3 H) 1.50 (br. s., 1 H) 1.78 - 2.03 (m, 2 H) 2.35 (s, 3 H) 2.56 - 2.90 (m, 4 H) 3.41 - 3.75 (m, 2 H) 5.70 (d, J=8.78 Hz, 1 H) 6.94 (d, J=7.78 Hz, 1 H) 7.10 - 7.20 (m, 1 H) 7.23 - 7.32 (m, 3 H) 7.36 (d, J=8.03 Hz, 1 H) 7.71 (d, J=8.03 Hz, 1 H)

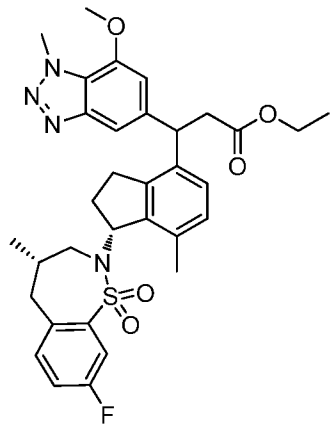
Intermediate 13: (Z)-ethyl 3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate



To a vial containing a mixture of ethyl (E)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (0.201 g, 0.769 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.038 g, 0.074 mmol), a solution of (S)-2-((R)-4-bromo-7-methyl-2,3-dihydro-1H-inden-1-yl)-8-fluoro-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (0.294 g, 0.671 mmol) in 1,4-dioxane (3.6 mL) was added followed by N-cyclohexyl-N-methylcyclohexanamine (0.175 mL, 0.817 mmol). The reaction mixture was heated at 90 °C. After 23 hr 30 min the reaction mixture was cooled, filtered, and concentrated to give 0.613 g of a brown foam. This was taken into ethyl acetate and adsorbed onto isolute and purified via silica gel chromatography to give 0.341 g of a white foam.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.72 (d, J=5.52 Hz, 3 H) 1.16 (t, J=7.03 Hz, 3 H) 1.72 (d, J=9.03 Hz, 1 H) 2.11 - 2.24 (m, 1 H) 2.26 - 2.38 (m, 1 H) 2.43 (br. s., 4 H) 2.63 (br. s., 1 H) 3.38 - 3.68 (m, 2 H) 3.89 (s, 3 H) 4.03 - 4.19 (m, 3 H) 4.45 (s, 3 H) 5.55 (d, J=8.28 Hz, 1 H) 6.14 (s, 1 H) 6.63 (s, 1 H) 7.04 - 7.25 (m, 4 H) 7.39 (s, 1 H) 7.66 (d, J=6.53 Hz, 1 H)

Intermediate 14: Ethyl 3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



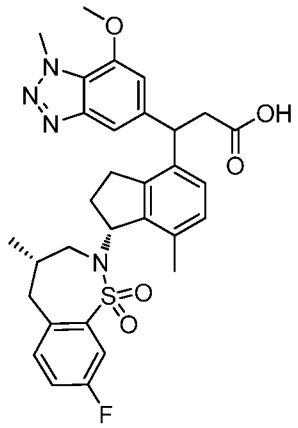
A suspension of ethyl (Z)-3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (0.341 g, 0.551 mmol) and 20% palladium hydroxide on carbon (0.187 g, 0.266 mmol) was kept under a hydrogen balloon. No progress after 16 hr 37 min. The suspension was filtered and concentrated to give 0.323 g of a white solid (39470-94-A1). This was taken into ethyl acetate and adsorbed onto isolute and purified via silica gel chromatography to give 0.198 g of a white solid. This was re-subjected to the reaction conditions as follows:

A suspension of ethyl (Z)-3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (0.198 g, 0.320 mmol) and 20% palladium hydroxide on carbon (0.178 g, 0.253 mmol) was kept under a hydrogen balloon. The reaction was followed by LC/MS. After ~17 hr 40 min additional 20% palladium hydroxide on carbon (0.179 g, 0.255 mmol) was added and the suspension kept under a balloon of hydrogen. After 90 hrs, the suspension was filtered and washed with a large quantity of ethyl acetate (Note: large amounts of ethyl acetate are required to wash the product from the catalyst) and concentrated to give 0. 173 g of a clear, colorless oil. 1H NMR is consistent with the desired product plus ethyl acetate and a small amount of starting olefin. This was taken into ethyl acetate and adsorbed onto isolute and purified via silica gel chromatography to give 0.078 g of a clear, colorless oil.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.33 (d, J=6.53 Hz, 2 H) 0.77 - 0.92 (m, 1 H) 1.08 - 1.20 (m, 3 H) 1.42 (d, J=15.31 Hz, 1 H) 1.63 (d, J=3.51 Hz, 2 H) 1.75 - 1.95 (m, 1 H) 2.11 - 2.24 (m, 1 H) 2.25 - 2.42 (m, 4 H) 2.58 (dd, J=17.07, 9.79 Hz, 1 H) 2.66 - 2.91 (m, 1 H) 2.96 - 3.17 (m, 2 H) 3.20 - 3.69 (m, 2 H) 3.87 (s, 3 H) 3.98 - 4.09 (m, 2 H) 4.35 - 4.44 (m, 3 H) 4.63 (t, J=7.78 Hz, 1 H) 5.58 (d, J=8.28 Hz, 1 H) 6.51 (s, 1 H) 7.02 - 7.20 (m, 3 H) 7.21 - 7.29 (m, 1 H) 7.29 - 7.43 (m, 1 H) 7.66 (dd, J=7.91, 2.64 Hz, 1 H)

Example 1

3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid – Stereoisomer 1 and 2.



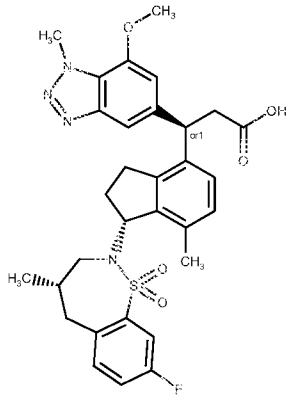
Batch 1:

To a solution of ethyl 3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.078 g, 0.126 mmol) in tetrahydrofuran (THF) (1mL) and at ambient temperature was added 1M lithium hydroxide (0.7mL, 0.700 mmol) followed by methanol (1 ml). After ~2.5 hrs, the reaction was acidified via addition of 1N HCl to pH 2-3 and extracted with ethyl acetate (2x) and concentrated to give 0.083 g of a clear, colorless residue. This was purified by reverse phase HPLC to give two fractions.

Batch 2:

To a solution of ethyl 3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.051 g, 0.082 mmol) in tetrahydrofuran (THF) (1mL) and at ambient temperature was added 1M lithium hydroxide (0.7mL, 0.700 mmol) followed by methanol (1 ml). The reaction was monitored by LC/MS. After ~2.5 hrs, the reaction was acidified via addition of 1N HCl to pH 2-3 and extracted with ethyl acetate (2x) and concentrated to give 0.056 g of a clear, colorless residue. This was purified by reverse phase HPLC to give two fractions. The individual fractions of batch 2 were combined with the respective fractions from batch 1.

Stereoisomer 1:



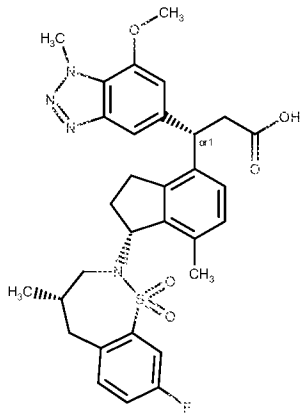
ISOMER 1

One set of combined fractions from the synthesis of 3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid (see above) gave 0.047 g of a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.25 (m, 1 H) 1.31 - 1.52 (m, 1 H) 1.72 - 2.13 (m, 2 H) 2.19 - 2.40 (m, 4 H) 2.63 - 2.87 (m, 3 H) 2.93 - 3.49 (m, 8 H) 3.81 - 3.98 (m, 3 H) 4.32 (s, 3 H) 4.48 - 4.66 (m, 1 H) 5.34 - 5.59 (m, 1 H) 6.79 (s, 1 H) 7.05 - 7.26 (m, 2 H) 7.29 - 7.50 (m, 3 H) 7.52 - 7.66 (m, 1 H) 12.03 - 12.52 (m, 1 H)

Example 2

Stereoisomer 2:



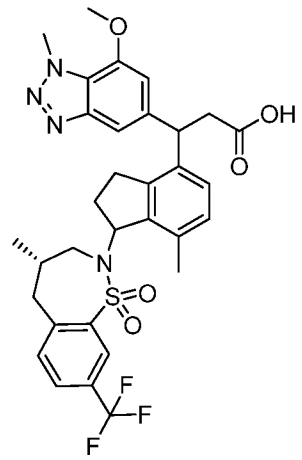
ISOMER 2

The second set of combined fractions from the synthesis of 3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid (see above) gave 0.020 g of a white solid.

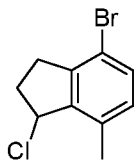
1H NMR (400 MHz, DMSO-d6) δ ppm 0.62 - 0.96 (m, 4 H) 1.18 - 1.45 (m, 2 H) 1.68 - 1.95 (m, 3 H) 2.16 - 2.35 (m, 4 H) 2.62 - 3.19 (m, 6 H) 3.81 - 4.01 (m, 4 H) 4.25 - 4.43 (m, 4 H) 4.48 - 4.66 (m, 1 H) 5.45 (br dd, J=9.03, 2.01 Hz, 1 H) 6.80 - 6.93 (m, 1 H) 6.99 - 7.16 (m, 1 H) 7.25 - 7.73 (m, 6 H)

Example 3:

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)propanoic acid



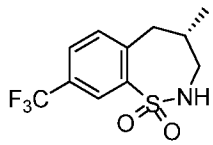
(a) 4-bromo-1-chloro-7-methyl-2,3-dihydro-1H-indene



To a solution of 4-bromo-7-methyl-2,3-dihydro-1*H*-inden-1-ol (300 mg, 1.3 mmol) in dichloromethane (DCM) (6.6 ml) at 0 °C was added thionyl chloride (289 µl, 4.0 mmol). After 2.5 h at 0 °C, 1H NMR of 0.3 mL aliquot showed complete consumption of R1 to P1. Concentrated in vacuo to give a cloudy orange oil (302.5 mg). This was used directly in the next step without further purification.

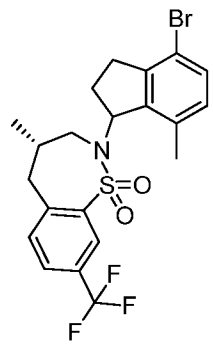
^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 2.35 - 2.40 (m, 3 H) 2.41 - 2.62 (m, 2 H) 3.00 (dd, *J*=16.69, 7.91 Hz, 1 H) 3.25 (dt, *J*=16.69, 8.47 Hz, 1 H) 5.54 (d, *J*=6.27 Hz, 1 H) 6.94 (d, *J*=7.78 Hz, 1 H) 7.37 (d, *J*=8.03 Hz, 1 H).

(b) (S)-4-Methyl-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide



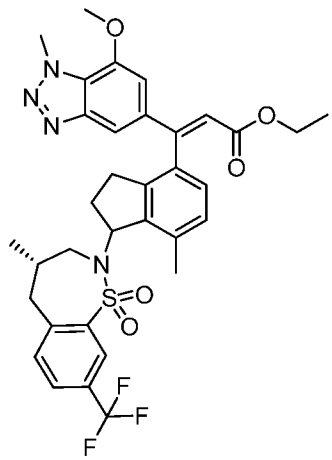
(S)-4-Methyl-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide of the invention was made using compounds described in WO 2017/060854 on page 137, published April 13, 2017, and incorporated herein by reference.

(c) (3S)-2-(4-bromo-7-methyl-2,3-dihydro-1H-inden-1-yl)-3-methyl-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide



To a solution of (*S*)-4-methyl-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (330 mg, 1.2 mmol) in *N,N*-dimethylformamide (DMF) (3.9ml) at 0 °C was added NaH (47.3 mg, 1.2 mmol). After 30 min at 0 °C, a solution of 4-bromo-1-chloro-7-methyl-2,3-dihydro-1*H*-indene (290.2 mg, 1.2 mmol) and TBAI (43.7 mg, 0.118 mmol) in *N,N*-dimethylformamide (DMF) (2.0 ml) was added and the resulting reaction mixture was immediately heated to 80 °C. After 30 min, the reaction contents were cooled to ambient temperature and partitioned with 30 mL EtOAc and 15 mL saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with 1 x 15 mL EtOAc. The combined organics were sequentially washed with 4 x 15 mL water, 1 x 15 mL brine. The combined organics were subsequently dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give an orange/red oil. Purification by silica gel chromatography (0-20% EtOAc:Hexane) provided the title compounds (diastereomeric mixture) as a thick, orange/red oil (354.9 mg). LC-MS *m/z* 488.1, 490.1 (M, M+2)$^+$, 1.54 min (diastereomer #1), 1.57 min (diastereomer #2).

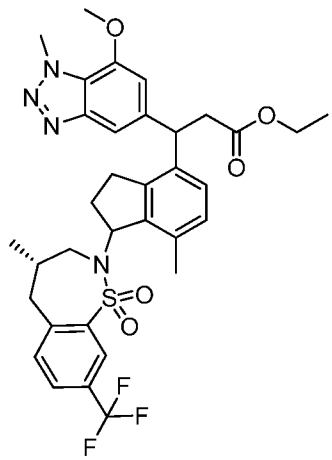
(d) (Z)-ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)acrylate



A vial containing a mixture of ethyl (E)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (0.201 g, 0.769 mmol), (4S)-2-(4-bromo-7-methyl-2,3-dihydro-1H-inden-1-yl)-4-methyl-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (0.338 g, 0.692 mmol), and bis(tri-t-butylphosphine)palladium(0) (0.037 g, 0.072 mmol), was purged with nitrogen after which time 1,4-dioxane (3.5 mL) was added followed by N-cyclohexyl-N-methylcyclohexanamine (0.170 mL, 0.794 mmol). The reaction mixture was heated at 90 °C. The solution was cooled and concentrated and the resulting brown residue taken into ethyl acetate. The suspension was filtered and the filtrate extracted with dilute HCl (1x), water (1x), brine (1x), dried over magnesium sulfate and concentrated to give 0.443 g of a brown colored foam. This was taken into ethyl acetate and adsorbed onto isolute and purified via silica gel chromatography to give 0.274 g of a light yellow solid. This was taken into ethanol and treated with activated charcoal and filtered and concentrated to give 0.269 g of a light yellow residue.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.77 (d, J=6.27 Hz, 3 H) 1.09 - 1.20 (m, 4 H) 1.27 (t, J=7.15 Hz, 3 H) 1.48 (d, J=14.05 Hz, 1 H) 1.67 (br. s., 2 H) 2.10 - 2.35 (m, 2 H) 2.38 - 2.85 (m, 5 H) 3.41 - 3.60 (m, 2 H) 3.91 (d, J=17.07 Hz, 3 H) 4.04 - 4.19 (m, 4 H) 4.46 (d, J=9.29 Hz, 4 H) 5.39 - 5.62 (m, 1 H) 6.14 (s, 1 H) 6.60 - 6.74 (m, 1 H) 6.89 - 7.26 (m, 2 H) 7.30 - 7.41 (m, 2 H) 7.66 (d, J=7.28 Hz, 1 H) 8.19 (br. s., 1 H)

(e) Ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)propanoate



Batch 1:

A suspension of ethyl (Z)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)acrylate (0.269 g, 0.402 mmol) and 20% palladium hydroxide on carbon (0.206 g, 0.293 mmol) was kept under a hydrogen balloon. After 3 hours the suspension was filtered through celite and concentrated to give 0.216 g of a tan colored solid. This was adsorbed onto isolute and purified via silica gel chromatography to give 0.142 g of a white foam.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.77 (d, J=6.27 Hz, 3 H) 1.16 (q, J=6.27 Hz, 3 H) 1.27 (t, J=7.15 Hz, 2 H) 1.33 (br. s., 1 H) 1.67 (br. s., 2 H) 1.96 (d, J=14.05 Hz, 1 H) 2.05 (s, 2 H) 2.10 - 2.84 (m, 6 H) 3.40 - 3.74 (m, 2 H) 3.91 (d, J=17.07 Hz, 3 H) 4.04 - 4.19 (m, 3 H) 4.47 (d, J=9.79 Hz, 3 H) 5.39 - 5.62 (m, 1 H) 6.14 (s, 1 H) 6.60 - 6.73 (m, 1 H) 6.89 - 7.25 (m, 2 H) 7.30 - 7.42 (m, 2 H) 7.66 (d, J=7.78 Hz, 1 H) 8.19 (br. s., 1 H)

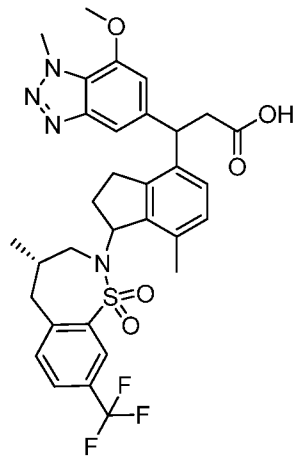
Batch 2:

A suspension of ethyl (Z)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)acrylate (0.142 g, 0.212 mmol) and 20% palladium hydroxide on carbon (0.241 g, 0.343 mmol) was kept under a hydrogen balloon. After 23 hr 20 min LC/MS showed mostly desired product mass with a little starting material remaining.

Additional 20% palladium hydroxide on carbon (0.168 g, 0.239 mmol) was added and the balloon re-filled with hydrogen. After ~48 hours the suspension was filtered through celite and concentrated to give 0.120 g of a clear, colorless oil. The celite was washed again with ethanol and the combined organics concentrated to give 0.113 g of a white foam. This was adsorbed onto isolute and purified via silica gel chromatography to give 0.089 g of a white foam.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.36 (d, J=6.53 Hz, 1 H) 0.50 (d, J=6.78 Hz, 1 H) 0.68 - 0.98 (m, 1 H) 1.06 - 1.20 (m, 3 H) 1.35 - 1.93 (m, 6 H) 1.96 - 2.50 (m, 4 H) 2.52 - 3.22 (m, 5 H) 3.27 - 3.63 (m, 2 H) 3.80 - 3.96 (m, 3 H) 3.98 - 4.15 (m, 2 H) 4.32 - 4.50 (m, 3 H) 4.54 - 4.85 (m, 2 H) 5.37 - 5.68 (m, 1 H) 6.41 - 6.71 (m, 1 H) 6.84 - 7.49 (m, 5 H) 7.58 - 7.78 (m, 1 H) 8.13 - 8.30 (m, 1 H)

(f) 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)propanoic acid

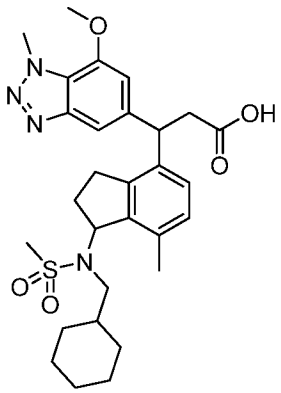


To a solution of ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)propanoate (0.089 g, 0.133 mmol) in tetrahydrofuran (THF) (2mL) and at ambient temperature was added 1M lithium hydroxide (1 mL, 1.000 mmol) followed by methanol (0.8 ml). After 2 hours the reaction was quenched via addition of 1N HCl to a pH of 1-2 and extracted with ethyl acetate. The organic phase was extracted with water (1x), dried over magnesium sulfate, filtered and concentrated to give 0.089 g of a white foam. This was lyophilized from acetonitrile and water to give 0.074 g of a white solid.

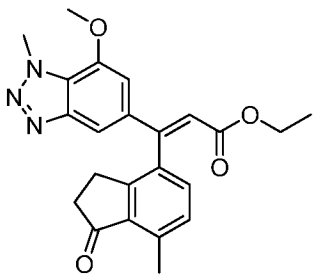
1H NMR (400 MHz, DMSO-d6) d ppm 0.26 (br. s., 1 H) 0.42 (d, J=6.27 Hz, 1 H) 0.67 (d, J=7.03 Hz, 1 H) 0.83 (br. s., 1 H) 0.92 - 1.19 (m, 1 H) 1.24 (br. s., 1 H) 1.44 (br. s., 2 H) 1.60 - 2.01 (m, 3 H) 2.17 - 2.43 (m, 3 H) 2.62 - 2.93 (m, 3 H) 2.96 - 3.24 (m, 3 H) 3.71 - 3.83 (m, 1 H) 3.84 - 3.96 (m, 3 H) 4.33 (d, J=5.77 Hz, 3 H) 4.57 (d, J=6.53 Hz, 1 H) 5.27 - 5.55 (m, 1 H) 6.73 - 6.97 (m, 1 H) 7.02 - 7.42 (m, 3 H) 7.59 - 7.78 (m, 1 H) 7.86 - 8.09 (m, 2 H) 11.67 (s, 1 H) 12.14 (br. s., 1 H)

Example 4:

3-(1-(N-(cyclohexylmethyl)methylsulfonamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid



(a) (Z)-ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-oxo-2,3-dihydro-1H-inden-4-yl)acrylate

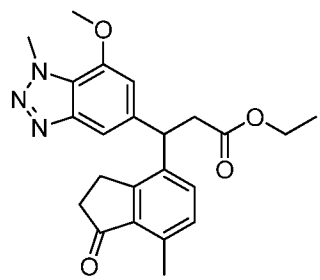


A vial containing a mixture of (E)-ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (4.973 g, 19.03 mmol), 4-bromo-7-methyl-2,3-dihydro-1H-inden-1-one (3.537 g, 15.71 mmol), and bis(tri-t-butylphosphine)palladium(0) (0.815 g, 1.595 mmol), was purged with nitrogen after which time 1,4-dioxane (70 mL) was added followed by N-cyclohexyl-N-methylcyclohexanamine (3.7 mL, 17.27 mmol). The reaction mixture was heated at 90 °C.

After 21 hr 40 mins the black colored solution was cooled and concentrated. The resulting solid was taken into ethyl acetate - a solid remained which was filtered. The filtrate was extracted with water (2x) and brine. The organic phase was dried over magnesium sulfate and concentrated over isolute and purified via silica gel chromatography to give 4.98 g of tan solid. This was taken into ethyl acetate and concentrated over isolute and purified again via silica gel chromatography to give 3.45 g of a tan foam.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.18 (t, J=7.03 Hz, 4 H) 1.59 (s, 6 H) 2.47 - 2.54 (m, 2 H) 2.61 (d, J=5.27 Hz, 2 H) 2.67 (s, 3 H) 3.93 (s, 3 H) 4.13 (q, J=7.11 Hz, 3 H) 4.43 - 4.51 (m, 4 H) 6.21 (s, 1 H) 6.68 (s, 1 H) 7.16 (d, J=7.53 Hz, 1 H) 7.39 - 7.49 (m, 2 H)

(b) Ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-oxo-2,3-dihydro-1H-inden-4-yl)propanoate

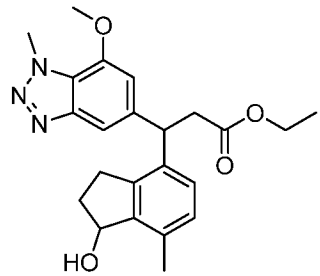


A suspension of (Z)-ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-oxo-2,3-dihydro-1H-inden-4-yl)acrylate (3.45 g, 8.51 mmol) and palladium hydroxide on carbon (0.560 g, 0.798 mmol) was kept under 32 PSI hydrogen. After 3.5 hours additonal palladium hydroxide on carbon (5.97 g, 8.51 mmol) was added and the suspension kept under 50 psi hydrogen. After a total of 19 hrs the reaction mixture was filtered through Celite and concentrated over isolute. The isolute was taken into ethyl acetate to extract the product, filtered, and the filtrate dried over magnesium sulfate and filtered. The filtrate was concentrated over isolute and purified via silica gel chromatography to give 1.929 g of a white foam. 1H NMR is consistent with the starting material. This was re-subjected to the reaction conditions as follows:

A suspension of (Z)-ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-oxo-2,3-dihydro-1H-inden-4-yl)acrylate (1.929 g, 4.76 mmol) and palladium hydroxide on carbon (2.504 g, 17.83 mmol) was kept under a hydrogen balloon. After 16 hr 40 mins the suspension was filtered over celite and concentrated to give 1.727 g of a white foam.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.16 (t, J=7.03 Hz, 3 H) 2.50 - 2.72 (m, 5 H) 2.77 - 2.90 (m, 1 H) 3.03 - 3.23 (m, 3 H) 3.91 (s, 3 H) 4.07 (q, J=6.94 Hz, 2 H) 4.42 (s, 3 H) 4.81 (t, J=8.03 Hz, 1 H) 6.58 (s, 1 H) 7.14 (d, J=7.53 Hz, 1 H) 7.39 - 7.46 (m, 2 H)

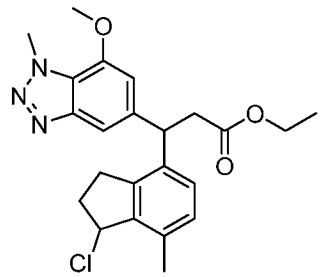
(c) Ethyl 3-(1-hydroxy-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To a solution of ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-oxo-2,3-dihydro-1H-inden-4-yl)propanoate (0.041 g, 0.101 mmol) in Ethanol (1 mL) was added sodium borohydride (0.00602 g, 0.159 mmol) at 0 °C. LC/MS after 25 and 50 mins showed starting material remaining. After 1hr 20 mins, additional sodium borohydride (0.00861 g, 0.228 mmol) was added. After an additional 42 mins, LC/MS showed consumption of starting material. After a total of 2hrs 50 min, the reaction was quenched with several drops of 1N HCl and diluted with ethyl acetate. The resulting solution was extracted with water (2x), brine, and the organic phase dried over magnesium sulfate and concentrated to give 0.032g of a clear, colorless oil.

1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.09 - 1.20 (m, 3 H) 1.22 - 1.33 (m, 1 H) 1.95 - 2.08 (m, 1 H) 2.19 - 2.44 (m, 4 H) 2.59 - 2.73 (m, 1 H) 2.91 (t, J=6.78 Hz, 1 H) 3.02 - 3.22 (m, 3 H) 3.90 (s, 3 H) 3.99 - 4.10 (m, 2 H) 4.40 (s, 3 H) 4.69 (t, J=7.53 Hz, 1 H) 5.29 (t, J=6.53 Hz, 1 H) 6.60 (br. s., 1 H) 7.03 (d, J=7.78 Hz, 1 H) 7.10 - 7.19 (m, 1 H) 7.41 (d, J=13.80 Hz, 1 H)

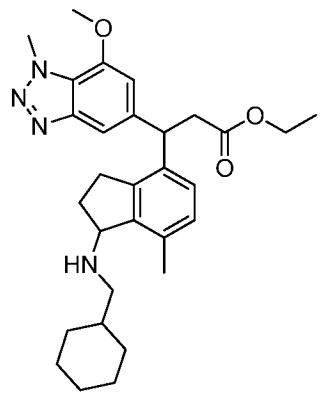
(d) Ethyl 3-(1-chloro-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To a solution of ethyl 3-(1-hydroxy-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.086 g, 0.210 mmol) in dichloromethane (DCM) (2 mL) was added thionyl chloride (0.030 ml, 0.411 mmol) at ambient temperature. After 40 minutes the solution was concentrated to give 0.113 g of a white solid. 1H NMR is consistent with the desired product. This was carried forward without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 1.11 - 1.23 (m, 4 H) 2.35 - 2.57 (m, 6 H) 2.88 - 3.26 (m, 5 H) 3.95 (d, *J*=12.30 Hz, 4 H) 4.07 (q, *J*=6.94 Hz, 3 H) 4.52 (br. s., 3 H) 4.73 (t, *J*=7.15 Hz, 1 H) 5.42 - 5.53 (m, 1 H) 6.60 - 6.81 (m, 1 H) 7.02 - 7.10 (m, 1 H) 7.13 (dd, *J*=7.53, 4.02 Hz, 1 H) 7.48 - 7.64 (m, 1 H)

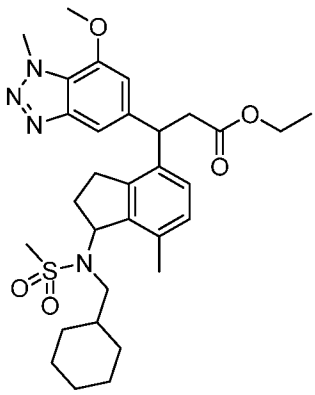
(e) Ethyl 3-(1-((cyclohexylmethyl)amino)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



A suspension of ethyl 3-(1-chloro-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.113 g, 0.264 mmol), cyclohexylmethanamine (0.063 mL, 0.485 mmol), sodium iodide (0.0065 g, 0.043 mmol), and potassium carbonate (0.058 g, 0.420 mmol) in acetonitrile (2 mL) was heated to 40 °C.

After 2 hrs 40 mins the reaction was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate (3x). The combined organics were dried over magnesium sulfate, filtered, and concentrated to give 0.137 g of a yellow oil. This was used in the next step without further purification.

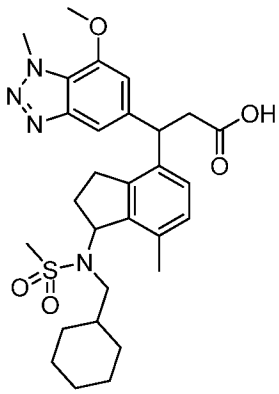
(f) Ethyl 3-(1-(N-(cyclohexylmethyl)methylsulfonamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To a solution of ethyl 3-(1-((cyclohexylmethyl)amino)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.137 g, 0.271 mmol) and triethylamine (0.06 mL, 0.430 mmol) in dichloromethane (DCM) (2 mL) at 0 °C was added methanesulfonyl chloride (0.020 mL, 0.257 mmol). After 35 minutes, additional methanesulfonyl chloride (0.020 mL, 0.257 mmol) was added. After a further 20 minutes, the reaction was quenched via addition of saturated sodium bicarbonate solution. The organic phase was diluted with ethyl acetate and extracted with water (1x), dilute HCl (1x), brine (1x), dried over magnesium sulfate, filtered and concentrated to give 0.137 g of a light yellow oil (N39470-55-A1). This was taken into ethyl acetate and concentrated over isolute and purified via silica gel chromatography to give 0.043 g of a clear, colorless, oil.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 0.09 (d, *J*=11.80 Hz, 1 H) 0.28 - 1.03 (m, 6 H) 1.16 (dt, *J*=10.35, 7.25 Hz, 3 H) 1.31 - 1.54 (m, 3 H) 2.19 - 2.57 (m, 5 H) 2.65 - 2.96 (m, 5 H) 3.01 - 3.21 (m, 3 H) 3.87 - 3.94 (m, 3 H) 4.05 (q, *J*=6.86 Hz, 2 H) 4.37 - 4.44 (m, 3 H) 4.60 - 4.72 (m, 1 H) 5.48 (d, *J*=8.53 Hz, 1 H) 6.55 - 6.64 (m, 1 H) 7.02 - 7.12 (m, 1 H) 7.15 - 7.29 (m, 2 H) 7.41 (s, 1 H)

(g) 3-(1-(N-(cyclohexylmethyl)methylsulfonamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid

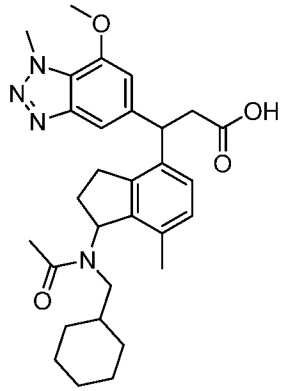


To a solution of ethyl 3-(1-(N-(cyclohexylmethyl)methylsulfonamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.043 g, 0.074 mmol) in tetrahydrofuran (THF) (1 mL) at ambient temperature was added lithium hydroxide (0.5 ml, 0.500 mmol) followed by methanol (0.2 ml). After 10 minutes, lithium hydroxide (0.2 ml, 0.200 mmol) was added. After 3hrs 30mins the reaction was quenched via addition of 1N HCl to pH ~2-3 and the resulting mixture extracted with ethyl acetate. The aqueous phase was extracted again with ethyl acetate and the combined organics were dried over magnesium sulfate and concentrated to give 0.042 g of white solid.

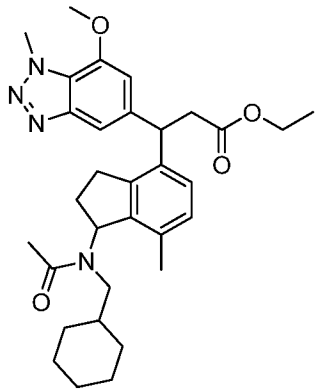
^{1}H NMR (400 MHz, DMSO-d_6) d ppm -0.27 - 1.03 (m, 8 H) 1.08 - 1.58 (m, 6 H) 2.03 - 2.19 (m, 2 H) 2.23 - 2.45 (m, 4 H) 2.67 (br. s., 1 H) 2.73 - 3.23 (m, 7 H) 3.86 - 3.98 (m, 3 H) 4.32 (d, *J*=9.79 Hz, 3 H) 4.49 - 4.68 (m, 1 H) 5.36 (d, *J*=8.28 Hz, 1 H) 6.81 - 7.13 (m, 2 H) 7.20 - 7.55 (m, 2 H) 12.11 (br. s., 1 H)

Example 5:

3-(1-(N-(cyclohexylmethyl)acetamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid, ethyl acetate solvate



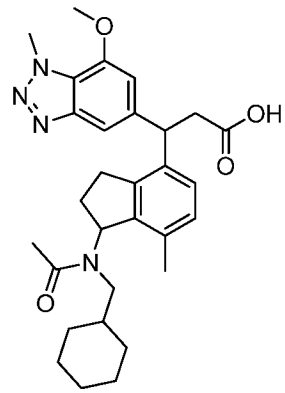
(a) Ethyl 3-(1-(N-(cyclohexylmethyl)acetamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To a solution of ethyl 3-(1-((cyclohexylmethyl)amino)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.074 g, 0.147 mmol) and triethylamine (0.060 ml, 0.430 mmol) in dichloromethane (DCM) (2 mL) at 0 °C was added acetyl chloride (0.03 mL, 0.421 mmol). After the addition, the solution was warmed to ambient temperature. After 50 min the reaction was quenched via addition of saturated sodium bicarbonate solution. The organic phase was extracted with dilute HCl, water (1x), brine (1x), dried over magnesium sulfate, filtered and concentrated over isolute and purified via silica gel chromatography to give 0.060 g of a white solid. Some N-(cyclohexylmethyl)acetamide present. This was used directly in the next step.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 0.31 - 1.10 (m, 13 H) 1.11 - 1.21 (m, 7 H) 1.99 (s, 1 H) 2.06 (d, *J*=8.28 Hz, 3 H) 2.11 - 2.23 (m, 7 H) 2.28 (br. s., 3 H) 2.79 (br. s., 3 H) 3.09 (t, *J*=7.65 Hz, 5 H) 3.83 - 3.96 (m, 6 H) 4.06 (d, *J*=7.03 Hz, 4 H) 4.40 (d, *J*=4.02 Hz, 6 H) 4.62 - 4.75 (m, 2 H) 5.35 (br. s., 1 H) 6.51 - 6.66 (m, 2 H) 6.95 - 7.15 (m, 2 H) 7.22 (d, *J*=7.53 Hz, 1 H) 7.34 - 7.47 (m, 2 H)

(b) 3-(1-(N-(cyclohexylmethyl)acetamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid, ethyl acetate solvate

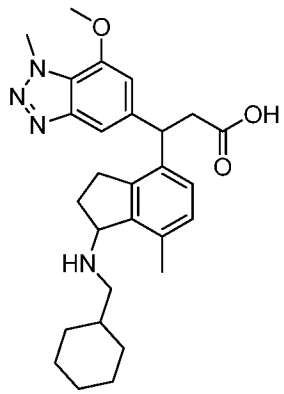


To a solution of ethyl 3-(1-(N-(cyclohexylmethyl)acetamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.060 g, 0.110 mmol) in tetrahydrofuran (THF) (1 mL) and methanol (0.5 ml) at ambient temperature was added lithium hydroxide (0.7 ml, 0.700 mmol). After ~ 3 hrs 30 mins the reaction was quenched via addition of 1N HCl to pH ~1-2 and the resulting mixture extracted with ethyl acetate. The organic phase was extracted with dilute HCl (1x), brine (1x), and dried over magnesium sulfate and concentrated to give 0.054 g of white solid. This was taken into ethyl acetate and extracted with saturated sodium bicarbonate solution (2x). The aqueous phase was acidified with 1N HCl to pH 1-2 and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated to give 0.036 g of a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) d ppm 0.04 - 1.65 (m, 12 H) 1.68 - 2.40 (m, 8 H) 2.64 - 3.22 (m, 5 H) 3.85 - 3.97 (m, 3 H) 4.03 (q, *J*=7.03 Hz, 1 H) 4.32 (d, *J*=8.28 Hz, 3 H) 4.58 (d, *J*=7.78 Hz, 1 H) 5.44 (d, *J*=6.78 Hz, 1 H) 6.77 - 6.91 (m, 1 H) 6.93 - 7.14 (m, 1 H) 7.16 - 7.50 (m, 2 H) 12.14 (br. s., 1 H)

Example 6

3-(1-((cyclohexylmethyl)amino)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid

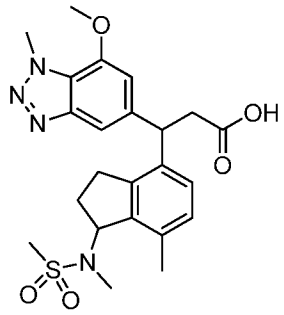


To a solution of ethyl 3-(1-((cyclohexylmethyl)amino)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (g) in tetrahydrofuran (THF) (1 mL) and methanol (0.5 ml) at ambient temperature was added lithium hydroxide (0.7 ml, 0.700 mmol). After ~ 4 hrs the reaction was quenched via addition of 1N HCl to pH ~1-2 and the resulting mixture extracted with ethyl acetate. The organic phase was concentrated to give 0.090 g of white solid. 1H NMR showed desired plus some ethyl acetate. This was purified via reverse phase HPLC using a Atlantics 20x100mm column and water / acetonitrile (15-45%) as mobile phase with flow rate of 18 mL/min over 10 mins. The combined fractions were lyophilized from MeCN and water to give 0.009 g of a white solid.

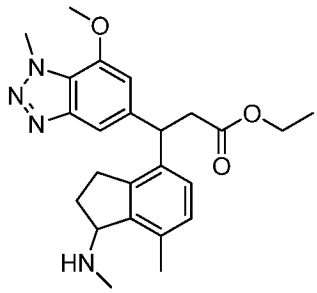
^{1}H NMR (400 MHz, DMSO-d_6) d ppm 0.82 (br. s., 2 H) 1.02 - 1.42 (m, 5 H) 1.47 - 1.82 (m, 6 H) 1.91 (d, *J*=5.77 Hz, 2 H) 2.18 - 2.41 (m, 6 H) 2.64 - 3.12 (m, 4 H) 3.91 (s, 3 H) 4.10 (d, *J*=7.03 Hz, 1 H) 4.33 (s, 3 H) 4.54 (br. s., 1 H) 6.74 - 7.04 (m, 2 H) 7.09 - 7.44 (m, 2 H)

Example 7

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylmethylsulfonamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid



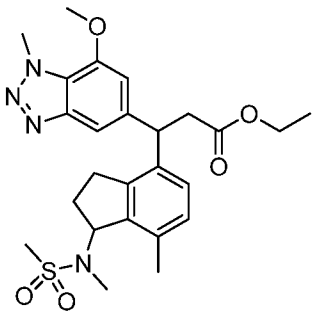
(a) Ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(methylamino)-2,3-dihydro-1H-inden-4-yl)propanoate



A suspension of ethyl 3-(1-chloro-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (0.096 g, 0.224 mmol), and methanamine (0.4 mL, 0.800 mmol) in acetonitrile (2 mL) was heated to 40 °C. After 2 hr 20 mins additional methanamine (0.4 mL, 0.800 mmol) was added and again after 4 hr 20 min - methanamine (0.4 mL, 0.800 mmol) was added. After 5 hr 45 min the heating was removed and stirring maintained at ambient temperature for 15 hr 30 min (overnight). The suspension was filtered and concentrated to give 0.074 g of light yellow solid. This was used in the next step without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 1.04 - 1.22 (m, 4 H) 2.05 - 2.25 (m, 3 H) 2.29 - 2.51 (m, 6 H) 2.87 - 3.22 (m, 4 H) 3.80 - 3.97 (m, 3 H) 3.99 - 4.17 (m, 2 H) 4.27 (br. s., 1 H) 4.40 (d, *J*=2.26 Hz, 3 H) 4.68 (d, *J*=4.02 Hz, 1 H) 6.59 (d, *J*=17.57 Hz, 1 H) 6.89 - 7.19 (m, 2 H) 7.41 (d, *J*=10.04 Hz, 1 H)

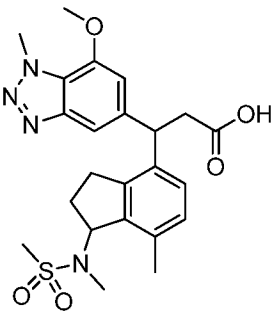
(b) Ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylmethylsulfonamido)-2,3-dihydro-1H-inden-4-yl)propanoate



To a solution of ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(methylamino)-2,3-dihydro-1H-inden-4-yl)propanoate (0.074 g, 0.175 mmol) and triethylamine (0.050 ml, 0.359 mmol) in dichloromethane (DCM) (2 mL) at 0 °C was added cyclohexanesulfonyl chloride (0.040 mL, 0.276 mmol). After the addition, the solution was warmed to ambient temperature. No reaction was seen after 40 minutes. To the solution was added methanesulfonyl chloride (0.030 mL, 0.385 mmol) at ambient temperature. After 1 hr 15 min LC/MS showed complete conversion to the methylsulfonamide product. The reaction was quenched via addition of saturated sodium bicarbonate solution. The organic phase was extracted with dilute HCl, extracted with water (1x), brine (1x), dried over magnesium sulfate, filtered and concentrated over isolute and purified via silica gel chromatography to give 0.039 g of a white solid. This was used directly in the next step.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 1.08 - 1.19 (m, 3 H) 1.55 - 1.73 (m, 1 H) 1.89 - 2.03 (m, 1 H) 2.23 - 2.42 (m, 5 H) 2.47 (s, 2 H) 2.62 - 2.78 (m, 1 H) 2.81 - 3.16 (m, 6 H) 3.89 (s, 3 H) 3.99 - 4.09 (m, 2 H) 4.41 (d, *J*=2.51 Hz, 3 H) 4.67 (t, *J*=7.78 Hz, 1 H) 5.50 - 5.66 (m, 1 H) 6.56 (d, *J*=5.02 Hz, 1 H) 7.00 - 7.13 (m, 1 H) 7.20 (t, *J*=8.53 Hz, 1 H) 7.38 (d, *J*=18.32 Hz, 1 H)

(c) 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylmethylsulfonamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid

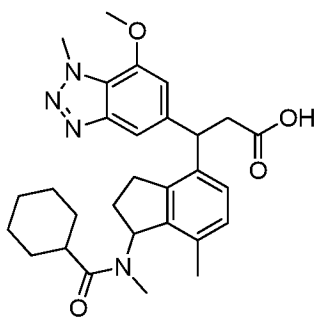


To a solution of ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylmethylsulfonamido)-2,3-dihydro-1H-inden-4-yl)propanoate (0.039 g, 0.078 mmol) in tetrahydrofuran (THF) (1 mL) and methanol (0.5 ml) at ambient temperature was added lithium hydroxide (0.7 ml, 0.700 mmol). After 1hr 6mins the reaction was quenched via addition of 1N HCl to pH ~2-3 and the resulting mixture extracted with ethyl acetate. The aqueous phase was extracted again with ethyl acetate and the combined organics were dried over magnesium sulfate and concentrated to give 0.036 g of white solid. The solid was pumped on the V10 evaporator on the Hi-Boil setting (2x) - afterwhich 0.034 g was obtained.

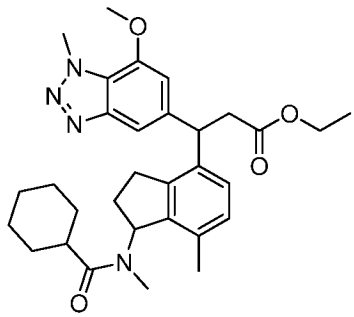
^{1}H NMR (400 MHz, DMSO-d_6) d ppm 1.99 (s, 2 H) 2.15 - 2.40 (m, 7 H) 2.71 - 2.85 (m, 1 H) 2.96 (d, *J*=11.54 Hz, 3 H) 3.03 - 3.14 (m, 2 H) 3.90 (d, *J*=11.80 Hz, 3 H) 4.34 (s, 3 H) 4.50 - 4.71 (m, 1 H) 5.27 - 5.51 (m, 1 H) 6.71 - 6.94 (m, 1 H) 6.99 - 7.16 (m, 1 H) 7.23 - 7.47 (m, 2 H) 12.03 - 12.29 (m, 1 H)

Example 8

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylcyclohexanecarboxamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid



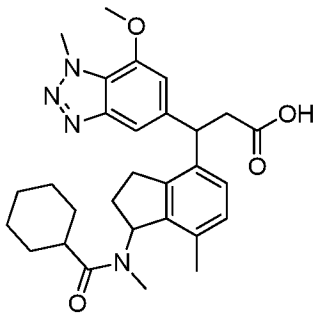
(a) Ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylcyclohexanecarboxamido)-2,3-dihydro-1H-inden-4-yl)propanoate



To a solution of ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(methylamino)-2,3-dihydro-1H-inden-4-yl)propanoate (0.085 g, 0.201 mmol) and triethylamine (0.060 ml, 0.430 mmol) in dichloromethane (DCM) (2 mL) at 0 °C was added cyclohexanecarbonyl chloride (0.07 mL, 0.201 mmol). After the addition, the solution was warmed to ambient temperature. After ~10 minutes the reaction was quenched and extracted with saturated sodium bicarbonate solution (2x). The organic phase was extracted with HCl (1N), dried over sodium sulfate, filtered and concentrated to give 0.099 g of a yellow oil. This was adsorbed onto isolute using ethyl acetate as solvent and purified via silica gel chromatography to give 0.044 g of a light yellow foam. LC/MS shows N-methylcyclohexanecarboxamide with desired product mass. This was used in the next step without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) d ppm 1.08 - 1.49 (m, 15 H) 1.65 - 1.93 (m, 13 H) 2.00 - 2.23 (m, 6 H) 2.30 - 2.56 (m, 6 H) 2.61 (s, 2 H) 2.66 - 2.86 (m, 3 H) 2.92 (br. s., 1 H) 3.08 (d, *J*=7.28 Hz, 4 H) 3.90 (d, *J*=13.80 Hz, 5 H) 4.06 (d, *J*=6.78 Hz, 3 H) 4.41 (d, *J*=4.77 Hz, 5 H) 4.68 (br. s., 2 H) 5.23 - 5.66 (m, 1 H) 6.33 (d, *J*=5.27 Hz, 1 H) 6.52 - 6.69 (m, 2 H) 6.97 - 7.08 (m, 2 H) 7.15 (dd, *J*=17.32, 7.78 Hz, 2 H) 7.29 - 7.36 (m, 1 H) 7.43 (s, 1 H)

(b) 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylcyclohexanecarboxamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid



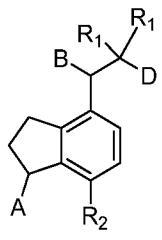
To a solution of ethyl 3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylcyclohexanecarboxamido)-2,3-dihydro-1H-inden-4-yl)propanoate (0.044 g, 0.083 mmol) in tetrahydrofuran (THF) (1 mL) and methanol (0.5 ml) at ambient temperature was added lithium hydroxide (0.7 ml, 0.700 mmol). After 1.5 hrs LC/MS showed a complete reaction and also showed N-methylcyclohexanecarboxamide as a side product. The reaction was acidified to pH 1-2 using 1N HCl then basified with saturated sodium bicarbonate solution and extracted with ethyl acetate (3x). The aqueous phase was then re-acidified with 1N HCl to pH 1-2 and extracted with ethyl acetate (2x). The organics were combined and extracted with brine (1x), dried over magnesium sulfate, filtered and concentrated to give 0.017 g of a light yellow solid. This was lyophilized from MeCN and water to give 0.013 g of a white solid. 1H NMR and LC/MS is consistent with the desired product plus a small amount of N-methylcyclohexanecarboxamide and putative indane alcohol.

^{1}H NMR (400 MHz, DMSO-d_6) d ppm 1.08 - 1.46 (m, 5 H) 1.67 (d, *J*=16.81 Hz, 5 H) 1.94 - 2.10 (m, 2 H) 2.12 - 2.44 (m, 3 H) 2.54 (s, 2 H) 2.76 - 3.21 (m, 4 H) 3.90 (d, *J*=5.77 Hz, 3 H) 4.34 (s, 3 H) 4.58 (br. s., 1 H) 5.69 (br. s., 1 H) 6.13 (br. s., 1 H) 6.78 - 6.91 (m, 1 H) 6.93 - 7.10 (m, 1 H) 7.18 - 7.45 (m, 2 H) 12.18 (br. s., 1 H)

Claims

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -(CH_2)$_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -(CH_2)$_2$-triazolyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C_{1-3}alkyl, -O-C_{1-3}alkyl,
-CN, -(CH_2)$_2$–O–(CH_2)$_2$-OR_3 and halo;

D is –C(O)OH, -C(O)NR_3R_4, -C(O)$NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -(CH_2)$_n$-O-(CH_2)$_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-

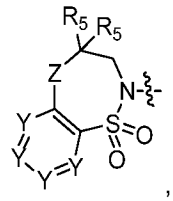
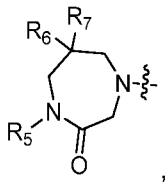
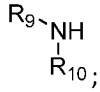
membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –C(O) or one $–S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from $-C_{1-5}$alkyl, $-C_{3-7}$cycloalkyl, $-C_{4-7}$heterocycloalkyl, $-(CH_2)$phenyl, halogen, $-NR_3R_5$, $-CHF_2$, $-CF_3$, and $-(CH_2)_n-O-(CH_2)_m-CH_3$;

A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from $-C_{1-3}$alkyl, $-C_{3-6}$spirocycloalkyl, halo, -CN, $-O-C_{1-3}$alkyl, $-CH_2-O-CH_3$, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from $-C_{1-3}$alkyl and $–C_{3-7}$cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from $-C_{1-3}$ alkyl and $-O-C_{1-3}$ alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

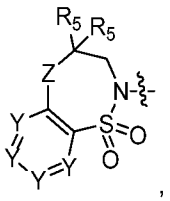
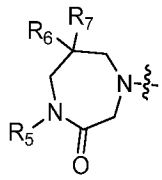
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -OMe,
-$C(O)NH_2$, -OCF_3 and -C_{1-4}alkylNR_7R_8;

R_8 is -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl,
-C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl, wherein each of -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl, -C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, -CF_3, -OCF_3,
-OCH_3, -C_{1-3}alkyl, -OC_{1-3}alkyl, -OC_{3-7}cycloalkyl, -OC_{3-7}hetercycloalkyl, -O-aryl and –O-heteroaryl;

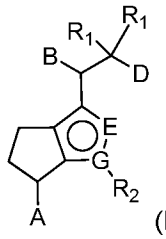
R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, $C(O)R_6$;

m is 0, 1 or 2; and

n is 1 or 2; or a pharmaceutically acceptable salt thereof.

2. A compound of Formula (II):



(II)

wherein:

B is benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl wherein each of benzotriazolyl, phenyl, triazolopyridinyl, -O-(CH_2)-triazolyl, or -$(CH_2)_2$-triazolyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from –C_{1-3}alkyl, -O-C_{1-3}alkyl,
-CN, -$(CH_2)_2$–O–$(CH_2)_2$-OR_3 and halo;

D is –C(O)OH, -C(O)NR_3R_4, -C(O)$NHSO_2CH_3$, –$SO_2NHC(O)CH_3$, -5-(trifluoromethyl)-4H-1,2,4-triazol-2-yl, –NR_3-C(O)-R_4, -NR_3-C(O)-NR_3R_4; -NR_3-C(O)-O-R_4 or tetrazolyl;

R_1 is independently hydrogen, -C_{1-3}alkyl, F, -C_{3-6}spirocycloalkyl, oxetane, or the two R_1 groups together with the carbon to which they are attached form a cyclopropyl group;

R_2 is hydrogen, methyl, -CF_3, or halo;

R_3 is hydrogen or -C_{1-3}alkyl;

R_4 is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-8}heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-SO_2C_{1-3}alkyl, -C_{1-3}alkyl-C_{4-8}heterocycloalkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl, wherein each of -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{4-7} heterocycloalkyl, -C_{1-5}alkoxy, -C_{1-3}alkyl-O-C_{1-3}alkyl, -C_{1-3}alkyl-NH-C_{1-3}alkyl, -C_{1-3}alkyl-C(O)NR_4R_5, aryl or heteroaryl is unsubstituted or substituted by one or two substituents selected from –OH, -CO_2H, -C(O)NR_4R_5,-C(O)OR_3, -N-C(O)-C_{1-3}alkyl, F, -CN, -CH-F_2, -CF_3, -$(CH_2)_n$-O-$(CH_2)_m$-CH_3, -C_{3-7}cycloalkyl and a 5-6-membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from O, N and S;

or R_3 and R_4 together with the nitrogen atom to which they are attached form a 5-8-membered heterocyclic ring, an 8-11-membered bicyclic heterocyclic ring or a 9-10-membered bridged bicyclic heterocyclic ring, wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally includes one –

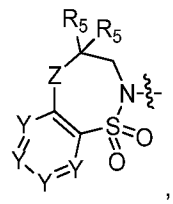
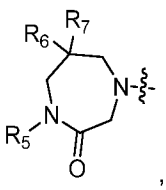
C(O) or one –$S(O)_2$, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring optionally contains one, two or three oxygen ring atoms, one, two or three sulfur ring atoms or one, two or three nitrogen ring atoms, and wherein each 5-8-membered ring, 8-11-membered bicyclic ring, or 9-10-membered bridged bicyclic ring is unsubstituted or substituted by one, two or three substituents independently selected from -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -C_{4-7}heterocycloalkyl, -(CH_2)phenyl, halogen, -NR_3R_5, -CHF_2, -CF_3, and -$(CH_2)_n$-O-$(CH_2)_m$-CH_3;

A is tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, phenyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl;

wherein each of tetrahydrobenzoxazepinyl, tetrahydro-pyrido-oxazepinyl, piperidinyl, tetrahydrobenzazepinyl, tetrahydropyrrolopyrazinyl, imidazopyridinyl, tetrahydrobenzodiazepinyl, piperidopyrimidinyl, dioxidotetrahydrothiophenyl, tetrahydroimidazodiazepinyl, oxazepane or morpholinyl is unsubstituted or substituted by 1, 2, or 3 substituents independently selected from -C_{1-3}alkyl, -C_{3-6}spirocycloalkyl, halo, -CN, -O-C_{1-3}alkyl, -CH_2-O-CH_3, and -OH;

and wherein the oxazepane is further unsubstituted or substituted by 1 or 2 substituents independently selected from -C_{1-3}alkyl and –C_{3-7}cycloalkyl;

and wherein the morpholinyl is further unsubstituted or substituted by phenyl which phenyl is unsubstituted or substituted by a substituent independently selected from -C_{1-3} alkyl and -O-C_{1-3} alkyl;

or A is  , or  , or  ;

Y is independently selected from N or CH;

E is independently S, O, N;

G is independently C, N;

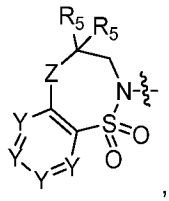
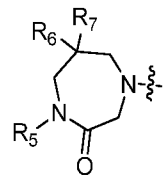
Z is O, CH_2, NR_5, S, S(O) or $S(O)_2$;

R_5 is independently selected from hydrogen or -C_{1-4}alkyl;

R_6 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_7 is hydrogen or -C_{1-4}alkyl;

or R_6 and R_7, together with the carbon to which they are attached form a C_3-C_5-membered cycloalkyl ring;

and, wherein when A is  , or  , it is unsubstituted or substituted with one, two or three substituents independently selected from halo, -CF_3, -C_{1-4}alkyl, -CN, -OMe,
-$C(O)NH_2$, -OCF_3 and -C_{1-4}alkylNR_7R_8;

R_8 is -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl,
-C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl, wherein each of -C_{1-3}alkyl, aryl, heteroaryl, -$C(O)C_{1-3}$alkyl, -SO_2C_{1-3}alkyl, -C(O)aryl, -C(O)heteroaryl, -SO_2aryl, -SO_2heteroaryl, -C_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}cycloalkyl, -C_{1-3}alkylC_{3-7}heterocycloalkyl, -C_{1-3}alkyl-heteroaryl or -C_{1-3}alkyl-aryl is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo, -CN, -CF_3, -OCF_3,
-OCH_3, -C_{1-3}alkyl, -OC_{1-3}alkyl, -OC_{3-7}cycloalkyl, -OC_{3-7}hetercycloalkyl, -O-aryl and –O-heteroaryl;

R_9 is hydrogen, -C_{1-5}alkyl or –$(CH_2)_m$-C_{3-5}cycloalkyl;

R_{10} is H, SO_2R_6, $C(O)R_6$;

m is 0, 1 or 2; and

n is 1 or 2; or a pharmaceutically acceptable salt thereof.

3. A compound which is:

3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid – Stereoisomer 1;

3-((R)-1-((S)-8-fluoro-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid – Stereoisomer 2;

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-((S)-4-methyl-1,1-dioxido-8-(trifluoromethyl)-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)-2,3-dihydro-1H-inden-4-yl)propanoic acid;

3-(1-(N-(cyclohexylmethyl)methylsulfonamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid;

3-(1-(N-(cyclohexylmethyl)acetamido)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid, ethyl acetate solvate;

3-(1-((cyclohexylmethyl)amino)-7-methyl-2,3-dihydro-1H-inden-4-yl)-3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid;

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylmethylsulfonamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid; and

3-(7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(7-methyl-1-(N-methylcyclohexanecarboxamido)-2,3-dihydro-1H-inden-4-yl)propanoic acid;

or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound of any one of claims 1–3 and a pharmaceutically acceptable excipient.

5. A method of treating respiratory and non-respiratory disorders, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-

induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disesase (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness which comprises administering to a human in need thereof, a compound of any one of claims 1-3.

6. The method according to claim 5 wherein the compound is administered orally.

7. The method according to claim 5 wherein the compound is administered intravenously.

8. The method according to claim 5 wherein the compound is administered by inhalation.

9. The method according to claim 5 wherein the disease is COPD.

10. The method according to claim 5 wherein the disease is heart failure.

11. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-3 for use in treating respiratory and non-respiratory disorders, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye conditions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

12. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-3 for use in treating COPD.

13. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-3 for use in treating heart failure.

14. Use of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-3 in the manufacture of a medicament for the treatment of respiratory and non-respiratory disorders, including COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection,

chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye conditions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

15. Use of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-3 in the manufacture of a medicament for the treatment of COPD.

16. Use of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-3 in the manufacture of a medicament for the treatment of heart failure.

17. A compound according to any one of claims 1-3 for use in therapy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/054067

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4192 A61K31/554 C07D417/08 C07D417/10 C07D249/18
A61P11/00 A61P9/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/203401 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]; ASTEX THERAPEUTICS LTD [GB]) 22 December 2016 (2016-12-22) claims 1-18; examples 1-87	1,3-17
A	WO 2016/203400 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]; ASTEX THERAPEUTICS LTD [GB]) 22 December 2016 (2016-12-22) claims 1-13; examples 1-27	1,3-17
A	WO 2015/092713 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]; ASTEX THERAPEUTICS LTD [GB]) 25 June 2015 (2015-06-25) claims 1-20; examples 198-218	1,3-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2019	26/08/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rufet, Jacques

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/054067

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2(completely); 1, 4-17(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 2(completely); 1, 4-17(partially)

The subject-matter of claims 1, 2 and 4 to 17 relates to an extremely large number of possible compounds, pharmaceutical compositions and uses thereof, due to the fact that formulas (I) and (II) of independent claims 1 and 2 respectively contain so many options, variables, possible attachment points for rings (e.g. rings for variables A or B). Support and disclosure within the meaning of Articles 6 and 5 PCT are to be found, however, for only a very small proportion of the compounds claimed, namely compounds of examples 1 to 8 according to formula (I) with a similar structure, wherein B is always a benzotriazolyl group, A a cyclic or acyclic nitrogen radical and D a -COOH group.

It is stressed that compounds of formula (II) according to independent claim 2 are not supported by the description. Thus no search has been carried out for the subject-matter of independent claim 2.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1 and 4 to 17 (PCT Guidelines 9.19 and 9.23).

The search of claims 1 and 4 to 17 was restricted to those claimed compounds/compositions which appear to be supported and a generalisation of their structural formulae, namely compounds of formula (I) of present claim 1, wherein A is a cyclic nitrogen atom or group NR9R10 as defined in claim 1.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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