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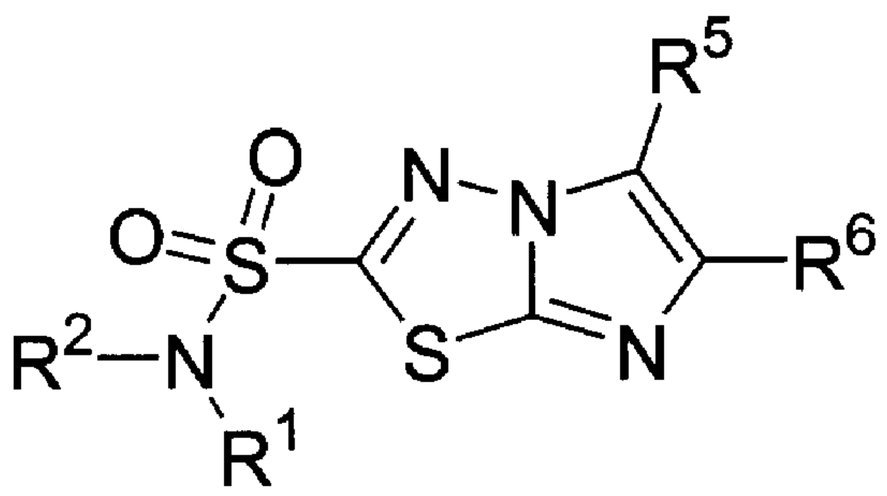

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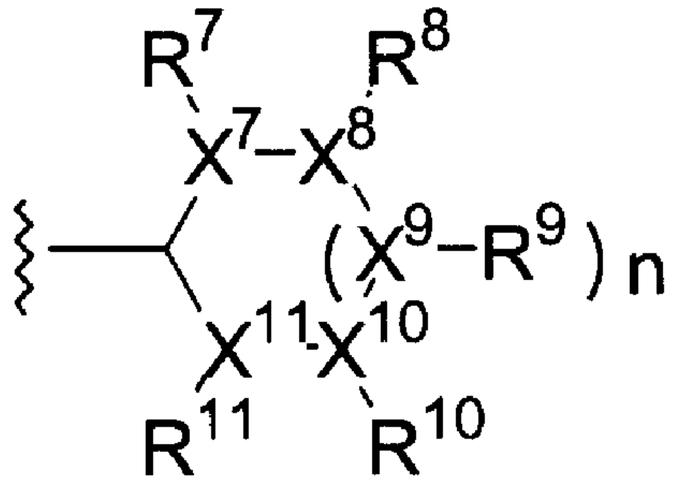

(57) Abrégé/Abstract:
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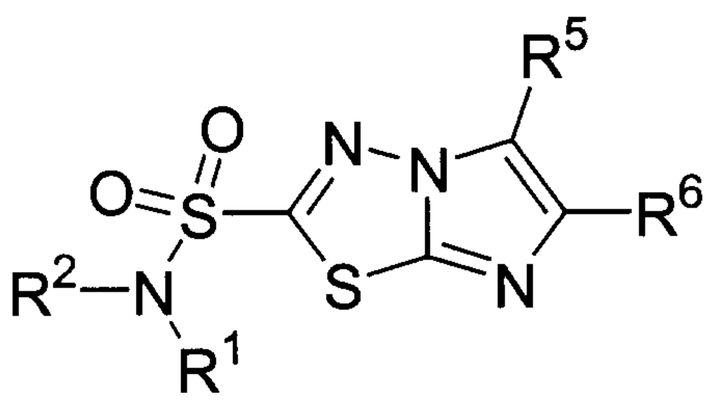
ABSTRACT

This invention relates to novel compounds of Formula I and the use of compounds of Formula I as neuroprotective agents in the treatment of neuronal disorders of the central and peripheral nervous systems. In Formula I, R^6 can be represented by W.



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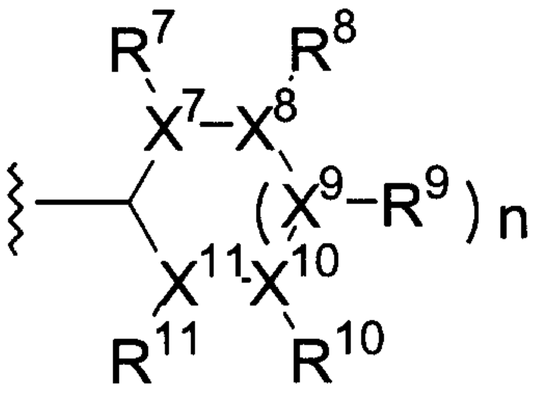
W =



Imidazo[2,1- *b*]thiadiazole Sulfonamides

FIELD OF THE INVENTION

The invention relates to compounds useful in prevention of neuronal cell loss or the treatment of nerve cell or axonal degradation, in either the central or peripheral nervous systems (CNS and PNS, respectively), resulting from such diseases as Alzheimer's, Huntington's, Parkinson's, muscular dystrophy, diabetes, HIV, from ischemic insults such as stroke in the brain (CNS), retinal ganglion loss following acute ocular stroke or hypertension as in glaucoma, and from infection by viruses such as Hepatitis C and Herpes Simplex, or for the treatment of neuropathies resulting from the use of chemo-therapeutic agents used in the treatment of HIV and proliferative disease such as cancer, for the treatment of inflammatory diseases.

BACKGROUND OF THE INVENTION

Various neurotrophins characterized by Neuronal Growth Factor (NGF), brain derived growth factor (BDNF), neurotrophin-3 (NT-3), and others (NT-4, CNTF, GDNF, IGF-1), have been identified as key survival factors for neurons. NGF plays a critical role in the development and maintenance of cholinergic forebrain neurons of the CNS and neurons of the peripheral nervous system (PNS); neurons of the PNS are characterized as small fiber sensory neurons associated with pain and temperature sensation, in addition to neurons of the sympathetic ganglia and dorsal root ganglia (SCGs and DRGs, respectively). BDNF plays a role in motor neuron survival. Both BDNF and NT-3 are expressed in the CNS and serve similar purposes in multiple subsets of cortical and hyppocampal neurons; neurons of the CNS are characterized by those found in the brain, spinal chord, and eye. The removal of these trophic factors from *in vitro* cellular media results in the degradation of the axonal processes, leading to apoptosis of cultured neurons.

Localized tissue loss of NGF, or reduced axonal retrograde transport of NGF to the cell body, have been causally implicated in the development of peripheral neuropathies and neuropathic pain regularly observed in diabetes and HIV patients. Several double blind Phase II clinical trials have found that the systemic administration of recombinant human NGF (rhNGF) (US 5,604,202) displayed beneficial effects on neuropathic pain, physiology, and cognition related to these diseases (Apfel, S. C. *et. al. JAMA*, 248(17), 2215-2221; Apfel, S. C. *Neurology* 51, 695-702, 1998; McAurthur, J. C. *et al. Neurology* 54, 1080-1088, 2000). Side effects related to rhNGF treatment included injection site pain, hyperalgesia, and other pain related symptoms. Despite these symptoms, a large number of patients continued rhNGF treatment after unblinding.

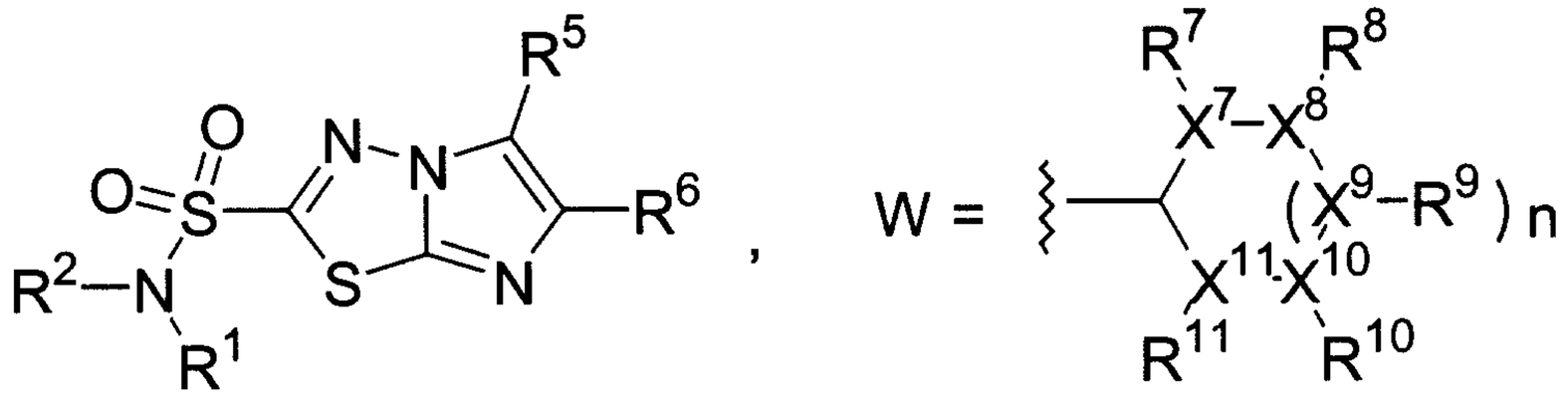
Various chemotherapeutic drugs such as Taxol™, cisplatin, vinblastine, and vincristine, cause dose dependent peripheral neuropathies, characterized by peripheral pain and loss of function. In many cases these neuropathies effectively limit the amount, and duration, of chemotherapy given to patients. For example, upwards of 50% of patients receiving Taxol™ chemotherapy experience severe, and cumulative, peripheral neuropathies. The progression of the neuropathy necessitates the use of a dosing regime which is characterized by three cycles of fourteen days of Taxol™ treatment, followed by 14 days of recovery. Regression of the neuropathy is often observed between treatment cycles and following the final treatment. The degree and duration of recovery varies largely between patients. In addition to peripheral neuropathies, cisplatin treatment invariably results in some form of auditory loss, especially in children, due to neuronal damage in the inner ear, with minimal recovery of the neurons after completion of treatment.

In order to identify compounds which mimic the positive effects of NGF on peripheral neurons, but which lack the inherent difficulties associated with the use of recombinant human proteins and the rhNGF related hyperalgesia, we have developed several *in vitro* screens using a variety of neurotoxic insults. PNS neurons such as the superior cervical ganglion (SCG) and dorsal root ganglion (DRG) undergo apoptosis when subjected to NGF

withdrawal. Treatment with chemotherapeutic agents such as Taxol™, cisplatin, vinblastine, vincristine, and anti-viral agents such as D4T, also induce neuronal apoptosis. Similarly, neurons of the CNS, such as cortical neurons, are sensitive to various neurotoxic agents such as β-amyloid, NMDA, osmotic shock, Taxol™ and cisplatin. Additionally, retinal ganglion neurons subjected to hypoxia undergo apoptosis.

Compounds which protect neurons from trophin withdrawal will be useful in the treatment of the peripheral neuropathies observed in diseases such as diabetes and HIV. Compounds which protect neurons from chemotherapeutic toxicity, if given concurrently with, or following, chemotherapeutic treatment will allow for the use of increasing concentrations of chemotherapeutics and/or extend the duration of chemotherapy treatments. Alternatively, enhanced recovery will be observed if such compounds are given during the recovery stages, and post treatment. These compounds will also be useful in the treatment of neurodegenerative diseases of the CNS in which diminished neurotrophin signaling is implicated, such as AD, PD, HD, stroke, MS, macular degeneration, glaucoma, optical stroke and retinal degeneration, and the like.

We have shown that compounds of Formula I protect SCG neurons from several neurotoxic insults, including NGF withdrawal and treatment with chemotherapeutics such as Taxol™, cisplatin, and vincristine.



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When such agents are administered to mice treated with Taxol™, either during or after a two week dosing period, marked improvements are observed in the animal's general health, weight gain, and gait, as compared to animals treated with Taxol™ alone.

Selected examples from Formula I have been previously described. Their uses include anti-bacterial agents (Gadad, A. K. *Eur J. Med. Chem.*, 35(9), 853-857, 2000), anti-proliferative agents (Gadad, A. K. *India. Arzneim.-Forsch.*, 49(10), 858-863, 1999), and as carbonic anhydrase (CA) inhibitors (Barnish, I. T., *et. al. J. Med. Chem.*, 23(2), 117-121, 1980; Barnish, I. T. *et. al* GB 1464259, abandoned; Supuran, C, T. *Met.-Based Drugs* 2(6), 331-336, 1995 – Co(II), Cu (II), Zn(II) complexes of compound 1). Barnish *et al.* demonstrated that certain compounds reduced the number and intensity of electroshock induced seizures in rats. This anti-seizure activity was linked to increased cerebral blood flow, attributed to the ability of these compounds to inhibit CA. No direct evidence of neuronal protection as a result of these compounds has been previously demonstrated *in vitro* or *in vivo* (ie. histology, neuronal cell count, etc.).

We have found that various aryl sulfonamide CA inhibitors do not protect SCG neurons from apoptosis. These finding indicate that the neuroprotection mediated by compounds represented by Formula I is independent of their CA activity. Additionally, we have prepared several synthetic derivatives of represented by Formula I which minimally inhibit CA, while retaining their neuroprotective capabilities.

There are several synthetic routes to compounds represented by Formula I which may be found in the above references. Also included are novel methods for the functionalization of compounds represented by Formula I.

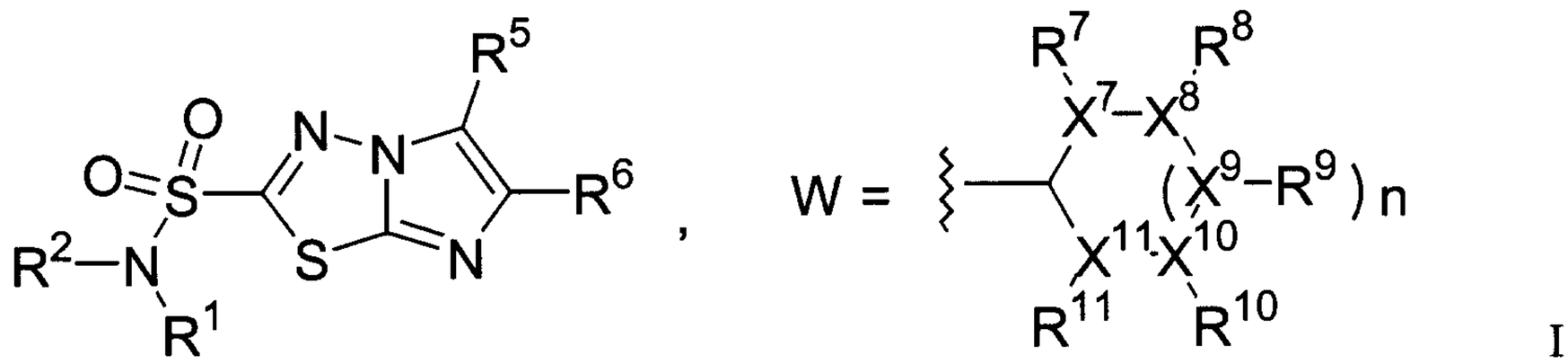
SUMMARY OF THE INVENTION

The present invention is directed, *inter alia*, to a select group of imidazo[2,1-*b*]thiadiazole sulfone compounds. These compounds are useful in the treatment of neurodegenerative diseases of the CNS and/or PNS, for the inhibition of various serine-threonine protein kinases, phosphatases, CA, for inhibiting the degradation, dysfunction, or loss of neurons of the CNS

and/or PNS, or enhancing the phenotype of neuronal cell types and preserving the axonal function of neuronal and synaptic processes of the CNS and/or of the PNS.

Also included are selected methods for the preparation of these compounds.

The imidazo[2,1-*b*]thiadiazole sulfonamide derivatives and precursors of the present invention include compounds of the Formula I:



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or pharmaceutically acceptable salts thereof wherein:

R^1 and R^2 are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl lower alkylcarbonyl, or wherein R^1 and R^2 are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

R^5 is selected from the group consisting of:

a) H, halogen, cyano, azide, thiocyanate, formyl, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

b) SO_nR^{12} wherein n=0, 1 or 2, and wherein R^{12} is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

c) OR^{13} wherein R^{13} is defined as R^{12} in b), or wherein R^{13} is defined as acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;

d) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl,or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system, or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

R^6 is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, substituted fluoroalkyl, adamantly, coumarinyl, substituted coumarinyl; or alternatively, R^6 is represented by W, wherein:

n represents 0 or 1;

the ring system containing X^7-X^{11} represents a 5 or 6 membered (n=0 or 1, respectively) aromatic or heteroaromatic ring system, in which X^7-X^{11} are independently chosen from C, N, S, O;

when X^7-X^{11} independently represents C, each respective R^7-R^{11} is independently chosen from the groups consisting of:

e) H, halogen, nitro, cyano, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl;

f) $SO_2NR^{16}R^{17}$ wherein R^{16} and R^{17} are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl,or wherein R^{16} and R^{17} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

g) SO_nR^{18} wherein n=0, 1 or 2, and wherein R^{18} is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

h) OR^{19} wherein R^{19} is defined as R^{12} in b), or wherein R^{19} is defined as fluoroaclkyl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;

i) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are as described in d), or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

j) CO_2R^{20} wherein R^{20} is defined as H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $NR^{14}R^{15}$, wherein R^{14} and R^{15} are individually chosen from the groups as defined in d);

when X^7-X^{11} represents N, that nitrogen may be attached to the adjacent atoms by either one single and one double bond (as in pyridinyl systems), or by two single bonds (as in indolyl or imidazolyl systems);

when X^7-X^{11} represents N, and that nitrogen is attached to the adjacent atoms by one single and one double bond (as in pyridinyl systems), the respective R^7-R^{11} represents a lone pair;

when X^1-X^5 represents N, and that nitrogen is attached to the adjacent atoms by two single bonds (as in indolyl or imidazolyl systems), the respective R^7-R^{11} is chosen from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, SO_2R^{18}, wherein R^{18} is defined as in g), COR^{18}, wherein R^{18} is defined as in g);

when n=0, R^7 and R^8, or R^8 and R^9 may be combined to form a fused 5,6, or 7 membered alkyl, substituted alkyl, heteroalky, substituted heteroalkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, heteroaryl ring system;

when n=1 and X^9 represents C, R^7 and R^8, or R^8 and R^{10} may be combined to form a fused 5, 6, or 7 membered alkyl, substituted alkyl, heteroalky, substituted heteroalkyl, aryl, substituted aryl, or heteroaryl ring system; and

R^7-R^{11} represents a lone pair when the respective X^7-X^{11} represents S or O.

The compounds represented by Formula I are hereinafter referred to as Compound (I).

DESCRIPTION OF FIGURES

Preferred embodiments of the present invention and data illustrating the efficacy of the invention will now be described, by way of example only, with reference to the attached Figures.

Figure 1 illustrates data showing protection of SCG neurons from Taxol™ induced killing. A comparison of AEG3482 in Taxol treated SCG neurons is provided, with addition of compound 1 at varying levels. p1 Sprague Dawley rat SCG neurons were cultured and incubated with NGF (50 ng/mL) for 5 days. Addition of Taxol™ (50 ng/mL) resulted in a 72% loss in viability as measured by MTS staining. Co-treatment with compound 1 resulted in 100% protection at 10 μM, with an IC_{50} of 3 μM.

Figure 2 illustrates weight loss induced by Taxol™ over time. Male Spraugue Dawley rats were treated with 50% HPDC vehicle (veh/veh), compound 1 dissolved in 50% HPDC at 1, 5, or 10 mg/kg (veh/1, veh/5, veh/10, respectively), or Taxol™ (9 mg/kg) + compound 1 dissolved in 50% HPDC at 1, 5, and 10 mg/kg (Tax/1, Tax/5, Tax/10) according to the dosing regime described in Example 123. Weight measurements were made every other day.

Figure 3 illustrates the gait disturbance induced by Taxol™. The effect of compound AEG3482 and Taxol on number of paw contact points is provided. Two days after the completion of drug treatments animal walking gait was analyzed according to a) total imprint area, and b) total number of contact points. Compound 1 prevented Taxol™ induced gait disturbance.

Figure 4 illustrates H/M wave disturbance induced by Taxol™. Two days after the completion of drug treatments the dorsal root ganglia and attached nerves were dissected bilaterally from L4 and L5 and their H/M wave conductance measured. Compound 1 caused a reversal in H/M wave disturbance induced by Taxol™.

Figure 5 illustrates the result of co-treatment of lung carcinoma HA460 and ovarian carcinoma OV2008 cell lines with Taxol™ and compound 1. HA460 and OV2008 cells were treated with Taxol™ and/or Taxol™ + compound 1 (AEG 3842). Compound 1 did not protect HA460 or OV2008 cells from Taxol™ induced apoptosis.

DETAILED DESCRIPTION OF THE INVENTION

In the definitions of the groups of Formula I, lower alkyl means a straight-chain or branched alkyl group having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-amyl, neopentyl, 1-ethylpropyl, hexyl, and octyl. The lower alkyl moiety of lower alkoxy, lower alkylsulfonyl, lower alkoxylcarbonyl, lower alkylaminocarbonyl has the same meaning as lower alkyl defined above. The acyl moiety of the acyl and the acyloxy group means a straight-chain or branched alkanoyl group having 1 to

6 carbon atoms, such as formyl, acetyl, propanoyl, butyryl, valeryl, pivaloyl and hexanoyl, and arylcarbonyl group described below, or a heteroarylcarbonyl group described below. The aryl moiety of the aryl, the arylcarbonyl and arylaminocarbonyl groups means a group having 6 to 16 carbon atoms such as phenyl, biphenyl, naphthyl, or pyrenyl. The heteroaryl moiety of the heteroaryl and the heteroarylcarbonyl groups contain at least one hetero atom from O, N, and S, and include pyridyl, pyrimidyl, pyrroleyl, furyl, benzofuryl, thienyl, benzothienyl, imidazolyl, triazolyl, quinolyl, iso-quinolyl, benzoimidazolyl, thiazolyl, benzothiazolyl, and indolyl. The aralkyl moiety of the aralkyl and the aralkyloxy groups having 7 to 15 carbon atoms, such as benzyl, phenethyl, benzhydryl, and naphthylmethyl. The substituted lower alkyl group has 1 to 3 independently-substitutuents, such as hydroxyl, lower alkyloxy, carboxyl, lower alkylcarbonyl, nitro, amino, mono- or di-lower alkylamino, dioxolane, dioxane, dithiolane, and dithione. The lower alkyl moiety of the substituted lower alkyl, and the lower alkyl moeity of the lower alkoxy, the lower alkoxycarbonyl, and the mono- and di-lower alkylamino in the substituents of the substituted lower alkyl group have the same meaning as lower alkyl defined above. The substituted aryl, the substituted heteroaryl and the substituted aralkyl groups each has 1 to 5 independently-selected substituents, such as lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, nitro, amino, mono or di-lower alkylamino, azido, and halogen. The lower alkyl moiety of the lower alkyl, the lower alkoxy, the lower alkylamino, and the mono- and di-lower alkylamino groups amoung the susbtituents has the same meaning as lower alkyl defined above. The heterocyclic group formed with a nitrogen atom includes pyrrolyl, piperidinyl, piperidino, morpholinyl, morpholino, thiomorpholino, N-methylpiperazinyl, indolyl, and isoindolyl. The cycloalkyl moeity means a cycloalkyl group of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, such as cycloalkyl groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-norbornyl, 1-adamantyl and the like. The fluoroalkyl moiety means a lower fluoroalkyl group in which one or more hydrogens of the corresponding lower alkyl group, as defined above, is replaced by a fluorine atom, such as CH_2F, CHF_2, CF_3, CH_2CF_3. The α-amino acid groups include alanine, aminobutyric acid, arganine, asparagine, aspartic acid, cystine, glutamic acid, glycine, histidine, isoleucine,

leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrocine, and valine, which may be in the L-form, or the D-form, or in the form of racemates. The polypeptide groups include any linear combination of the above α-amino acids. Halogen includes fluorine, chlorine, bromine, and iodine.

Some of the compounds described herein contain one or more chiral centres and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic, resolved and enantiomerically pure forms, and pharmaceutically acceptable salts thereof.

The term "subject" or "patient" as used herein refers to mammals including humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

The pharmaceutical compositions of the invention are administered to subjects in effective amounts. An effective amount means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of or diagnose the particular condition or symptoms of the particular condition being treated. In general, an effective amount for treating a neurological disorder is that amount necessary to affect any symptom or indicator of the condition In general, an effective amount for treating neuropathies and neuropathic pain will be that amount necessary to favorably affect mammalian cancer cell proliferation *in situ*. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular condition being treated, the particular drug selected, the severity of

the condition being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Oral routes are preferred.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 1000 mg/kg per day. It is expected that IV doses in the range of about 1 to 1000 mg/m2 per day will be effective. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the conjugates of the invention into association with a carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the active compounds of the

invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

A long-term sustained release implant also may be used. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the compounds of the invention.

When administered, the Formulations of the invention are applied in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, *p*-toluenesulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and a salt (1-2% W/V); citric acid and a salt (1-3% W/V); and phosphoric acid and a salt (0.8-2% W/V), as well as others known in the art.

Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V), as well as others known in the art.

Suitable carriers are pharmaceutically acceptable carriers. The term pharmaceutically acceptable carrier means one or more compatible solid or liquid filler, dilutants or encapsulating substances that are suitable for administration to a human or other animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions are capable of being commingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy. Carrier Formulations suitable for oral, subcutaneous, intravenous, and intramuscular administration etc., are those which are known in the art.

The compounds of the invention may be delivered with other therapeutic agents. The invention additionally includes co-administration of compound I of the invention with other compounds known to be useful in treating neurodegenerative diseases, typified by but not limited to, acetylcholinesterase inhibitors for treating AD, such as tacrine, doneprizil, and rivastigmin, and L-dopa for treating PD, and ACE inhibitors and insulin for the treatment of diabetes.

In the case of peripheral neuropathy induced by a toxic agent, compound I would be delivered separately before, simultaneously with (ie. in the form of anti-cancer coctails, see below), or after exposure to the toxic agent. Preferably, compound I and the chemotherapeutic agent are

each administered at effective time intervals, during an overlapping period of treatment in order to prevent or restore at least a portion of the neurofunction destroyed by the neurotoxic or chemotherapeutic agent. The chemotherapeutic can be any chemotherapeutic agent that causes neurotoxicity, such as dideoxyinosine, deoxy cytizine, D4T, cisplatin, etoposide, vincristine, or Taxol™, Taxoter™, are representative of the classes of agents induce neuropathies.

By "toxic agent" or "neurotixic agent" is meant a substance that through its chemical action injures, impairs, or inhibits the activity of a component of the nervous system. The list of neurotoxic agents that cause neuropathies is lengthy (see a list of candidate agents provided in **Table 1**). Such neurotoxic agents include, but are not limited to, neoplastic agents such as vincristine, vinblastine, cisplatin, Taxol™, or dideoxy-compounds, eg., dideoxyinosine; alcohol; metals; industrial toxins involved in occupational or environmental exposure; contaminants in food or medicinals; or over-doses of vitamines or therapeutic drugs, eg. Antibiotics such as penicillin or chloramphenicol, or mega-doses of vitamins A, D, or B6.

Table 1

Neurotoxic Agents

AGENT	ACTIVITY	AGENT	ACTIVITY
acetazolimide	diuretic	imipramine	antidepressant
acrylamide	flocculant, grouting agent	indomethacin	anti-inflammatory
adriamycin	antineoplastic	inorganic lead	toxic metal in paint, etc.
alcohol (ie. ethanol)	solvent, recreational drug	iso-niazid	antituberculousis
almitine	respiratory stimulant	lithium	antidepressant
amiodarone	antiarrthymic	methylmercury	industrial waste
amphotericin	antimicrobial	metformin	antidiabetic
arsenic	herbicide, insecticide	methylhydrazine	synthetic intermediate
aurothioglucose	antirheumatic	metronidazole	antiprotozoal
barbiturates	anticonvulsive, sedative	misonidazole	radiosensitizer
buckthorn	toxic berry	nitrofurantoin	urinary antiseptic

carbamates	insecticide	nitrogen mustard	antineoplastic, nerve gas
carbon disulfide	industrial applications	nitous oxide	anesthetic
chloramphenicol	antibacterial	organophosphates	insecticides
chloroquine	antimalarial	ospolot	anticonvulsant
chlorestyramine	antihyperlipoproteinemic	penicillin	antibacterial
cisplatin	antineoplastic	perhexiline	antiarrhythmic
clioquinol	amebicide, antibacterial	perhexiline maleate	antiarrythmic
colestipol	antihyperlipoproteinemic	phenytoin	anticonvulsant
colchicine	gout suppressant	platnim	drug component
colistin	antimicrobial	primidone	anticonvulsant
cycloserine	antibacterial	procarbazine	antineoplastic
cytarabine	antineoplastic	pyridoxine	vitamin B6
dapsone	dermatological including leprosy	sodium cyanate	antisickling
dideoxycytidine	anatineoplastic	streptomycin	antimicrobial
dideoxyinosine	antineoplastic	sulphonamides	antimicrobial
dideoxythymidine	antiviral	suramin	anteneoplastic
disulfiram	antialcohol	tamoxifen	antineoplastic
doxorubicin	antineoplastic	Taxol™	antineoplastic
ethambutol	antibacterial	thalidomide	antileprous
ethionamide	antibacterial	thallium	rat poison
glutethimide	sedative, hypnotic	triamterene	diuretic
gold	antirheumatic	trimethyltin	toxic metal
hexacarbons	solvents	L-trypophan	health food additive
hormonal contraceptives		vincristine	antineoplastic
hexamethylolmelamine	fireprooing, crease proofing	vinblastine	antineoplastic
hydralazine	antihypertensive	vindesine	antineoplastic
hydroxychloroquine	antirheumatic	vitamine A or D	mega doses

Several neurotoxic agents and protocols may be used to induce apoptosis in SCG neurons. Several of these insults include the withdrawal of trophic support (for example NGF), treatment with neurotoxic chemotherapeutics such as Taxol™, cisplatin, vincristine, or

vinblastine, and treatment with neurotoxic anti-virals such as D4T. Selected compounds represented by Formula I have been found to inhibit apoptosis induced by the above insults.

Neurotrophins are critical to the growth, development, and survival of small fiber neurons of the PNS. SCG neurons are neurons of the PNS that undergo apoptosis upon NGF withdrawal. In a typical experiment SCG neurons are cultured in the presence of NGF, which induces survival and neurite out-growth. After 5 days the media is changed to one containing no NGF, resulting in the apoptosis of up to 90% of the neurons after 48 hours. The addition of selected compounds of Formula I to the final cellular media provides upwards of 100% protection, at drug concentrations ranging from 1 to 50 μM (see Example 119).

Taxol™ is regularly used in breast cancer chemotherapy. In cancer cells Taxol™ binds to the cyto-skeletal protein tubulin, thereby inhibiting normal microtubular assembly and inducing cellular apoptosis. Despite its potency as an anti-tumour agent, Taxol™ is also toxic to neurons, inducing dose limiting peripheral neuropathies. The addition of Taxol™ (100 ng/mL) to cultured SCG neurons induces the degradation or loss of upwards of 80 % of the neurons. The addition of selected compounds of Formula I to the cellular media, concurrently with Taxol™, protects upwards of 100% of the neurons, at drug concentrations ranging from 1 to 50 μM (see Example 120 and **Figure 1**).

The mechanism of Cisplatin's anti-cancer action is not fully understood, but is believed to involve DNA binding and cleavage. Cisplatin is highly toxic to neurons. The addition of cisplatin (3 μg/mL) to cultured SCG neurons induces apoptosis of upwards of 80% of the neurons. The addition of selected compounds of Formula I to the cellular media, concurrently with cisplatin, protects upwards of 100% of the neurons, at drug concentrations ranging from 1 to 50 μM (see Example 121).

Similarly, vincristine and vinblastine are commonly used anti-tumour agents whose mode of action involves tubulin binding. As above, the addition of vincristine (100 ng/mL) to cultured

SCG neurons induces apoptosis of upwards of 80% of the neurons. The addition of selected compounds of Formula I to the cellular media, concurrently with vincristine, protects upwards of 100% of the neurons, at drug concentrations ranging from 1 to 50 μM (see Example 122).

Taken together, compound of Formula I display remarkable neuroprotective capabilities, against a wide range of insults in both the CNS and the PNS. One of the intended uses of these agent is in the conjugation with chemotherapeutic agents. If compound represented by Formula I were to protect cancer cells from the same chemotherapeutic agents, it would have limited value. Two pieces of evidence suggest these compounds do not protect cancer cells from chemotherapeutics. Selected compounds represented by Formula I have previously been shown to be anit-proliferative (Gadad, A. K. *India. Arzneim.-Forsch.*, 49(10), 858-863, 1999), suggesting these compounds will be beneficial when used in conjunction with other chemotherapeutic agents. Additionally, we have shown that compound 1 displays no protection when human ovarian carcinoma cells (OV2008) and human lung carcinoma cells (HA460) were treated with Taxol™ and/or cisplatin (see Example 124 and Figure 5).

Compound 1 and several of its derivatives have been reported to be potent inhibitors of carbonic anhydrase (CA) (Barnish, I. T., *et. al. J. Med. Chem.*, 23(2), 117-121, 1980). CA plays an important role in maintaining both intra- and extra-cellular pH levels. In an effort to determine whether the neuroprotective profile of compound 1 was due to CA inhibition, a number of well-known, cell permeable, aryl sulfonamide CA inhibitors were evaluated against the Taxol™ killing of SCGs. Dorzolamide, (Ponticello, G. S., *et. al J. Med. Chem.*, **1987**, *30*, 591) aminobenzolamide *N*-acetylaminobenzolamide, acetazolamide, methazolamide, (see Marten, T. H. *J. Glaucoma*, **1995**, *4*, 49) all failed to inhibit Taxol™ induced killing of SCGs at concentrations as high as 50 μM. Based on these results it is clear that although compound 1 is a known CA inhibitor, the primary mechanism by which it is protecting neurons appears to be independent of CA inhibition.

Adenovirus overexpression of Erk1 and Erk2, two members of the MAP kinase family of signaling proteins, have been shown to stimulate neuronal out-growth and the formation of

new synaptic connections in primary neurons of the PNS and CNS. Additionally, the Erks protect cultured neurons from a number of insults including neurotrophin withdrawal (Bonni, A., *et al., Science, **1999***, 286, 1358-1362). A dramatic increase in Erk activity was observed in both PC12 cells and in primary cultures of sympathetic neurons when treated with compound 1. The activity of Akt, however, remained unchanged when both PC12 cells and SCGs were treated with compound 1. Akt is activated by NGF and has been demonstrated to be neuroprotective in both PNS and CNS neurons. Compound 1, therefore, protects neurons by activating a subset of NGF-stimulated signaling pathways.

Taxol™ commonly causes dose dependent peripheral neuropathies during cancer treatment. When treated with Taxol™ (9 mg/kg in Cremophor EL and ethanol) twice weekly for 3 weeks, Sprague Dawley rats displayed acute symptoms of chemotoxicity, characterized by reduced appetite, weight loss, gait disturbance (a general marker of Taxol™ induced peripheral neuropathy), and general poor health (see Example 123). For example, over a thirteen day period control animals gained an average of 50 g, whereas the Taxol™ treated animals displayed no weight gain (see Figure 2). All of the Taxol™ treated animals developed peripheral neuropathies, characterized by 'tip toe walking'. The extent of this neuropathy was analyzed by quantifying the refracted light captured by a video camera as the animals walked over a glass plate. This data was analyzed by Northern Eclipse software. The Taxol™ treated animals displayed a 46 % reduction in foot-pad contact with the glass plate, as compared to control animals (see Figures 3 and 4).

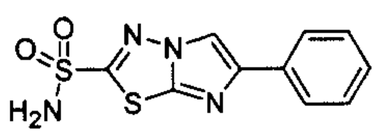
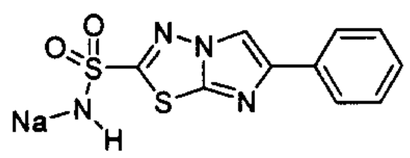
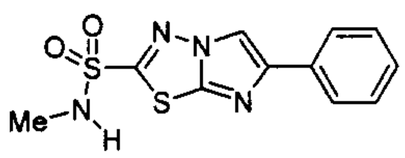
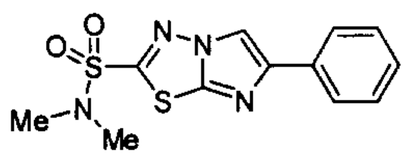
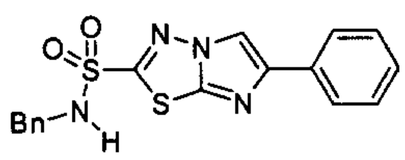
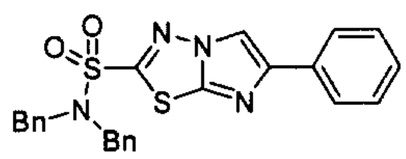
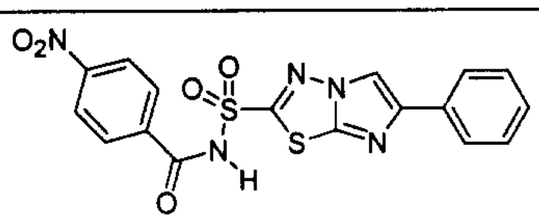
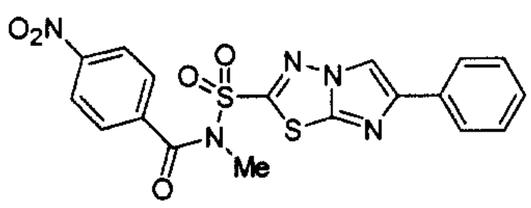
When compound 1 (5 mg/kg) was given with Taxol™ (9 mg/kg) on a bi-weekly schedule, the animals displayed greatly improved health. This was characterized by moderate weight gain (Figure 2) and a reduction in the severity of the peripheral neuropathies; a 23 % loss in foot pad contact was observed, as compared to a 46 % loss in the animals treated with Taxol™ alone (see Figures 3 and 4). No acute signs of toxicity were observed in animals in acute toxicity studies with compound 1 alone (1, 5, and 10 mg/kg for 3 weeks).

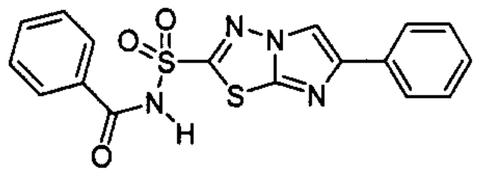
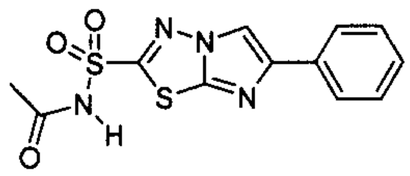
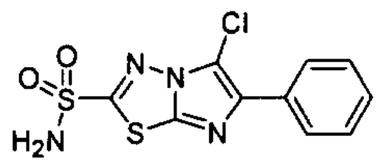
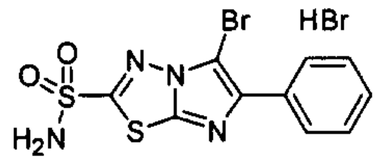
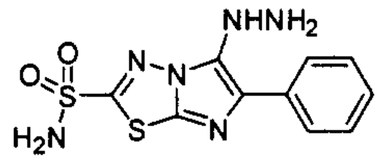
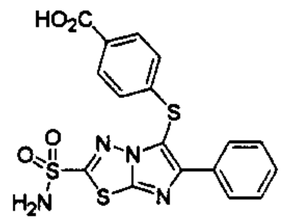
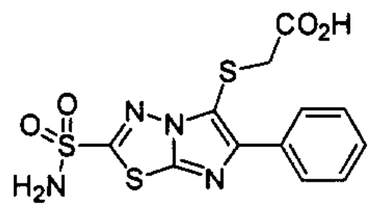
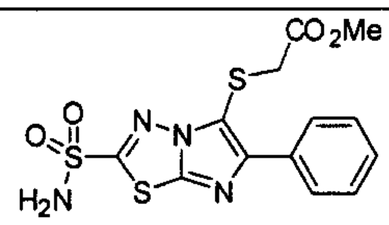
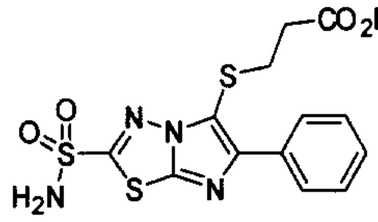
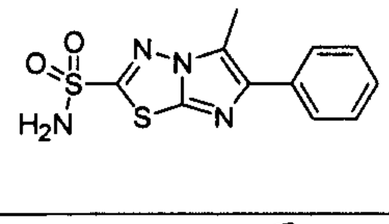
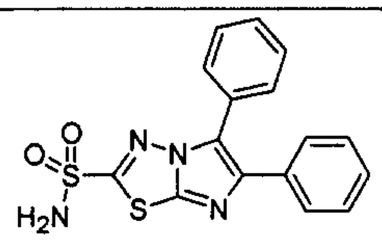
For any of the compounds having the structure of Formula I which bear similarity to those known in the art, the use of these compounds for treatment and/or prevention of neurological disorders, cancer, inflammation, or symptoms related thereto are encompassed by the invention.

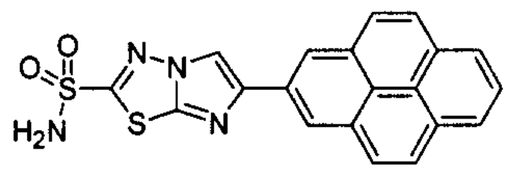
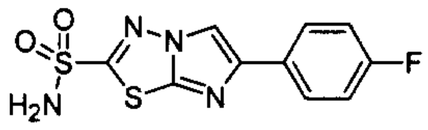
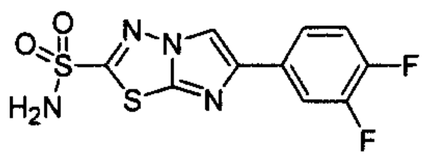
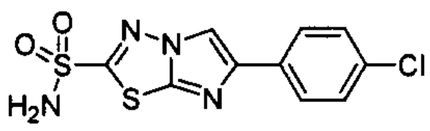
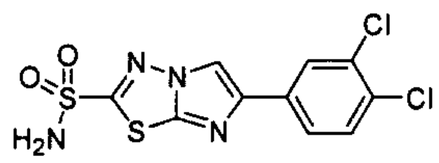
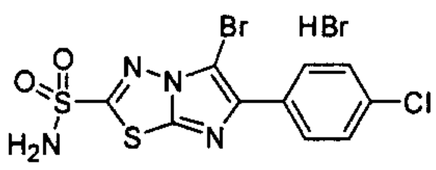
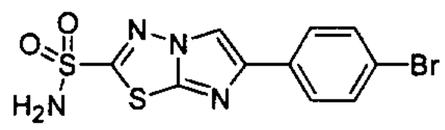
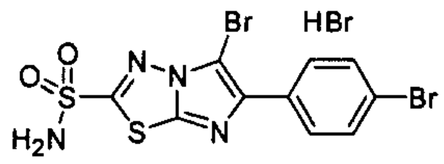
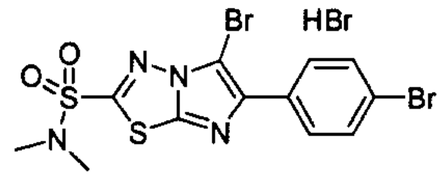
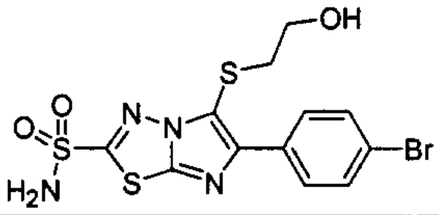
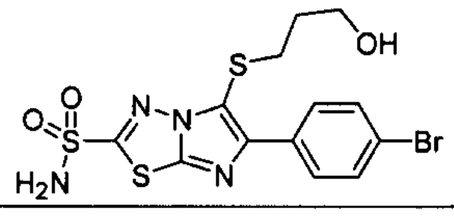
Examples of Formula I are provided in Table 2.

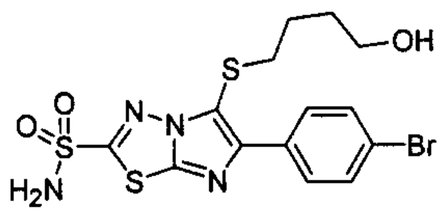
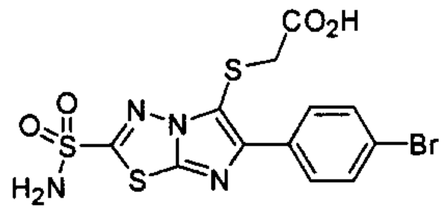
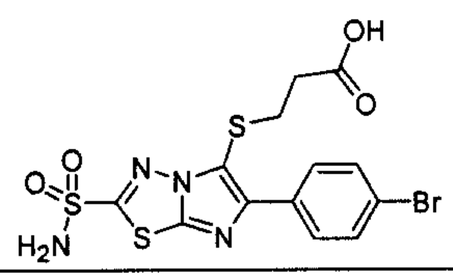
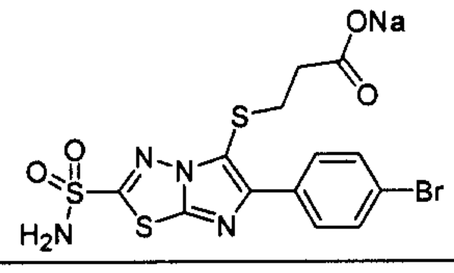
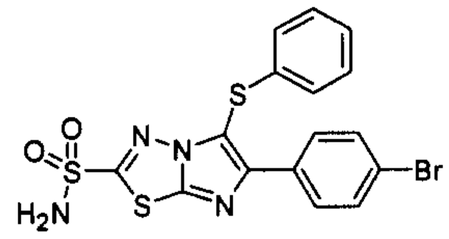
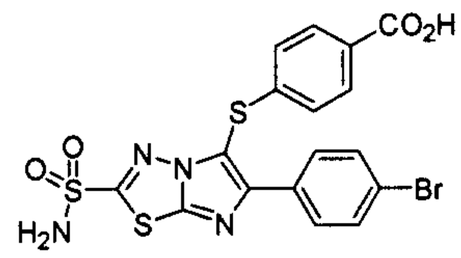
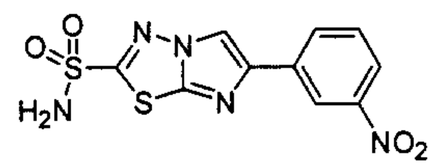
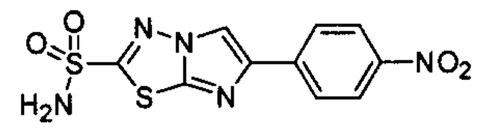
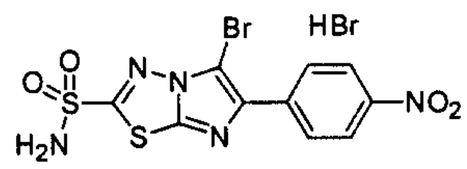
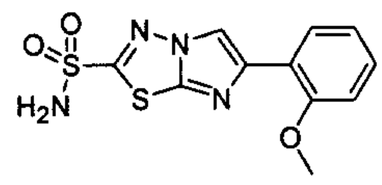
Table 2

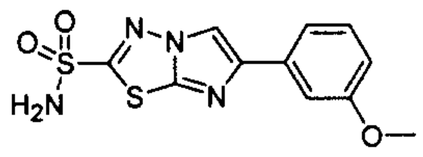
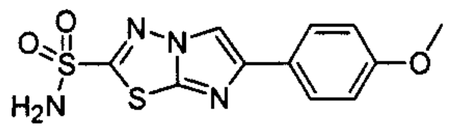
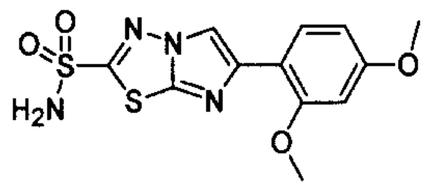
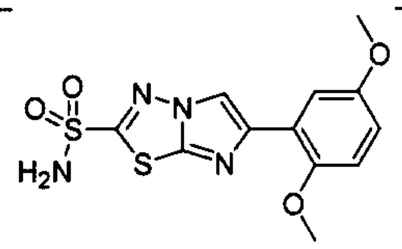
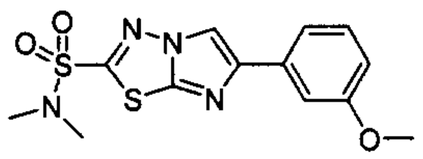
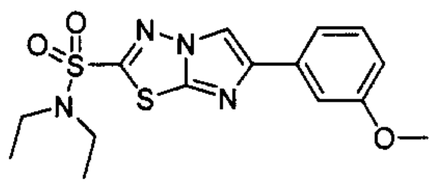
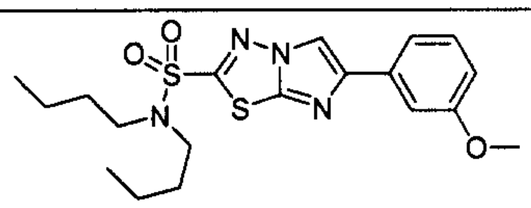
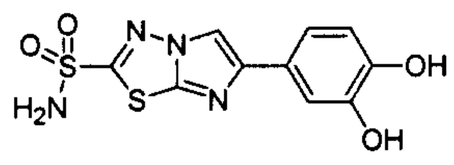
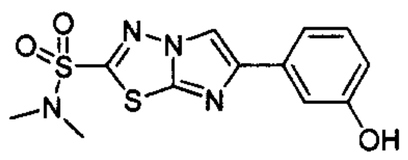
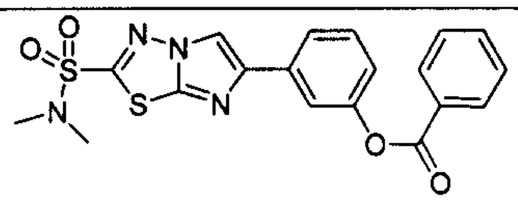
Exemplary Compounds of Formula I

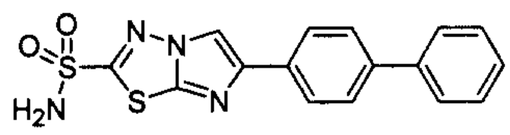
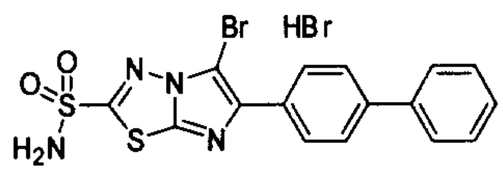
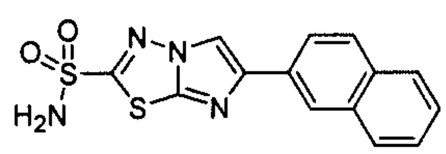
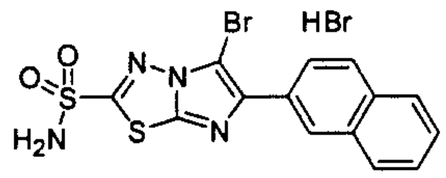
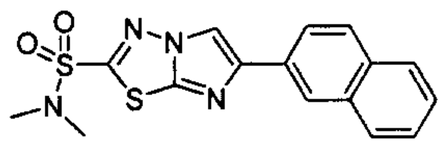
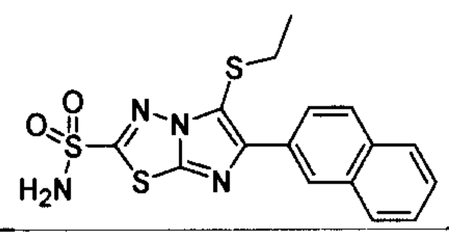
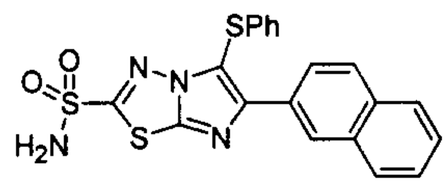
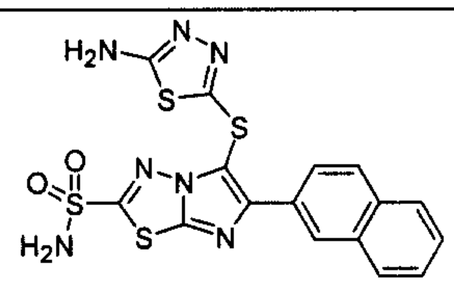
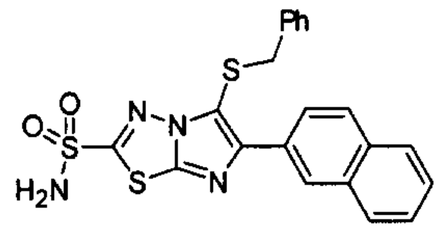
Compound	Structure
1	
2	
3	
4	
5	
6	
7	
8	

9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	

20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	

31	
32	
33	
34	
35	
36	
37	
38	
39	
40	

41	
42	
43	
44	
45	
46	
47	
48	
49	
50	

51	
52	
53	
54	
55	
56	
57	
58	
59	
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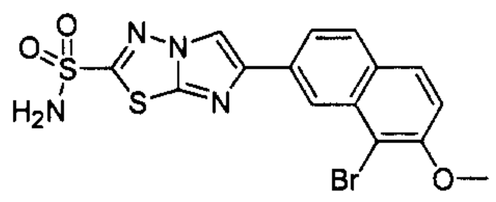
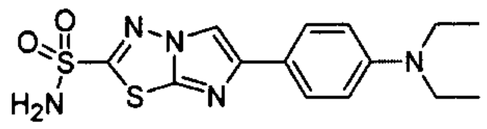
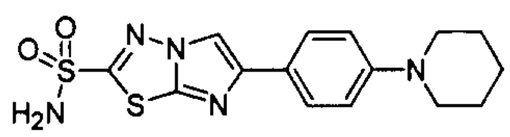
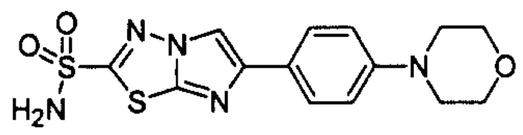
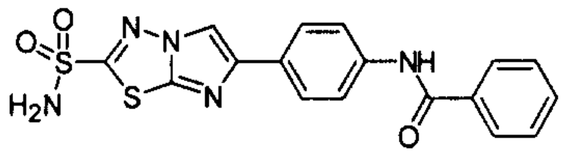
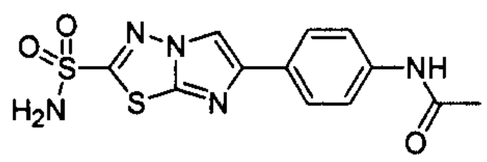
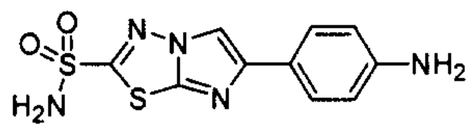
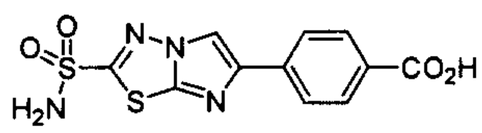
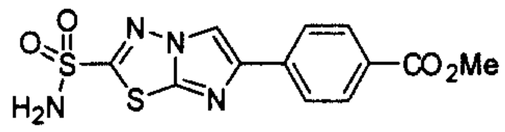
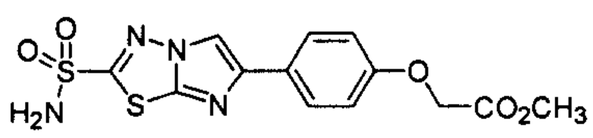
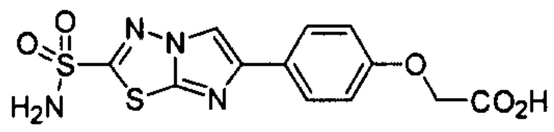
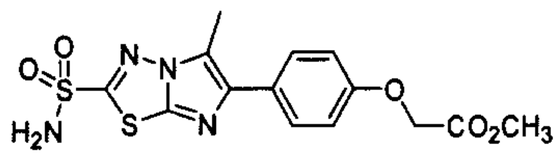
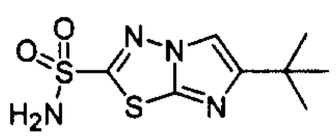
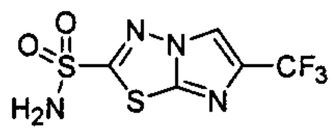
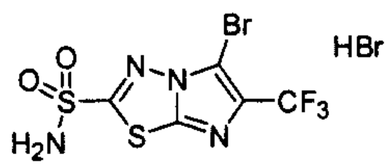
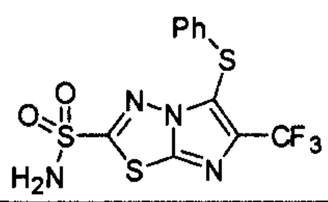
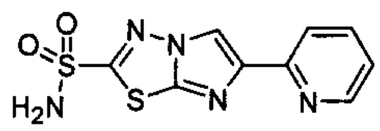
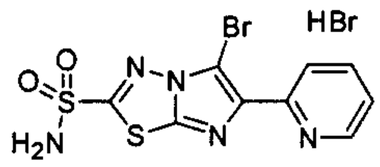
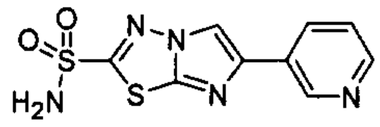
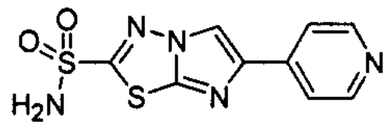
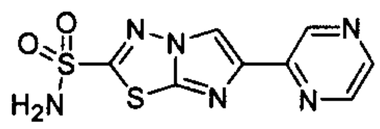
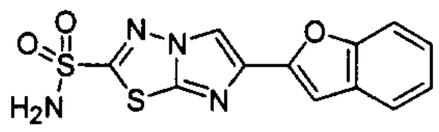
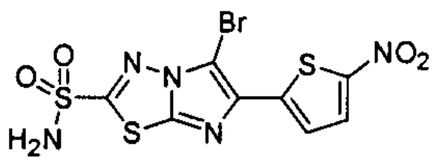
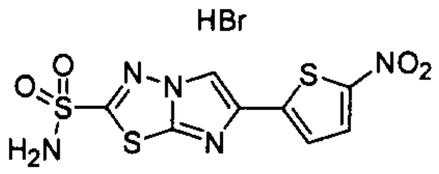
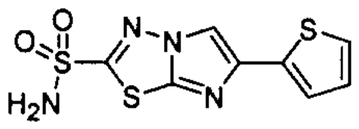
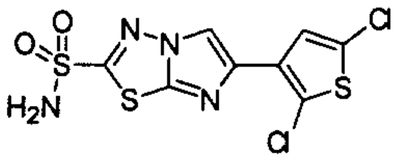
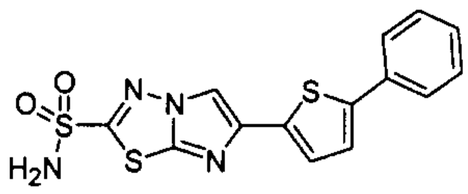
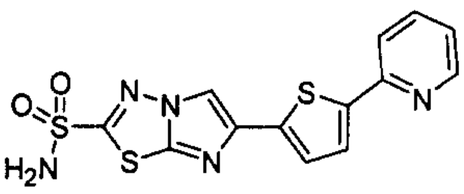
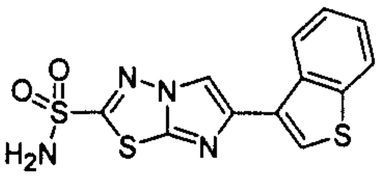
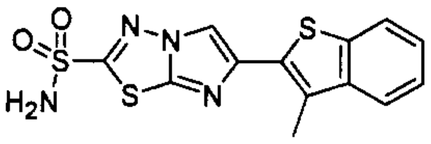
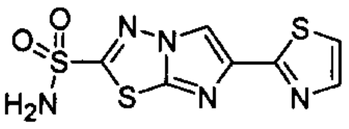
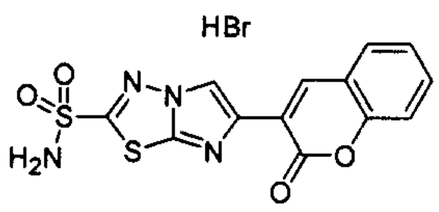
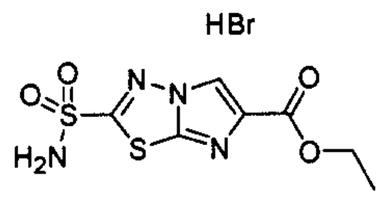
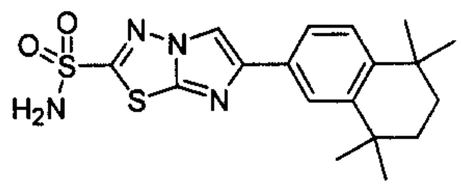
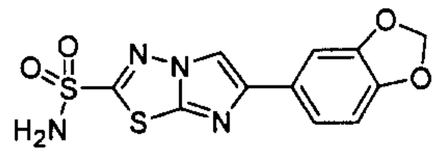
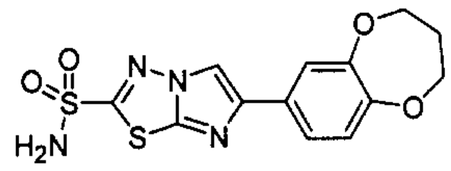
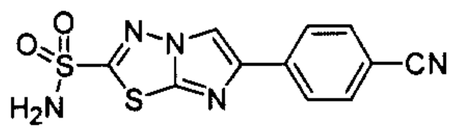
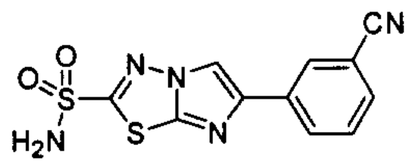
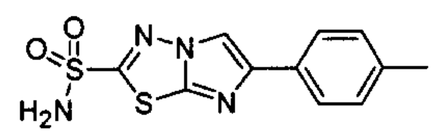
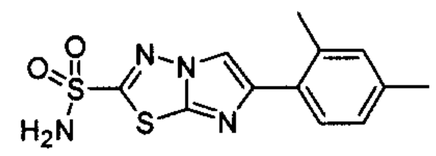
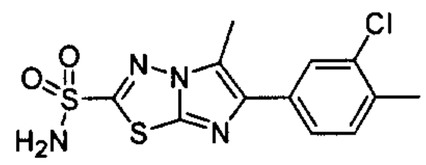
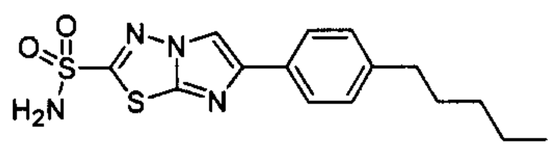
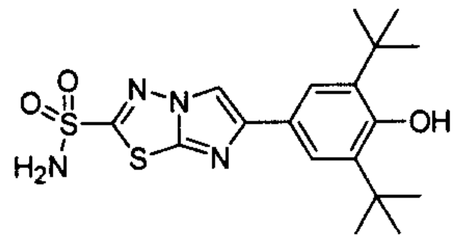
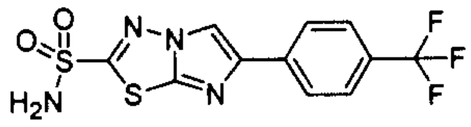
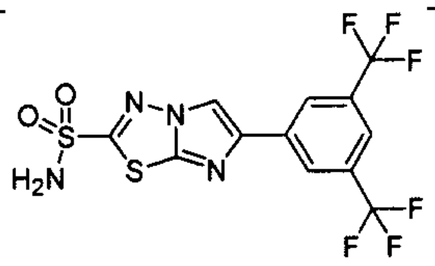
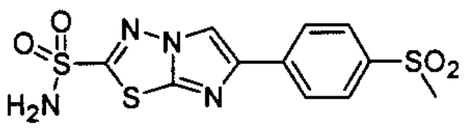
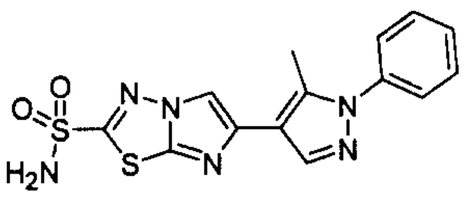
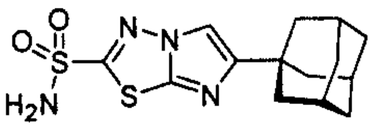
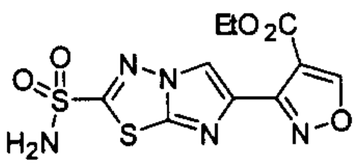
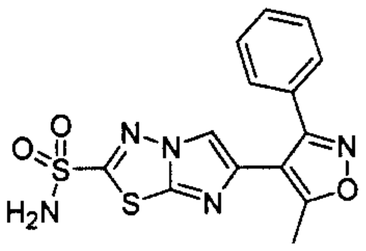
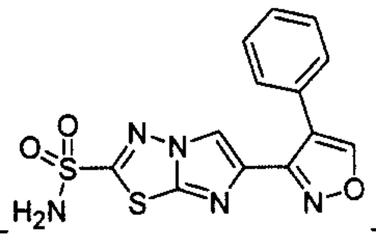
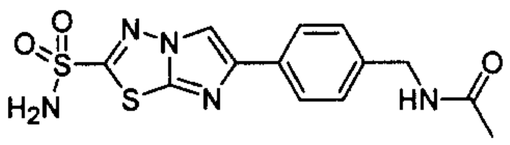
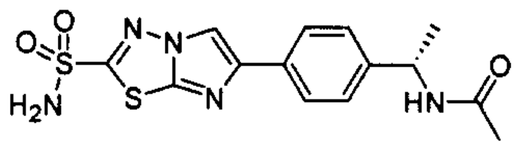
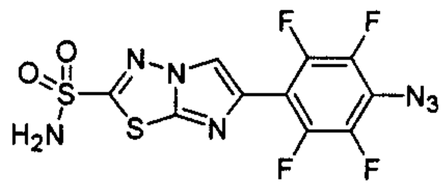
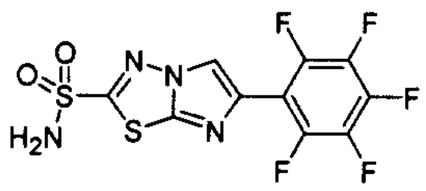
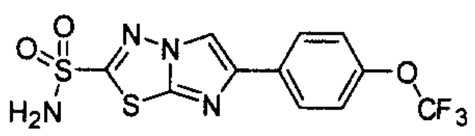
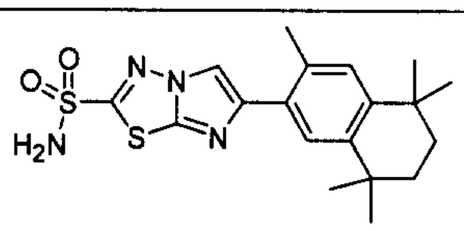
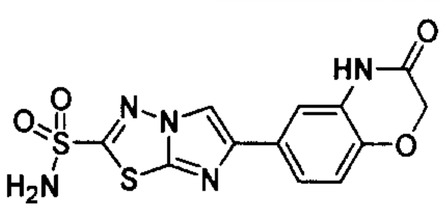
61	
62	
63	
64	
65	
66	
67	
68	
69	
70	

71	
72	
73	
74	
75	
76	
77	
78	
79	
80	
81	

82	
83	
84	
85	
86	
87	
88	
89	
90	
91	
92	

93	
94	
95	
96	
97	
98	
99	
100	
101	
102	

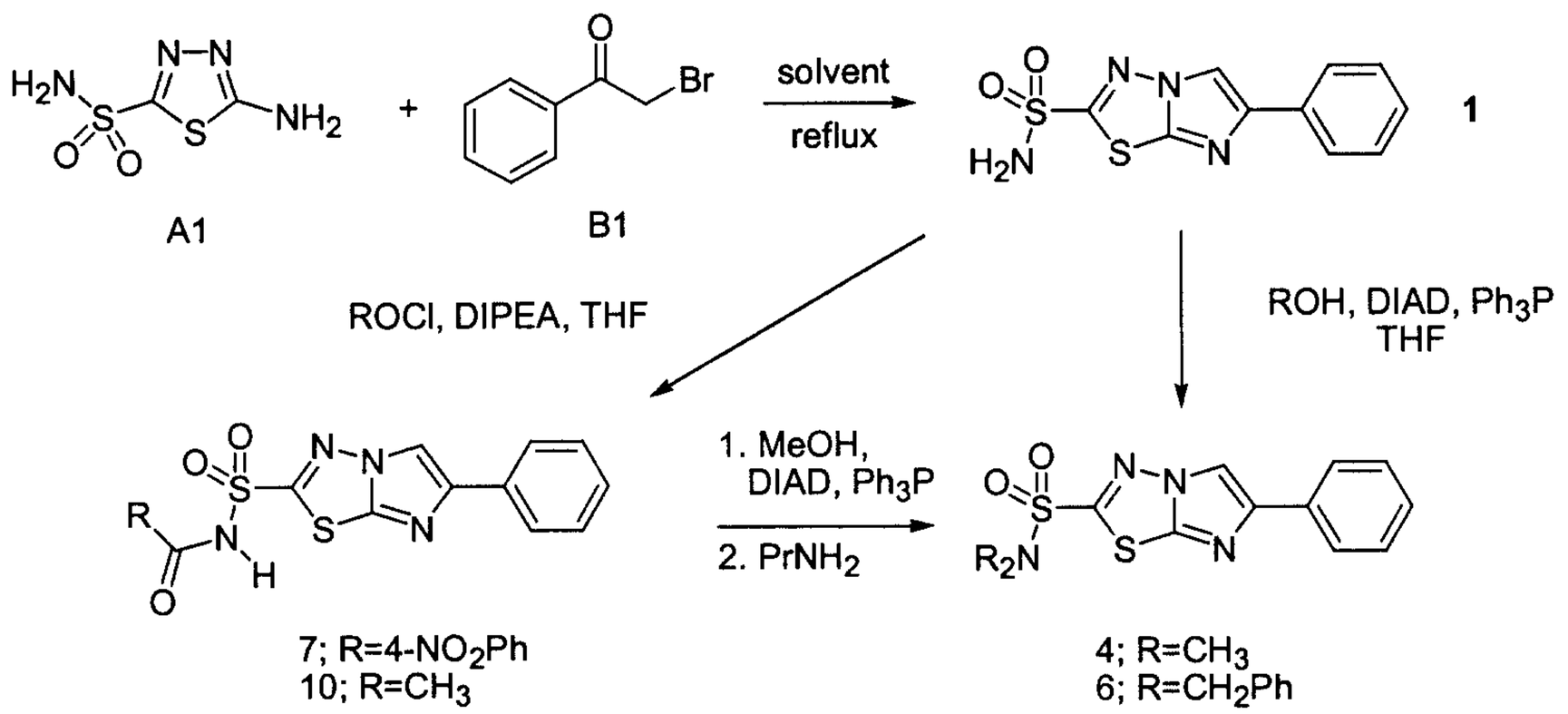
103	
104	
105	
106	
107	
108	
109	
110	
111	
112	

113	
114	
115	
116	
117	
118	

Selected Synthetic Procedures

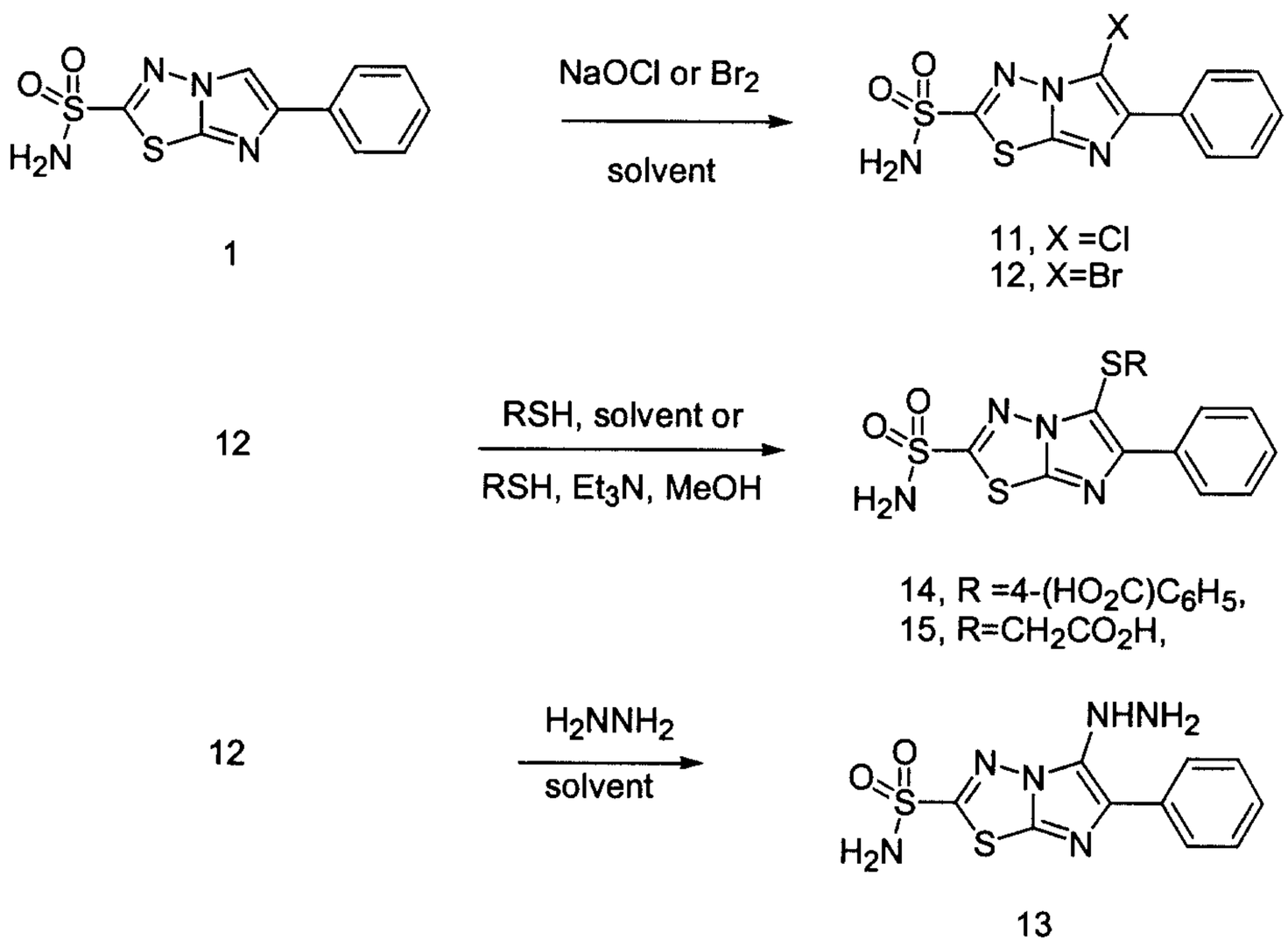
2-Amino-5-thiadiazole sulfonamide, intermediate A1, was prepared by the acid hydrolysis of acetazolamide. Selected 2-bromoaryl ketones were purchased from either Aldrich Chemical Co. or from Maybridge Inc.

Compound 1 was prepared in good yield by refluxing intermediate A1, with 2-bromoacetophenone, intermediate B1, in either alcohol or 1,4-dioxane, for 48 hours.



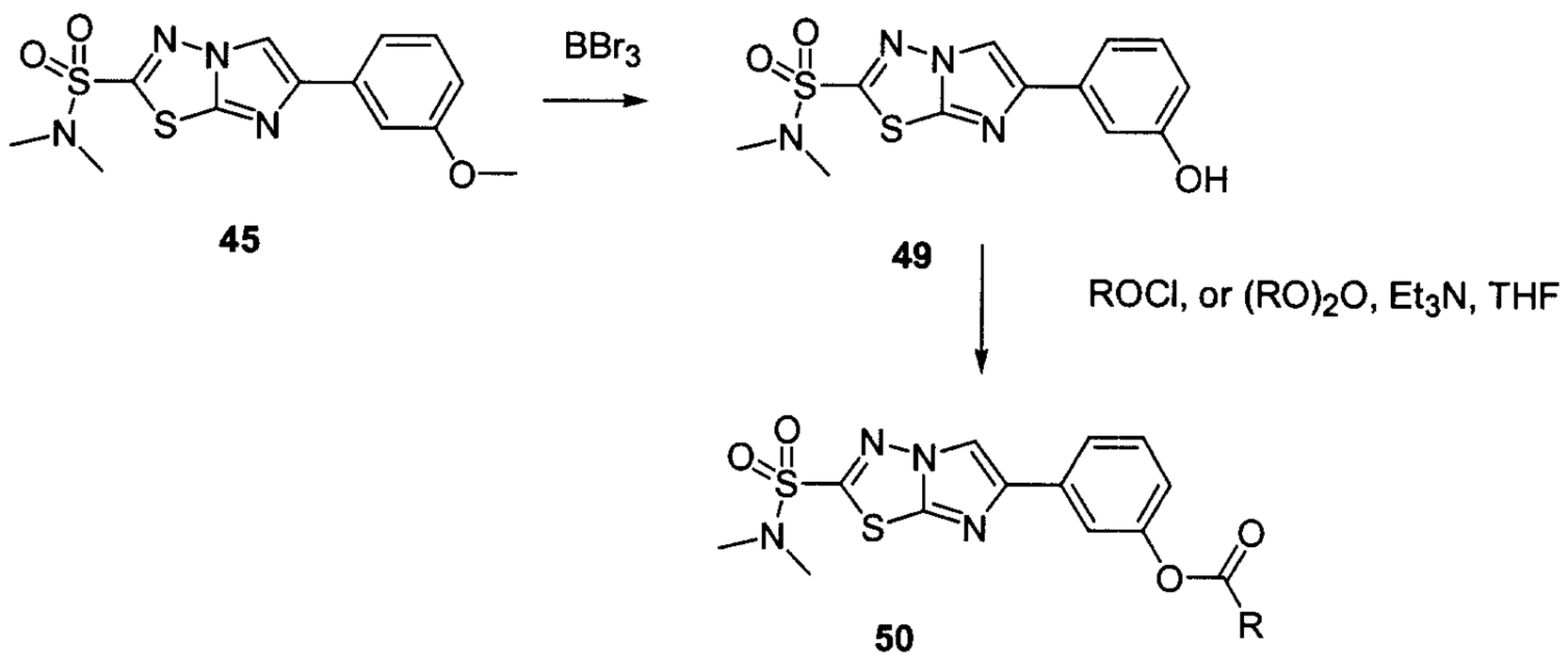
Compound 1 was acylated by treatment with 1 equiv of acid chloride and base to provide compounds 7 and 10. Compound 1 was either mono- or dialkylated by the treatment of compound 1 with the appropriate alcohol (1 or 2 equiv), triphenyphosphine, and DIAD or polymer supported DIAD to yield compounds such as 4 and 6. The conversion of compound 7 to compound 4, Mitsunobu followed by de-acylation with $PrNH_2$, proceeds in good yield. This last series of reactions also works on solid phase.

Compound 1 was readily functionalized at the imidazole methine position by treatment with NaOCl or Br_2, to provide compounds 11 and 12, respectively. Subsequent treatment of the bromo derivative, compound, with aromatic or alkyl thiols provided the desired thio ethers such as compounds 14 and 15.



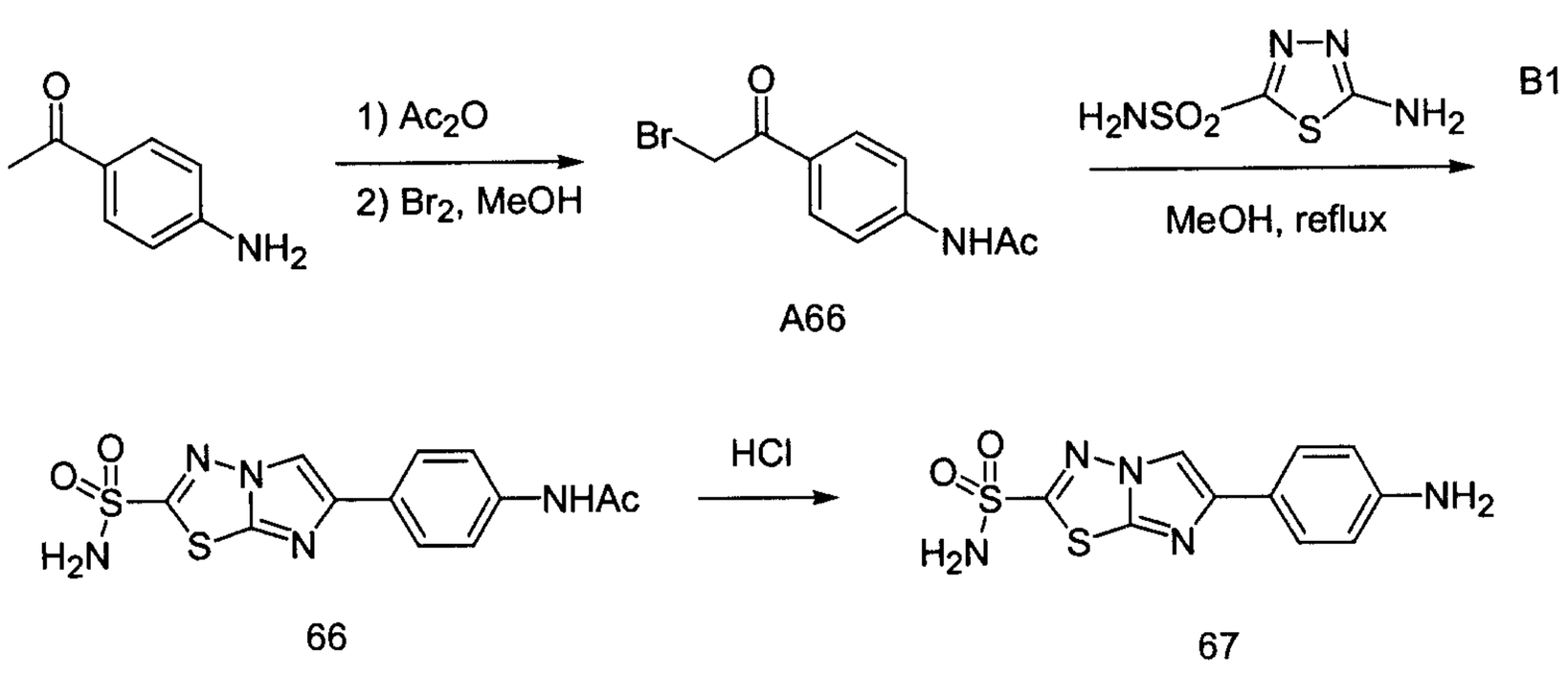
Treatment of compound 12 with hydrazine provided compounds 13.

Demethylation of compound 45 with BBr_3 provides the phenolic compound 49. Acylation of compound 49 with benzoyl chloride provides compound 50.



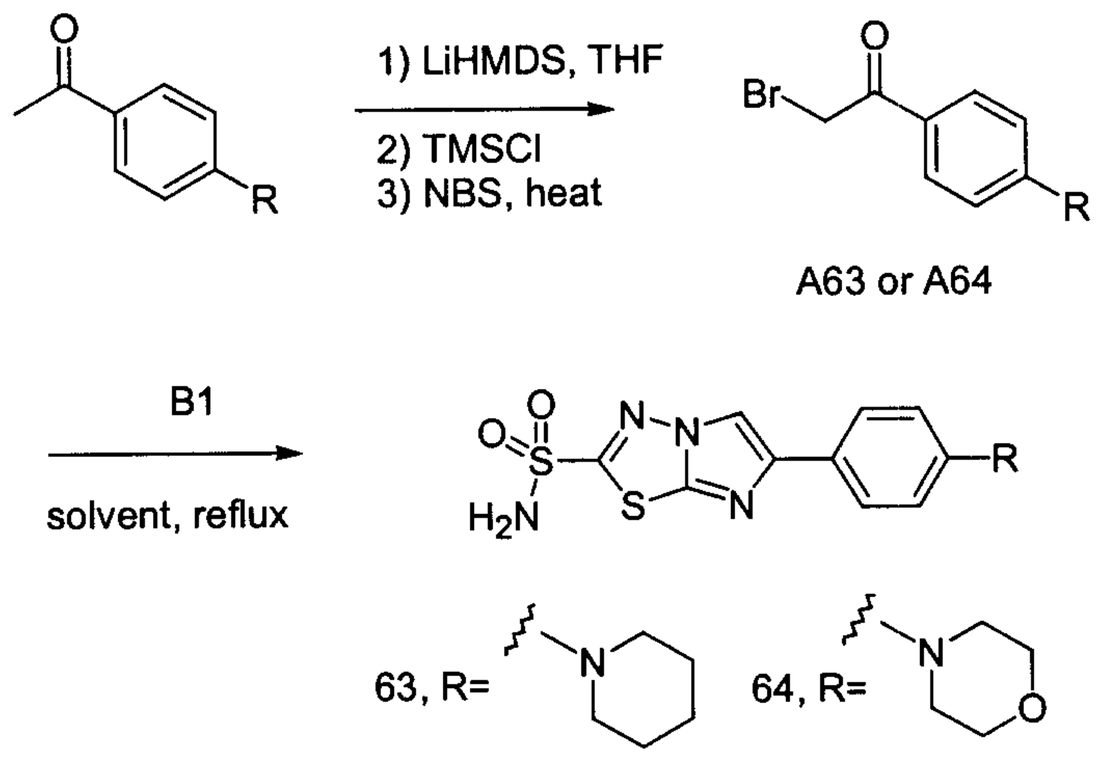
In several cases the requisite 2-bromoacetophenones were commercially available. In other cases they were prepared by the treatment of an appropriately substituted acetophenone with

bromine, in an appropriate solvent, as exemplified below. Acylation of 4-aminoacetophenone was followed by bromination in MeOH to provide intermediate A66. Condensation of intermediate A65 with intermediate B1, yielded the desired compound 66.



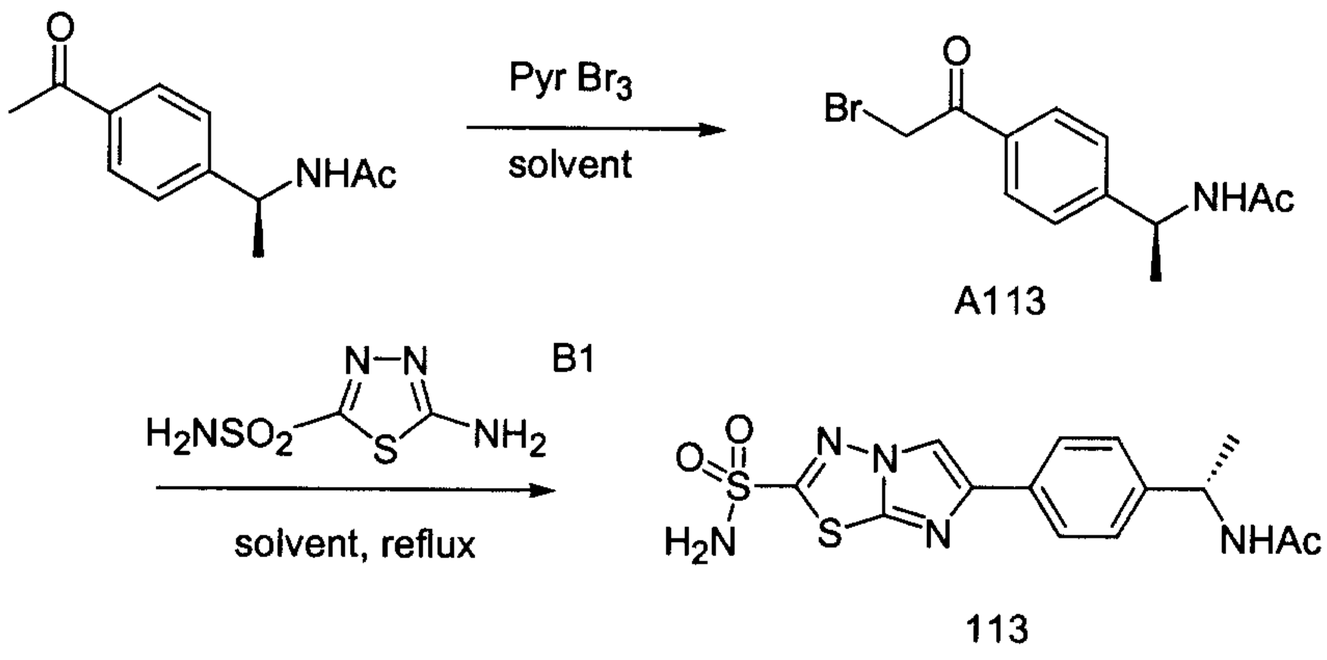
Treatment of compound 66 with methanolic HCl provided compound 67.

Several α-bromoketones were prepared by bromination of the appropriate enol silyl ether. Therefore, deprotonation of either 4'-piperidenylaceophenone or 4'-morpholinoacetophenone with LiHMDS, silation with TMSCl, and quenching with *N*-bromosuccinamide, yielding the desired α-bromoketone intermediates A63 and A64, respectively, as shown below.

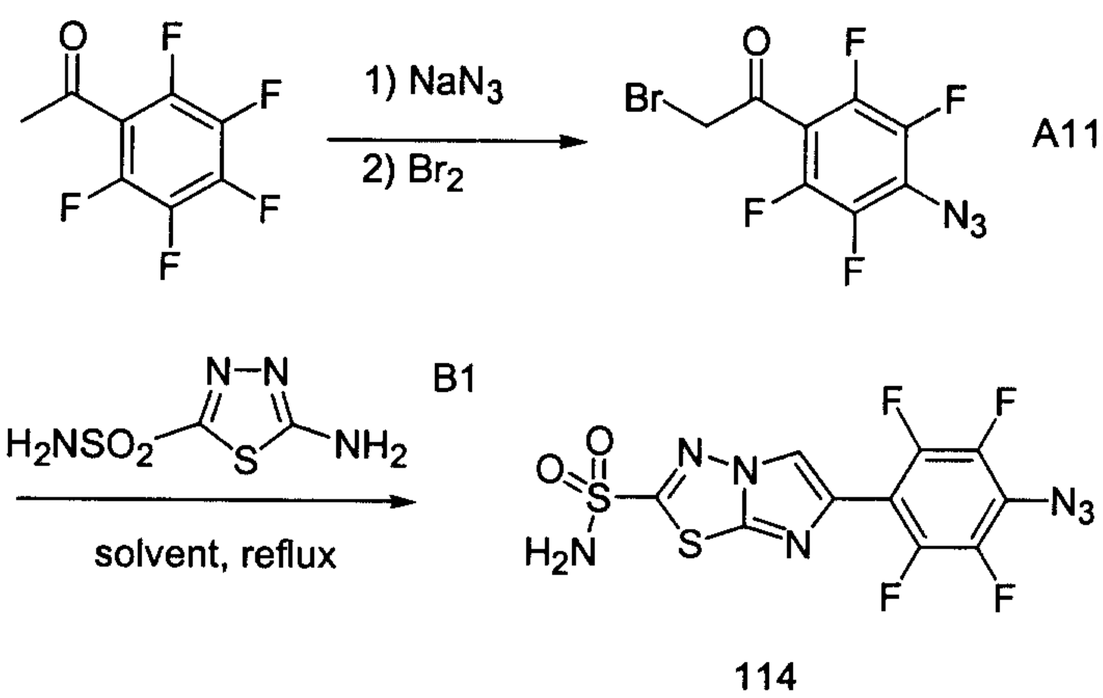


Condensation of A63 and A64 with B1, provided compounds 63 and 64, respectively.

Treatment of selected aryl ketones with bromine or pyridinium perbromide also provided the desired 2-bromoacetophenones, which were again condensed with 2-amino-1,3,4-thiadiazole-5-sulfonamide to provide the desired 6-aryl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamides, as shown below for compound 113.



Compound 114 was prepared using the following strategy. 2',3',4',5', 6'-Pentafluoroacetophenone was treated with sodium azide, followed by bromide, to provide 2-bromo-4'-azido-2',3',5',6'-tetrafluoroacetophenone, A107 (Keana, J. F. W.; Cai, S. X. *J. Org. Chem.*, **1990**, *55*, 3640). Condensation of A114 with B1 to provided compound 114.



Selected Compound Syntheses

Example 1: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromoacetophenone (4.00 g, 20.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (3.60 g, 20.0 mmol) were refluxed in ethanol (150 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 1 as a white crystalline solid (2.50 g, 44 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.89 (s, 1H), 8.72 (br s, 2H), 7.90 (d, 2H), 7.43 (t, 2H), 7.32 (t, 1H).

Example 2: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide sodium salt

Compound 1 (200 mg, 0.71 mmol) was added to a solution of sodium hydroxide (28 mg, 0.71 mmol) in 4:1 MeOH/H_2O (5 mL). The solution was stirred overnight at room temperature before the solvent was removed under reduced pressure to provide compound 2 as a white solid (240 mg, 111%). ^{1}H NMR (200 MHz, DMSO-d^6) δ 8.59 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.32 (m, 3H).

Example 3: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N*-methylsulfonamide

Compound 1 (110 mg, 0.50 mmol), methanol (30 mg, 0.5 mmol), and triphenylphosphine (130 mg, 0.5 mmol) were combined in THF (5 mL). This solution was added to a reaction vessel containing polymer supported DIAD (500 mg, 0.50 mmol). After being shaken overnight, the solid resin was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting semi-solid was purified by silica gel chromatography, eluting with 10% ethyl acetate/hexane, to provide compound 2 as a white solid. ^{1}H NMR (200MHz, acetone-d^6) δ 8.58 (s, 1H), 7.98 (d, 2H), 7.42 (t, 2H), 7.31 (t, 1H), 2.93 (s, 3H).

Example 4: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 1 (140 mg, 0.5 mmol), methanol (64 mg, 2.0 mmol), and triphenylphosphine (525 mg, 2.0 mmol) were combined in THF (2 mL) and treated with DIAD (200 μL, 2.0 mmol).

The resulting solution was stirred over night. The resulting solid was filtered and washed with THF (2 x 3 mL) to provide compound 4 as a white crystalline solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.92 (s, 1H), 8.91 (d, 2H), 7.44 (t, 2H), 7.34 (t, 1H), 2.93 (s, 6H).

Example 5: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N*-benzylsulfonamide

Compound 1 (140 mg, 0.5 mmol), benzyl alcohol (103 μL, 1.0 mmol), and triphenylphosphine (210 mg, 0.8 mmol) were combined in THF (10 ml) and treated with DIAD (158 μL, 0.8 mmol). The resulting solution was stirred for several minutes. Solvent was removed under reduced pressure. The resulting semi-solid was purified by column chromatography on silica gel, eluting with 10:2:88 ethyl acetate/acetic acid/hexane. Recrystallization of the resulting solid from methanol provided compound 5 as a white crystalline solid (97 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.6 (t, 1H), 8.9 (s, 1H), 7.9 (d, 2H), 7.5-7.2 (m, 8H), 4.3 (d, 2H).

Example 6: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2- *N,N*-dibenzylsulfonamide

Compound 1 (140 mg, 0.5 mmol), benzyl alcohol (103 μL, 1.0 mmol), and triphenylphosphine (393 mg, 1.5 mmol) were combined in THF (10 ml) and treated with DIAD (295 μL, 1.5 mmol). The resulting solution was stirred overnight. Solvent was removed under reduced pressure and the resulting semi-solid was dissolved in ethyl acetate. This solution was washed with aqueous sodium hydroxide solution (1mg/ml), dried over magnesium sulfate and concentrated under reduced pressure to a white semi-solid. Upon addition of methanol a voluminous white precipitate appeared. This was collected by suction filtration and washed with a small portion of methanol to afford compound 64 as a shiny, off white solid (156 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.9 (s, 1H), 7.9 (d, 2H), 7.5-7.1 (m, 12H), 4.6 (s, 4H)

Example 7: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N*-(4-nitrobenzoyl)sulfonamide

Compound 1 (27.9 mg, 0.1 mmol) and DIPEA (35 μL, 0.2 mmol) were dissolved in THF (3 ml) and treated with 4-nitrobenzoyl chloride (61.2 mg, 0.33 mmol). After stirring for 2 hours

at room temperature, solvent was removed under reduced pressure. The resultant oil was chased with two portions of toluene (2 x 5ml). Upon addition of ethyl acetate a precipitate appeared and was collected by suction filtration. Recrystallization from dichloromethane afforded compound 7 as a pale green solid (22 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.7 (s, 1H), 8.3-8.1(m, 4H), 7.9 (d, 2H), 7.5-7.2 (m, 3H).

Example 8: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-(*N*-methyl-*N*-(4-nitrobenzoyl)sulfonamide

Compound 7 (107 mg, 0.25 mmol), methanol (20 µl, 0.5 mmol), and triphenylphosphine (98 mg, 0.375 mmol) were combined in 1,4-dioxane (5 ml) and treated with DIAD (74 µl, 0.375 mmol). After several minutes of stirring, solvent was removed under reduced pressure and the resulting oil was purified by silica gel chromatography, eluting with hexane followed by 10% ethyl acetate in hexane. Recrystallization of the resulting solid from dichloromethane provided compound 8 as a white crystalline solid (42 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.0 (s, 1H), 8.3 (d, 2H), 8.0-7.8 (m, 4H), 7.6-7.3 (m, 3H), 3.4 (s, 3H)

Example 9: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N*-benzoylsulfonamide

Compound 1 (140 mg, 0.5 mmol) and DIPEA (174 µL, 1.0 mmol) were dissolved in THF (5 ml) and treated with benzoyl chloride (174 µL, 1.5 mmol). The resulting suspension was stirred for 30 minutes and the solvent removed under reduced pressure. The reaction mixture was chased with two portions of toluene (2 x 5ml). The resulting oil was purified by silica gel chromatography, eluting with 2:1:97 methanol/acetic acid/ dichloromethane, to provide compound 9 as an off white powder (73 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.7 (s, 1H), 8.0-7.8 (m, 4H), 7.5-7.2 (m, 6H)

Example 10: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N*-acetylsulfonamide

Compound 1 (140 mg, 0.5 mmol) and DIPEA (174 µL, 1.0 mmol) were dissolved in THF (5 ml) and treated with acety chloride (174 µL, 2.0 mmol). The resulting suspension was stirred for 60 minutes before standard aqueous workup and purification by silica gel

chromatography, eluting with 5% methanol/dichloromethane, to provide compound 9 as a light brown solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 8

Example 11: 5-Chloro-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-sulfonamide

Compound 1 (250 mg, 0.891 mmol) was dissolved in 10:1 THF/water (22 mL) and treated with 40 % sodium hypochlorite (1 mL). The solution was stirred for 3 hours before the volatiles were removed under reduced pressure to provide a light yellow solid (310 mg, 98%). ^{1}H NMR (200MHz, DMSO-d^6) δ 7.96 (m, 2H), 7.43 (t, 2H), 7.39 (t, 1H).

Example 12: 5-Bromo-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 1 (5.00 g, 17.8 mmol) in AcOH (200 mL) was treated with bromine (0.96 mL, 18.7 mmol). The solution was stirred overnight and the formation of a white precipitate was observed. The solvent was evaporated and the solid was suspended in MeOH (50 mL). That suspension was put in the fridge for one hour and filtered to provide compound 12 as a white powder (4.8 g, 76 % after 3rd crop). ^{1}H NMR (200 MHz, DMSO) : δ 8.82 (s, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.46 (m, 3H).

Example 13: 5-Hydrazino-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 12 (150 mg, 0.34 mmol) was suspended in MeOH (3 mL) and treated with hydrazine (1.70 mL, 1.0M in THF, 1.7 mmol). The solution was stirred overnight and the formation of a beige precipitate was observed. The solution was put in the fridge for one hour to increase the precipitation. The solid was filtered with cold MeOH and dried under vacuum to provide compound 13 as a white solid (36 mg, 34 %). ^{1}H NMR (200 MHz, DMSO-d^6) δ 7.92 (d, J = 8.3 Hz, 2H), 7.38 (m, 3H), 6.70 (m, 2H), 5.28 (m, 2H).

Example 14: 5-(4-Carboxyphenylthio)-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 12 (200 mg, 0.450 mmol) was suspended in methanol (5 mL) and treated with triethylamine (197 µL, 1.59 mmol), providing a clear solution. 4-Mercaptobenzoic acid (105 mg, 0.680 mmol) was added resulting in the formation of a white precipitate. Filtration, washing with methanol (3 x 5 mL), provided compound 14 was a green solid (75 mg, 38 %). ^{1}H NMR (200 MHz, DMSO) : δ 8.96 (m, 4H), 7.80 (m, 2H), 7.42 (m, 3H).

Example 15: 5-()-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 12 (1.0 g, 1.9 mmol) was suspended in methanol (30 mL) and treated with triethylamine (938 µL, 6.70 mmol), providing a clear solution. Mercaptoethanol (200 µL, 2.90 mmol) was added resulting in the formation of a white precipitate. Filtration, washing with methanol (3 x 5 mL), provided compound 15 was a white solid (545 mg, 76 %). ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 7.93 (dd, J = 1.4, 8.4 Hz, 2H), 7.41 (m, 3H), 3.83 (s, 2H).

Example 16: 5-(methoxycarbonylmethanethiol)-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole sulfonamide

Compound 12 (220 mg, 0.50 mmol) was suspended in methanol (5 mL) and treated with triethylamine (243 µL, 1.75 mmol), providing a clear solution. Methyl thioglycolate (67 µL, 0.75 mmol) was added resulting in the formation of a white precipitate after overnight stirring. Filtration, washing with methanol (3 x 5 mL), provided compound 229-063 as a white powder (190 mg, 99%). ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 7.94 (td, J = 1.5, 6.7 Hz, 2H), 7.43 (m, 3H), 4.30 (s, 2H), 3.71 (s, 3H). ^{13}C NMR (50 MHz, DMSO) δ 168.4, 144.3, 141.1, 132.7, 128.7, 128.0, 126.3, 124.7, 92.7, 52.8, 35.3.

Example 17: 5-(2-methoxycarbonylethanethiol)-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole sulfonamide

Compound 12 (220 mg, 0.50 mmol) was suspended in methanol (5 mL) and treated with triethylamine (243 µL, 1.75 mmol), providing a clear solution. Methyl 3-mercaptopropionate (83 µL, 0.75 mmol) was added resulting in the formation of a white precipitate after overnight stirring. Filtration, washing with methanol (3 x 5 mL), provided compound 229-064 as a

white powder (142 mg, 71%). ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 7.94 (td, J = 1.5, 7.0 Hz, 2H), 7.43 (m, 3H), 3.62 (s, 3H), 3.49 (t, J = 6.9 Hz, 2H), 2.90 (t, J = 6.7 Hz, 2H); ^{13}C NMR (50 MHz, DMSO) : δ 171.5, 161.4, 144.1, 141.0, 132.8, 128.7, 128.0, 126.3, 92.9, 51.8, 33.4, 29.3.

Example 18: 5-Methyl-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromopropiophenone (1.07 mg, 5.00 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (900 mg, 5.0 mmol) were refluxed in ethanol (25 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 16 as a white crystalline solid (100 mg). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 8.75 (br s, 3H), 7.75 (d, 2H), 7.45 (t, 2H), 7.30 (t, 1H), 2.65 (s, 3H).

Example 19: 5,6-Diphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Desyl bromide (550 mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2 mmol) were refluxed in ethanol (20ml) for 60 hrs. Solvent was removed under reduced pressure. Purification by silica gel chromatography, eluting with 30:0.1:70 ethyl acetate/ acetic acid/ hexane, and recrystallization from dichloromethane gave compound 17 as a white crystalline solid (175 mg). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 8.8-8.6 (s, 2H), 7.7-7.4 (m, 7H), 7.4-7.2 (m, 3H).

Example 20: 6-pyrenylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-(Bromoacetyl)-pyrene (646mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360mg, 2 mmol) were refluxed in ethanol (20 ml) for 60 hrs. Solvent was removed under reduced pressure. The resulting solid was purified by silica gel chromatography, eluting with solvent gradient of 30-100% ethyl acetate/hexane, to afford compound 18 as a brownish orange solid (4.5 mg). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 9.0 (s, 1H), 8.8 (s, 2H), 8.50-8.00 (m, 9H).

Example 21: 6-(4-Fluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-fluoroacetophenone (1.08 g, 5.0 mmol) 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (900 mg, 5.0 mmol) were refluxed in ethanol (25 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 19 as a white crystalline solid (17 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.87 (s, 1H), 8.74 (br s, 2H), 7.40 (m, 2H), 7.28 (m, 2H).

Example 22: 6-(3,4-Difluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Chloro-3',4'-difluoroacetophenone (190 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (150 mg, 1.0 mmol), and CETAB (437 mg, 1.20 mmol) were refluxed in dioxane (5 mL) for 48 hrs. The solvent was removed under reduced pressure and the resulting solid was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 20 (173 mg, 57%) as a white crystalline solid. ^{1}H NMR (200MHz, acetone-d^6) δ 8.41 (d, 1H), 8.26 (m, 1H), 7.92 (br s, 2H), 7.24-7.08 (m, 2H).

Example 23: 6-(4-Chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 21 was obtained from Talon.

Example 24: 6-(3,4-Dichlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-3',4'-dichloroacetophenone (267 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (180 mg, 1.00 mmol) were refluxed in ethanol (20 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 22 as a white crystalline solid (91 mg, 26 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.01 (s, 1H), 8.74 (s, 2H), 8.13 (d, 1H), 7.89 (dd, 1H), 7.70 (d, 1H).

Example 25: 5-Bromo-6-(4-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 23 was obtained from Talon.

Example 26: 6-(4-Bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-bromoacetophenone (2.78 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 12.0 mmol) were refluxed in 1,4-dioxane (25 mL) for 16 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 24 as a white crystalline solid (3.60 g). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.92 (s, 1H), 8.75 (br s, 2H), 7.85 (d, 2H), 7.62 (d, 2H).

Example 27: 5-Bromo-6-(4-bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 24 (100 mg, 0.278 mmol) was suspended in acetic acid (5 mL) and treated with neat bromine (16 μL, 0.306 mmol). The reaction mixture was stirred overnight and volatiles were removed under reduced pressure to provide compounds 24 as a light orange solid (143 mg, 99%).

^{1}H NMR (200MHz, DMSO-d^6) δ 8.82 (s, 2H), 7.92 (d, 2H), 7.68 (d, 2H).

Example 28: 6-(4-Bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide hydrobromide

6-(4-Bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide (100 mg, 0.258 mmol) was suspended in acetic acid (5 mL) and treated with neat bromine (18 μL, 0.315 mmol). The reaction mixture was stirred overnight and volatiles were removed under reduced pressure to provide compounds 24 as a light orange solid (140 mg, 99%). ^{1}H NMR (200MHz, DMSO-d^6) δ 7.84 (d, 2H), 7.63 (d, 2H), 2.93 (s, 6H).

Example 29: 5-(2-Hydroxyethanethiol)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 26 (250 mg, 0.48 mmol) was suspended in methanol (8 mL) and treated with triethylamine (235 μL, 1.68 mmol), providing a clear solution. Mercaptoethanol (56 μL, 0.72 mmol) was added resulting in the formation of a white precipitate. Filtration, washing with methanol (3 x 5 mL), provided compound 29 was a white solid (130 mg, 67%).

^{1}H NMR (200 MHz, DMSO-d^6) δ 7.92 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 7.9 Hz, 2H), 5.20 (t, J = 6.0 Hz, 1H), 3.74 (q, J = 6.7 Hz, 2H), 3.40 (t, J = 6.7 Hz, 2H).

Example 30: 5-(3-Hydroxypropanethiol)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 27 (250 mg, 0.48 mmol) was suspended in methanol (8 mL) and treated with triethylamine (235 μL, 1.68 mmol), providing a clear solution. Mercaptopropanol (62 μL, 0.72 mmol) was added resulting in the formation of a white precipitate. Filtration, washing with methanol (3 x 5 mL), provided compound 30 as a green solid. ^{1}H NMR (200 MHz, DMSO) : δ 7.86 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 4.66 (t, J = 5.2 Hz, 1H), 3.52 (q, J = 5.7 Hz, 2H), 3.32 (q, J = 4.8 Hz, 2H), 1.88 (quintet, J = 6.5 Hz, 2H); ^{13}C NMR (50 MHz, DMSO) : δ 162.4, 144.0, 140.0, 132.0, 131.6, 127.9, 120.9, 93.1, 58.9, 31.7, 31.0.

Example 31: 5-(4-Hydroxybutylthio)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 27 (250 mg, 0.48 mmol) was suspended in methanol (8 mL) and treated with triethylamine (235 μL, 1.68 mmol), providing a clear solution. Mercaptobutanol (75 μL, 0.72 mmol) was added resulting in the formation of a white precipitate. Filtration, washing with methanol (3 x 5 mL), provided compound 31 as a green solid. ^{1}H NMR (200 MHz, DMSO-d^6) δ 7.89 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 4.46 (t, J = 4.9 Hz, 1H), 3.38 (m, 4H), 1.80 (q, J = 6.4 Hz, 2H), 1.57 (m, 2H); ^{13}C NMR (50 MHz, DMSO-d^6) δ 162.0, 144.0, 139.5, 132.0, 131.0, 128.0, 121.0, 93.0, 60.0, 34.0, 31.0, 25.0.

Example 32: 5-(Carboxymethylthio)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 27 (250 mg, 0.48 mmol) was suspended in methanol (8 mL) and treated with triethylamine (235 μL, 1.68 mmol), providing a clear solution. 2-Mercaptoacetic acid (63 μL, 0.72 mmol) was added. After stirring overnight the volatiles were removed and methanol (5 mL) added to the residue. Filtration, washing with methanol (3 x 5 mL), provided compound

32 was a white solid (151 mg , 70 %). ^{1}H NMR (200 MHz, DMSO-d^6) δ 7.87 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 4.06 (s, 2H).

Example 33: 5-(3-Carboxyethylthio)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 27 (250 mg, 0.48 mmol) was suspended in methanol (8 mL) and treated with triethylamine (235 µL, 1.68 mmol), providing a clear solution. 3-Mercaptopropionic acid (63 µL, 0.72 mmol) was added. The solution was stirred overnight at room temperature under argon before the solvent was evaporated. MeOH (4 mL) were added and the solution was put in the fridge for one hour to help precipitation. The solid was filtered with cold MeOH and dried under vacuum to give 132 mg (59 %) of compound 33as a white powder. ^{1}H NMR (200 MHz, DMSO-d^6) δ 7.89 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 7.3 Hz, 2H), 3.45 (t, J = 6.7 Hz, 2H), 2.80 (t, J = 6.7 Hz, 2H).

Example 34: 5-(3-Carboxyethanethio)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide mono sodium salt

To a suspension of compound 33 (117 mg, 0.25 mmol) in a mixture of 4:1 MeOH/water (5 mL) was added sodium hydroxide (10 mg, 0.25 mmol). The solution was stirred overnight before the solvents were evaporated. The solid obtained was dried under vacuum to give compounds 34 as a white powder (115 mg, 94 %). ^{1}H NMR (200 MHz, D_2O) δ 7.30 (d, J = 7.4 Hz, 2H), 7.04 (d, J = 7.4 Hz, 2H), 3.18 (m, 2H), 2.54 (m, 2H).

Example 35: 5-(Phenylthio)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 27 (250 mg, 0.48 mmol) was suspended in methanol (8 mL) and treated with triethylamine (235 µL, 1.68 mmol), providing a clear solution. Benzenethiol (75 µL, 0.72 mmol) was added resulting in the formation of a white precipitate. Filtration, washing with methanol (3 x 5 mL), provided compound 35 was a white solid. ^{1}H NMR (200 MHz, DMSO-d^6) δ 7.99 (d, J = 8.5 Hz, 2H), 7.84 (m, 2H), 7.63 (m, 5H).

Example 36: 5-(4-Carboxyphenylthio)-6-(4-bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 27 (250 mg, 0.48 mmol) was suspended in methanol (8 mL) and treated with triethylamine (235 μL, 1.68 mmol), providing a clear solution. 4-Mercaptobenzoic acid (112 mg, 0.72 mmol was added resulting in the formation of a gray precipitate. The solution was cooled to –4 °C, filtration, and washed with methanol (3 x 5 mL), providing compound 36 as a gray solid (215 mg, 87 %). ^{1}H NMR (200 MHz, DMSO-d^6) δ 8.01 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H).

Example 37: 6-(3-Nitrophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-3'-nitroacetophenone (224 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.20 mmol) were refluxed in 1,4-dioxane (7 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 37 as a yellow crystalline solid (54 mg, 15 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.12 (s, 1H), 8.75 (br s, 2H), 8.70 (t, 1H), 8.31 (d, 1H), 8.14 (d, 1H), 7.72 (t, 1H).

Example 38: 6-(4-Nitrophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-nitroacetophenone (2.44 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.50 g, 10.0 mmol) were refluxed in 1,4-dioxane (20 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 38 as a white crystalline solid (2.40 g, 67 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.18 (s, 1H), 8.69 (br s, 1H), 8.35 (d, 2H), 8.16 (d, 2H).

Example 39: 5-Bromo-6-(4-nitrophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 39 was obtained from Talon.

Example 40: 6-(2-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-2'-methoxyacetophenone (916 mg, 4.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (720 mg, 4.0 mmol) were refluxed in ethanol (20 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 40 as a white crystalline solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 9.68 (br s, 1H), 8.78 (br s, 2H), 8.12 (d, 1H), 7.34 (t, 1H), 7.11 (d, 1H), 7.05 (t, 1H), 3.96 (s, 3H).

Example 41: 6-(3-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-3'-methoxyacetophenone (1.00 g, 4.37 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (786 mg, 4.37 mmol) were refluxed in 1,4-dioxane (25 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 41 as a white crystalline solid (375 mg, 28 %).
^{1}H NMR (200MHz, DMSO-d^6) δ 8.60 (s, 1H), 7.87 (br s, 2H), 7.56 (d, 1H), 7.52 (dt, 1H), 7.35 (t, 1H), 6.90 (ddd, 1H), 3.85 (s, 3H).

Example 42: 6-(4-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-methoxyacetophenone (2.29 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 12.0 mmol) were refluxed in 1,4-dioxane (25 mL) for 24 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 42 as a white crystalline solid (2.65 g, 86 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.83 (s, 1H), 8.00 (d, 2H), 7.13 (d, 2H), 3.88 (s, 3H).

Example 43: 6-(2,4-Dimethoxyphenyl)imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-2',4'-dimethoxyacetophenone (259 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-2-sulfonamide (180 mg, 1 mmol) were refluxed in ethanol for 5 days. After cooling the resulting precipitate was filtered and washed with methanol, providing 43 (56 mg) as a beige powder. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.69 (br s, 2H), 8.47 (s, 1H), 8.06 (d, J=8.8 Hz, 1H), 6.66 (s, 1H), 6.62 (d, J=2.4 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H).

Example 44: 6-(2,5-Dimethoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-2',5'-dimethoxyacetophenone (261 mg, 1.00 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.20 mmol) were refluxed in 1,4-dioxane (7 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 44 as a white crystalline solid (15.5 mg, 5 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.72 (br s, 2H), 8.60 (s, 1H), 7.70 (d, 1H), 7.04 (d, 1H), 6.87 (dd, 1H), 3.89 (s, 3H), 3.74 (s, 3H).

Example 45: 6-(3-Methoxyphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 41 (212 mg, 0.851 mmol), methanol (103 μL. 2.55 mmol), and triphenylphosphine (669 mg, 2.55 mmol) were combined in THF (10 mL) and treated with DIAD (502 uL, 2.55 mmol). The resulting solution was stirred over night. Solvent was removed under reduced pressure and the resulting semi-solid was triturated with methanol to provide compound 45 as a white crystalline solid (244 mg, 85 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.12 (s, 1H), 7.40 (dd, 1H), 7.38 (d, 1H), 7.33 (t, 1H), 6.88 (ddd, 1H), 3.87 (s, 3H), 3.02 (s, 6H).

Example 46: 6-(3-Methoxyphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-diethylsulfonamide

Compound 41 (50 mg, 0.162 mmol), ethanol (28 μL, 0.486 mmol), and triphenylphosphine (127 mg, 0.86 mmol) were combined in THF (10 mL) and treated with DIAD (96 μL, 0.468 mmol). The resulting solution was stirred over night. Solvent was removed under reduced pressure and the resulting semi-solid was triturated with diethyl ether to provide compound 46 as a white crystalline solid (19.6 mg, 33 %). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.06 (s, 1H). 7.38 (d, 2H), 7.35 (t, 1H), 6.88 (d, 1H), 3.88 (s, 3H), 3.45 (q, 4H), 1.35 (t, 6H).

Example 47: 6-(3-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2- *N,N*-dibutylsulfonamide

Compound 41 (50 mg, 0.162 mmol), butanol (44 μL, 0.486 mmol), and triphenylphosphine (127 mg, 0.486 mmol) were combined in THF (10 mL) and treated with DIAD (96 μL, 0.486 mmol). The resulting solution was stirred over night. The solvent was removed under reduced pressure and the resulting semi-solid was purified by silica gel chromatography, eluting with 10 % ethyl acetate/hexane, to provide compound 47 as a light yellow solid (49 mg, 72 %). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.38 (d, 2H), 7.35 (t, 1H), 3.89 (s, 3H), 3.34 (t, 4H), 1.67 (m, 4H), 1.36 (m, 3H), 0.93 (t, 6H).

Example 48: 6-(3,4-Dihydroxyphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Chloro-3',4'-dihydroxyacetophenone (186 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (150 mg, 1.0 mmol), and CETAB (10 mg) were refluxed in dioxane (5 mL) for 48 hrs. The solvent was removed under reduced pressure and the resulting solid was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 48 (11 mg, 4%) as a white crystalline solid. ^{1}H NMR (200MHz, acetone-d^6) δ 8.38 (s, 1H), 8.10 (br s, 2H), 7.84 (br s, 2H), 7.44 (d, 1H), 7.39 (dd, 1H), 6.88 (d, 1H).

Example 49: 6-(3-Hydroxyphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 45 (420 mg, 1.24 mmol) was suspended in methylenechloride (10 mL) and treated with a BBr_3 (6.20 mL, 1.0M in CH_2Cl_2, 6.20 mmol). The reaction mixture was stirred overnight before being quenched with water (1 mL), followed by saturated $NaHCO_3$ (10 mL). The resulting mixture was diluted with ethyl acetate (20 mL) and subjected to standard workup. The organic layer provided a off yellow solid which was further purified by recrystallization from methanol to provide compounds 49 was a gray solid (14 mg, 32 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.50 (br s, 1H), 8.83 (s, 1H), 7.30 (m, 2H), 7.25 (t, 1H), 6.71 (dd, 1H), 2.93 (s, 6H).

Example 50: 6-(3-Benzoyloxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 49 (20 mg, 0.062 mmol) was dissolved in THF (2 mL) and treated with triethylamine (10 mL, 0.068 mmol) followed by benzoyl chloride (9 mL, 0.068 mmol). The reaction mixture was stirred for 4 hours before a second equiv of triethylamine and benzoyl chloride were added. Standard aqueous workup and purification by silica gel chromatography, eluting with 30% ethyl acetate/hexane, provided compound 50 as a white solid (16 mg, 62 %). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.22 (m, 2H), 8.12 (s, 1H), 7.77-7.60 (m, 3H), 7.58-7.44 (m, 3H), 7.22 (m, 1H).

Example 51: 6-(Biphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-phenylacetophenone (1.38 g, 5.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (0.90 g, 5.0 mmol) were refluxed in ethanol (20 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 51 as a white solid (0.75 g, 45 %). ^{1}H NMR (200 MHz, DMSO-d^6) δ 8.95 (s, 1H), 8.74 (s, 2H), 8.00 (d, J = 8.6 Hz, 2H), 7.74 (m, 4H), 7.44 (m, 3H).

Example 52: 5-Bromo-6-(biphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 51 (1.00 g, 2.80 mmol) was suspended in AcOH (20 mL) and treated with bromine (172 μL, 3.4 mmol). The solution was stirred overnight and the formation of a white precipitate was observed. The solvent was evaporated and the solid was dissolved in 10 mL MeOH. That suspension was put in the fridge for one hour to increase precipitation. Successive precipitations and filtrations provided compound 52 as a yellow powder (1.10 g, 79 %). ^{1}H NMR (200 MHz, DMSO) δ 8.82 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.45 (m, 3H).

Example 53: 6-(2-Naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromonaphthone (2.50 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 1.2 mmol) were refluxed in1,4-dioxane (20 mL) for 96 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 53 as a tan

crystalline solid (2.36 g, 38 %) in two crops. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.99 (s, 1H), 8.74 (br s, 2H), 8.42 (s, 1H), 8.05 (d, 1H), 7.96-7.89 (m, 2H), 7.51 (m, 2H).

Example 54: 5-Bromo-6-(biphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 53 (192 mg, 0.582 mmol) was suspended in acetic acid (10 mL) and treated with neat bromine (31 μL, 0.612 mmol). After stirring overnight the volatiles were removed under reduced pressure, to provide compound 54 as a tan solid (279 mg, 93 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.83 (br s, 2H), 8.42 (s, 1H), 8.04 (d, 1H), 7.98-7.80 (m, 3H), 7.48 (m, 2H).

Example 55: 6-(2-Naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 53 (330 mg, 1.0 mmol), methanol (180 μL, 4.40 mmol), and triphenylphosphine (1.15 g, 4.40 mmol) were combined in THF (10 mL) and treated with DIAD (1.90 mL, 4.40 mmol). The resulting solution was stirred over night. The solvent was removed under reduced pressure and the resulting semi-solid was triturated with diethyl ether, to provide compound 55 as a white crystalline solid (268 mg, 75 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.02 (s, 1H), 8.45 (s, 1H), 8.07-7.83 (m, 3H), 7.56 (m, 2H), 2.91 (s, 6H).

Example 56: 5-Ethylthio-6-(2-naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole

Compound 54 (100 mg, 0.204 mmol), ethanethiol (100 mL), and triethylamine (500 mL) were combined in methanol (10 mL) and refluxed for 16 hours. The resulting suspension was partitioned between hot ethyl acetate and water. The organic layer was separated, dried over anhydrous $MgSO_4$, and solvent removed under reduced pressure. Recrystallization of the resulting solid with acetone, provided compounds 56 as a white solid (57 mg, 66 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.48 (s, 1H), 8.12 (d, 1H), 8.02-7.95 (m, 3H), 7.53 (m, 2H), 3.36 (q, 2H), 1.42 (t, 3H).

Example 57: 5-Thiophenyl-6-(2-naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 54 (100 mg, 0.204 mmol) and mercaptobenzene (28 uL, 0.269 mmol) were combined in THF (10 mL) and refluxed for 16 hours, followed by 72 hours at room temperature. Volatiles were removed under reduced pressure and the resulting residue was triturated with diethyl ether to provide compound 57 as a yellow solid (62 mg, 69 % yield). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.82 (br s, 2H), 8.58 (s, 1H), 8.19 (d, 1H), 7.92 (d, 1H), 7.83 (m, 2H), 7.53 (m, 2H), 7.38-7.12 (m, 5H).

Example 58: 5-(*S*-(2-Thio-5-amino-1,3,4-thiadiazolyl)-6-(2-naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 54 (102 mg, 0.208 mmol) and 5-amino-1,3,4-thiadiazole-2-thiol (37 mg, 0.275 mmol) were combined in a 2:1 mixture of ethyl acetate/methanol (15 mL) and refluxed for 16 hours, followed by 72 hours at room temperature. Volatiles were removed under reduced pressure and the resulting residue was recrystallized from methanol to provide compound 58 as a yellow solid (32 mg, 34 % yield). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.86 (br s, 2H), 8.66 (s, 1H), 8.28 (d, 1H), 8.02 (d, 1H), 7.98 (m, 2H), 7.57 (m, 2H), 7.36 (br s, 2H).

Example 59: 5-Benzylthio-6-(2-naphtyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 54 (127 mg, 0.26 mmol) was suspended in methanol (5 mL) and treated with triethylamine (126 μL, 0.91 mmol), providing a clear solution. Benzyl mercaptan (46 μL, 0.0.39 mmol) was added. The solution was stirred overnight at room temperature under argon before the solvent was evaporated. MeOH (4 mL) were added and the solution was put in the fridge for one hour to help precipitation. The solid was filtered with cold MeOH and dried under vacuum to give 110 mg (94 %) of compound 59 as a white powder. ^{1}H NMR (200 MHz, DMSO-d^6) δ 8.47 (s, 1H), 8.12 (dd, J = 1.7, 8.7 Hz, 1H), 7.96 (m, 4H), 7.54 (m, 4H), 7.36 (m, 3H), 4.61 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d^6) δ 161.3, 141.0, 136.0, 132.9, 132.4, 130.3, 129.4, 128.7, 128.2, 128.0, 127.7, 126.7, 126.5, 125.0, 124.2, 93.2, 37.7.

Example 60: 5-(2-Phenethylthio)-6-(2-naphthyl))imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Example 61: 6-(2-(6-methoxy-7-bromonaphthyl))imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 2-Acetyl-6-methoxyacetophenone (1.00 g, 5.0 mmol) was dissolved in methanol (5 mL) and was treated with bromine (500 μL, 10.0 mmol). The reaction was stirred at room temperature for 2 hours before the volatiles were removed *in vacuo* to provide a 95:5 mixture of 2,7'-dibromo-6'-methoxylnaphone and 2-acetyl-6-methoxyacetophenone. This crude mixture was advanced to the next step without further purification. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.75 (s, 1H), 8.20 (d, 1H), 8.10 (d, 1H), 8.07 (dd, 1H), 7.64 (d, 1H), 5.01 (s, 2H), 4.03 (s, 3H).

Step 2: To the crude mixture obtained above was added 5-amino-1,3,4-thiadiazole-2-sulfonamide (740 mg, 5.0 mmol) and methanol (20 mL). The resulting suspension was refluxed for 48 hours, cooled on ice and the solid filtered off, to provide compound 61 as a white solid (230 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.95 (s, 1H), 8.76 (d, 1H), 8.44 (s, 1H), 8.11 (s, 2H), 8.02 (d, 1H), 7.52 (d, 1H), 3.99 (s, 3H).

Example 62: 6-(4-(Dimethylamino)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Example 63: 6-(4-Piperidinophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step1: 4'-Piperidinoacetophenone (203 mg, 1.00 mmol) was dissolved in THF (5 mL) and treated with lithium bis(trimethylsilyl)amide (1.10 mL, 1.0M in THF, 1.10 mmol). The solution was stirred for 30 minutes prior to the addition of chlorotrimethylsilane (140 μL, 1.10 mmol). After stirring for an additional 30 minutes *N*-bromosuccinamide (300 mg, 1.73 mmol) was added and the mixture was refluxed from 4 hours. Standard aqueous/ethyl acetate workup provided a yellow solid which was further purified by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, to provide 2-bromo-4'-piperidinoacetophenone as an off

white solid (209 mg, 74 %). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.75 (d, 2H), 6.84 (d, 2H), 4.61 (s, 2H), 3.40 (m, 4H), 1.68 (m, 6H).

Step 2: 2-Bromo-4'-piperidinoacetophenone (209 mg, 0.74 mol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (220 mg, 1.48 mmol) were suspended in 1,4-dioxane (10 mL) and refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 63 as a yellow solid (8.0 mg, 2.7 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.68 (s, 3H), 7.75 (d, 2H), 6.98 (d, 2H), 3.23 (m , 4H), 1.57 (m, 6H).

Example 64: 6-(4-Morpholinophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step1: 4'-Morpholinoacetophenone (218 mg, 1.0 mmol) was dissolved in THF (5 mL) and treated with lithium bis(trimethylsilyl)amide (1.1 mL, 1.0M in THF, 1.1 mmol). The solution was stirred for 30 minutes prior to the addition of chlorotrimethylsilane (140 μL, 1.1 mmol). After stirring for an additional 30 minutes *N*-bromosuccinamide (300 mg, 1.73 mmol) was added and the mixture was refluxed from 4 hours. Standard aqueous/ethyl acetate workup provided a yellow solid, which was identified as a 3:1 mixture of 2-bromo-4'-morpholinoacetophenone and starting material. ^{1}H NMR (200MHz, $CDCl_3$) δ 7.86 (d, 2H), 6.84 (d, 2H), 4.62 (s, 2H), 3.84 (t, 4H), 3.32 (t, 4H).

Step 2: The crude 2-Bromo-4'-morpholinoacetophenone from above and 5-amino-1,3,4-thiadiazole-2-sulfonamide (100 mg, 0.66 mmol) were suspended in 1,4-dioxane (10 mL) and refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 64 as a yellow solid (23 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.67 (s, 3H), 7.74 (d, 2H), 6.99 (d, 2H), 3.75 (t, 4H), 3.13 (t, 4H).

Example 65: 6-(4-Benzoylamidophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4-Aminoacetophenone (1.35 g, 10.0 mmol) was dissolved in dichloromethane (10 mL) and treated with benzoyl chloride (1.74 mL, 15.0 mmol). The mixture was stirred for 16 hours at which time a white precipitate had formed. The solid was removed by

filtration, washing with dichloromethane (3 x 20 mL) to provide 4-acetamidoacetophenone as a white sold (2.74 g). ^{1}H NMR (200MHz, DMSO-d^6) δ 10.53 (s, 1H), 7.92 (s, 7H), 7.54 (m, 3H), 2.50 (s, 3H).

Step 2: 4-Benzoylamidoacetophenone (2.55 g) was dissolved in acetic acid (25 mL) and was treated with pyridinium tribromine (3.00 g, 8.0 mmol). The reaction was stirred at room temperature for 24 hours before the volatiles were removed *in vacuo* to provide 2-bromo-4'-benzoylamidoacetophenone. This crude mixture was advanced to the next step without further purification. ^{1}H NMR (200MHz, DMSO-d^6) δ 10.61 (s, 1H), 8.96 (d, 2H), 8.61 (t, 1H), 8.15-8.00 (m, 7H), 4.86 (s, 2H).

Step 3: To the crude mixture obtained above was added 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.50 mg, 10.0 mmol) and methanol (20 mL). The resulting suspension was refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was triturated from acetone to provide compound 65 as a yellow solid (120 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 10.35 (s, 1H), 8.82 (s, 1H), 8.70 (br s, 2H), 7.92 (d, 2H), 7.82 (s, 5H), 7.54 (d, 2H).

Example 66: 6-(4-Acetamidophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4-Aminoacetophenone (13.51 g, 100 mmol) was dissolved in dichloromethane (10 mL) and treated with acetic anhydride (14.20 mL, 150 mmol). The mixture was stirred for 16 hours at which time a white precipitate had formed. The solid was removed by filtration, washing with dichloromethane (3 x 20 mL) to provide 4-acetamidoacetophenone as a white sold (14.62 g, 83%). An additional 1.30 g (9 %) was recovered from the filtrate by titurating the residue with dichloromethane (20 mL). ^{1}H NMR (200MHz, DMSO-d^6) δ 10.25 (br s, 1H), 7.89 (d, 2H), 7.67 (d, 2H), 2.49 (s, 3H), 2.06 (s, 3H).

Step 2: 4-Acetamidoacetophenone (1.00 g, 5.0 mmol) was dissolved in methanol (5 mL) and was treated with bromine (500 μL, 10.0 mmol). The reaction was stirred at room temperature for 2 hours before the volatiles were removed *in vacuo* to provide 2-bromo-4'-acetamidoacetophenone. This crude mixture was advanced to the next step without further

purification. ^{1}H NMR (200MHz, DMSO-d^6) δ 10.37 (br s, 1H), 7.93 (d, 2H), 7.72 (d, 2H), 4.81 (s, 2H), 2.07 (s, 3H).

Step 3: To the crude mixture obtained above was added 5-amino-1,3,4-thiadiazole-2-sulfonamide (740 mg, 5.0 mmol) and methanol (20 mL). The resulting suspension was refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 66 as a yellow solid (60 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.62 (br s, 2H), 8.52 (s, 1H), 7.69 (br d, 1H), 7.56 (s, 2H), 6.61 (d, 2H), 2.08 (s, 3H).

Example 67: 6-(4-Aminophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 66 (60 mg) was suspended in methanol (10 mL) and treated with 6N HCl (1 mL). The suspension was refluxed for 16 hours until all solids had dissolved. The solvent was removed under reduced pressure and the residue was suspended in water (10 mL), neutralized with saturated aqueous $NaHCO_3$. The resulting precipitate was extracted with ethyl acetate to provide compound 67 as a yellow solid (15 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.65 (br s, 2H), 8.53 (s, 1H), 7.58 (d, 2H), 6.58 (d, 2H), 5.32 (br s, 2H).

Example 68: 6-(4-carboxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4-Acetylbenzoic acid (186 mg, 1.14 mmol) was dissolved in warm acetic acid (5 mL) and treated with bromine (58 mL, 1.14 mmol). The solution was stirred overnight before being cooled on ice. The resulting solid was filtered, washed with 1:1 methanol/water (3 x 10 mL) and dried *in vacuo* to provide 4-(2-bromoacetyl)benzoic acid as a white solid (102 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.07 (s, 4H), 4.98 (s, 2H).

Step 2: 4-(2-bromoacetyl)benzoic acid (102 mg) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (75 mg, 0.42 mmol) were refluxed together in methanol (20 mL) for 48 hours. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 5 mL) to provide compound 68 as a white crystalline solid (16 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.02 (s, 1H), 8.00 (s, 4H).

Example 69:

Step1: 4-Acetylbenzoic acid (1.00 g, 6.09 mmol) was suspended in methanol (10 mL). Hydrochloric acid (500 μL) was added. The reaction mixture was refluxed overnight. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 2 mL) to provide methyl 4-acetylbenzoate as a white solid (799 mg, 74%). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.12 (d, J = 8.9Hz, 2H), 8.01 (d, J = 8.9Hz, 2H), 3.95 (s, 3H), 2.65 (s, 3H).

Step2 Methyl 4-acetylbenzoate (200 mg, 1.12 mmol) was suspended in chloroform (5mL) and treated with pyridinium tribromide (359 mg, 1.12mmol). The reaction mixture was stirred overnight. One half equivalent of pyridinium tribromide (179 mg, 0.56 mmol) was added to the reaction mixture and stirred for two days. The solvent was removed under reduced pressure. Standard aqueous/ethyl acetate workup provided a brown solid, which was identified as a 8:12:3 mixture of starting material, methyl 4-(2-bromoacetyl)benzoate and methyl 4-(2.2-dibromoacetyl)benzoate compound. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.08 (d, J = 6.7Hz, 4H), 4.98 (s, 2H), 3.87 (s, 3H).

Step 3 Methyl 4-(2-bromoacetyl)benzoate (100 mg, 0.39 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (70mg, 0.39 mmol) were refluxed together in methanol (10 mL) for 48 hours. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 2 mL) to provide compound 69 as a white solid (12.9 mg, 9.35%). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.03 (s, 1H), 8.70 (br s, 2H), 8.03 (s, 4H), 3.85 (s, 3H).

Example 70:

Step 1: 4-Hydroxyacetophenone (5.00 g, 36.7 mmol) was dissolved in THF (100 mL) and cooled on ice. Sodium bis(trimethylsilyl)amide (40.5 mL, 1.0M in THF, 40.5 mmol) was added and the solution was warmed to room temperature. After stirring for 2 hours the solution was cooled on ice and ethyl bromoacetate (6.14 mL, 55.1 mmol) was added. The solution was stirred over night. Standard aqueous workup provided the desired ester as a clear oil, which was dissolved in 3:2:1 THF/methanol/1.0M NaOH (36 mL). After stirring over night the solution was diluted with diethyl ether and water. The aqueous layer was

separated, washed with diethyl ether, and acidified. The resulting solid was extracted with ethyl acetate to provide 2-(4-acetylphenoxy)acetic acid as a white solid (2.91 g).

Step 2: 2-(4-acetylphenoxy)acetic acid (2.81 g, 14.5 mmol) was dissolved in acetic acid (100 mL) and treated with bromine (740 μL, 14.5 mmol) and stirred 48 hours. Bromine (370 mL, 7.25 mmol) was added and solution was stirred for an additional 16 hours. Volatiles were removed under reduced pressure to provide a brown solid which was titurated with diethyl ether to provide 2-(4-(2-bromoacetyl)phenoxy)acetic acid (1.82 g) as a light brown solid.

Step 3: 2-(4-(2-Bromoacetyl)phenoxy)acetic acid (1.00 g, 3.66 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (659 mg, 3.66 mmol) were refluxed together in methanol (20 mL) for 48 hours. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 5 mL) to provide compound 70 as a white crystalline solid (578 mg, 44 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.69 (s, 1H), 7.65 (d, 2H), 7.02 (d, 2H), 4.83 (s, 2H), 3.70 (s, 3H), 2.64 (s, 3H).

Example 71:

Compound 70 (50 mg, 0.14 mmol) was dissolved in 3:2:1 THF/methanol/1M NaOH (9 mL) and stirred over night. The resulting solution was diluted with ethyl acetate and water. The aqueous layer was washed with ethyl acetate and acidified to yield a white suspension. The suspension was extracted with ethyl acetate, the organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure to provide compound 71 as a white solid (10.2 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.74 (s, 1H), 7.80 (d, J=8.8Hz, 2H), 6.96 (d, J=8.8Hz, 2H), 4.66 (s, 2H).

Example 72:

4-(2-Bromopropionyl)phenylacetic acid (256 mg, 1.0 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (185 mg, 1.22 mmol) were refluxed together in methanol (20 mL) for 48 hours. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 5 mL) to provide compound 72 as a white crystalline solid (22 mg, 7 %). ^{1}H

NMR (200MHz, DMSO-d^6) δ 8.69 (s, 1H), 7.65 (d, 2H), 7.02 (d, 2H), 4.83 (s, 2H), 3.70 (s, 3H), 2.64 (s, 3H).

Example 73: 6-*tert*-Butylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-3,3-dimethylacetone (900 mg, 5.0 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide hydrochloride (900 mg, 5.0 mmol) were refluxed together in methanol (20 mL) for 48 hours. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 5 mL) to provide compound 73 as a white crystalline solid (276 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.62 (br s, 2H), 8.02 (s, 1H), 1.23 (s, 9H).

Example 74: 6-Trifluoromethylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-3,3,3-trifluoroacetone (1.44 g, 9.69 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.85 g, 9.69 mmol) were refluxed together in 1,4-dioxane (20 mL) for 5 days. The resulting suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 74 as a white crystalline solid (650 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.09 (s, 1H), 8.82 (br s, 2H).

Example 75: 5-Bromo-6-trifluoromethylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 74 (430 mg, 1.59 mmol) was suspended in acetic acid (10 mL) and treated with bromine (244 μL, 4.76 mmol). After stirring stirring overnight the volatiles were removed under reduced pressure to provide a 1:1 mixture of compounds 74 and 75. The above process was repeated to provide compound 75 as a white solid (477 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.89 (s, 2H).

Example 76: 5-Phenylthio-6-trifluoromethylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 75 (100 mg, 0.231 mmol), triethylamine (97 mL, 0.694 mmol), and benzenethiol (26 mL, 0.254 mmol) were stirred together in methanol (5 mL) for 48 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 7:3 hexane/ethyl acetate, to provide compound 76 as a white semi-solid (55 mg). ^{1}H NMR (200MHz, $CDCl_3$) δ 7.69 (d, 2H), 7.57 (m, 3H).

Example 77: 6-(2-Pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-(2-bromoacetyl)pyridine (2.5 g, 12.4 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (2.2 g, 12.4 mmol) were refluxed in methanol (75 mL) for 48 hrs. After evaporation of methanol 1M sodium hydroxide (25 mL) was added and the resulting solution was washed with ether (3 x 20 mL). The aqueous layer was acidified to a pH of 7 with 1M hydrochloric acid and extracted with ethyl acetate (3 x 25 mL). The solid obtained from the organic layers was recrystallized in acetone to provide compound 77 as a light brown powder (84 mg, 2.4 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.82 (s, 1H), 8.74 (br s, 2H), 8.58 (d, J = 5.5 Hz, 1H), 7.92 (m, 2H), 7.33 (m, 1H).

Example 78: 5-Bromo-6-(2-pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 77 (50 mg, 0.18 mmol) was suspended in acetic acid (5 mL) and treated with bromine (10 μL, 0.20 mmol). After stirring overnight the volatiles were removed under reduced pressure and the solid was dried under vacuum to provide compound 78 as a yellow solid (54 mg, 84 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.84 (s, 2H), 8.67 (d, J = 4.6 Hz, 1H), 8.02 (m, 2H), 7.43 (m, 1H); ^{13}C NMR (50 MHz, DMSO) δ 166.9, 147.1, 146.0, 142.6, 137.9, 124.8, 122.4, 98.7.

Example 79: 6-(3-Pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Example 80: 6-(4-Pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(4-pyridinyl)-1-ethanone hydrobromide (100 mg, 0.356 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (64 mg, 0.356 mmol) were refluxed in 1,4-dioxane (5 mL) for 48 hours. The resulting solid was isolated by filtration and recrystallized from methanol to provide compounds 80 as a brown solid (129 mg, 42 % yield). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.52 (s, 1H), 8.90 (d, 2H), 8.84 (s, 2H), 8.39 (d, 2H).

Example 81: 6-(2-Pyrimidenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step1: Acetylpyrazine (244 mg, 2.0 mmol) was suspended in glacial acetic acid (10 mL) and treated with pyridinium tribromide (640 mg, 2.0 mmol). The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide 2-(2-bromoacetyl)pyrazine as a brown solid (154 mg, 38%). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.16 (d, J = 1.5Hz, 1H), 8.94 (d, J = 2.4Hz, 1H), 8.82 (dd, J = 1.5, 2.4Hz, 1H), 4.99 (s, 2H).

Step 2 2-(2-Bromoacetyl)pyrazine (154 mg, 0.764 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (138 mg, 0.764 mmol) were refluxed together in methanol (10 mL) for 48 hours. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 2 mL) to provide compound 81 as a brown solid (6.6 mg, 3.1%). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.19 (s, 1H), 8.98 (s,1H), 8.78 (s, 2H), 8.65 (d, J = 1.5Hz, 1H), 8.59 (d, J = 2.7Hz, 1H).

Example 82: 6-(Benzo[b]furan-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-(1-benzofuran-2-yl)-2-bromoethan-1-one (100 mg, 0.41 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.41 mmol) were refluxed in ethanol (5 mL) for 30 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 82 as an off white powder (47 mg, 33 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.86 (s, 1H), 8.77 (br s, 2H), 7.65 (m, 2H), 7.29 (m, 3H).

Example 83: 6-(5-Nitro-2-thiophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Purchased from Talon.

Example 84: 5-Bromo-6-(5-Nitro-2-thiophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Purchased from Talon.

Example 85: 6-(2-Thiophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Acetylthiophene (252 mg, 2.0 mmol) was dissolved in acetic acid (5 mL) and treated with bromine (100 μL, 2.0 mmol). The solution was stirred overnight before the volatiles were removed under reduced pressure to provide a white solid, which contained a 3:1 mixture of (2-bromoacetyl)thiophene and starting material. This crude mixture was refluxed in methanol (10 mL) with 5-amino-1,3,4-thiadiazole-2-sulfonamide (300 mg, 2.0 mmol) for 5 days. The resulting solid was filtered, washing with methanol (3 x 5 mL) to provide compounds 85 as a light pink solid (60.5 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.70 (s, 1H), 7.48 (m, 2H), 7.11 (t, 1H).

Example 86: 6-(2,5-Dichlorothiophen-2-yl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 3-Acetyl-2,5-dichlorothiophene (195 mg, 1.0 mmol) was dissolved in acetic acid (5 mL) and treated with solid pyridinium tribromide (319 mg, 1.0 mmol). The solution was stirred at room temperature for 48 hours. The solvent was removed under reduced pressure. Aqueous work-up yielded an orange solid which contained a 10:1 mixture of 3-(2-bromoacetyl)-2,5-dichlorothiophene and 3-(2,2-dibromoacetyl)-2,5-dichlorothiophene. The crude product was advanced to the next step without further purification. ^{1}H NMR (200MHz, DMSO-d^6) δ 7.65 (s, 1H), 4.76 (s, 2H).

Step 2: The crude mixture above and 2-amino-1,3,4-thiadiazole-2-sulfonamide (150 mg, 1.0 mmol) were refluxed together in methanol (5 mL) for 48 hours. Filtration provided compound 86 as a white solid (7.7 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.83 (s, 1H), 8.78 (br s, 2H), 7.53 (s, 1H).

Example 87: 6-(5-Phenylthiophen-2-yl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(5-phenyl-2-thienyl)-1-ethanone (100 mg, 0.36mmol) and 2-amino-1,3,4-thiadiazole-2-sulfonamide were refluxed in ethanol for 120 hours. The volatiles were removed *in vacuo*. The residue was purified by column chromatography on silica gel using 20% ethyl acetate/1% acetic acid in hexane followed by 30% ethyl acetate/1% acetic acid in hexane as eluant. Triturating with diethyl ether provided compound 87 (7 mg) as an orange solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.82 (s, 1H), 8.70 (br s, 2H), 7.70-7.20 (m, 7H).

Example 88: 6-(5-(2-Pyridyl)-2-thiophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Example 89: 6-(Benzo[b]thiophen-3-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-Benzo[b]thiophen-3-yl-2-bromoethan-1-one (125 mg, 0.5 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.5 mmol) were refluxed in ethanol (10 mL) for 72 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 89 as a white crystalline solid (63 mg, 39 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.91 (s, 1H), 8.74 (br s, 2H), 8.52 (d, 1H), 8.13 (s, 1H), 8.05 (d, 1H), 7.50-7.42 (m, 2H).

Example 90: 6-(3-Methylbenzo[b]thiophen-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3-methylbenzo[b]thiophen-2-yl)ethan-1-one (125 mg, 0.5 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.5 mmol) were refluxed in ethanol (10 mL) for 72 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 90 as a white crystalline solid (63 mg, 39 %).

Example 91: 5-(Thiaxol-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step1 2-Acetylthiazole (400 μL, 3.86 mmol) was suspended in chloroform (10 mL) and treated with pyridinium tribromide (1.23 g, 3.86 mmol). The reaction mixture was stirred for two days. The solvent was removed under reduced pressure. Standard aqueous/ethyl acetate workup provided a dark orange solid, which was identified as a 8:1 mixture of 2-(2-bromoacetyl)thiazole and starting material. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.30 (d, J = 2.1Hz, 1H), 8.18 (d, J = 2.1Hz, 1H), 4.93 (s, 2H).

Step 2 2-(2-Bromoacetyl)thiazole (206 mg, 1.0 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (180mg, 1.0 mmol) were refluxed together in methanol (10 mL) for 72 hours. The resulting suspension was cooled to –10 °C, filtered and the solid washed with cold methanol (3 x 2 mL) to provide compound 91 as a white solid (15.6 mg, 5.4%). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.90 (s, 1H), 8.74 (br s, 2H), 7.90 (d, J = 3.1Hz, 1H), 7.75 (d, J = 3.3Hz, 1H).

Example 92: 6-(coumaran-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Purchased from Talon.

Example 93: 6-(Ethyl carboxy)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Purchased from Talon.

Example 94: 6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-one (250 mg, 0.81 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (146 mg, 0.81 mmol) were refluxed in ethanol (10 mL) for 60 hours. Solvent was evaporated under reduced pressure and the resulting solid suspended in ethanol (3 ml). The precipitate was collected by suction filtration and washed with ethanol to provide compound 94 (45 mg) as an off white solid. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.8 (s, 1H), 8.6 (br s, 2H), 7.8 (br s, 1H), 7.6 (dd, 1H), 7.3 (d, 1H), 1.6 (s, 4H), 1.3 (s, 6H), 1.2 (s, 6H)

Example 95: 6-(1,3-Benzodioxol-5-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-(1,3-benzodioxol-5-yl)-2-bromoethan-1-one (100 mg, 0.41 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.41 mmol) were refluxed in ethanol (5 mL) for 30 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 95 as a pale yellow powder (40 mg, 44 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.75 (s, 1H), 8.69 (s, 2H), 7.43 (m, 2H), 6.97 (d, J = 8.6 Hz, 1H), 6.04 (s, 2H).

Example 96: 6-(3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)ethan-1one (542 mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2 mmol) were refluxed in ethanol (10ml) for 60 hours. The resulting mixture was cooled on ice and the resulting precipitate collected by suction filtration, giving 96 (310 mg) as a yellow powder. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.8 (s, 1H), 8.7 (br s, 2H), 7.4 (m, 2H), 7.0 (d, 1H), 4.2-4.0 (m, 4H), 2.2-2.0 (m, 2H).

Example 97: 6-(4-cyanophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

4-(2-bromoacetyl)benzonitrile (448 mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2 mmol) were refluxed in ethanol for 60 hours. The resulting mixture was cooled on ice and the precipitate collected by suction filtration to provide 97 (300 mg) as a white powder. ^{1}H NMR (200MHz, DMSO-d^6) δ 9.07 (s, 1H), 8.77 (br s, 2H), 8.09 (d, 2H), 7.90 (d, 2H).

Example 98: 6-(3-cyanophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

3-(2-bromoacetyl)benzonitrile (100 mg, 0.45 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (80 mg, 0.45 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide

compound 98 as a white crystalline solid (78 mg, 57 %). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 9.03 (s, 1H), 8.76 (s, 2H), 8.32 (s, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.71 (m, 2H); ^{13}C NMR (50 MHz, DMSO) δ 164.9, 145.8, 144.6, 134.6, 131.3, 130.2, 129.4, 128.3, 118.7, 112.4, 112.1.

Example 99: 6-(4-Methylphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(4-methylphenyl)ethan-1one (213 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (148 mg, 1 mmol) were refluxed in ethanol (10 mL) for 60 hours. Solvent was removed under reduced pressure. The suspension was cooled to –4 °C, filtered and washed with cold methanol (3 x 5 mL), to provide compound 99 (118 mg, 42 %) as a white powder. ^{1}H NMR (200MHz, DMSO-d^{6}) δ 8.80 (s, 1H), 8.71 (s, 2H), 7.78 (d, 2H), 7.23 (d, 2H), 2.31 (s, 3H).

Example 100: 6-(2,4-dimethylphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(2,4-dimethylphenyl)ethan-1-one (227 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-2-sulfonamide (180 mg, 1 mmol) were refluxed in ethanol for 5 days. The volatiles were removed *in vacuo*. The residue was purified by column chromatography on silica using 30% ethyl acetate/1% acetic acid in hexane as eluant. Recrystallization from dichloromethane gave 100 (30 mg) as a white powder. ^{1}H NMR (200MHz, DMSO-d^{6}) δ 8.71 (br s, 2H), 8.52 (s, 1H), 7.70 (d, J=7.6 Hz, 1H), 7.10 (s, 1H), 7.06 (s, 1H), 2.46(s, 3H), 2.29 (s, 3H).

Example 101: 6-(3-chloro-4-methylphenyl)-5-methylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3-chloro-4-methylphenyl)propan-1-one (262 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.0 mmol) were refluxed in ethanol (10 mL) for 5 days. The resulting solution was concentrated and the crude material was purified by column chromatography on silica gel, eluting with 25:75 ethyl acetate/hexanes to provide compound 229-047 as a yellow powder (38 mg, 11 %). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 8.72 (s, 2H), 7.74 (m, 1H), 7.59 (m, 1H), 7.48 (m, 1H), 2.68 (s, 3H), 2.39 (s, 3H).

Example 102: 6-(4-Pentylphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(4-pentylphenyl)ethan-1-one (269 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.0 mmol) were refluxed in ethanol (10 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 102 as a white powder (180 mg, 51 %). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 8.81 (s, 1H), 8.71 (s, 2H), 8.79 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 2.54 (t, J = 7.0 Hz, 2H), 1.57 (quintet, J = 7.6 Hz, 2H), 1.27 (m, 4H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) : δ 164.0, 147.1, 145.3, 142.5, 130.9, 128.9, 125.2, 110.7, 34.9, 30.9, 30.6, 22.0, 14.0.

Example 103: 6-(3,4-Di-*tert*-butyl-4-hydroxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3,4-di-*tert*-butyl-4-hydroxyphenyl)ethan-1-one (327 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (148 mg, 1 mmol) were refluxed in ethanol (10 mL) for 60 hours. Solvent was removed under reduced pressure. The resulting solid was suspended in methanol (5 mL) and stirred for 30 minutes prior to suction filtration, washing twice for cold methanol (2 mL), to provide compound 103 (93 mg, 24 %) as a white powder. ^{1}H NMR (200MHz, DMSO-d^{6}) δ 8.72 (s, 1H), 8.68 (s, 2H), 7.63 (s, 2H), 1.41 (s, 9H).

Example 104: 6-(4-(Trifluoromethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-[4-(trifluoromethyl)phenyl]ethan-1-one (534 mg, 2.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2.0 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 104 as a white powder (270 mg, 39 %). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 9.05 (s, 1H), 8.74 (s, 2H), 8.10 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H).

Example 105: 6-(3,5-di(trifluoromethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-[3,5-di(trifluoromethyl)phenyl]ethan-1-one (670 mg, 2.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2.0 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 105 as a white powder (292 mg, 70 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.26 (s, 1H), 8.77 (s, 2H), 8.54 (s, 2H), 8.04 (s, 1H).

Example 106: 6-(4-(methylsulfonyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-[4-(methylsulfonyl)phenyl]ethan-1-one (100 mg, 0.36 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (65 mg, 0.36 mmol) were refluxed in ethanol (5 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 106 as a white powder (55 mg, 43 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.08 (s, 1H), 8.76 (s, 2H), 8.15 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.1 Hz, 2H), 3.23 (s, 3H).

Example 107: 6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethan-1-one (100 mg, 0.36 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (65 mg, 0.36 mmol) were refluxed in ethanol (5 mL) for 45 hrs. Solvent was evaporated and the solid was recrystallized from ethanol to provide compound 107 as a beige powder (30 mg, 28 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.71 (s, 2H), 8.55 (s, 1H), 7.98 (s, 1H), 7.52 (m, 5H), 2.56 (s, 3H).

Example 108: 6-(1-adamantyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-(1-Adamantyl)-2-bromoethan-1-one (514 mg, 2.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2.0 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 108 as a white powder (120 mg, 18 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.64 (s, 2H), 8.03 (s, 1H), 2.03 (m, 3H), 1.90 (m, 6H), 1.72 (m, 6H).

Example 109: 6-(Ethyl isoxazol-5-yl-3-carboxylate)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Ethyl 5-(2-bromoacetyl)isoxazole-3-carboxylate (100 mg, 0.38 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (70 mg, 0.38 mmol) were refluxed in ethanol (5 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 229-053 as an orange powder (21 mg, 16 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 9.14 (s, 1H), 8.82 (s, 2H), 7.16 (s, 1H), 4.39 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

Example 110: 6-(5-Methyl-3-phenylisoxazol-4-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(5-methyl-3-phenylisoxazol-4-yl)ethan-1-one (100 mg, 0.36 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (65 mg, 0.36 mmol) were refluxed in ethanol (5 mL) for 60 hrs. Solvent was evaporated and the crude solid was purified by flash chromatography using 35 : 65 ethyl acetate : hexanes to provide compound 110 as a yellowish powder (64 mg, 50 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.73 (br s, 2H), 8.25 (s, 1H), 7.58 (m, 2H), 7.45 (m, 3H), 2.56 (s, 3H).

Example 111: 6-(4-Phenylisoxazol-3-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Example 112: 6-(4-(Acetamidomethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: Benzylamine (10.0 g, 9.51 mmol) was dissolved in methylenechloride (100 mL) and cooled on ice. Acetic anhydride (13.50 mL, 14.27 mmol) was added and the solution was stirred at room temperature for 3 hours. Volatiles were removed under reduced pressure, and standard aqueous workup with ethyl acetate provided *N*-acetylbenzylamine as a

white solid (14.0 g, 99%). ^{1}H NMR (200MHz, $CDCl_3$) δ 7.25 (m, 5H), 4.33 (d, 2H), 1.94 (s, 3H).

Step 2: *N*-acetylbenzylamine (5.00 g, 33.5 mmol) was dissolved in methylene chloride (100 mL) and treated with acetyl chloride (3.57 mL, 50.3 mmol) and cooled on ice. Aluminum chloride (6.70 g, 50.3 mmol) was added in 1g portions over 30 minutes. The resulting mixture was refluxed overnight, before being poured into ice water and exracted with methylene chloride. The resulting semi-solid was purified by silica gel chromatography to yield a white semi-solid, which was approximately 80% 1-acetyl-4-(acetaminomethyl)benzene by ^{1}H NMR. The crude material (236 mg, 1.23 mmol) was dissolved in acetic acid and treated with pyridinium tribromide (395 mg, 1.23 mmol). The solution was stirred overnight to provide a white solid which was isolated by filtration, to provide 1-(2-bromoacetyl)-4-(acetaminomethyl)benzene as a white solid (150 mg, 45%). ^{1}H NMR (200MHz, DMSO-d^6) δ 10.30 (s, 1H), 8.46 (br s, 1H), 7.92 (d, J=8.2Hz, 2H), 7.37 (d, J=8.2Hz, 2H), 4.88 (s, 2H), 4.28 (d, J=5.5 Hz, 2H), 1.87 (s, 3H).

Step 3: 1-(2-Bromoacetyl)-4-(acetaminomethyl)benzene (150 mg, 0.556 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (82 mg, 0.556 mmol) were combined and refluxed in methanol (10 mL) for 48 hours. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography, eluting with 10:1 methylene chloride/methanol, to provide compound 112 as a yellow solid (125 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.81 (s, 2H), 8.48 (br t, 1H), 7.92 (d, J=8.2Hz, 2H), 7.35 (d, J=8.2Hz, 2H), 4.27 (d, J=5.5Hz, 2H), 1.87 (s, 3H).

Example 113: 6-(4-(*S*-1-acetamidoethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-(*S*-1-acetamidoethyl)acetophenone (426 mg, 1.5 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (222 mg, 1.5 mmol) were refluxed in ethanol (10 mL) for 60 hours. The resulting solution was cooled to –4 °C for 2 hours and the resulting solid was filtered, washing twice for cold methanol (2 mL), to provide compound 113 (172 mg, 34 %) as white

crystals. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.82 (s, 1H), 8.70 (s, 2H), 8.28 (d, 1H), 7.83 (d, 2H), 7.34 (d, 2H), 4.91 (dt, 1H), 1.83 (s, 3H), 1.33 (d, 3H).

Example 114: 6-(4-Azido-2,3,5,6-tetraflourophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-azido-2',3',5',6'-tetrafluoroacetophenone (Keana, J. F. W.; Cai, S. X. *J. Org. Chem.*, **1990**, *55*, 3640) (353 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (148 mg, 1 mmol) were refluxed in ethanol (10 mL) for 60 hours. The resulting solid was filtered, washing twice for cold methanol (2 mL), to provide compound 114 (102 mg, 25 %) as a white powder. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.81 (t, J=2.0Hz, 1H), 8.79 (br s, 2H).

Example 115: 6-(2,3,4,5,6-Pentafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(pentafluorophenyl)ethan-1-one (2.89 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 10.0 mmol) were refluxed in ethanol (20 mL) for 60 hrs. Solvent was evaporated and the crude solid was purified by flash chromatography using 20 : 80 : 0.1 ethyl acetate : hexanes : acetic acid to provide compound 115 as white needles (125 mg, 3.4 %). ^{1}H NMR (200MHz, DMSO-d^6) δ 8.82 (s, 1H), 8.78 (s, 2H).

Example 116: 6-(4-trifluoromethoxy)imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-[4-(trifluoromethoxy)phenyl]ethan-1-one (250 mg, 1.13 mmol) and 2-amino-1,3,4-thiadiazole-2-sulfonamide (204 mg, 1.1.3 mmol) were refluxed in ethanol for 60 hours. The resulting precipitate was collected by suction filtration and was washed with cooled ethanol, providing 116 as a white powder. 1H NMR (200MHz, DMSO-d6) δ 8.93(s, 1H), 8.73(br s, 2H), 8.00 (d, J=8.8 Hz, 2H), 7.43 (d, J=8.4 Hz).

Example 117: 6-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Step 1: 1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethylnaphthalene was prepared according to published procedure (*J Med. Chem.*, **1994**, 37, 2930)

Step 2: 7-Acetyl-1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene was prepared according to published procedure (US Patent 2,897,237, 1959)

Step 3: 7-Acetyl-1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene (1.81g, 7.43 mmol) was dissolved in ice cooled diethyl ether (100 ml). Bromine (383 uL, 7.43 mmol) in diethyl ether (10ml) was added dropwise to the solution and external cooling was used to prevent the reaction mixture from exceeding 20 °C. Once all bromine had been added, one drop of glacial acetic acid was added and the mixture was warmed to room temperature. After stirring for 2 hours at room temperature, the reaction mixture was washed with water (3 x 15ml) and dried over $MgSO_4$. Volatiles were removed *in vacuo* to afford a 9:1 mixture of 7-bromoacetyl-1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene and 7-dibromoacetyl-1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene which was used in the next step without further purification.

Step 4: To the crude material obtained in the previous step was added 5-amino-1,3,4-thiadiazole-2-sulfonamide (2.04 g, 6.29 mmol) and ethanol (20 ml). The mixture was refluxed for 60 hours. The resulting solid was filtered and washed with cooled ethanol to provide compound 117 as a white powder. ^{1}H NMR (200MHz, DMSO-d^6) δ 8.75 (br s, 2H), 8.65 (s, 1H), 7.76 (s, 1H), 7.20 (s, 1H), 2.40 (s, 3H), 1.63 (s, 4H), 1.24 (br s, 12H).

Example 118:

6-(Chloroacetyl)-2-*H*-1,4-benzoxazin-3(4*H*)-one (248 mg, 1.1 mmol), *n*-Bu_4NI (405 mg, 1.1 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (148 mg, 1.0 mmol) were refluxed together in methanol (12 mL) for 4 days. The resulting precipitate was isolated by filtration, washing with cold methanol, to provide compounds 118 as a white solid (58 mg). ^{1}H NMR (200MHz, DMSO-d^6) δ 10.84 (s, 1H), 8.79 (s, 3H), 7.48 (s, 1H), 7.42 (d, 2H), 7.00 (d, 2H), 4.58 (s, 2H).

Example 119: NGF Withdrawal Assay

SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 5,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs), at 37 °C, under a 5% CO_2 atmosphere. After 4 days the cells were washed 4 times with Ultraculture media (as above but containing no NGF or serum). At this time compound was added and the cells were maintained serum and NGF free for 48 hours, at which time viability was assessed using Alamar Blue (Medicorp) staining.

Table 3

Protection of SCG neurons against NGF withdrawal

Entry	Compound	IC_{50} (± 1 μM)
1	1	25
2	51	15
2	52	10
3	94	5
4	115	6

Example 110: *In Vitro* Taxol™ killing of SCG neurons

SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 10,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs) at 37 °C, under a 5% CO_2 atmosphere. After 5 days the cells were treated with compound and Taxol™ (50 ng/mL). Viability was assessed 48 hours later using MTS (Promega) staining.

Table 4

Protection of SCG neurons against Taxol™ killing

Entry	Compound	IC_{50} (± 1 μM)
1	1	5
2	2	5
3	3	5
4	4	10
5	11	6
6	12	3
7	18	20
8	19	20
9	20	10
10	21	6
11	22	10
12	23	5
13	24	7
14	25	3
15	26	5
16	27	2
17	28	15
18	37	10
19	38	4
20	39	3
21	40	15
22	41	5
23	42	5
24	43	15
25	44	30
26	45	10
27	46	20
28	48	20
29	49	20
30	50	25
31	51	5
32	52	1
33	53	4
34	54	2
35	57	6
36	58	6
37	59	>30

38	61	5
39	63	20
40	64	7
41	67	20
42	69	25
43	70	>30
44	73	30
45	74	10
46	75	1
47	76	>30
48	77	5
49	78	3
50	79	5
51	81	5
52	85	5
53	87	9
54	89	7
55	90	7
56	91	5
57	92	8
58	93	>30
59	94	1
60	95	8
61	96	10
62	97	3
63	98	3
64	99	7
65	100	4
66	101	20
67	102	8
68	103	15
69	104	5
70	105	10
71	106	10
72	108	25
73	109	>30
74	110	20
75	113	30
76	114	1
77	115	1
78	116	5
79	117	3
80	118	>30

Example 121: *In Vitro* Cisplatin killing of SCG neurons

SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 10,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs) at 37 °C, under a 5% CO_2 atmosphere. After 5 days the cells were treated with compound and cisplatin (3 μg/mL). Viability was assessed 48 hours later using MTS (Promega) staining.

Table 5

Protection of SCG Neurons Against Vincristine Killing

Entry	Compound	IC_{50} (± 1 μM)
1	1	5

Example 122: *In Vitro* Vincristine killing of SCG neurons.

SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 10,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs) at 37 °C, under a 5% CO_2 atmosphere. After 5 days the cells were treated with compound and vincristine (50 ng/mL). Viability was assessed 48 hours later using MTS (Promega) staining.

Table 6

Protection of SCG Neurons Against Vincristine Killing

Entry	Compound	IC_{50} (± 1 μM)
1	1	10

Example 123: Protection of Sprague Dawley rats from Taxol™ induced neuropathies. Adult Sprague Dawley rats were treated with Taxol™ (IP, 9 mg/kg in Cremophor EL and ethanol) twice weekly for 3 weeks (J. Neuro-Oncology (1999) 41: 107-116). Compound was administered 1 hour prior to Taxol™ treatment (IP, 1, 5 and 10 mg/kg in hydroxypropyl-β-cyclodextrin). Taxol™ treated control animals were treated with saline solution at the same time of Compound treated animals. Non-treated control animals were treated with saline solution as above. Weight gain was measured every second day, starting at Day 1. Gait analysis was measured by quantifying the refracted light captured by a video camera as the animals walked over a glass plate, 2 days after the final Taxol™ treatment (Physiology and Behavior (1994), 55(4): 723-726; Med. Sci. Res. (1988) 16: 901-902). This data was analyzed by Northern Eclipse software. H/M wave recovery was analyzed using standard procedures 2 days after the final Taxol™ treatment (Muscle Nerve (1998) 21: 1405-1413; Annals of Neurology (1998) 43 (1): 46-55).

Figure 2 illustrates weight loss induced by Taxol™ over time. Male Spraugue Dawley rats were treated with 50% HPDC vehicle (veh/veh), compound 1 dissolved in 50% HPDC at 1, 5, or 10 mg/kg (veh/1, veh/5, veh/10, respectively), or Taxol™ (9 mg/kg) + compound 1 dissolved in 50% HPDC at 1, 5, and 10 mg/kg (Tax/1, Tax/5, Tax/10) according to the dosing regime described in Example 123. Weight measurements were made every other day.

Figure 3 illustrates the gait disturbance induced by Taxol™. The effect of compound AEG3482 and Taxol on number of paw contact points is provided. Two days after the completion of drug treatments animal walking gait was analyzed according to a) total imprint area, and b) total number of contact points. Compound 1 prevented Taxol™ induced gait disturbance.

Figure 4 illustrates H/M wave disturbance induced by Taxol™. Two days after the completion of drug treatments the dorsal root ganglia and attached nerves were dissected

bilaterally from L4 and L5 and their H/M wave conductance measured. Compound 1 caused a reversal in H/M wave disturbance induced by Taxol™.

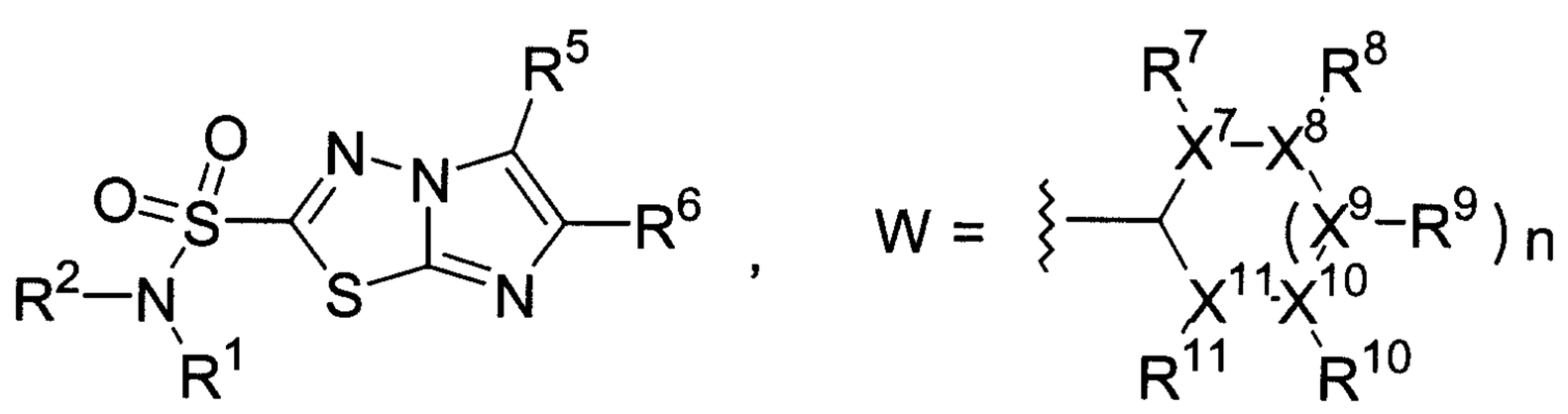
Example 124: Taxol™ Killing of HA460 and OV2008 cells.

HA460 and OV2008 cells were cultured at 1.0×10^4 and 1.25×10^4 cells per well, respectively. Cells were allowed to grow for 16 hours and treated with compound 1 for 1 hour prior to the addition of Taxol (15 nM). After 48 hours the cellular viability is determined using MTS staining.

Figure 5 illustrates the result of co-treatment of HA460 and OV2008 cancer cell line with Taxol™ and compound 1. HA460 and OV2008 cells were treated with Taxol™ and/or Taxol™ + compound 1. Compound 1 did not protect HA460 or OV2008 cells from Taxol™ induced apoptosis.

CLAIMS

1. Imidazo[2,1-*b*]thiadiazole sulfone analogues and precursor compounds of Formula I:



I

or pharmaceutically acceptable salts thereof wherein:

R^1 and R^2 are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl lower alkylcarbonyl, or wherein R^1 and R^2 are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

R^5 is selected from the group consisting of:

e) H, halogen, cyano, azide, thiocyanate, formyl, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

f) SO_nR^{12} wherein n=0, 1 or 2, and wherein R^{12} is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

g) OR^{13} wherein R^{13} is defined as R^{12} in b), or wherein R^{13} is defined as acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;

h) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl,or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system, or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

R^6 is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, substituted fluoroalkyl, adamantly, coumarinyl, substituted coumarinyl;

alternately, R^6 is represented by W, wherein:
n represents 0 or 1;
the ring system containing X^7-X^{11} represents a 5 or 6 membered (n=0 or 1, respectively) aromatic or heteroaromatic ring system, in which X^7-X^{11} are independently chosen from C, N, S, O;
when X^7-X^{11} independently represents C, each respective R^7-R^{11} is independently chosen from the groups consisting of:

e) H, halogen, nitro, cyano, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl;
f) $SO_2NR^{16}R^{17}$ wherein R^{16} and R^{17} are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl,

arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl,or wherein R^{16} and R^{17} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

g) SO_nR^{18} wherein n=0, 1 or 2, and wherein R^{18} is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

h) OR^{19} wherein R^{19} is defined as R^{12} in b), or wherein R^{19} is defined as fluoroaclkyl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;

k) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are as described in d), or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

l) CO_2R^{20} wherein R^{20} is defined as H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $NR^{14}R^{15}$, wherein R^{14} and R^{15} are individually chosen from the groups as defined in d);

when X^7-X^{11} represents N, that nitrogen may be attached to the adjacent atoms by either one single and one double bond (as in pyridinyl systems), or by two single bonds (as in indolyl or imidazolyl systems);

when X^7-X^{11} represents N, and that nitrogen is attached to the adjacent atoms by one single and one double bond (as in pyridinyl systems), the respective R^7-R^{11} represents a lone pair;

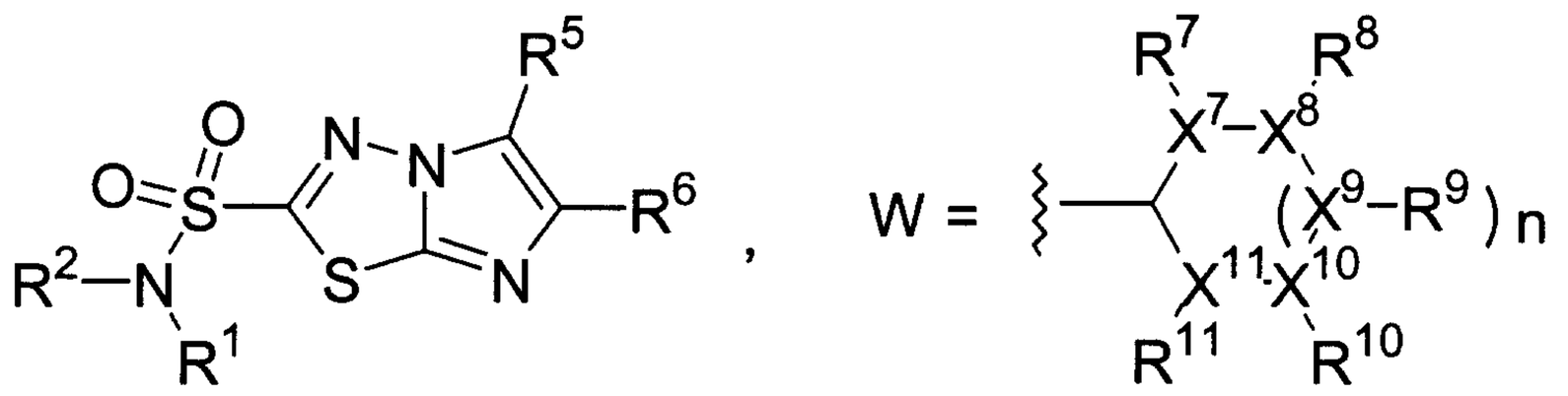
when X^1-X^5 represents N, and that nitrogen is attached to the adjacent atoms by two single bonds (as in indolyl or imidazolyl systems), the respective R^7-R^{11} is chosen from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, SO_2R^{18}, wherein R^{18} is defined as in g), COR^{18}, wherein R^{18} is defined as in g);

when n=0, R^7 and R^8, or R^8 and R^9 may be combined to form a fused 5,6, or 7 membered alkyl, substituted alkyl, heteroalky, substituted heteroalkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, heteroaryl ring system;

when n=1 and X^9 represents C, R^7 and R^8, or R^8 and R^{10} may be combined to form a fused 5, 6, or 7 membered alkyl, substituted alkyl, heteroalky, substituted heteroalkyl, aryl, substituted aryl, or heteroaryl ring system; and

R^7-R^{11} represents a lone pair when the respective X^7-X^{11} represents S or O.

2. Imidazo[2,1-*b*]thiadiazole sulfonamide derivatives and precursors of Formula I:



I

or pharmaceutically acceptable salts thereof wherein:

R^1 and R^2 are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl lower alkylcarbonyl, or wherein R^1 and R^2 are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

R^5 is selected from the group consisting of:

i) H, halogen, cyano, azide, thiocyanate, formyl, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

j) SO_nR^{12} wherein n=0, 1 or 2, and wherein R^{12} is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl,

heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

k) OR^{13} wherein R^{13} is defined as R^{12} in b), or wherein R^{13} is defined as acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;

l) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl,or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system, or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

R^6 is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, substituted fluoroalkyl, adamantly, coumarinyl, substituted coumarinyl;

alternately, R^6 is represented by W, wherein:

n represents 0 or 1;

the ring system containing X^7-X^{11} represents a 5 or 6 membered (n=0 or 1, respectively) aromatic or heteroaromatic ring system, in which X^7-X^{11} are independently chosen from C, N, S, O;

when X^7-X^{11} independently represents C, each respective R^7-R^{11} is independently chosen from the groups consisting of:

e) H, halogen, nitro, cyano, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl,

lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl;

f) $SO_2NR^{16}R^{17}$ wherein R^{16} and R^{17} are individually selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl,or wherein R^{16} and R^{17} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

g) SO_nR^{18} wherein n=0, 1 or 2, and wherein R^{18} is selected from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

h) OR^{19} wherein R^{19} is defined as R^{12} in b), or wherein R^{19} is defined as fluoroaclkyl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;

m) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are as described in d), or wherein R^{14} and R^{15} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;

n) CO_2R^{20} wherein R^{20} is defined as H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $NR^{14}R^{15}$, wherein R^{14} and R^{15} are individually chosen from the groups as defined in d);

when X^7-X^{11} represents N, that nitrogen may be attached to the adjacent atoms by either one single and one double bond (as in pyridinyl systems), or by two single bonds (as in indolyl or imidazolyl systems);

when X^7-X^{11} represents N, and that nitrogen is attached to the adjacent atoms by one single and one double bond (as in pyridinyl systems), the respective R^7-R^{11} represents a lone pair; when X^1-X^5 represents N, and that nitrogen is attached to the adjacent atoms by two single bonds (as in indolyl or imidazolyl systems), the respective R^7-R^{11} is chosen from the groups consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, SO_2R^{18}, wherein R^{18} is defined as in g), COR^{18}, wherein R^{18} is defined as in g);

when n=0, R^7 and R^8, or R^8 and R^9 may be combined to form a fused 5,6, or 7 membered alkyl, substituted alkyl, heteroalky, substituted heteroalkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, heteroaryl ring system;

when n=1 and X^9 represents C, R^7 and R^8, or R^8 and R^{10} may be combined to form a fused 5, 6, or 7 membered alkyl, substituted alkyl, heteroalky, substituted heteroalkyl, aryl, substituted aryl, or heteroaryl ring system; and

R^7-R^{11} represents a lone pair when the respective X^7-X^{11} represents S or O,

with the proviso that compounds 1, 11, 12, 18, 21, 32, 25, 26, 27, 38, 39, 40, 42, 44, 51, 52, 66, 67, 73, 79, 84, 85, 92, 93, 99, and 108 of Table 2 are excluded.

3. Imidazo[2,1-*b*]thiadiazole sulfonamide derivatives identified as compounds 4, 5, 6, 13, 14, 15, 116, 17, 18, 19, 20, 22, 24, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37,41, 43, 45, 45, 46, 47, 48, 49, 50, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 80, 81, 82, 83, 86, 87, 88, 89, 90, 91, 94, 95, 96, 97, 98, 100, 101, 102, 103, 104, 105, 106, 107, 109, 110, 111, 112, 113, 114, 115, 116, 117, and 118 of Table 2.

4. Use of a compound according to any one of claims 1 to 3 for the prevention or treatment of a condition selected from the group consisting of neurodegenerative diseases of both the central and peripheral nervous systems, inflammatory diseases, conditions resulting in loss of growth and cellular differentiation control, and cancer.

5. Use of a compound according to any one of claims 1 to 3 in combination with a known therapeutic for the treatment of a condition selected from the group consisting of neurodegenerative diseases of both the central and peripheral nervous systems, inflammatory diseases, conditions resulting in loss of growth and cellular differentiation control, and cancer.

6. Treatment or prevention of a condition selected from the group consisting of neurodegenerative diseases of both the central and peripheral nervous systems, inflammatory diseases, conditions resulting in loss of growth and cellular differentiation control, and cancer by administration of an effective amount of the compound according to claims 1, 2 and 3 to a patient in need thereof.

7. Use of a compound according to any one of claims 1 to 3 for altering signal transduction.

8. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to any one of claims 1 to 3 in combination with a pharmaceutically acceptable carrier.

9. A pharmaceutical package comprising the pharmaceutical composition according to claim 8 in combination with directions for use.

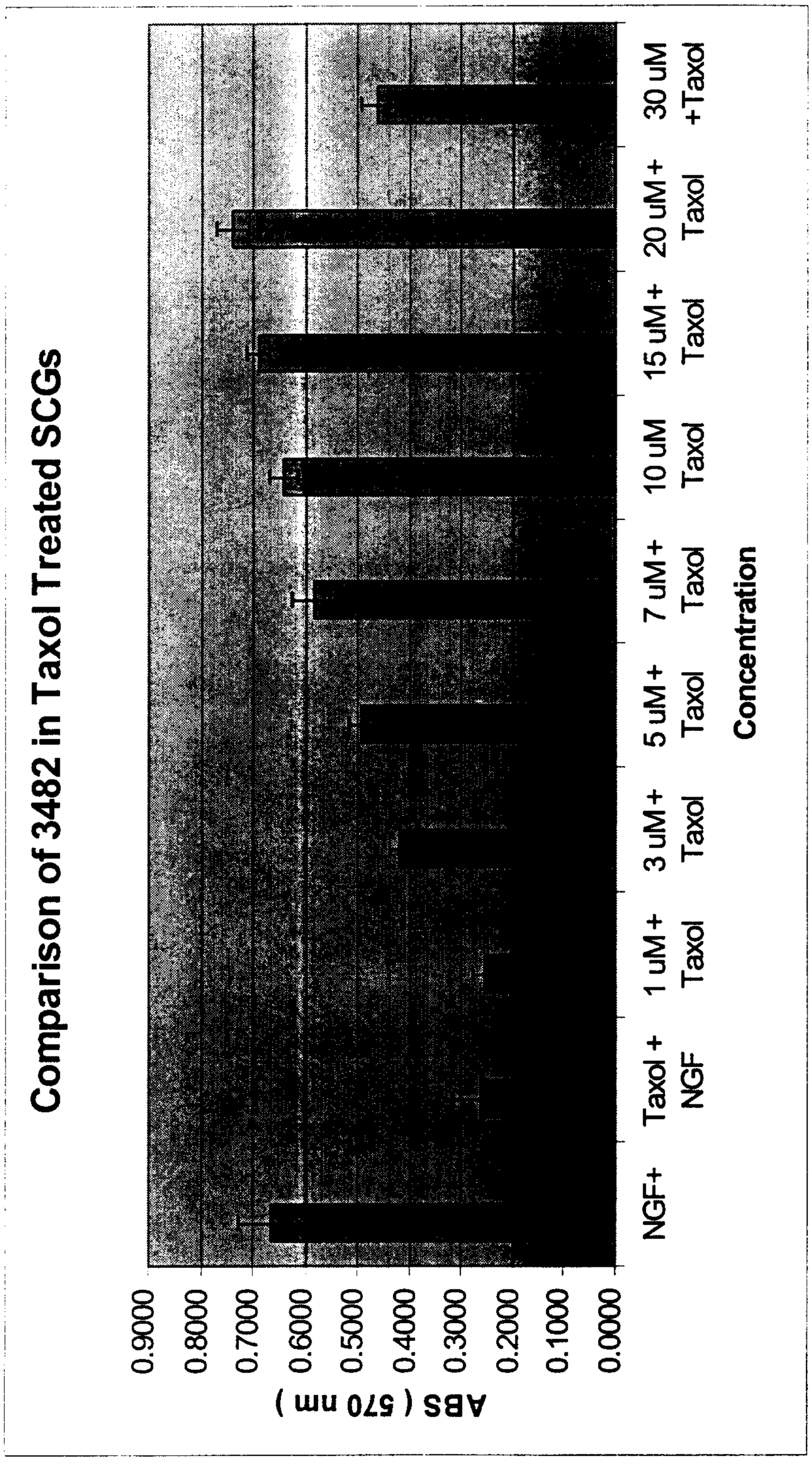


FIG. 1

Borden Ladner Gervais LLP / s.r.l.

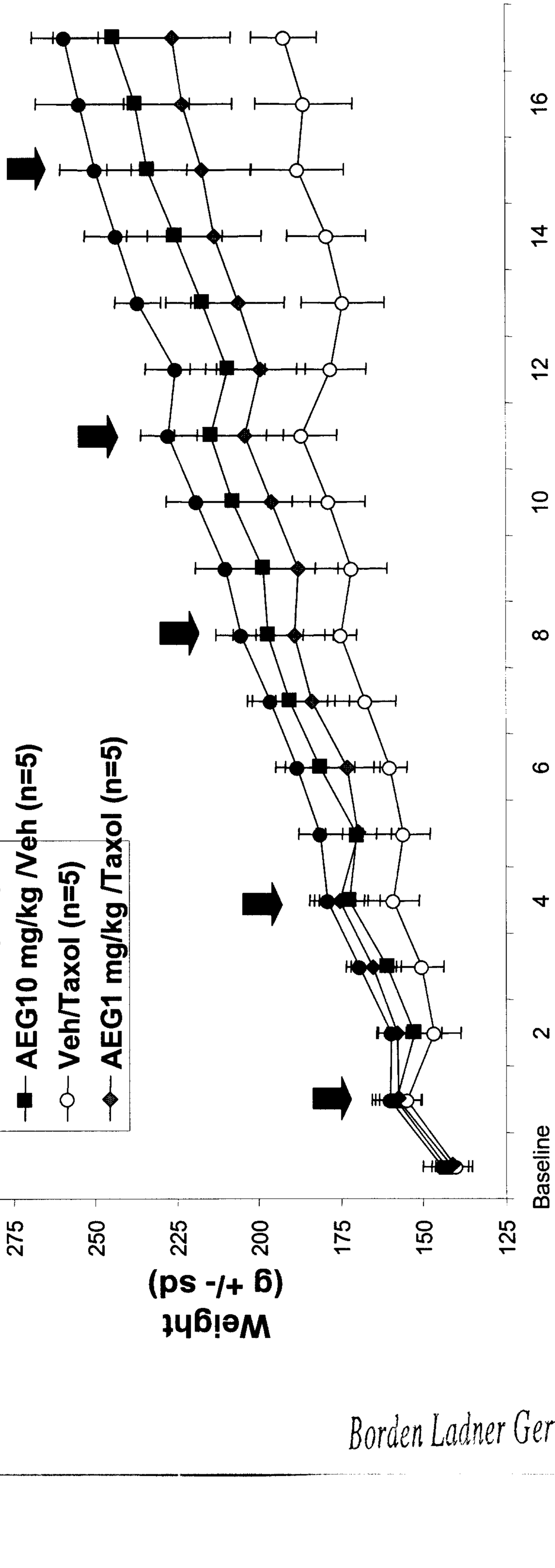

Veh/Veh (n=5)
AEG10 mg/kg /Veh (n=5)
Veh/Taxol (n=5)
AEG1 mg/kg /Taxol (n=5)
Weight
(g +/- sd)
300
275
250
225
200
175
150
125
Baseline
2
4
6
8
10
12
14
16
Day

FIG. 2

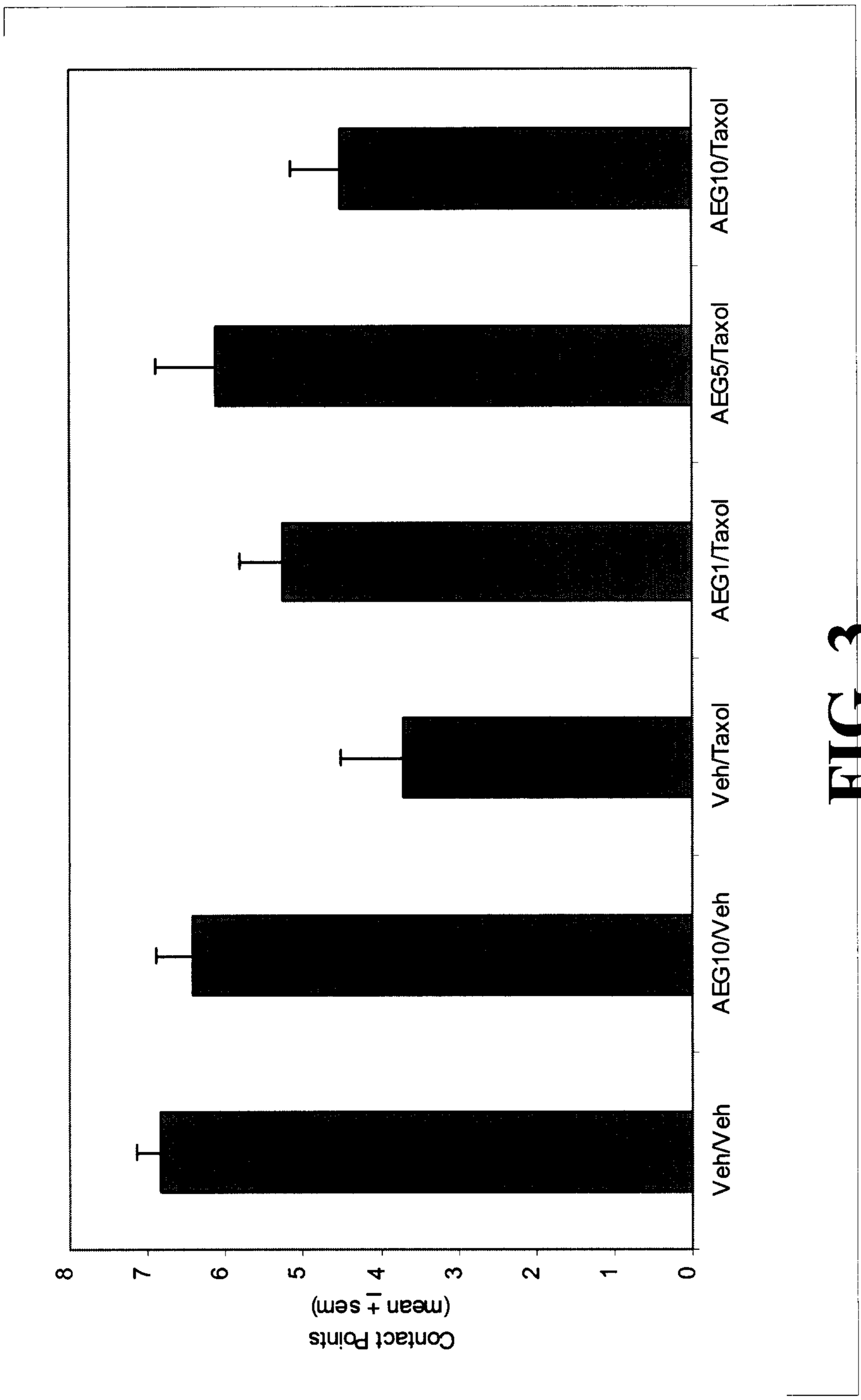

Effect of AEG3482 and Taxol on Number of Paw Contact Points
(mean ± sem)
Contact Points
0
1
2
3
4
5
6
7
8
Veh/Veh
AEG10/Veh
Veh/Taxol
AEG1/Taxol
AEG5/Taxol
AEG10/Taxol

FIG. 3

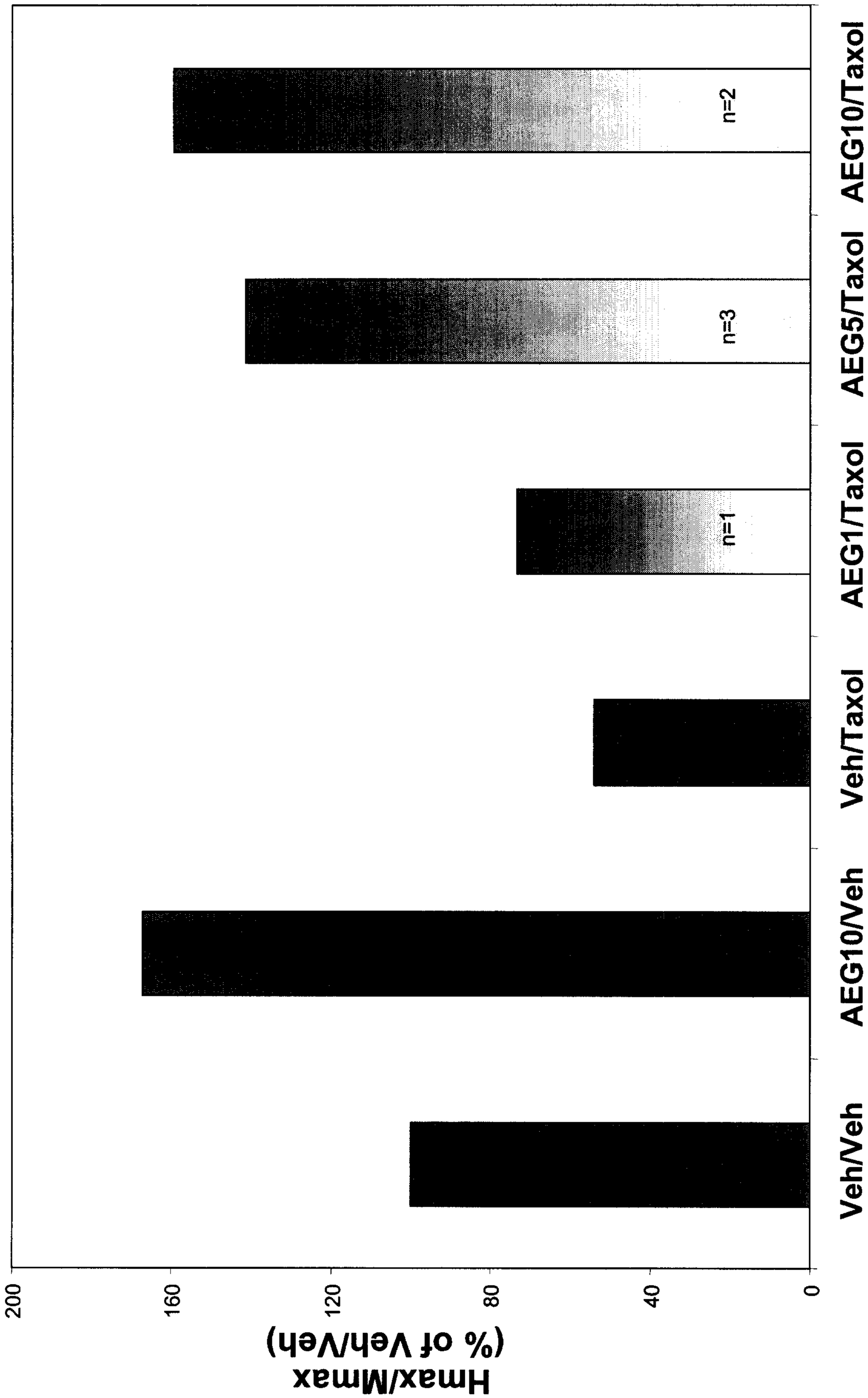
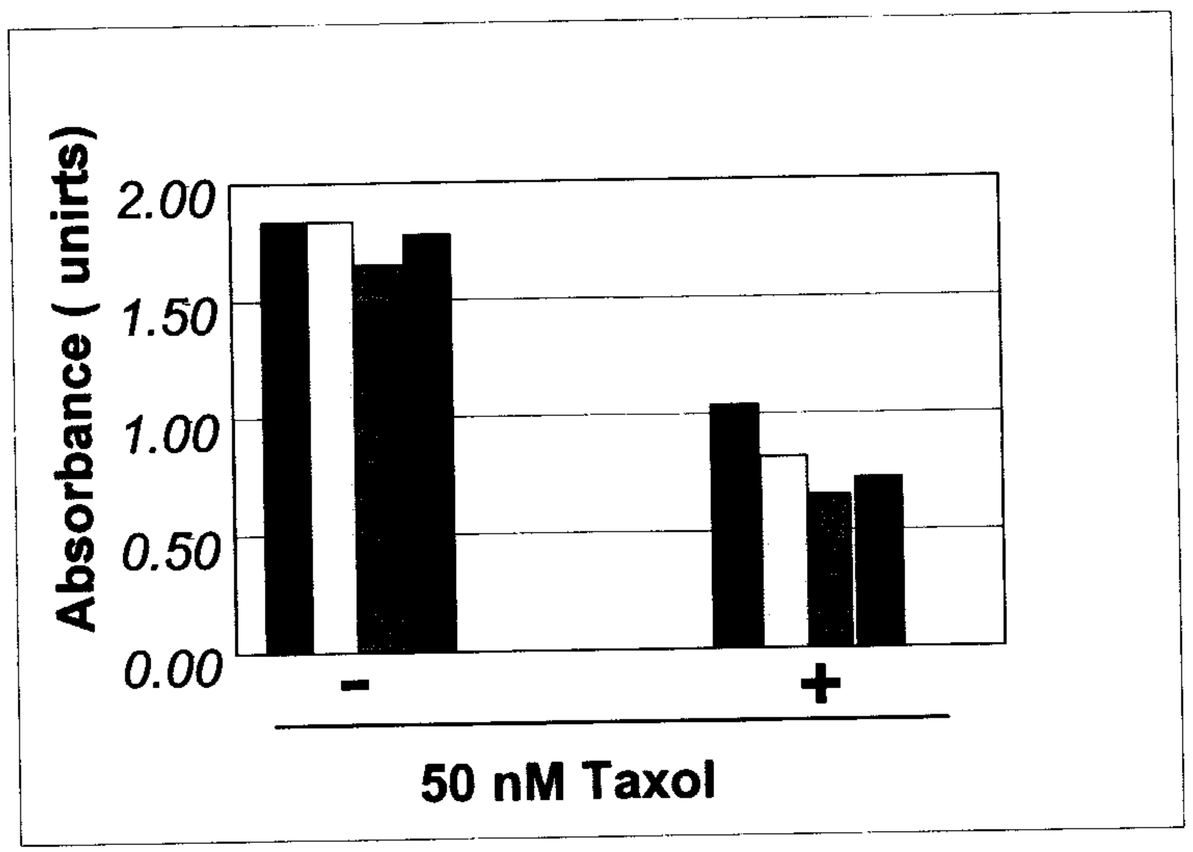
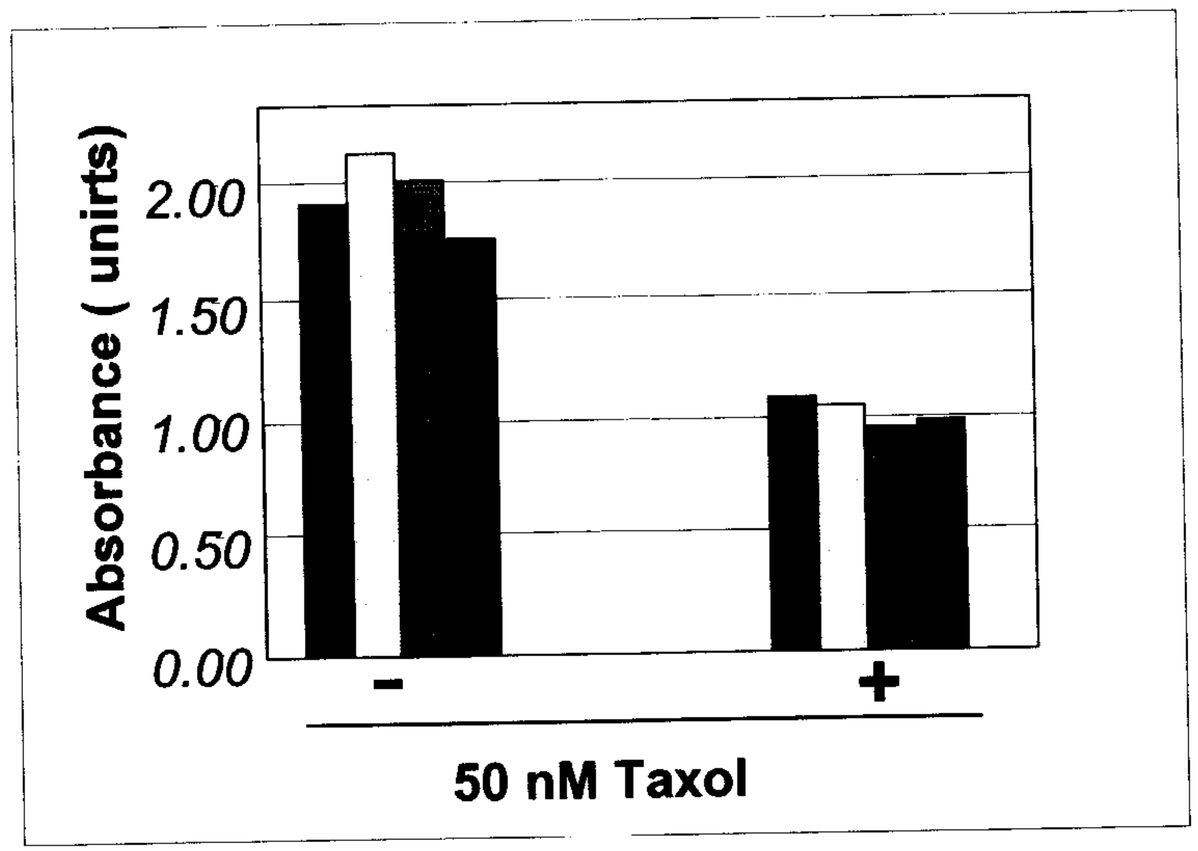

Hmax/Mmax
(% of Veh/Veh)
200
160
120
80
40
0
Veh/Veh
AEG10/Veh
Veh/Taxol
AEG1/Taxol
AEG5/Taxol
AEG10/Taxol
n=1
n=3
n=2

FIG. 4





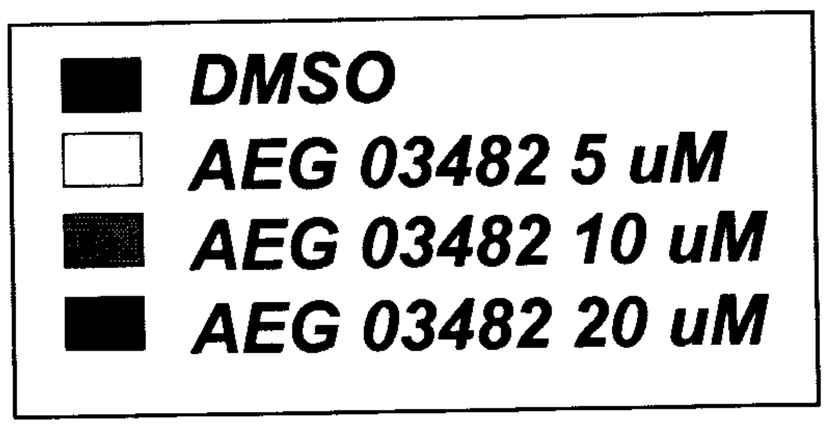


FIG. 5

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