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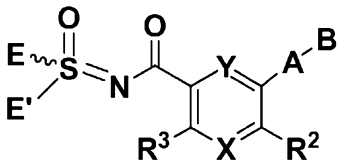

(I)

(57) Abstract: The present invention relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Formula (I)

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SULFOXIMINES AS KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Cross Reference To Related Applications

This application is based on, and claims the benefit of, U.S. Provisional Application No. 60/866,080, filed November 16, 2006, and which is incorporated herein by reference.

1. Field Of The Invention

The present invention relates to novel compounds capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction. The present invention is also directed to methods of regulating, modulating or inhibiting tyrosine kinases, whether of the receptor or non-receptor class, for the prevention and/or treatment of disorders related to unregulated tyrosine kinase signal transduction, including cell growth, metabolic, and blood vessel proliferative disorders.

2. Description Of The Related Art

Protein tyrosine kinases (PTKs) comprise a large and diverse class of proteins having enzymatic activity. The PTKs play an important role in the control of cell growth and differentiation.

For example, receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic homeostasis, and responses to the extracellular microenvironment).

With respect to receptor tyrosine kinases, it has been shown also that tyrosine phosphorylation sites function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Several intracellular substrate proteins that associate with receptor tyrosine kinases (RTKs) have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain but serve as adapters and associate with catalytically active molecules. The specificity of the interactions between receptors or proteins and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate

phosphorylation profiles. These observations suggest that the function of each receptor tyrosine kinase is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

Aberrant expression or mutations in the PTKs have been shown to lead to either uncontrolled cell proliferation (e.g. malignant tumor growth) or to defects in key developmental processes. Consequently, the biomedical community has expended significant resources to discover the specific biological role of members of the PTK family, their function in differentiation processes, their involvement in tumorigenesis and in other diseases, the biochemical mechanisms underlying their signal transduction pathways activated upon ligand stimulation and the development of novel drugs.

Tyrosine kinases can be of the receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular).

The RTKs comprise a large family of transmembrane receptors with diverse biological activities. The intrinsic function of RTKs is activated upon ligand binding, which results in phophorylation of the receptor and multiple cellular substrates, and subsequently in a variety of cellular responses.

At present, at least nineteen (19) distinct RTK subfamilies have been identified. One RTK subfamily, designated the HER subfamily, is believed to be comprised of EGFR, HER2, HER3 and HER4. Ligands to the Her subfamily of receptors include epithelial growth factor (EGF), TGF-α, amphiregulin, HB-EGF, betacellulin and heregulin.

A second family of RTKs, designated the insulin subfamily, is comprised of the INS-R, the IGF-1R and the IR-R. A third family, the "PDGF" subfamily includes the PDGF α and β receptors, CSFIR, c-kit and FLK-II. Another subfamily of RTKs, identified as the FLK family, is believed to be comprised of the Kinase insert Domain-Receptor fetal liver kinase-1 (KDR/FLK-1), the fetal liver kinase 4 (FLK-4) and the fms-like tyrosine kinase 1 (flt-1). Each of these receptors was initially believed to be receptors for hematopoietic growth factors. Two other subfamilies of RTKs have been designated as the FGF receptor family (FGFR1, FGFR2, FGFR3 and FGFR4) and the Met subfamily (c-met and Ron).

Because of the similarities between the PDGF and FLK subfamilies, the two subfamilies are often considered together. The known RTK subfamilies are identified in Plowman et al, 1994, DN&P 7(6): 334-339, which is incorporated herein by reference.

The non-receptor tyrosine kinases represent a collection of cellular enzymes which lack extracellular and transmembrane sequences. At present, over twenty-four individual non-receptor

tyrosine kinases, comprising eleven (11) subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been identified. At present, the Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs and include Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. A more detailed discussion of non-receptor tyrosine kinases is provided in Bolen, 1993, Oncogen 8: 2025-2031, which is incorporated herein by reference.

Many of the tyrosine kinases, whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways leading to cellular signal cascades leading to pathogenic conditions, including cancer, psoriasis and hyper immune response.

In view of the surmised importance of PTKs to the control, regulation and modulation of cell proliferation the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify receptor and non-receptor tyrosine kinase "inhibitors" using a variety of approaches, including the use of mutant ligands (U.S. Patent No. 4,966,849), soluble receptors and antibodies (PCT Application No. WO 94/10202; Kendall & Thomas, 1994, Proc. Nat'l Acad. Sci 90: 10705-09; Kim, et al, 1993, Nature 362: 841-844), RNA ligands (Jellinek, et al, Biochemistry 33: 10450-56); Takano, et al, 1993, Mol. Bio. Cell 4:358A; Kinsella, et al, 1992, Exp. Cell Res. 199: 56-62; Wright, et al, 1992, J. Cellular Phys. 152: 448-57) and tyrosine kinase inhibitors (PCT Application Nos. WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Patent No. 5,330,992; Mariani, et al, 1994, Proc. Am. Assoc. Cancer Res. 35: 2268).

More recently, attempts have been made to identify small molecules which act as tyrosine kinase inhibitors. For example, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT Application No. WO 92/20642), vinylene-azaindole derivatives (PCT Application No. WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (U.S. Patent No. 5,330,992) have been described generally as tyrosine kinase inhibitors. Styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1), seleoindoles and selenides (PCT Application No. WO 94/03427), tricyclic polyhydroxylic compounds (PCT Application No. WO 92/21660) and benzylphosphonic acid compounds (PCT Application No. WO 91/15495) have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer.

The identification of effective small compounds which specifically inhibit signal transduction by modulating the activity of receptor and non-receptor tyrosine kinases to regulate and modulate abnormal or inappropriate cell proliferation is therefore desirable and one object of this invention.

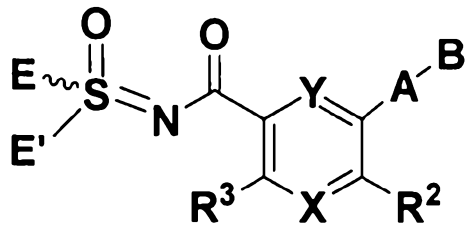
In addition, certain small compounds are disclosed in U.S. Patents 5,792,783; 5,834,504; 5,883,113; 5,883,116 and 5,886,020 as useful for the treatment of diseases related to unregulated TKS transduction. See also Patents and PCT Published Patent Application WO 02/29630;

6,599,173; 6,765,012; 6,699,863; 6,541,504 and 6,747,025. These patents are hereby incorporated by reference in its entirety for the purpose of disclosing starting materials and methods for the preparation thereof, screens and assays to determine a claimed compound's ability to modulate, regulate and/or inhibit cell proliferation, indications which are treatable with said compounds, formulations and routes of administration, effective dosages, etc.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to organic molecules capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction. Such compounds are useful for the treatment of diseases related to unregulated TKS transduction, including cell proliferative diseases such as cancer, atherosclerosis, restenosis, metabolic diseases such as diabetes, inflammatory diseases such as psoriasis and chronic obstructive pulmonary disease, vascular proliferative disorders such as diabetic retinopathy, age-related macular degeneration and retinopathy of prematurity, autoimmune diseases and transplant rejection.

A first aspect of the invention provides a compound represented by the general formula I or a pharmaceutically acceptable salt thereof



I

wherein:

X is CR^4 or N;

Y is CR^1 or N;

$\mathbf{R^1}$ is selected from the group consisting of hydrogen, alkyl, halogen, OR^4, CN, NO_2, COR^4, $(CH_2)_aOR^4$, $(CH_2)_an(R^4)_2$, $C(O)N(R^4)_2$ and $N(R^4)_2$;

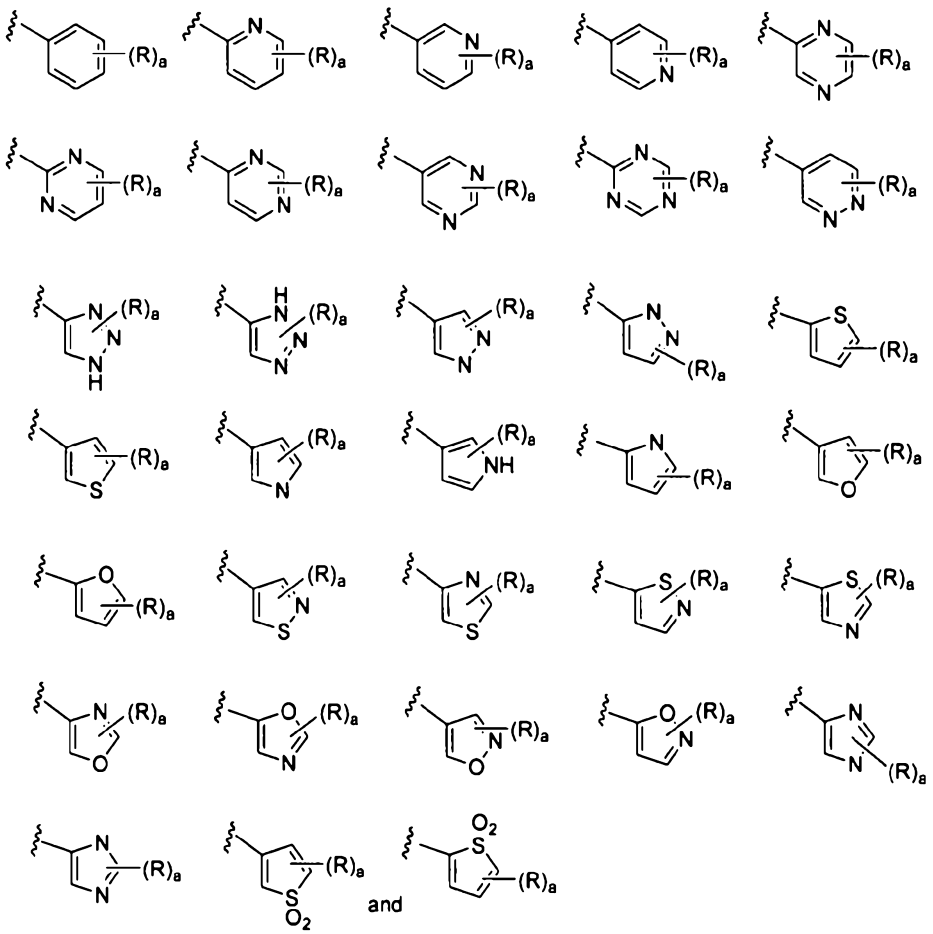
$\mathbf{R^2}$ is selected from the group consisting of hydrogen, halogen, alkyl, OR^4, CN, NO_2, $SO_2N(R^4)_2$, COR^4, $(CH_2)_aOR^4$, $(CH_2)_an(R^4)_2$, $C(O)N(R^4)_2$, $N(R^4)_2$ and $N(R^6)(CR^7R^8)_aR^{10}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, OR^4, CN, NO_2, $SO_2N(R^4)_2$, COR^4, $(CH_2)_aOR^4$, $(CH_2)_an(R^4)_2$, $C(O)N(R^4)_2$, $N(R^4)_2$ and $N(R^6)(CR^7R^8)_aR^{10}$;

R^4 is hydrogen or C_1 to C_4 alkyl;

A is $C\equiv C$;

B is a carbocyclic aryl or heterocyclic aryl selected from the group consisting of:



and

R is selected from the group consisting of halogen, alkyl, CF_3, OCF_3, OCF_2H, CH_2CN, CN, SR^6, $OP(O)(OR^6)_2$, OCH_2O, HC=N-NH, N=CH-S, $(CR^7R^8)_aC(O)R^6$, $O(CR^7R^8)_aC(O)R^6$, $N(R^6)(CR^7R^8)_aC(O)R^6$, $C(O)(CR^7R^8)_aC(O)R^6$, $S(O)_e(CR^7R^8)_aC(O)R^6$, $(CR^7R^8)_aC(O)OR^6$, $O(CR^7R^8)_aC(O)OR^6$, $N(R^6)(CR^7R^8)_aC(O)OR^6$, $C(O)(CR^7R^8)_aC(O)OR^6$, $S(O)_e(CR^7R^8)_aC(O)OR^6$, $O(CR^7R^8)_aC(O)N(R^6)_2$, $N(R^6)(CR^7R^8)_aC(O)N(R^6)_2$, $C(O)(CR^7R^8)_aC(O)N(R^6)_2$, $S(O)_e(CR^7R^8)_aC(O)N(R^6)_2$, $(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $O(CR^7R^8)_bN(R^6)C(O)N(R^6)_2$, $N(R^6)(CR^7R^8)_bN(R^6)C(O)N(R^6)_2$, $C(O)(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $S(O)_e(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $O(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $N(R^6)(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $C(O)(CR^7R^8)_aC(O)N(OR^6)(R^6)$,

$S(O)_e(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $(CR^7R^8)_a(OR^6)$, $O(CR^7R^8)_a(OR^6)$, $N(R^6)(CR^7R^8)_a(OR^6)$, $C(O)(CR^7R^8)_a(OR^6)$, $S(O)_e(CR^7R^8)_a(OR^6)$, $(CR^7R^8)_aN(R^6)_2$, $O(CR^7R^8)_bN(R^6)_2$, $N(R^6)(CR^7R^8)_bN(R^6)_2$, $C(O)(CR^7R^8)_aN(R^6)_2$, $S(O)_e(CR^7R^8)_aN(R^6)_2$, $(CR^7R^8)_aR^6$, $O(CR^7R^8)_aR^6$, $N(R^6)(CR^7R^8)_aR^6$, $C(O)(CR^7R^8)_aR^6$ and, $S(O)_e(CR^7R^8)_aR^6$;

E is a 5 or 6 membered carbocyclic aryl or heterocyclic aryl group which may be substituted with one or more group selected from halogen, trihalomethyl, hydroxyl, SH, NO_2, thioether, cyano, alkoxy, alkyl and amino;

E' is selected from the group consisting of alkyl, CF_3, $(CR^7R^8)_aC(O)OR^{10}$, $(CR^7R^8)_aC(O)N(R^{10})_2$, $(CR^7R^8)_aC(O)N(OR^{10})(R^{10})$, $(CR^7R^8)_a(OR^{10})$, $(CR^7R^8)_aN(R^{10})_2$, and $(CR^7R^8)_aR^{10}$;

$\mathbf{R^7}$ and $\mathbf{R^8}$ are selected from the group consisting of H, halogen, hydroxyl, and alkyl or CR^7R^8 may represent a carbocyclic ring of from 3 to 6 carbons; and being optionally substituted with one or more group/atom selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethylamino and SH;

$\mathbf{R^{10}}$ is selected from the group consisting of hydrogen, halogen, alkyl, hydroxyl, hydroxymethyl, carbocyclic aryl, heterocyclic aryl, $(CR^7R^8)_aC(O)OR^6$, $(CR^7R^8)_aC(O)R_6$, $(CR^7R^8)_aC(O)N(R^6)_2$, $(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $(CR^7R^8)_a(OR^6)$, $(CR^7R^8)_aN(R^6)_2$ and $(CR^7R^8)_aR^6$, the aryl groups being optionally susbstituted with one or more group selected from the group consisting of halogen, trihalomethyl, hydroxyl, SH, NO_2, thioether, cyano, alkoxy, alkyl and amino;

$\mathbf{R^6}$ is selected from the group consisting of hydrogen, carboalkyl, alkylamine, alkylhydroxy, and alkyloxyalkyl or R^6 is a 5 or 6 membered carbocyclic or heterocyclic group optionally substituted with one or more group/atom selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethylamino and SH;

the alkyl groups may be substituted with one or more group/atom selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethylamino and SH;

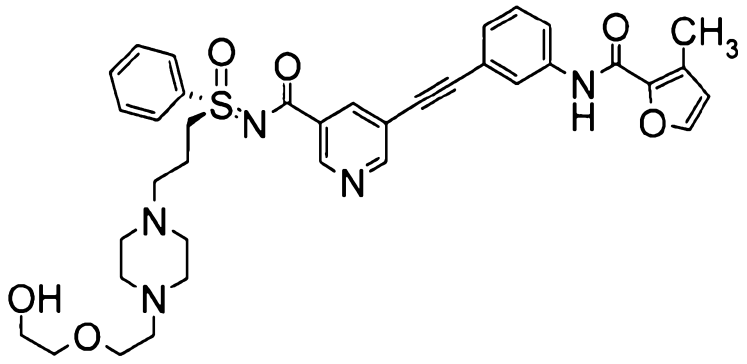
the heterocyclic aryl groups of E and R^{10} and the heterocyclic groups of R^6 contain 1 to 3 heteroatoms in the rings;

a is 0 or an integer of from 1 to 5;

b is an integer of from 2 to 5; and

e is 0 or an integer of from 1 to 2.

A second aspect of the invention provides a compound or a pharmaceutically acceptable salt thereof selected from the following compounds:



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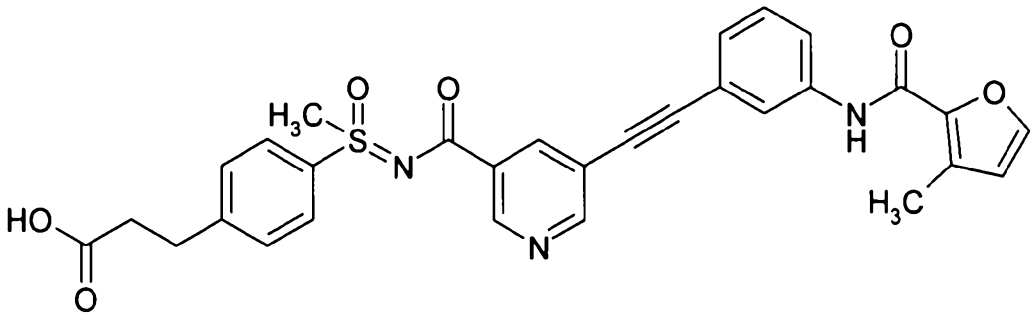

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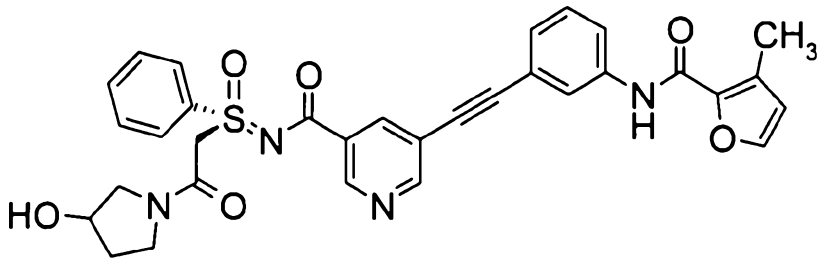

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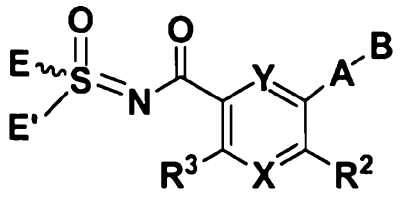
A third aspect of the invention provides a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as defined in the first or second aspect and a pharmaceutically acceptable carrier or excipient.

A fourth aspect of the invention provides a method for treating a disease related to unregulated tyrosine kinase signal transduction, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound as defined in the first aspect or second aspect or a pharmaceutical composition as defined in the third aspect.

A fifth aspect of the invention provides use of a compound as defined in the first aspect or second aspect or a pharmaceutical composition as defined in the third aspect in the manufacture of a medicament for the treatment of a disease related to unregulated tyrosine kinase signal transduction.

A sixth aspect of the invention provides a compound as defined in the first aspect or second aspect or a pharmaceutical composition as defined in the third aspect for use in treating a disease related to unregulated tyrosine kinase signal transduction.

In one illustrative embodiment, the compounds of the present invention have the following general formula I:



I

wherein:

X is CR^4 or N;

Y is CR^1 or N;

R^1 is selected from the group consisting of hydrogen, alkyl, halogen, OR^4, CN, NO_2, COR^4, $(CH_2)_aOR^4$, $(CH_2)_aN(R^4)_2$, $C(O)N(R^4)_2$ and $N(R^4)_2$;

R^2 is selected from the group consisting of hydrogen, halogen, alkyl, OR^4, CN, NO_2, $SO_2N(R^4)_2$, COR^4, $(CH_2)_aOR^4$, $(CH_2)aN(R^4)_2$, $C(O)N(R^4)_2$, $N(R^4)_2$ and $N(R^6)(CR^7R^8)_aR^{10}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, OR_4, CN, NO_2, $SO_2N(R^4)_2$, COR^4, $(CH_2)_aOR^4$, $(CH_2)_aN(R^4)_2$, $C(O)N(R^4)_2$, $N(R^4)_2$ and $N(R^6)(CR^7R^8)_aR^{10}$;

R^4 is hydrogen or C_1 to C_4 alkyl;

A is selected from the group consisting of $C\equiv C$, CH=CH, CH_2CH_2, CH_2O, CF_2O, OCH_2, OCF_2, O, $N(R^4)$, C(O), $S(O)_e$, $NR^7C(O)$, $C(O)NR^7$ and $N(R^7)C(O)NR^7$;

B is selected from the group consisting of hydrogen, alkyl and alkyloxyalkyl or **B** may be a 5 or 6 membered carbocyclic aryl or heterocyclic aryl group;

E is a 5 or 6 membered carbocyclic aryl or heterocyclic aryl group;

E' is selected from the group consisting of alkyl, CF_3,

$(CR^7R^8)_aC(O)OR^{10}$, $(CR^7R^8)_aC(O)N(R^{10})_2$, $(CR^7R^8)_aC(O)N(OR^{10})(R^{10})$, $(CR^7R^8)_a(OR^{10})$, $(CR^7R^8)_aN(R^{10})_2$, and $(CR^7R^8)_aR^{10}$; wherein $\mathbf{R^7}$ and $\mathbf{R^8}$ are selected from the group consisting of H, halogen, hydroxyl, and alkyl or CR^7R^8 may represent a carbocyclic ring of from 3 to 6 carbons; and

$\mathbf{R^{10}}$ is selected from the group consisting of hydrogen, halogen, alkyl, hydroxyl, hydroxymethyl, carbocyclic aryl, heterocyclic aryl, $(CR^7R^8)_aC(O)OR^6$, $(CR^7R^8)_aC(O)R^6$, $(CR^7R^8)_aC(O)N(R^6)_2$, $(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $(CR^7R^8)_a(OR^6)$, $(CR^7R^8)_aN(R^6)_2$ and $(CR^7R^8)_aR^6$, wherein R^6 is selected from the group consisting of hydrogen, carboalkyl, alkylamine, alkylhydroxy, and alkyloxyalkyl or R^6 is a 5 or 6 membered carbocyclic or heterocyclic group;

a is 0 or an integer of from 1 to 5;

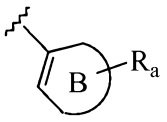
b is an integer of from 2 to 5;

c is 0 or an integer of from 1 to 4;

d is 0 or an integer of from 1 to 5;

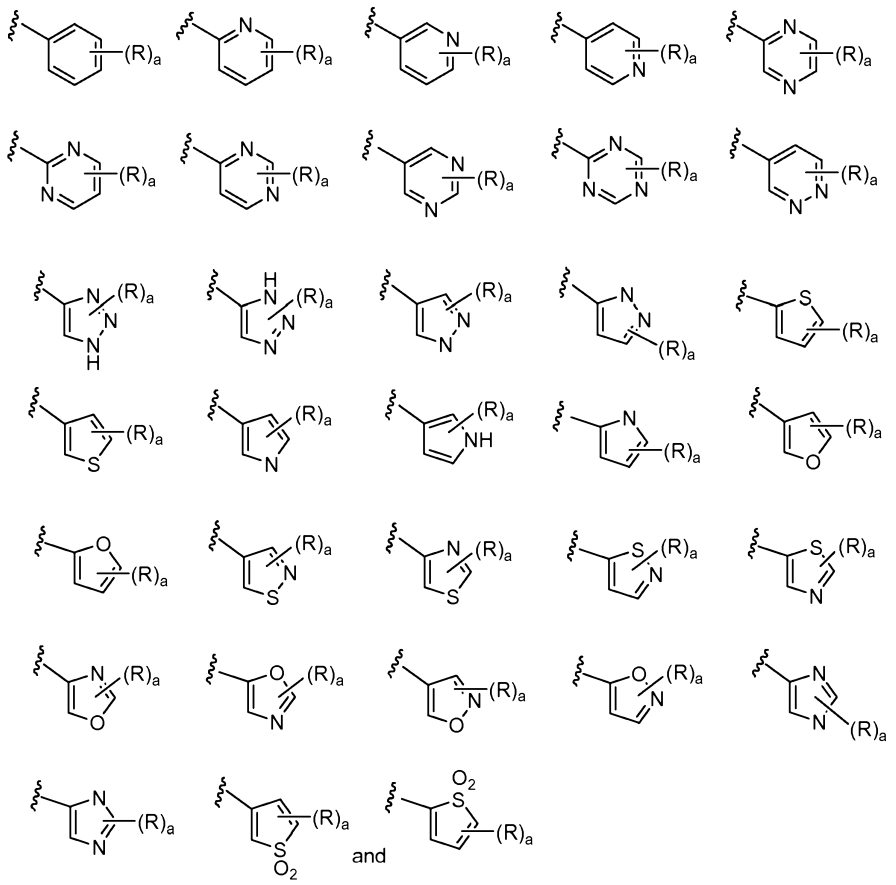
e is 0 or an integer of from 1 to 2 and further including prodrugs, pharmaceutically acceptable salts, racemic mixtures and enantiomers of said compound.

Preferably, B is a carbocyclic aryl or heterocyclic aryl represented by formula II below:



II

wherein said carbocyclic aryl and heterocyclic aryl groups are selected from the group consisting of:



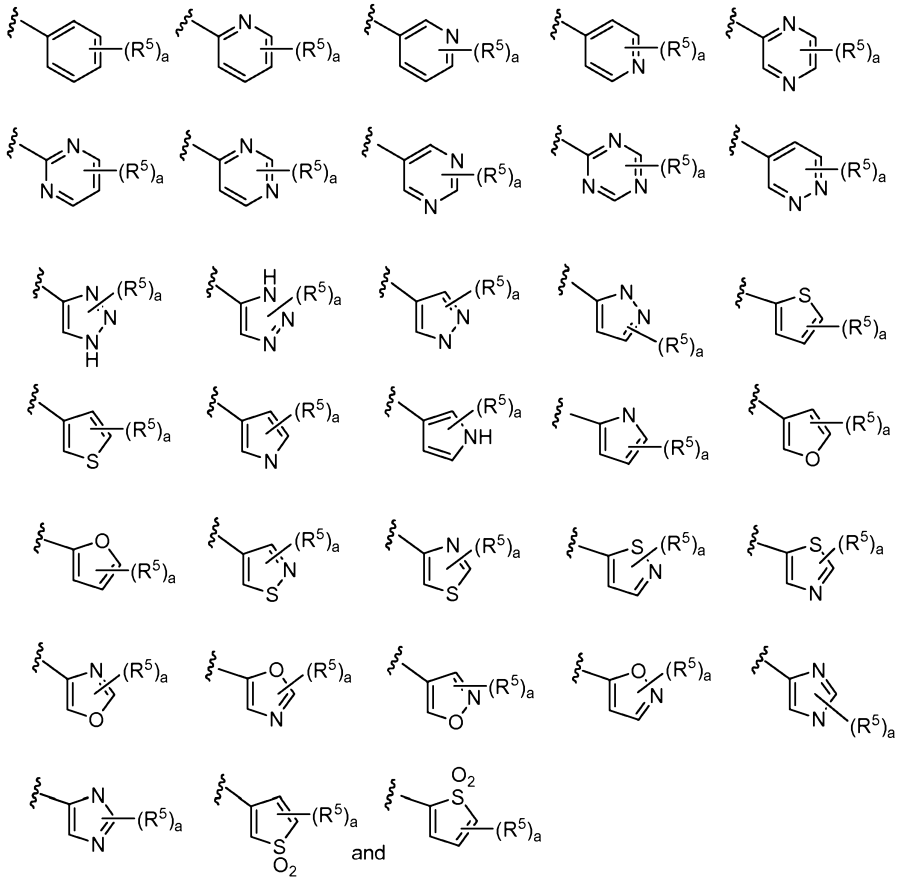
and

wherein R is selected from the group consisting of halogen, alkyl, CF_3, OCF_3, OCF_2H, CH_2CN, CN, SR^6, $OP(O)(OR^6)_2$, OCH_2O, HC=N-NH, N=CH-S,

$(CR^7R^8)_aC(O)R^6$, $O(CR^7R^8)_aC(O)R^6$, $N(R^6)(CR^7R^8)_aC(O)R^6$, $C(O)(CR^7R^8)_aC(O)R^6$, $S(O)_e(CR^7R^8)_aC(O)R^6$,$(CR^7R^8)_aC(O)OR^6$, $O(CR^7R^8)_aC(O)OR^6$, $N(R^6)(CR^7R^8)_aC(O)OR^6$, $C(O)(CR^7R^8)_aC(O)OR^6$, $S(O)_e(CR^7R^8)_aC(O)OR^6$, $(CR^7R^8)_aC(O)N(R^6)_2$, $O(CR^7R^8)_aC(O)N(R^6)_2$, $N(R^6)(CR^7R^8)_aC(O)N(R^6)_2$, $C(O)(CR^7R^8)_aC(O)N(R^6)_2$, $S(O)_e(CR^7R^8)_aC(O)N(R^6)_2$, $(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $O(CR^7R^8)_bN(R^6)C(O)N(R^6)_2$, $N(R^6)(CR^7R^8)_bN(R^6)C(O)N(R^6)_2$, $C(O)(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $S(O)_e(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $O(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $N(R^6)(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $C(O)(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $S(O)_e(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $(CR^7R^8)_a(OR^6)$, $O(CR^7R^8)_a(OR^6)$, $N(R^6)(CR^7R^8)_a(OR^6)$, $C(O)(CR^7R^8)_a(OR^6)$, $S(O)_e(CR^7R^8)_a(OR^6)$, $(CR^7R^8)_aN(R^6)_2$, $O(CR^7R^8)_bN(R^6)_2$, $N(R^6)(CR^7R^8)_bN(R^6)_2$, $C(O)(CR^7R^8)_aN(R^6)_2$

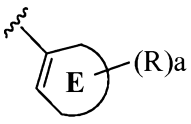
$S(O)_e(CR^7R^8)_aN(R^6)_2$, $(CR^7R^8)_aR^6$, $O(CR^7R^8)_aR^6$, $N(R^6)(CR^7R^8)_aR^6$, $C(O)(CR^7R^8)_aR^6$ and, $S(O)_e(CR^7R^8)_aR^6$.

Most preferably $\mathbf{R^6}$ is selected from the group consisting of hydrogen, alkyl, dilower alkyl amine or a heterocyclic group represented by the list below or $N(R^6)_2$ may represent a 3 to 7 membered heterocyclic group,



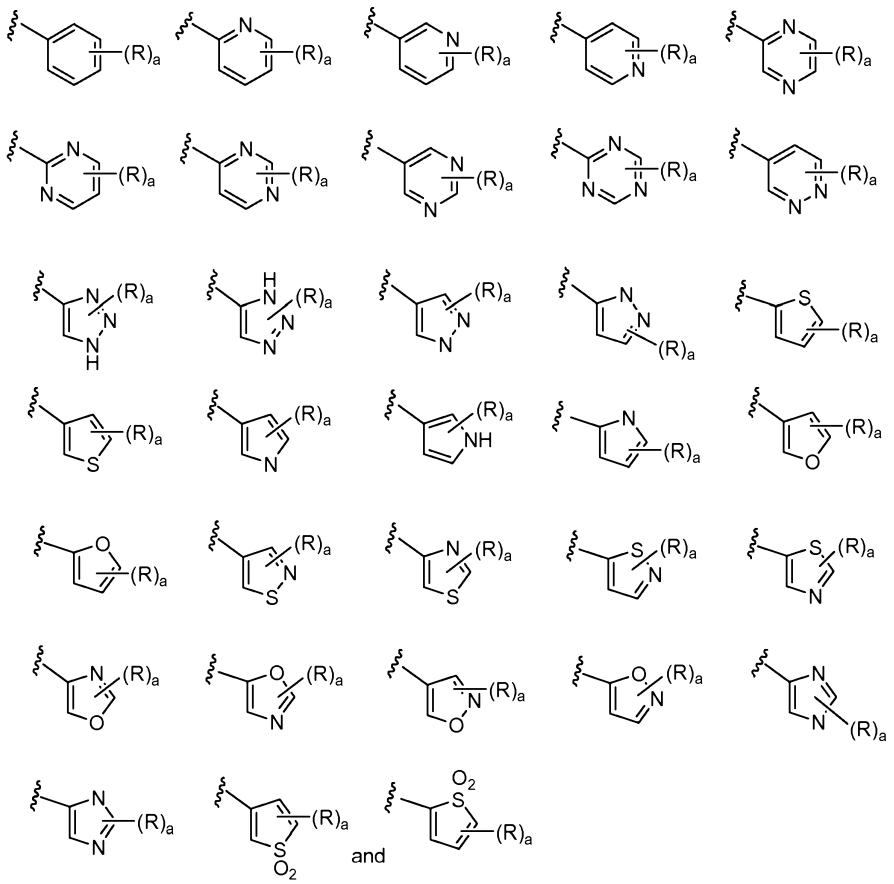
wherein R^5 is hydrogen, halogen, simple alkyl, CF_3, hydroxyl, OR^7, $N(R^7)_2$ or NO2.

Preferably, **E is** a 5 or 6 membered carbocyclic aryl or heterocyclic aryl represented by formula III below:



III

wherein said carbocyclic aryl and heterocyclic aryl is selected from the group consisting of:



Compounds of formula I below are useful as kinase inhibitors. As such compounds of formula I will be useful for treating diseases related to unregulated tyrosine kinase signal transduction, for example, cancer, blood vessel proliferative disorders, fibrotic disorders, and neurodegenerative diseases. In particular compounds of the present invention are useful for treatment of mesangial cell proliferative disorders and metabolic diseases, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetis mellitus, wound healing, inflammation and neurodegenerative diseases.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is further directed to pharmaceutical compositions comprising a pharmaceutically effective amount of the above-described compounds and a pharmaceutically acceptable carrier or excipient. Such a composition is believed to modulate signal transduction by a tyrosine kinase, either by inhibition of
catalytic activity, affinity to ATP or ability to interact with a substrate.

More particularly, the compositions of the present invention may be included in methods for treating diseases comprising proliferation, fibrotic or metabolic disorders, for example cancer,

fibrosis, psoriasis, atherosclerosis, arthritis, and other disorders related to abnormal vasculogenesis and/or angiogenesis, such as diabetic retinopathy.

The following defined terms are used throughout this specification:

"Me" refers to methyl.

"Et" refers to ethyl.

"tBu" refers to t-butyl.

"iPr" refers to i-propyl.

"Ph" refers to phenyl.

"Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Alkyl" refers to a straight-chain, branched or cyclic saturated aliphatic hydrocarbon. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. Typical alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl and the like. The alkyl group may be optionally substituted with one or more substituents are selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Alkenyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon group containing at least one carbon-carbon double bond. Preferably, the alkenyl group has 1 to 12 carbons. More preferably it is a lower alkenyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. The alkenyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Alkynyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon containing at least one carbon-carbon triple bond. Preferably, the alkynyl group has 1 to 12 carbons. More preferably it is a lower alkynyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. The alkynyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Alkoxyl" refers to an "O-alkyl" group.

"Aryl" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups. The aryl group may be optionally substituted with one or more substituents selected from the group consisting of halogen, trihalomethyl, hydroxyl, SH, OH, NO_2, amine, thioether, cyano, alkoxy, alkyl, and amino.

"Alkaryl" refers to an alkyl that is covalently joined to an aryl group. Preferably, the alkyl is a lower alkyl.

"Carbocyclic ring" refers to a substituted or unsubstituted cyclic radical, including cycloalkyl, cycloalkenyl and carbocyclic aryl wherein the ring atoms are carbon and said substituents are selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Carbocyclic aryl" refers to an aryl group wherein the ring atoms are carbon.

"Heterocyclic ring" refers to a substituted or unsubstituted cyclic radical including cycloalkyl, cycloalkenyl and heterocyclic aryl wherein 1 to 3 of the ring atoms are heteroatoms and the remainder of the ring atoms are carbon substituents are selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethyl amino, and SH.

"Heterocyclic aryl" refers to an aryl group having from 1 to 3 heteroatoms as ring atoms, the remainder of the ring atoms being carbon. Heteroatoms include oxygen, sulfur, and nitrogen. Thus, heterocyclic aryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like.

"Hydrocarbyl" refers to a hydrocarbon radical having only carbon and hydrogen atoms. Preferably, the hydrocarbyl radical has from 1 to 20 carbon atoms, more preferably from 1 to 12 carbon atoms and most preferably from 1 to 7 carbon atoms.

"Substituted hydrocarbyl" refers to a hydrocarbyl radical wherein one or more, but not all, of the hydrogen and/or the carbon atoms are replaced by a halogen, nitrogen, oxygen, sulfur or phosphorus atom or a radical including a halogen, nitrogen, oxygen, sulfur or phosphorus atom, e.g. fluoro, chloro, cyano, nitro, hydroxyl, phosphate, thiol, etc.

"Amide" refers to -C(O)-NH-R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Thioamide" refers to -C(S)-NH-R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

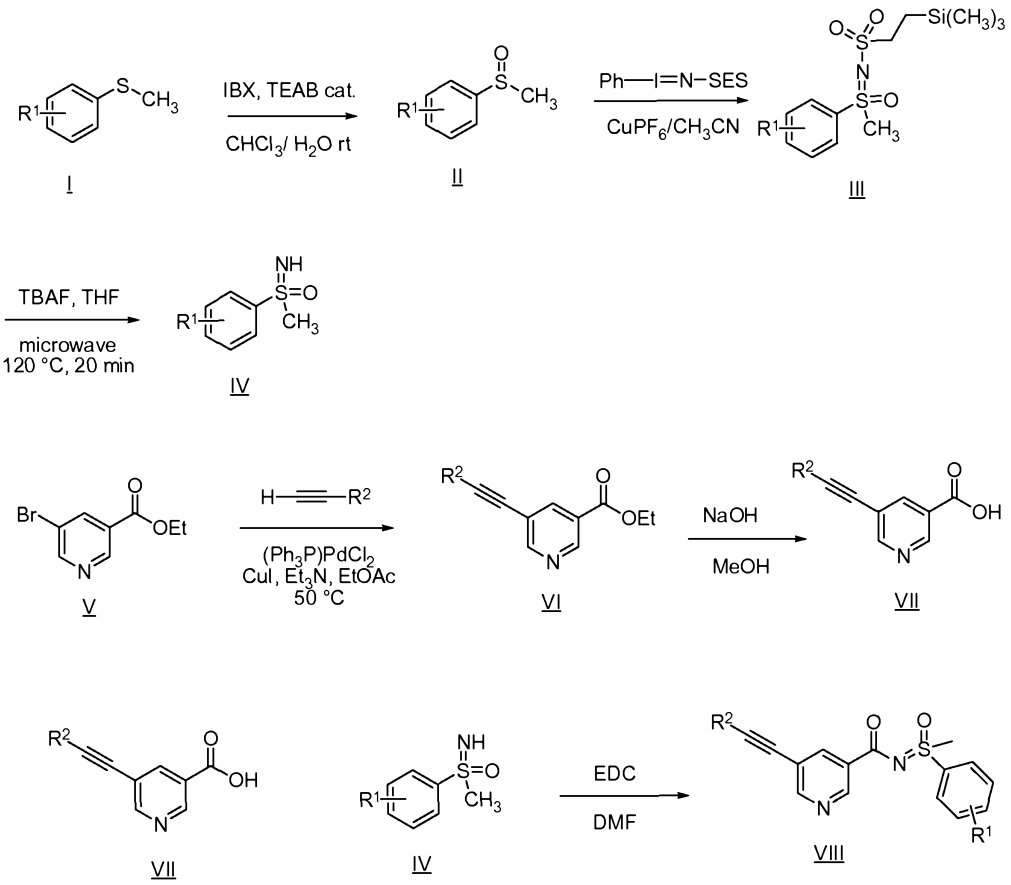
"Amine" refers to a -N(R'')R''' group, wherein R'' and R''' are independently selected from the group consisting of alkyl, aryl, and alkylaryl.

"Thioether" refers to -S-R'', wherein R'' is alkyl, aryl, or alkylaryl.

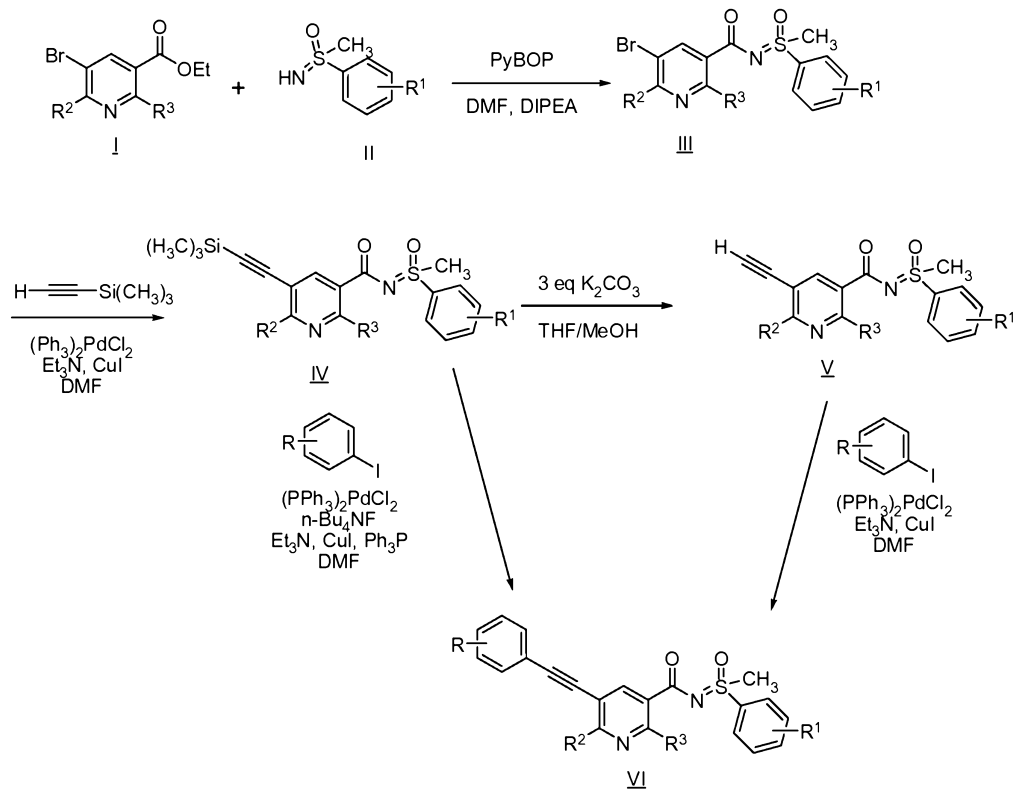
"Sulfonyl" refers to -$S(O)_2$-R'''', where R'''' is aryl, C(CN)=C-aryl, CH_2CN, alkyaryl, sulfonamide, NH-alkyl, NH-alkylaryl, or NH-aryl.

The compounds of this invention may be prepared by the general scheme set forth in Scheme 1.

Scheme 1 - General Route to Acyl Sulfoximines

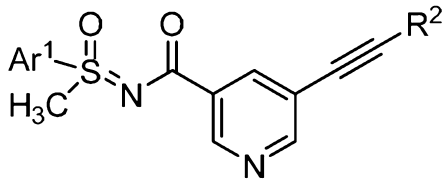


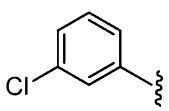
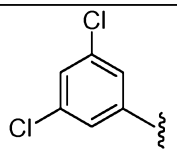
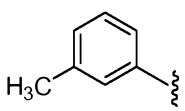
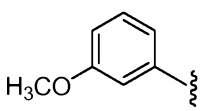
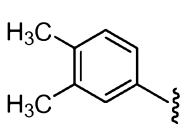
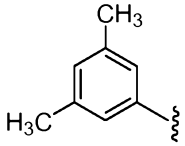
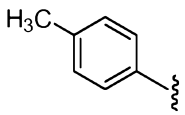
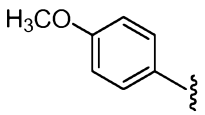
Scheme 2 - General Route to Acyl Sulfoximines

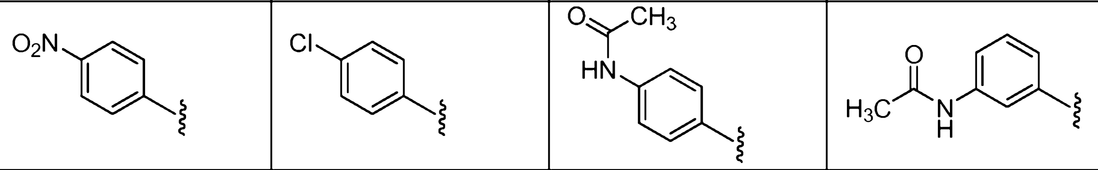
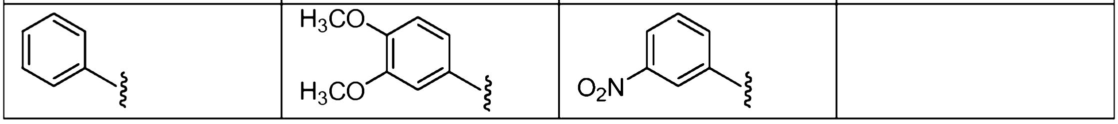


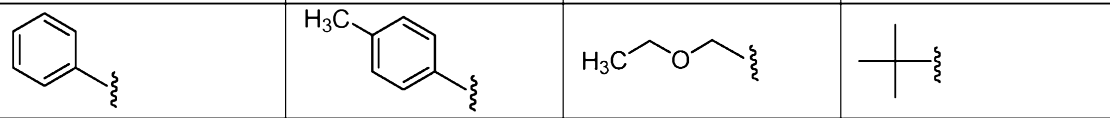
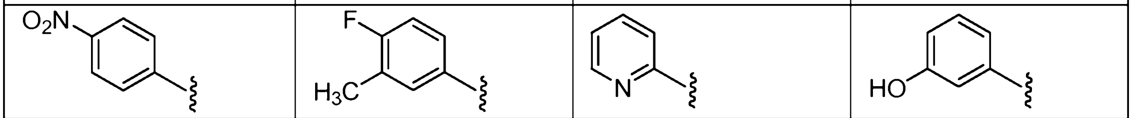
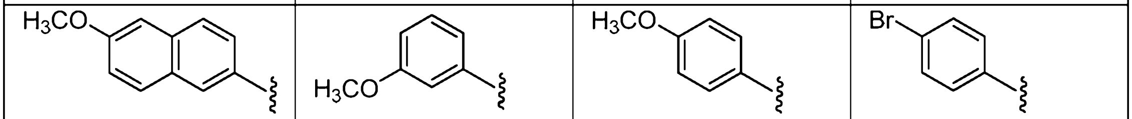
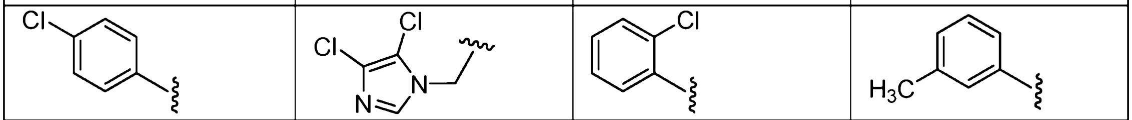
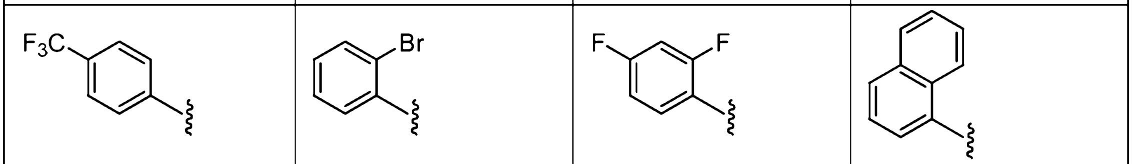
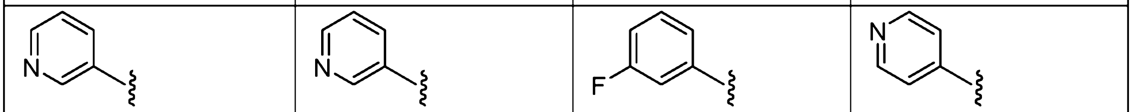
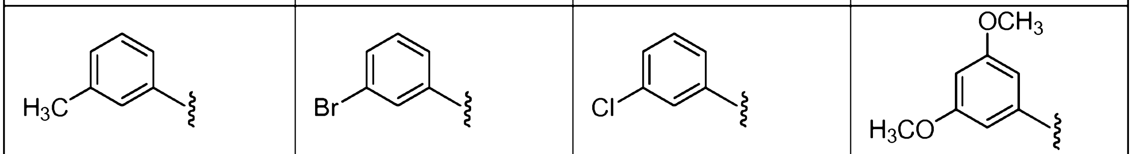
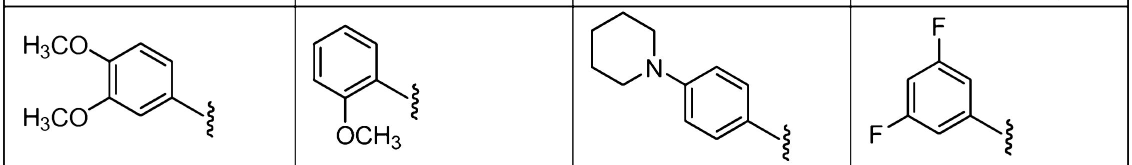
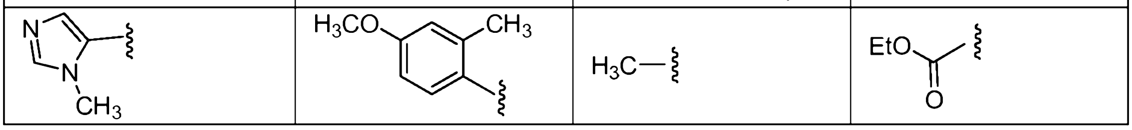
In particular the compounds of the present invention are selected from the compounds of Table 1, Table 2 and Table 2.1 below. In table 1 the compounds of the present invention are exemplified by any combination of Ar^1 and R^2 attached to the core template illustrated.

Table 1 -



Ar^1 Substitution			
			
			

Ar^1 Substitution			
			
			

R^2 Substitution			
			
			
			
			
			
			
			
			
			

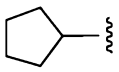
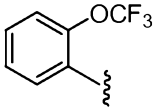
R^2 Substitution			
			

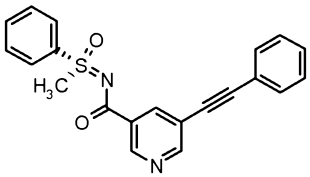
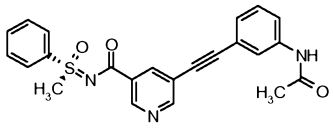
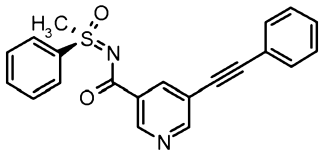
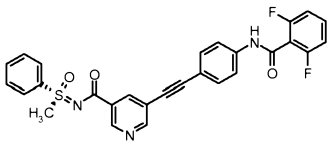
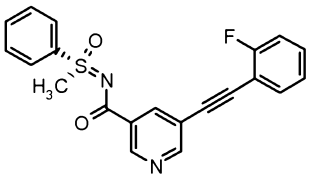
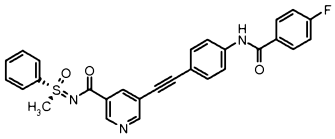
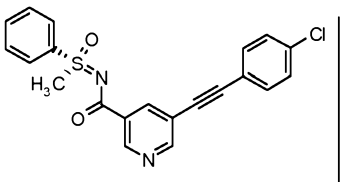
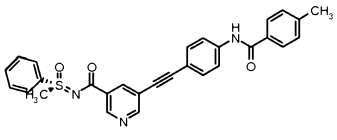
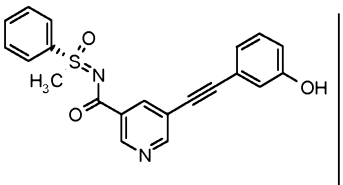
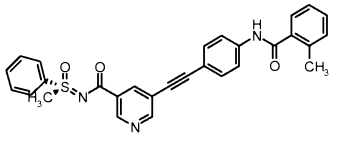
Table 2			
Example Number	**Structure**	**Example Number**	**Structure**
Example 423		Example 450	
Example 424		Example 451	
Example 425		Example 452	
Example 426		Example 453	
Example 427		Example 454	

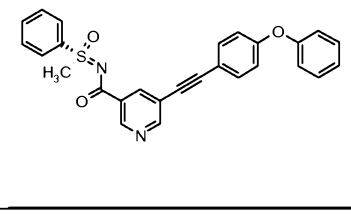
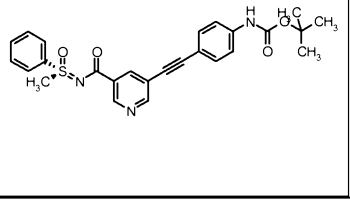
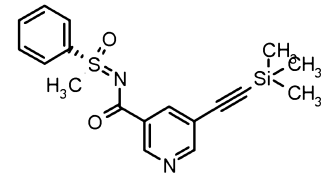
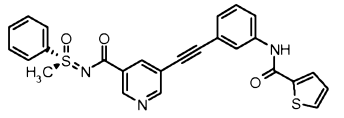
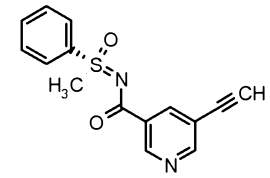
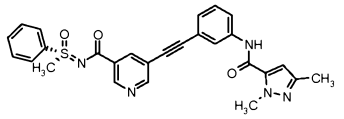
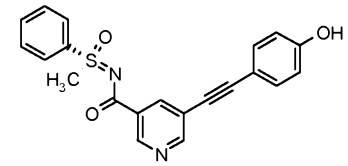
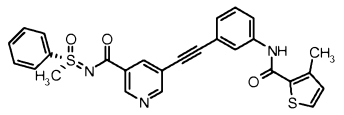
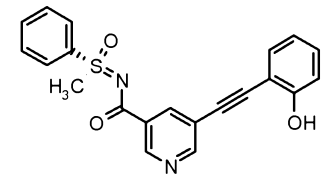
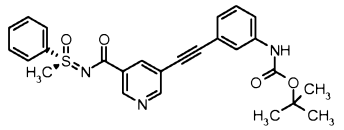
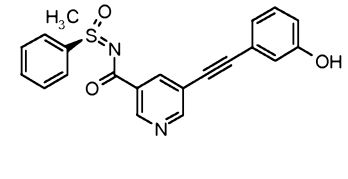
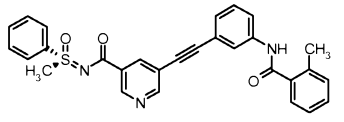
Table 2			
Example Number	**Structure**	**Example Number**	**Structure**
Example 428		Example 455	
Example 429		Example 456	
Example 430		Example 457	
Example 431		Example 458	
Example 432		Example 459	
Example 433		Example 460	

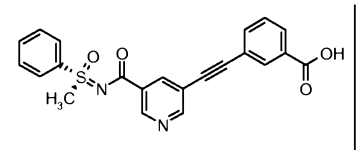
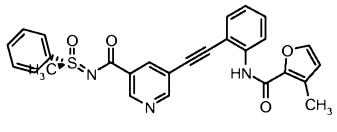
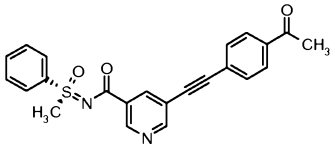
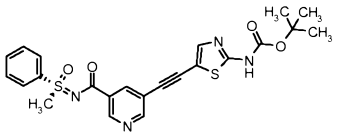
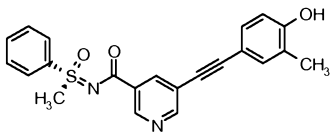
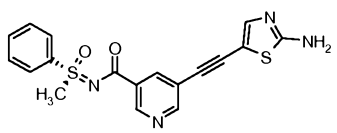
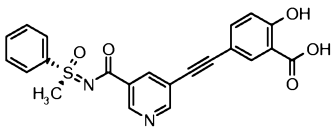
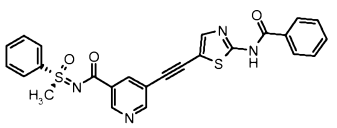
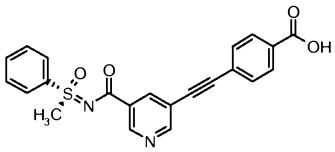
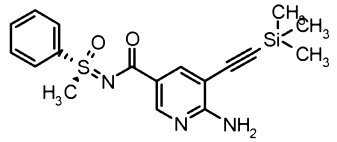
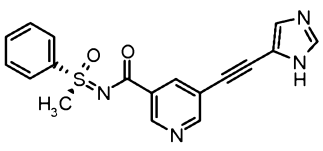
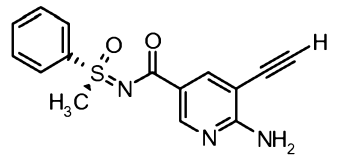
Table 2			
Example Number	**Structure**	**Example Number**	**Structure**
Example 434		Example 461	
Example 435		Example 462	
Example 436		Example 463	
Example 437		Example 464	
Example 438		Example 465	
Example 439		Example 466	

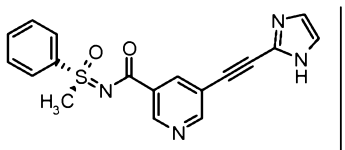
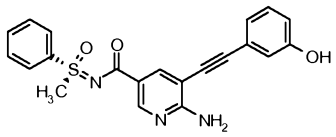
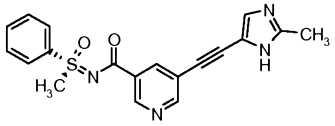
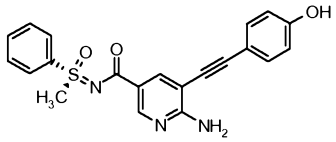
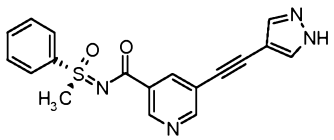
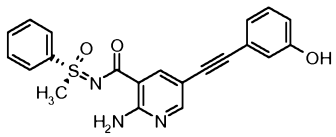
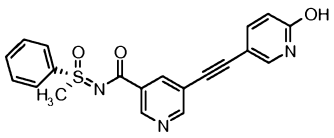
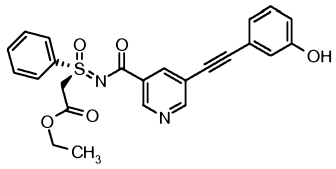
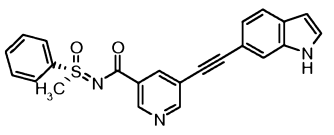
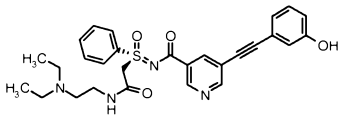
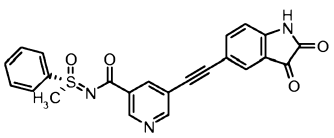
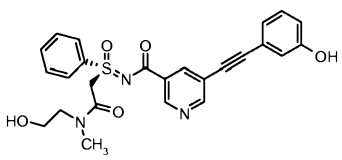
Table 2			
Example Number	**Structure**	**Example Number**	**Structure**
Example 440		Example 467	
Example 441		Example 468	
Example 442		Example 469	
Example 443		Example 470	
Example 444		Example 471	
Example 445		Example 472	

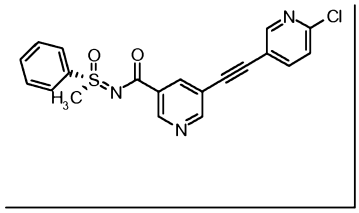
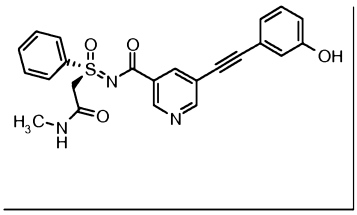
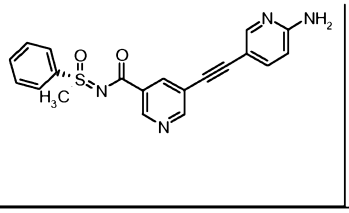
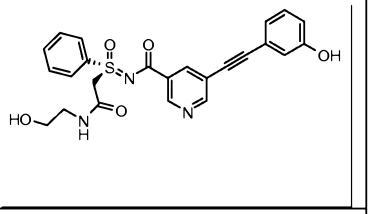
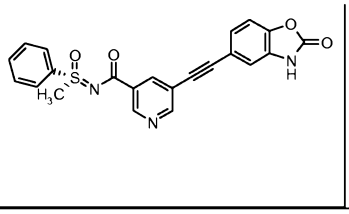
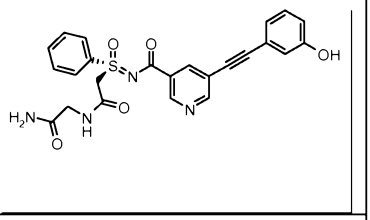
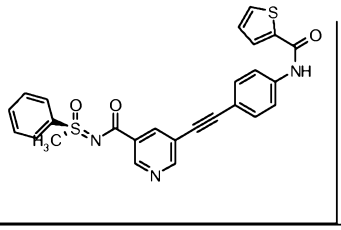
Table 2			
Example Number	**Structure**	**Example Number**	**Structure**
Example 446		Example 473	
Example 447		Example 474	
Example 448		Example 475	
Example 449			

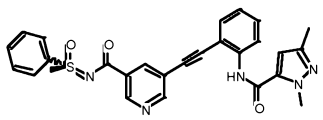
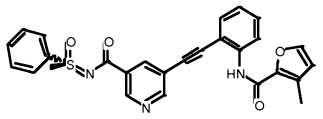
	Table 2-1
Example #	**Structure**
476	
477	

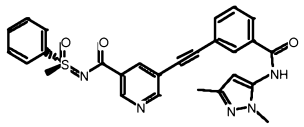
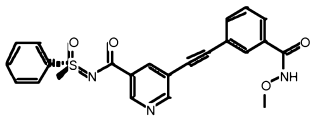
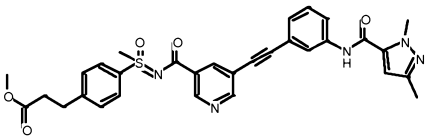
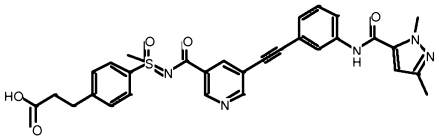
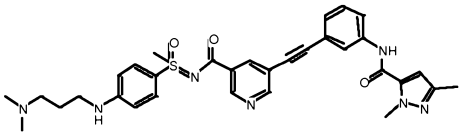
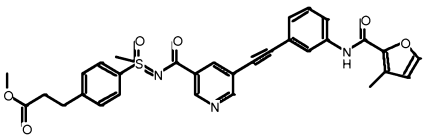
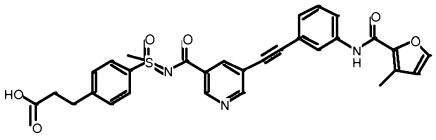
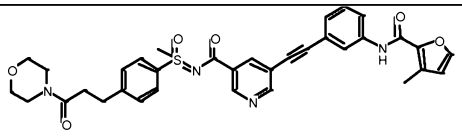
Table 2-1	
Example #	Structure
478	
479	
480	
481	
482	
483	
484	
485	

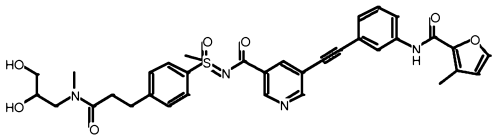
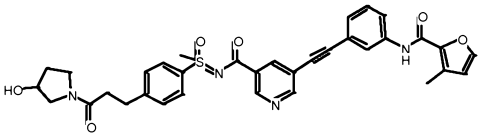
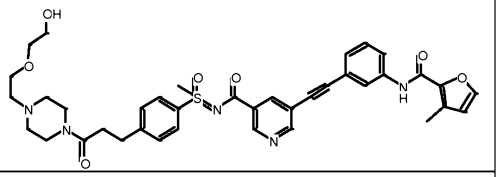
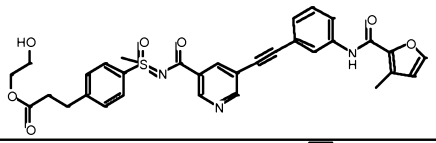
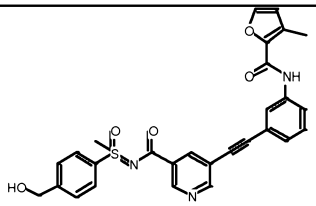
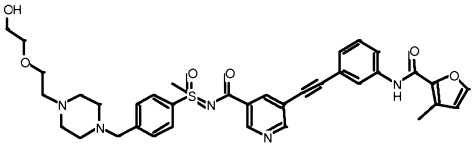
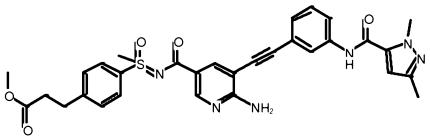
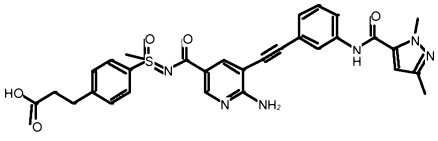
	Table 2-1
Example #	Structure
486	
487	
488	
489	
490	
491	
492	
493	

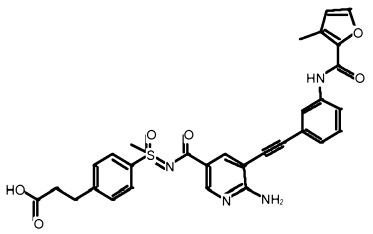
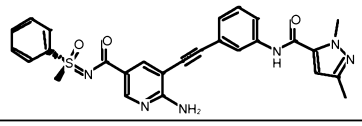
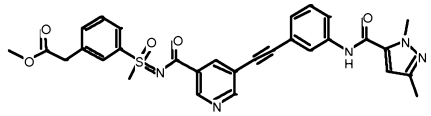
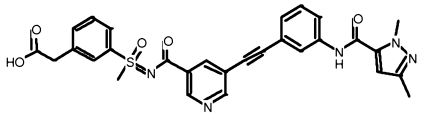
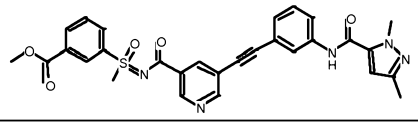
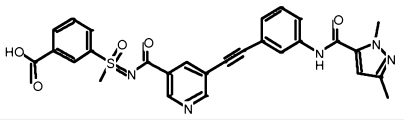
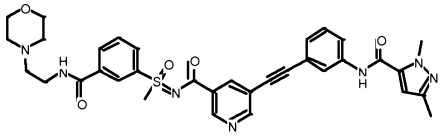
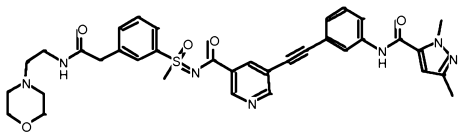
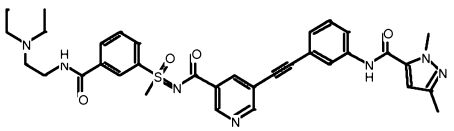
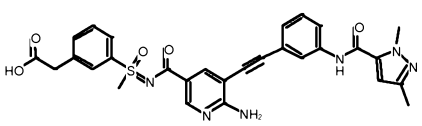
	Table 2-1
Example #	Structure
494	
495	
496	
497	
498	
499	
500	
501	
502	
503	

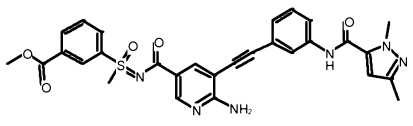
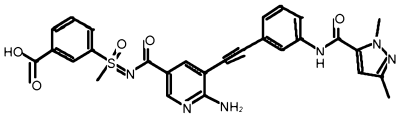
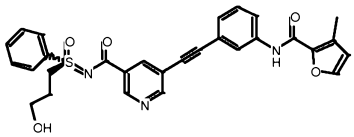
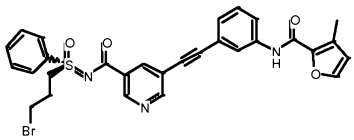
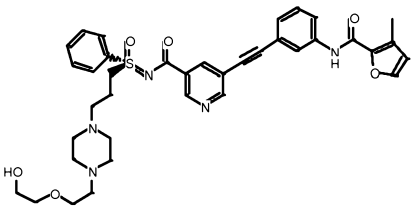
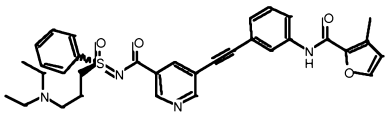
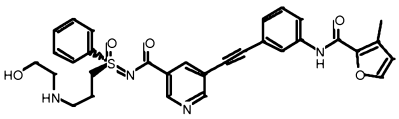
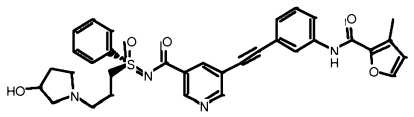
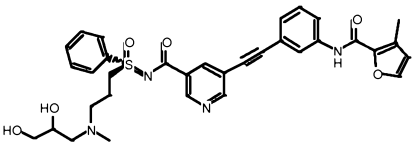
	Table 2-1
Example #	Structure
504	
505	
506	
507	
508	
509	
510	
511	
512	

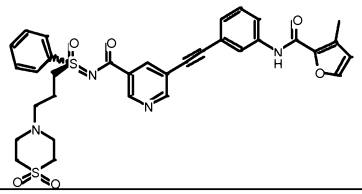
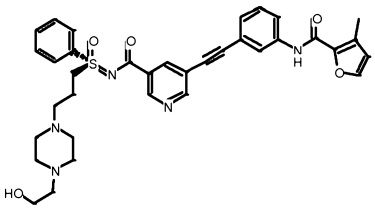
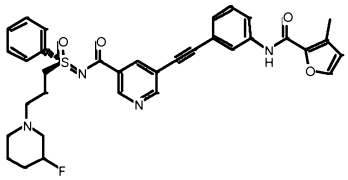
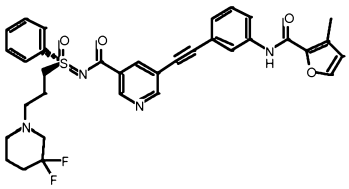
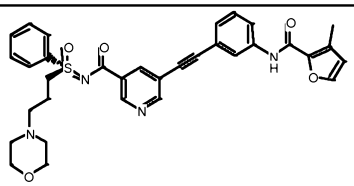
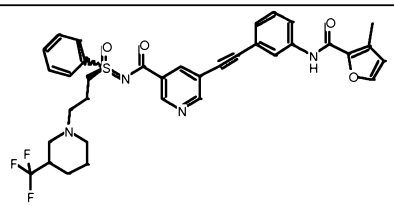
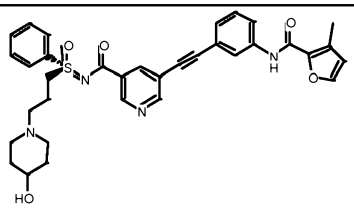
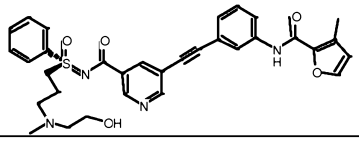
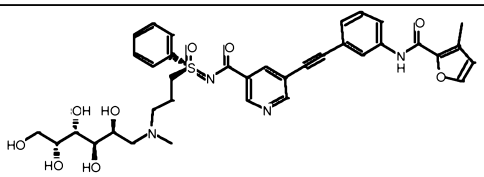
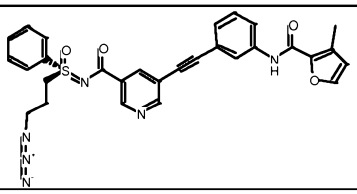
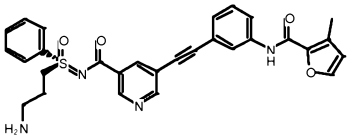
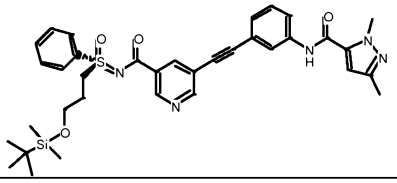
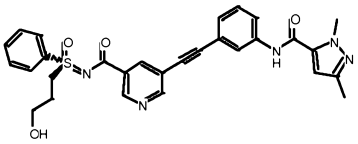
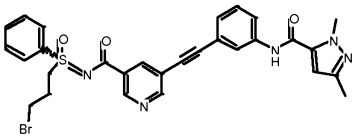
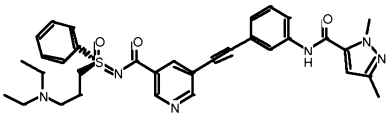
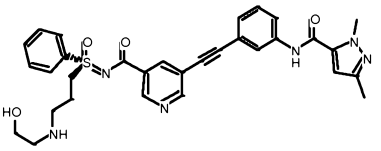
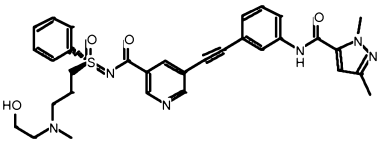
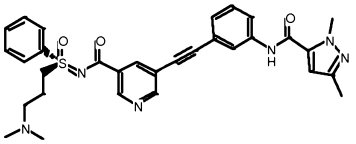
	Table 2-1
Example #	Structure
513	
514	
515	
516	
517	
518	
519	
520	

	Table 2-1
Example #	Structure
521	
522	
523	
524	
525	
526	
527	
528	
529	
530	

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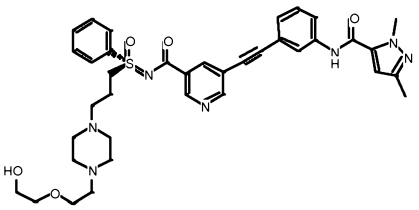
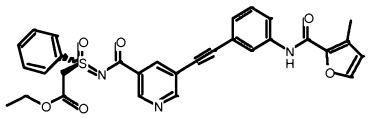
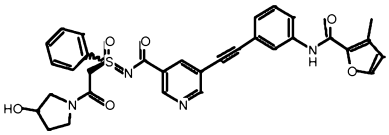
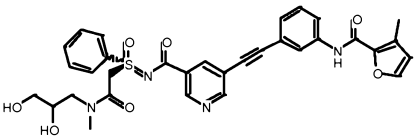
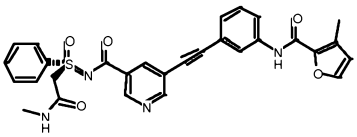
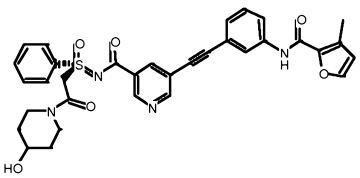
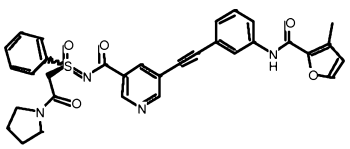
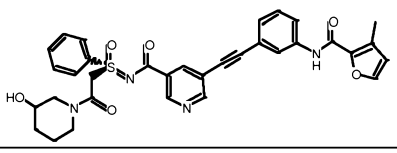
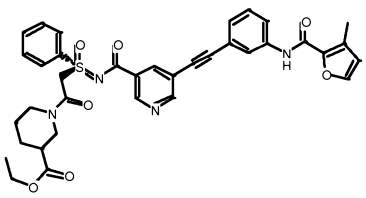
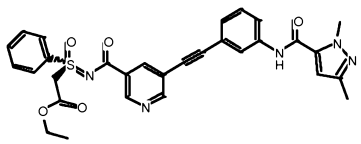
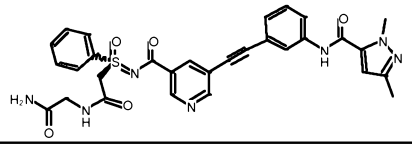
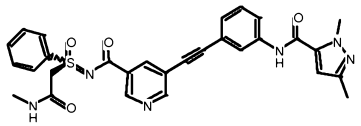
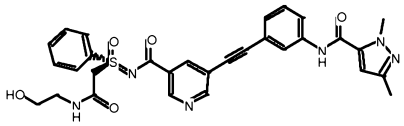
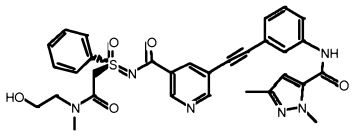
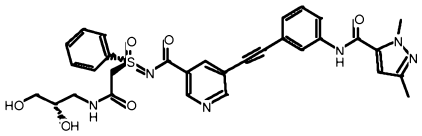
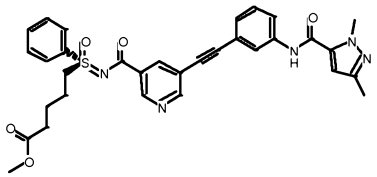
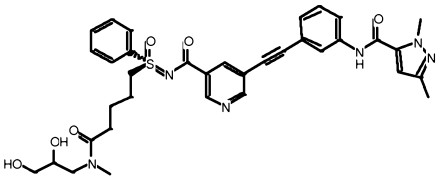
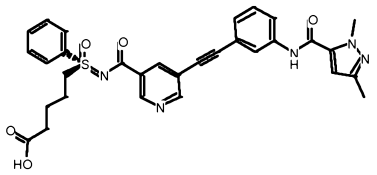
Example #	Structure
531	
532	
533	
534	
535	
536	
537	
538	
539	

Table 2-1	
Example #	Structure
540	
541	
542	
543	
544	
545	
546	
547	
548	

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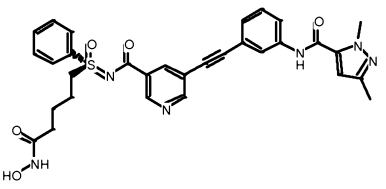
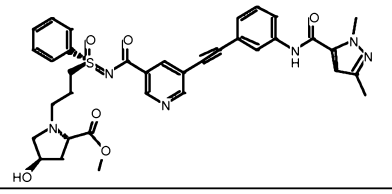
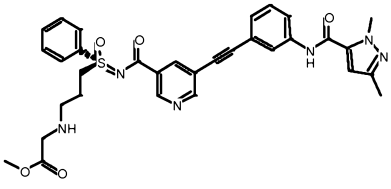
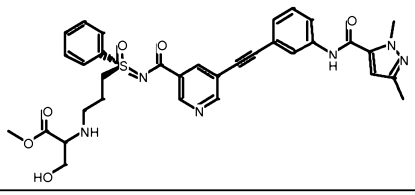
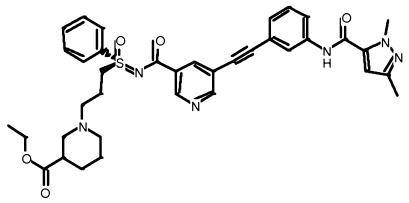
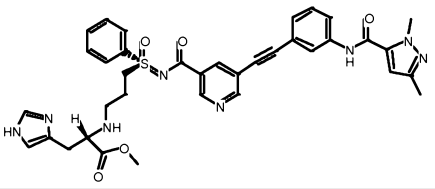
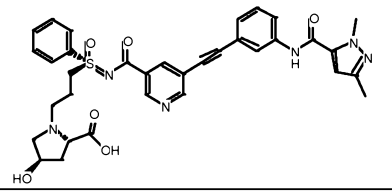
Example #	Structure
549	
550	
551	
552	
553	
554	
555	

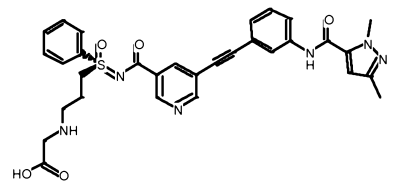
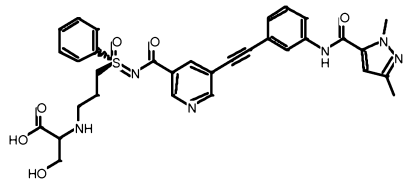
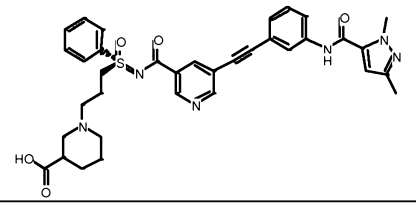
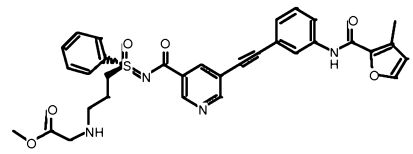
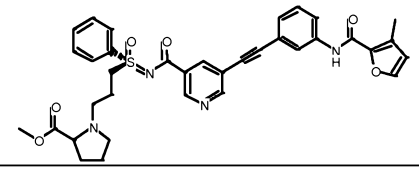
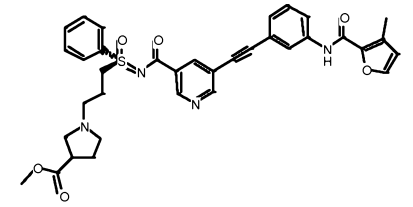
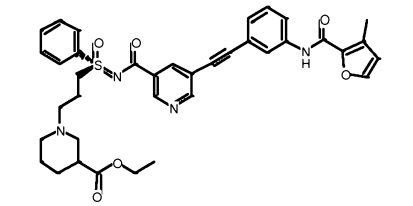
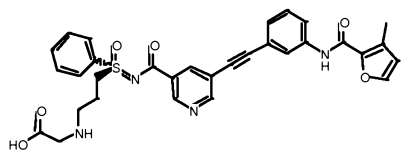
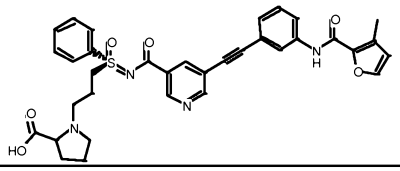
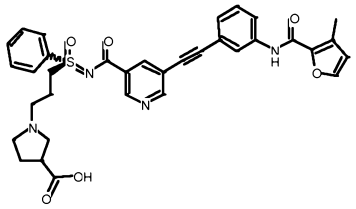
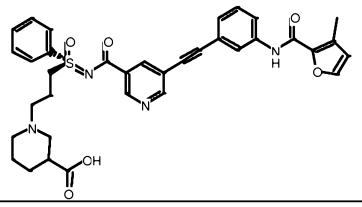
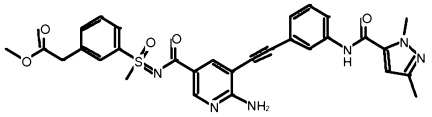
	Table 2-1
Example #	Structure
556	
557	
558	
559	
560	
561	
562	
563	

Table 2-1	
Example #	Structure
564	
565	
566	
567	

The present invention relates to compounds capable of regulating and/or modulating tyrosine kinase signal transduction and more particularly receptor and non-receptor tyrosine kinase signal transduction.

Receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects and responses to the extracellular microenvironment).

It has been shown that tyrosine phosphorylation sites in growth factor receptors function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Several intracellular substrate proteins that associate with receptor tyrosine kinases have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain but serve as adapters and associate with catalytically active molecules. The specificity of the interactions between receptors and SH2 domains of their

substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. These observations suggest that the function of each receptor tyrosine kinase is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

Tyrosine kinase signal transduction results in, among other responses, cell proliferation, differentiation and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis, e.g. macular degeneration).

This invention is therefore directed to compounds which regulate, modulate and/or inhibit tyrosine kinase signal transduction by affecting the enzymatic activity of the RTKs and/or the non-receptor tyrosine kinases and interfering with the signal transduced such proteins. More particularly, the present invention is directed to compounds which regulate, modulate and/or inhibit the RTK and/or non-receptor tyrosine kinase mediated signal transduction pathways as a therapeutic approach to cure many kinds of solid tumors, including but not limited to carcinoma, sarcoma, leukemia, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreas cancers, colon cancers, blood cancers, lung cancers and bone cancers.

Biological data for the compounds of the present invention was generated by use of the following assays.

VEGF Stimulated Ca^{++} Signal in vitro

Automated FLIPR (Fluorometric Imaging Plate Reader) technology was used to screen for inhibitors of VEGF induced increases in intracellular calcium levels in fluorescent dye loaded endothelial cells. HUVEC (human umbilical vein endothelial cells) (Clonetics) were seeded in 96-well fibronectin coated black- walled plates overnight @ 37°C/5%CO2. Cells were loaded with calcium indicator Fluo-4 for 45 minutes at 37°C. Cells were washed 4 times (Original Cell Wash, Labsystems) to remove extracellular dye. For screening, cells were pre-incubated with test agents for 30 minutes, at a single concentration (10 uM) or at concentrations ranging from 0.01 to 10.0

uM followed by VEGF stimulation (5ng/mL). Changes in fluorescence at 516 nm were measured simultaneously in all 96 wells using a cooled CCD camera. Data were generated by determining max-min fluorescence levels for unstimulated, stimulated, and drug treated samples. IC_{50} values for test compounds were calculated from % inhibition of VEGF stimulated responses in the absence of inhibitor.

Protocol for KDR Assay:

The cytoplasmic domain of the human VEGF receptor (VEGFR-2) was expressed as a Histidine-tagged fusion protein following infection of insect cells using an engineered baculovirus. His-VEGFR-2 was purified to homogeneity, as determined by SDS-PAGE, using nickel resin chromatography. Kinase assays were performed in 96 well microtiter plates that were coated overnight with 30µg of poly-Glu-Tyr (4:1) in 10mM Phosphate Buffered Saline (PBS), pH 7.2-7.4. The plates were incubated with 1% BSA and then washed four times with PBS prior to starting the reaction. Reactions were carried out in 120µL reaction volumes containing 3.6µM ATP in kinase buffer (50mM Hepes buffer pH 7.4, 20mM $MgCl_2$, 0.1 mM $MnCl_2$ and 0.2 mM Na_3VO_4). Test compounds were reconstituted in 100% DMSO and added to the reaction to give a final DMSO concentration of 5%. Reactions were initiated by the addition 0.5 ng of purified protein. Following a ten minute incubation at 25^0 C., the reactions were washed four times with PBS containing 0.05% Tween-20. 100µl of a monoclonal anti-phosphotyrosine antibody-peroxidase conjugate was diluted 1:10000 in PBS-Tween-20 and added to the wells for 30 minutes. Following four washes with PBS-Tween-20, 100µl of 0-Phenylenediamine Dihydrochloride in Phosphate-citrate buffer, containing urea hydrogen peroxide, was added to the wells for 7 minutes as a colorimetric substrate for the peroxidase. The reaction was terminated by the addition of 100µl of 2.5N H_2SO_4 to each well and read using a microplate ELISA reader set at 492 nm. IC_{50} values for compound inhibition were calculated directly from graphs of optical density (arbitrary units) versus compound concentration following subtraction of blank values.

The invention is further illustrated by the following non-limiting examples.

The invention is further illustrated by the following non-limiting examples.

Example 1

N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide

Step 1 - Representative procedure for the preparation of sulfoxides

Methyl phenyl sulfoxide

To a stirred suspension of iodoxybenzoic acid (3.7 g, 13.2 mmol, 1.1 eq) in 100:1 $CHCl_3/H_2O$ (25 mL) was added tetraethylammonium bromide (TEAB) (126 mg, 5 mol%), followed by the addition of *p*-tolyl sulfide (1.66 g, 12 mmol) in one portion. The mixture was stirred at room temperature for approximately 30 minutes until consumption of sulfide was observed (TLC, hexanes/EtOAc 1/1). The residual solids were removed by filtration and washed with $CHCl_3$ (40 mL). The combined filtrate was washed successively with saturated aq. $NaHCO_3$ (30 mL), saturated aq. NaCl (30 mL), dried over sodium sulfate, and concentrated to provide the crude product. Purification by silica gel column chromatography (50% hexanes/EtOAc elution) afforded the title compound (1.68 g, yield 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 2.71 (s, 3H), 2.42 (s, 3H); ESI-MS m/z 154.7 $(M+H)^+$.

Step 2 - Representative procedure for the preparation of subtitituted sulfoximines

S-methyl-S-(4-methoxyphenyl)-N-[[2-(trimethylsilyl)ethyl]sulfonyl]sulfoximine

To a solution of 1-methanesulfinyl-4-methoxy-benzene (1.51 g, 8.88 mmol) in dry acetonitrile (35 mL), was added $CuPF_6(CH_3CN)_4$ (165 mg, 0.44 mmol, 0.05 eq.). The mixture was cooled to 0 °C and [N-(2-(trimethylsilyl)ethanesulfonyl)imino]phenyl-iodinate (3.75 g, 9.8 mmol, 1.1 eq.) (prepared by the method described in J. Org. Chem. 1999, 64, 5304-5307) was added. The reaction mixture was allowed to warm to room temperature, stirred for 20 h and the solvent then evaporated. The residue was dissolved in EtOAc (50 mL) and filtered through a pad of silica gel. The ethyl acetate solution was evaporated and the residue was triturated with hexanes to provide the title compound as a white solid (3.0 g, recovery 96%, purity >95% by HPLC). If required, the compound can be further purified by silica gel column chromatography (50% hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 3.41 (s, 3H), 3.16-3.10 (m, 2H), 1.18-1.12 (m, 2H), 0.04 (s, 9H); ESI-MS m/z 349.9 $(M+H)^+$.

Step 3 - Representative procedure for the deprotection of (trimethylsilyl)ethyl]sulfonyl substituted sulfoximines

S-(4-methoxyphenyl)-S-methyl-sulfoximine

A mixture of S-methyl-S-(4-methoxyphenyl)-N-[[2-(trimethylsilyl)ethyl]sulfonyl]-sulfoximine (2.9 g, 8.3 mmol) and 1.0 M of TBAF (12.5 mL, 12.5 mmol, 1.5eq.) was heated in a microwave at 120 °C for 20 minutes. After cooling to room temperature, the solvent was evaporated and the resulting mixture was purified by silica gel column chromatography (elution with 100% EtOAc) to

provide the title compound (1.46 g, yield 96 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 9 Hz, 2H), 3.87 (s, 3H), 3.08 (s, 3H); ESI-MS m/z 186.1 $(M+H)^+$.

Step 4 - Representative procedure for the Sonagashira reaction of ethyl 5-bromonicotinate with acetylenes

5-Phenylethynyl-nicotinic acid ethyl ester

To a solution of ethyl 5-bromonicotinate (1.15 g, 5 mmol) in ethyl acetate (20 mL) under an N_2 atmosphere, was added triethylamine (1.1 mL, 7.5 mmol, 1.5 eq.), phenyl acetylene (0.766 g, 7.5 mmol, 1.5 eq.), dichloro-*bis*(triphenylphosphine)-palladium(II) (176 mg, 0.25 mmol, 0.05 eq.), and copper iodide (10 mg, 0.05 mmol, 0.01 eq). The reaction mixture was heated at 50 °C for 20 h before being cooled to room temperature, filtered through a pad of celite, and solvent evaporated to provide a dark brown oil. Silica gel column chromatography (9/1 - 4/1 hexanes/EtOAc elution) provided the title compound as a pale yellow oil (1.26 g, yield 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, J = 1.8 Hz, 1H), 8.87 (d, J = 2.1 Hz, 1H), 8.39 (dd, J =1.8, 2.1 Hz, 1H), 7.56-7.53 (m, 2H), 7.40-7.30 (m, 3H), 4.42 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2Hz, 3H); ESI-MS m/z 251.9 $(M+H)^+$.

Step 5 - Representative procedure for nicotinic acid ester hydrolysis

5-Phenylethynyl-nicotinic acid

To a solution of 5-phenylethynyl-nicotinic acid ethyl ester (1.17 g, 4.64 mmol) in methanol (10 mL) was added 5 N aqueous sodium hydroxide (2 mL, 10 mmol). The mixture was stirred at room temperature for approximately 20 h, before the reaction mixture was diluted with water (3 mL) and extracted with hexanes/EtOAc (95/5) (10 mL). The aqueous solution was acidified with 1 N HCl to pH 4. The white precipitate that formed was collected by filtration, washed with water (2 mL), and dried under vacuum to provide the title compound as a white solid (987 mg, yield 95%). ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.02 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.4 Hz, 1H), 8.34 (dd, J = 1.8, 2.4 Hz, 1H), 7.63-7.60 (m, 2H), 7.48-7.44 (m, 3H); ESI-MS m/z 223.9 $(M+H)^+$.

Step 6 – Representative procedure for coupling of substituted sulfoximine's to substituted nicotinic acids

N-[1-(4-Methoxy-phenyl)-methylsulfoximine]-5-phenylethynyl-nicotinamide

A solution of 5-phenylethynyl-nicotinic acid (0.1 mmol) and S-(4-methoxyphenyl)-S-methyl-sulfoximine (0.1 mmol), 1-hydroxybenzotriazole (0.15 mmol) in dimethyformamide (1.5 mL) was

treated with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (0.15 mmol) in dimethyformamide (1.5 mL). The reaction mixture was shaken at room temperature for 20 hours and concentrated. The residue was purified by high pressure liquid chromatography (phenomenex Luna C18 5 μm column, gradient elution, acetonitrile/10 mM aqueous ammonium carbonate) and concentrated to give the title compound.

Examples 2-422

Examples 2 through 422 (table 5) were prepared by the methods described in Example 1 by employing appropriate combinations of the aryl sulfides illustrated in table 3 and the acetylenes illustrated in table 4.

Table 3. Aryl Sulfide Reagents

CAS Number	Reagent	CAS Number	Reagent
623-13-2	METHYL P-TOLYL SULFIDE	68121-46-0	3,5-DICHLOROTHIOANISOLE
1879-16-9	1-METHOXY-4-(METHYLTHIO)BENZENE		3-METHYLTHIOANISOLE
701-57-5	4-NITROTHIOANISOLE	2388-74-1	3-METHOXY THIOANISOLE
123-09-1	4-CHLOROTHIOANISOLE		3,4-DIMETHYLTHIOANISOLE
10352-44-0	4-ACETAMIDOTHIOANISOLE		3,5-DIMETHYLTHIOANISOLE
2524-78-9	3-ACETAMIDOTHIOANISOLE	100-68-5	THIOANISOLE
4867-37-2	3-CHLOROTHIOANISOLE		3,4-DIMETHOXYTHIOANISOLE
2524-76-7	3-NITRO THIOANISOLE		

Table 4	Acetylene Reagents		
CAS #	Reagent	CAS #	Reagent
126716-66-3	PHENYLACETYLENE	15727-65-8	1-ETHYNYLNAPHTHALENE
766-97-2	4-ETHYNYLTOLUENE	121697-66-3	3-ETHYNYLPYRIDINE
627-41-8	METHYL PROPARGYL ETHER	927-74-2	3-BUTYN-1-OL
917-92-0	3,3-DIMETHYL-1-BUTYNE	2561-17-3	3-FLUOROPHENYLACETYLENE
937-31-5	4-NITROPHENYLACETYLENE	2510-22-7	4-ETHYNYLPYRIDINE
351002-93-2	4-ETHYNYL-1-FLUORO-2-METHYLBENZENE	766-47-2	2-ETHYNYLTOLUENE
1945-84-2	2-ETHYNYLPYRIDINE	766-81-4	1-BROMO-3-ETHYNYL-BENZENE
10401-11-3	3-HYDROXYPHENYLACETYLENE	766-83-6	3'-CHLOROPHENYL ACETYLENE

Table 4	Acetylene Reagents		
CAS #	Reagent	CAS #	Reagent
129113-00-4	2-ETHYNYL-6-METHOXYNAPHTHALENE	171290-52-1	1-ETHYNYL-3,5-DIMETHOXYBENZENE
768-70-7	1-ETHYNYL-3-METHOXYBENZENE	4302-52-7	3',4'-DIMETHOXYPHENYL ACETYLENE
768-60-5	1-ETH-1-YNYL-4-METHOXYBENZENE	767-91-9	1-ETHYNYL-2-METHOXYBENZENE
766-96-1	1-BROMO-4-ETHYNYLBENZENE	41876-66-8	4'-N-PIPERIDINOPHENYL ACETYLENE
	4,5-DICHLORO-1-PROP-2-YNYLIMIDAZOLE	151361-87-4	1-ETHYNYL-3,5-DIFLUORO-BENZENE
873-73-4	1-CHLORO-4-ETHYNYLBENZENE		5-ETHYNYL-1-METHYL-1H-IMIDAZOLE
873-31-4	1-CHLORO-2-ETHYNYLBENZENE	74331-69-4	1-ETHYNYL-4-METHOXY-2-METHYLBENZENE
766-82-5	M-TOLYLACETYLENE	74-99-7	PROPYNE
705-31-7	4'-TRIFLUOROMETHYLPHENYL ACETYLENE	922-67-8	METHYL PROPIOLATE
766-46-1	1-BROMO-2-ETHYNYLBENZENE	930-51-8	CYCLOPENTYLACETYLENE
302912-34-1	1-ETHYNYL-2,4-DIFLUORO-BENZENE		1-ETHYNYL-2-(TRIFLUOROMETHOXY)BENZENE

Table 5	
Example	Example Name
Example 2	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 3	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 4	5-(3,3-dimethylbut-1-yn-1-yl)-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 5	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 6	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 7	5-[(3-hydroxyphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 8	5-[(6-methoxy-2-naphthyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 9	5-[(3-methoxyphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 10	5-[(4-methoxyphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 11	5-[(4-bromophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 12	5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 13	5-[(4-chlorophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 14	5-[(2-chlorophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 15	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 16	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 17	5-[(2,4-difluorophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 18	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 19	5-[(3-fluorophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 20	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 21	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 22	5-[(3-bromophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 23	5-[(3-chlorophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 24	5-[(3,5-dimethoxyphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 25	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 26	5-[(2-methoxyphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 27	N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-piperidin-1-ylphenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 28	5-[(3,5-difluorophenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 29	5-[(4-methoxy-2-methylphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 30	5-[(4-fluoro-3-methylphenyl)ethynyl]-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 31	5-(4-hydroxybut-1-yn-1-yl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 32	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 33	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 34	5-(3-methoxyprop-1-yn-1-yl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 35	5-(3,3-dimethylbut-1-yn-1-yl)-N-[methyl(oxo)phenyl-λ^6sulfanylidene]nicotinamide
Example 36	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 37	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 38	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 39	5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 40	5-[(6-methoxy-2-naphthyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 41	5-[(3-methoxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 42	5-[(4-methoxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 43	5-[(4-bromophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 44	5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 45	5-[(4-chlorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 46	5-[(2-chlorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 47	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 48	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 49	5-[(2-bromophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 50	5-[(2,4-difluorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 51	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 52	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 53	5-[(3-fluorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 54	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 55	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 56	5-[(3-bromophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 57	5-[(3-chlorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 58	5-[(3,5-dimethoxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 59	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 60	5-[(2-methoxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 61	N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(4-piperidin-1-ylphenyl)ethynyl]nicotinamide
Example 62	5-[(3,5-difluorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 63	5-[(4-methoxy-2-methylphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 64	5-[(4-fluoro-3-methylphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide
Example 65	5-(4-hydroxybut-1-yn-1-yl)-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 66	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 67	5-(3-methoxyprop-1-yn-1-yl)-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 68	5-(3,3-dimethylbut-1-yn-1-yl)-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 69	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 70	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 71	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 72	5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 73	5-[(6-methoxy-2-naphthyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 74	5-[(3-methoxyphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 75	5-[(4-methoxyphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 76	5-[(4-bromophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 77	5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 78	5-[(4-chlorophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 79	5-[(2-chlorophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 80	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 81	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide

Table 5	
Example	Example Name
Example 82	5-[(2-bromophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 83	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 84	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 85	5-[(3-fluorophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 86	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 87	N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 88	5-[(3-bromophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 89	5-[(3-chlorophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 90	5-[(3,5-dimethoxyphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 91	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 92	5-[(2-methoxyphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 93	5-[(3,5-difluorophenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 94	5-[(1-methyl-1H-imidazol-5-yl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 95	5-[(4-methoxy-2-methylphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 96	5-[(4-fluoro-3-methylphenyl)ethynyl]-N-[methyl(4-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 97	5-(4-hydroxybut-1-yn-1-yl)-N-[(4-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 98	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 99	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide

Table 5	
Example	Example Name
Example 100	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 101	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 102	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3,3-dimethylbut-1-yn-1-yl)nicotinamide
Example 103	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 104	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 105	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 106	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide
Example 107	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 108	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 109	5-[(4-bromophenyl)ethynyl]-N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 110	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]nicotinamide
Example 111	5-[(4-chlorophenyl)ethynyl]-N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 112	5-[(2-bromophenyl)ethynyl]-N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 113	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2,4-difluorophenyl)ethynyl]nicotinamide
Example 114	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 115	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 116	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 117	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 118	5-[(3-bromophenyl)ethynyl]-N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 119	5-[(3-chlorophenyl)ethynyl]-N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 120	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,5-dimethoxyphenyl)ethynyl]nicotinamide
Example 121	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,4-dimethoxyphenyl)ethynyl]nicotinamide
Example 122	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methoxyphenyl)ethynyl]nicotinamide
Example 123	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,5-difluorophenyl)ethynyl]nicotinamide
Example 124	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 125	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide
Example 126	N-[(4-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide
Example 127	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 128	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(phenylethynyl)nicotinamide
Example 129	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 130	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 131	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(3,3-dimethylbut-1-yn-1-yl)nicotinamide
Example 132	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 133	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-prop-1-yn-1-ylnicotinamide
Example 134	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(pyridin-2-ylethynyl)nicotinamide
Example 135	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(6-methoxy-2-naphthyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 136	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 137	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 138	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-bromophenyl)ethynyl]nicotinamide
Example 139	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-chlorophenyl)ethynyl]nicotinamide
Example 140	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-chlorophenyl)ethynyl]nicotinamide
Example 141	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 142	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 143	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-bromophenyl)ethynyl]nicotinamide
Example 144	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2,4-difluorophenyl)ethynyl]nicotinamide
Example 145	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(1-naphthylethynyl)nicotinamide
Example 146	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(pyridin-3-ylethynyl)nicotinamide
Example 147	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 148	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(pyridin-4-ylethynyl)nicotinamide
Example 149	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 150	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-bromophenyl)ethynyl]nicotinamide
Example 151	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-chlorophenyl)ethynyl]nicotinamide
Example 152	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3,5-dimethoxyphenyl)ethynyl]nicotinamide
Example 153	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-methoxyphenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 154	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3,5-difluorophenyl)ethynyl]nicotinamide
Example 155	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 156	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide
Example 157	N-{[4-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide
Example 158	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 159	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(phenylethynyl)nicotinamide
Example 160	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 161	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 162	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(3,3-dimethylbut-1-yn-1-yl)nicotinamide
Example 163	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 164	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-prop-1-yn-1-ylnicotinamide
Example 165	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(pyridin-2-ylethynyl)nicotinamide
Example 166	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-hydroxyphenyl)ethynyl]nicotinamide
Example 167	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(6-methoxy-2-naphthyl)ethynyl]nicotinamide
Example 168	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 169	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 170	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-bromophenyl)ethynyl]nicotinamide
Example 171	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]nicotinamide

Table 5	
Example	Example Name
Example 172	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-chlorophenyl)ethynyl]nicotinamide
Example 173	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-chlorophenyl)ethynyl]nicotinamide
Example 174	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 175	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 176	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-bromophenyl)ethynyl]nicotinamide
Example 177	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2,4-difluorophenyl)ethynyl]nicotinamide
Example 178	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(1-naphthylethynyl)nicotinamide
Example 179	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(pyridin-3-ylethynyl)nicotinamide
Example 180	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 181	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-(pyridin-4-ylethynyl)nicotinamide
Example 182	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 183	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-bromophenyl)ethynyl]nicotinamide
Example 184	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3-chlorophenyl)ethynyl]nicotinamide
Example 185	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3,5-dimethoxyphenyl)ethynyl]nicotinamide
Example 186	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3,4-dimethoxyphenyl)ethynyl]nicotinamide
Example 187	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(2-methoxyphenyl)ethynyl]nicotinamide
Example 188	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-piperidin-1-ylphenyl)ethynyl]nicotinamide
Example 189	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(3,5-difluorophenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 190	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 191	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide
Example 192	N-{[3-(acetylamino)phenyl](methyl)oxo-λ^6-sulfanylidene}-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide
Example 193	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 194	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 195	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 196	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 197	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3,3-dimethylbut-1-yn-1-yl)nicotinamide
Example 198	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 199	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 200	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 201	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide
Example 202	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(6-methoxy-2-naphthyl)ethynyl]nicotinamide
Example 203	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 204	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 205	5-[(4-bromophenyl)ethynyl]-N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 206	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]nicotinamide
Example 207	5-[(4-chlorophenyl)ethynyl]-N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 208	5-[(2-chlorophenyl)ethynyl]-N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 209	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 210	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 211	5-[(2-bromophenyl)ethynyl]-N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 212	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2,4-difluorophenyl)ethynyl]nicotinamide
Example 213	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 214	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 215	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 216	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 217	5-[(3-bromophenyl)ethynyl]-N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 218	5-[(3-chlorophenyl)ethynyl]-N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 219	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,5-dimethoxyphenyl)ethynyl]nicotinamide
Example 220	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,4-dimethoxyphenyl)ethynyl]nicotinamide
Example 221	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methoxyphenyl)ethynyl]nicotinamide
Example 222	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-piperidin-1-ylphenyl)ethynyl]nicotinamide
Example 223	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,5-difluorophenyl)ethynyl]nicotinamide
Example 224	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 225	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 226	N-[(3-chlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide
Example 227	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 228	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 229	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 230	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 231	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3,3-dimethylbut-1-yn-1-yl)nicotinamide
Example 232	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 233	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 234	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide
Example 235	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(6-methoxy-2-naphthyl)ethynyl]nicotinamide
Example 236	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 237	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 238	5-[(4-bromophenyl)ethynyl]-N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 239	5-[(4-chlorophenyl)ethynyl]-N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 240	5-[(2-chlorophenyl)ethynyl]-N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 241	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 242	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 243	5-[(2-bromophenyl)ethynyl]-N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 244	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2,4-difluorophenyl)ethynyl]nicotinamide
Example 245	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 246	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 247	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 248	5-[(3-bromophenyl)ethynyl]-N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 249	5-[(3-chlorophenyl)ethynyl]-N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 250	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,5-dimethoxyphenyl)ethynyl]nicotinamide
Example 251	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,4-dimethoxyphenyl)ethynyl]nicotinamide
Example 252	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methoxyphenyl)ethynyl]nicotinamide
Example 253	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3,5-difluorophenyl)ethynyl]nicotinamide
Example 254	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 255	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide
Example 256	N-[(3,5-dichlorophenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide
Example 257	5-(4-hydroxybut-1-yn-1-yl)-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 258	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 259	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 260	5-(3-methoxyprop-1-yn-1-yl)-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 261	5-(3,3-dimethylbut-1-yn-1-yl)-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 262	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 263	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 264	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 265	5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 266	5-[(6-methoxy-2-naphthyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 267	5-[(3-methoxyphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 268	5-[(4-methoxyphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 269	5-[(4-bromophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 270	5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 271	5-[(4-chlorophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 272	5-[(2-chlorophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 273	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 274	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 275	5-[(2-bromophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 276	5-[(2,4-difluorophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 277	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 278	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 279	5-[(3-fluorophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 280	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 281	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 282	5-[(3-bromophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 283	5-[(3-chlorophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 284	5-[(3,5-dimethoxyphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 285	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 286	5-[(2-methoxyphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 287	N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]-5-[(4-piperidin-1-ylphenyl)ethynyl]nicotinamide
Example 288	5-[(3,5-difluorophenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 289	5-[(1-methyl-1H-imidazol-5-yl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 290	5-[(4-methoxy-2-methylphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 291	5-[(4-fluoro-3-methylphenyl)ethynyl]-N-[methyl(3-methylphenyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 292	5-(4-hydroxybut-1-yn-1-yl)-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 293	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 294	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 295	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 296	5-(3,3-dimethylbut-1-yn-1-yl)-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 297	N-[(3-methoxyphenyl)(methyl)oxo-λ6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide

Table 5	
Example	Example Name
Example 298	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 299	5-[(3-hydroxyphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 300	5-[(6-methoxy-2-naphthyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 301	5-[(3-methoxyphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 302	5-[(4-methoxyphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 303	5-[(4-bromophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 304	5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 305	5-[(4-chlorophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 306	5-[(2-chlorophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 307	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 308	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 309	5-[(2-bromophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 310	5-[(2,4-difluorophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 311	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 312	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 313	5-[(3-fluorophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 314	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 315	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 316	5-[(3-bromophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 317	5-[(3-chlorophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 318	5-[(3,5-dimethoxyphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 319	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 320	5-[(2-methoxyphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 321	5-[(3,5-difluorophenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 322	N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 323	5-[(4-methoxy-2-methylphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 324	5-[(4-fluoro-3-methylphenyl)ethynyl]-N-[(3-methoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 325	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 326	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 327	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 328	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 329	5-(3,3-dimethylbut-1-yn-1-yl)-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 330	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 331	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 332	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 333	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 334	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(6-methoxy-2-naphthyl)ethynyl]nicotinamide
Example 335	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 336	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 337	5-[(4-bromophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 338	5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 339	5-[(4-chlorophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 340	5-[(2-chlorophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 341	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 342	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 343	5-[(2-bromophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 344	5-[(2,4-difluorophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 345	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 346	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 347	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 348	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 349	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 350	5-[(3-bromophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 351	5-[(3-chlorophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 352	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 353	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methoxyphenyl)ethynyl]nicotinamide
Example 354	5-[(3,5-difluorophenyl)ethynyl]-N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 355	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 356	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide
Example 357	N-[(3,4-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide
Example 358	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 359	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 360	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 361	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 362	5-(3,3-dimethylbut-1-yn-1-yl)-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 363	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 364	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 365	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 366	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(6-methoxy-2-naphthyl)ethynyl]nicotinamide
Example 367	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 368	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 369	5-[(4-bromophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 370	5-[3-(4,5-dichloro-1H-imidazol-1-yl)prop-1-yn-1-yl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 371	5-[(4-chlorophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 372	5-[(2-chlorophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 373	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 374	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 375	5-[(2-bromophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 376	5-[(2,4-difluorophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 377	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 378	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 379	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 380	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 381	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 382	5-[(3-bromophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 383	5-[(3-chlorophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 384	5-[(3,5-dimethoxyphenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 385	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 386	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methoxyphenyl)ethynyl]nicotinamide
Example 387	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-piperidin-1-ylphenyl)ethynyl]nicotinamide

Table 5	
Example	Example Name
Example 388	5-[(3,5-difluorophenyl)ethynyl]-N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 389	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(1-methyl-1H-imidazol-5-yl)ethynyl]nicotinamide
Example 390	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide
Example 391	N-[(3,5-dimethylphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide
Example 392	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(4-hydroxybut-1-yn-1-yl)nicotinamide
Example 393	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide
Example 394	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methylphenyl)ethynyl]nicotinamide
Example 395	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3-methoxyprop-1-yn-1-yl)nicotinamide
Example 396	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(3,3-dimethylbut-1-yn-1-yl)nicotinamide
Example 397	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-nitrophenyl)ethynyl]nicotinamide
Example 398	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-prop-1-yn-1-ylnicotinamide
Example 399	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-2-ylethynyl)nicotinamide
Example 400	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide
Example 401	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(6-methoxy-2-naphthyl)ethynyl]nicotinamide
Example 402	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methoxyphenyl)ethynyl]nicotinamide
Example 403	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxyphenyl)ethynyl]nicotinamide
Example 404	5-[(4-bromophenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 405	5-[(4-chlorophenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide

Table 5	
Example	Example Name
Example 406	5-[(2-chlorophenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 407	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(3-methylphenyl)ethynyl]nicotinamide
Example 408	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-{[4-(trifluoromethyl)phenyl]ethynyl}nicotinamide
Example 409	5-[(2-bromophenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 410	5-[(2,4-difluorophenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 411	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(1-naphthylethynyl)nicotinamide
Example 412	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-3-ylethynyl)nicotinamide
Example 413	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ6-sulfanylidene]-5-[(3-fluorophenyl)ethynyl]nicotinamide
Example 414	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-(pyridin-4-ylethynyl)nicotinamide
Example 415	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(2-methylphenyl)ethynyl]nicotinamide
Example 416	5-[(3-bromophenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 417	5-[(3-chlorophenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 418	5-[(3,5-dimethoxyphenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 419	5-[(3,4-dimethoxyphenyl)ethynyl]-N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]nicotinamide
Example 420	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-piperidin-1-ylphenyl)ethynyl]nicotinamide
Example 421	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-methoxy-2-methylphenyl)ethynyl]nicotinamide
Example 422	N-[(3,4-dimethoxyphenyl)(methyl)oxo-λ^6-sulfanylidene]-5-[(4-fluoro-3-methylphenyl)ethynyl]nicotinamide

Example 423

(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide

To a slurry of 5-(2-phenyleth-1-ynyl)nicotinic acid (339 mg, 1.5mmol) in 6.0 mL THF at room temperature was added 1, 1'-carbonyldiimidazole (271 mg, 1.7 mmol). After stirring 1.25 hour, a solution of (S)-(+)-S-methyl-S-phenylsulfoximine (260 mg, 1.7 mmol) in 1.5mL THF was added and the mixture heated at 50 °C for 22 hours. Then an additional 50 mg (0.32 mmol) (S)-(+)-S-methyl-S-phenylsulfoximine was added and heating continued at 60 °C for 3.5 hours. The reaction was quenched with $NaHCO_3$ solution and then extracted into EtOAc. The EtOAc layer was washed with $NaHCO_3$ solution, H_2O, brine, dried with anhydrous Na_2SO_4 and concentrated. The yellow oil obtained was chromatographed eluting with hexane/EtOAc to give N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide as a white foam (303mg, 55%).

Example 424

(R)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(phenylethynyl)nicotinamide

In a manner similar to that described in Example 423, 5-(2-phenyleth-1-ynyl)nicotinic acid and (R)-(-)-S-methyl-S-phenylsulfoximine were reacted to give the title compound as a white foam (54mg, 25%).

Example 425

5-[(2-fluorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

Step 1

(S)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a solution of 5-bromonicotinic acid (1.21g, 6.0 mmol), N, N-diisopropylethylamine (2.1 mL, 12.0 mmol), and (S)-(+)-S-methyl-S-phenylsulfoximine (931 mg, 6.0 mmol) in DMF (11.0mL) cooled to 0 °C was treated with 1-benzotriazolyloxytripyrrolidinylphosphonium hexafluorophosphate (PyBOP) (3.43 g, 6.6 mmol). The reaction mixture was stirred 10 minutes, the ice bath removed, and the reaction continued at room temperature for 2 hours. The mixture was taken up in EtOAc and washed with H_2O, Na_2CO_3 solution, brine, AcOH solution, H_2O, Na_2CO_3 solution, brine, dried with anhydrous Na_2SO_4 and concentrated. The residual brown oil was purified by chromatography (silica gel, hexane/EtOAc). The product containing eluent was

concentrated and then triturated with hexane to give the title compound as an off-white solid (1.88 g, 92%).

Step 2

(S)-5-[(2-fluorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

A mixture of (S)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (105 mg, 0.31mmol) and 1-ethynyl-2-fluorobenzene (75 mg, 0.62 mmol) in 2.0 mL EtOAc was degassed with argon at 70 °C. Upon cooling to room temperature the reaction mixture was treated with triethylamine (0.16 mL, 1.1 mmol), dichlorobis(triphenylphosphine)palladium(II) (22 mg, 0.031 mmol) and copper(I)iodide (2 mg, 0.012 mmol). The reaction was heated at 70 °C for 20 hours then partitioned between EtOAc and H_2O. The EtOAc layer was washed with acetic acid solution, saturated $NaHCO_3$, brine, dried with anhydrous Na_2SO_4 and concentrated. The dark film obtained was purified by chromatography (silica gel, hexane/EtOAc) to give the title compound as a tan foam (110 mg, 94%).

Example 426

(S)-5-[(4-chlorophenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 425 a mixture of (S)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 4-chloro-1-ethynylbenzene were reacted to give the title compound as white needles (60 mg, 49%).

Example 427

(S)-5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 425, a mixture of (S)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 3-hydroxy-1-ethynylbenzene were reacted to give the title compound as an off-white solid (19 mg, 17%).

Example 428

(S)-5-[(4-phenoxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 425 a mixture of (S)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 1-ethynyl-4-phenoxybenzene were reacted to give the title compound as an off-white solid (95 mg, 68%).

Example 429

(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide

To a degassed solution of 10.0 mL DMF at room temperature was added (S)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (1.02 g, 3.0 mmol), triethylamine (1.3 mL, 9.0 mmol), trimethylsilylacetylene (0.83 mL, 6.0mmol), and dichlorobis(triphenylphosphine)palladium(II) (211 mg, 0.3 mmol). After 15 minutes added copper(I)iodide (29 mg, 0.15 mmol) and continued reaction for 4 hours. The reaction was then partitioned between EtOAc and H_2O. The EtOAc layer was washed with saturated $NaHCO_3$, brine, dried with anhydrous Na_2SO_4 and rotary evaporated to 20ml volume. The solution was placed overnight in the refrigerator and the resulting solid filtered and rinsed with 40% EtOAc/hexane to give The title compound (674 mg) as a tan solid. The filtrate was evaporated and purified by chromatography (silica gel, eluting with hexane/EtOAc) to give an additional 301 mg of the title compound. The product lots were combined and purified by chromatography (silica gel, eluting with hexane/EtOAc) to give the title compound as a tan solid (959 mg, 90%).

Example 430

(S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

A solution of (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (806 mg, 2.3 mmol) in 70 mL THF/methanol (1:1 ratio) at room temperature was degassed with argon. The solution was cooled to 0 °C and K_2CO_3 (937 mg, 6.8 mmol) added. After 5 minutes the solution was decanted from the solids and partitioned between EtOAc and H_2O. The EtOAc layer was washed with brine, dried with anhydrous Na_2SO_4 and concentrated. The brown oil was purified by chromatography (silica gel, $CHCl_3$/EtOAc) to the title compound as a thick pale orange oil (630 mg, 98 %).

Example 431

(S)-5-[(4-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a degassed solution of 1.3 mL DMF at room temperature containing (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (63 mg, 0.22 mmol), 4-iodophenol (121 mg,

0.55 mmol), and triethylamine (0.09 mL, 0.66 mmol) was added dichlorobis(triphenylphosphine)palladium(II) (15 mg, 0.022 mmol) and copper(I)iodide (4 mg, 0.022 mmol). After proceeding for 1 hour the reaction was partitioned between EtOAc and H_2O. The mixture was filtered to remove an insoluble brown precipitate and the EtOAc layer was washed with H_2O, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The brown film was chromatographed eluting with $CHCl_3$/EtOAc to give a yellow solid which was recrystallized from $CHCl_3$/hexane to give the title compound as an off-white solid (38 mg, 45%).

Example 432

(S)-5-[(2-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 431 a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 1-ethynyl-2-hydroxybenzene were reacted to give the title compound as a white solid (6 mg, 7%).

Example 433

Step 1

(R)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a solution of 5-bromonicotinic acid (303 mg, 1.5mmol), N, N-diisopropylethylamine (0.523 mL, 3.0mmol), and (R)-(-)-S-methyl-S-phenylsulfoximine (233 mg, 1.5 mmol) in DMF (3.0 mL) cooled to 0 °C was added 1-benzotriazolyloxytripyrrolidinylphosphonium hexafluorophosphate (PyBOP) (859 mg, 1.65 mmol). The solution was stirred 10 minutes, the ice bath removed, and the reaction continued at room temperature for 2.5 hours. The mixture was taken up in EtOAc and washed with H_2O, Na_2CO_3 solution, brine, AcOH solution, H_2O, Na_2CO_3 solution, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The brown oil was chromatographed eluting with hexane/EtOAc to give the title compound as a yellow solid (478 mg, 94%).

Step 2

(R)-5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a degassed solution of 2.0 mL DMF at room temperature containing (R)-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (105 mg, 0.31mmol), 3-hydroxyphenylacetylene (73 mg, 0.62 mmol) and triethylamine (0.13 mL, 0.93mmol) was added

dichlorobis(triphenylphosphine)palladium(II) (22 mg, 0.031 mmol) and copper(I)iodide (3 mg, 0.016 mmol). The reaction was stirred at room temperature for 1.5 hours. Additional 3-hydroxyphenylacetylene was added (30 mg, 0.25 mmol) and the reaction was stirred at room temperature for an additional 3.5 hours. After proceeding for 5 hours the reaction was partitioned between EtOAc and H_2O and the EtOAc layer washed with H_2O, brine, dried with anhydrous Na_2SO_4 and concentrated. The residual dark oil was purified by chromatography (silica gel, $CHCl_3$/EtOAc) and the product containing fractions were concentrated. The resulting solid was triturated with EtOAc/hexane to give the title compound as an off-white solid (37 mg, 32 %).

Example 434

(S)-3-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}benzoic acid

A mixture of (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (54 mg, 0.15 mmol), 3-iodobenzoic acid (56 mg, 0.23 mmol), dichlorobis(triphenylphosphine)palladium(II) (11 mg, 0.02 mmol), triphenylphosphine (1.0 mg, .004 mmol) and triethylamine (0.073 mL, 0.53mmol) in 1.5 mL DMF at room temperature was degassed using vacuum and a H_2/N_2 (1:1) mixture and then copper(I)iodide (2 mg, 0.01 mmol) added. The reaction was heated to 60 °C then tetrabutylammonium fluoride (1.0 M in THF, 0.15 ml) added over 3.5 minutes. After 25 minutes the reaction was partitioned between EtOAc and dilute AcOH. The EtOAc layer was collected and washed with H_2O, brine, dried with anhydrous Na_2SO_4 and concentrated to a yellow solid. The solid was triturated with EtOAc at room temperature to give the title compound as a yellow solid (45 mg, 74%).

Example 435

(S)-5-[(4-acetylphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 434 a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 4-iodoacetophenone were reacted to give the title compound as a light yellow foam (52 mg, 86%).

Example 436

(S)-5-[(4-hydroxy-3-methylphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 434, a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 4-iodo-2-methylphenol were reacted to give the title compound as a light yellow solid (43 mg, 73%).

Example 437

(S)-2-hydroxy-5-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}benzoic acid

In a manner similar to that describe in Example 434, a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 5-iodosalicyclic acid were reacted to give the title compound as a light tan solid (28 mg, 45%).

Example 438

(S)-4-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}benzoic acid

In a manner similar to that describe in Example 434, a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 4-iodobenzoic acid were reacted to give the title compound as a light yellow solid (30 mg, 49%).

Example 439

(S)-5-(1H-imidazol-5-ylethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 434, a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 5-iodo-1H-imidazole were reacted to give the title compound as a white foam (24 mg, 46%).

Example 440

(S)-5-(1H-imidazol-2-ylethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 434, a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ6-sulfanylidene]nicotinamide and 2-iodo-1H-imidazole were reacted to give the title compound as a white solid (15 mg, 29%).

Example 441

(S)-5-[(2-methyl-1H-imidazol-5-yl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 434, a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 5-iodo-2-methyl-1H-imidazole were reacted to give the title compound as an off-white foam (28 mg, 51%).

Example 442

(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-(1H-pyrazol-4-ylethynyl)nicotinamide

In a manner similar to that describe in Example 431 a mixture of (S)-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 4-iodopyrazole were reacted to give the title compound as a white film (15 mg, 17%).

Example 443

(S)-5-[(6-hydroxypyridin-3-yl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

A solution of (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]-nicotinamide (150 mg, 0.42 mmol) and 2-hydroxy-5-iodopyridine (105.4 mg, 0.46 mmol) in DMF (2.1 mL) was degassed (vacuum and argon). The resulting solution was treated tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.021 mmol), triethylamine (0.08 mL, 0.55 mmol), and CuI (8 mg, 0.042 mmol). The reaction mixture was then heated to 85 °C and tetrabutylammonium fluoride (1.0 M solution in THF, 0.46 mL, 0.46 mmol) was added dropwise over 10 min. The reaction was allowed to be stirred at 85 °C for 2 hours. The reaction mixture was partitioned between EtOAc and H_2O. The organic extracts and associated solid were collected and concentrated. The residue was purified by chromatography (silica gel, gradient elution MeOH-$CHCl_3$: 1:100-1:4). The product containing fractions were collected, concentrated, and the brown solid residue was triturated with a combination of MeOH and EtOAc. The resulting mixture was filtered and the filtrate allowed to stand at room temperature. The solid which precipitated from solution was collected and dried to give the title compound as a white solid (11 mg).

Example 444

(S)-5-(1H-indol-6-ylethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that described in Example 443, (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (150 mg, 0.42 mmol) and 6-bromoindole (90.7 mg, 0.46 mmol) were reacted to give the title compound (30 mg).

Example 445
(S)-5-[(2,3-dioxo-2,3-dihydro-1H-indol-5-yl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that described in Example 443, (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (150 mg, 0.42 mmol) and 5-bromoisatin (116 mg, 0.46 mmol) were reacted to give the title compound as a reddish oil (40 mg).

Example 446
(S)-5-[(6-chloropyridin-3-yl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that described in Example 443, (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (250 mg, 0.70 mmol) and 2-chloro-5-iodopyridine (173 mg, 0.70 mmol) were reacted to give the title compound as white solid (250 mg).

Example 447
(S)-5-[(6-aminopyridin-3-yl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that described in Example 443, (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (100 mg, 0.28 mmol) and 2-amino-5-iodopyridine (69.3 mg, 0.31 mmol) were reacted to give the title compound as light yellow solid (89 mg).

Example 448
(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)ethynyl]nicotinamide

In a manner similar to that described in Example 443, (S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (150 mg, 0.42 mmol) and 5-bromo-2-benzoxazolinone (102 mg, 0.46 mmol) were reacted to give the title compound as light yellow solid (71 mg).

Example 449
(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({4-[(2-thienylcarbonyl)amino]phenyl}ethynyl)nicotinamide.

In a 4 mL vial, thiophene-2-carboxylic acid (4-ethynyl-phenyl)-amide (0.100 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were added and dissolved into EtOAc (2 mL). The mixture was then degassed for ~20 min after which NEt_3 (0.141 mL, 1.035 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (20.7 mg, 0.0295 mmol) and CuI (2.8 mg, 0.148 mmol). The reaction mixture was allowed to stir at 50 °C for 3 hours after which the reaction mixture was extracted twice with EtOAc (~5 mL) and of water (~5 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4(s) and then concentrated *in vacuo*. The crude residue was then purified by chromatography (silica gel, gradient elution, 25% EtOAc/hexanes to 100% EtOAc/hexanes). The product containing fractions were concentrated to give the title compound as a tan solid (87 mg, 0.18 mmol, 61%).

Example 450

(S)-5-{[3-(acetylamino)phenyl]ethynyl}-N-[methyl(oxo)phenyl-λ6-sulfanylidene]nicotinamide.

In a manner similar to that described in Example 449, N-(3-ethynyl-phenyl)-acetamide (0.0469 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were reacted to give the title compound as a solid (83 mg, 0.20 mmol, 67%).

Example 451

(S)-5-({4-[(2,6-difluorobenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that described in Example 449, N-(4-ethynyl-phenyl)-2,6-difluoro-benzamide (0.114 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl- λ^6-sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were reacted to give the title compound as a solid (113 mg, 74%)

Example 452

(S)-5-({4-[(4-fluorobenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide.

In a manner similar to that described in Example 449, N-(4-ethynyl-phenyl)-4-fluoro-benzamide (0.106 g, 0.443 mmol) and 5-bromo-*N*-[methyl(oxo)phenyl-λ^6-

sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were reacted to give the title compound as a solid (106 mg, 72%).

Example 453

(S)-5-({4-[(4-methylbenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that described in Example 449, N-(4-ethynyl-phenyl)-4-methyl-benzamide (0.104 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were reacted to give the title compound as a solid (118 mg, 81%).

Example 454

(S)-5-({4-[(2-methylbenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide.

In a manner similar to that described in Example 449, N-(4-ethynyl-phenyl)-2-methyl-benzamide (0.104 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were reacted to give the title compound (109 mg, 75%).

Example 455

tert-butyl (4-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}phenyl)carbamate

Step 1

tert-butyl 4-ethynylphenylcarbamate.

A dry 25mL flask was charged with 3-ethynyl-phenylamine (0.100 g, 0.855 mmol) and then THF (5 mL) was added. Di-tert-butyl dicarbonate (0.242 g, 1.11 mmol) was added to the THF solution followed by NEt_3 (0.231mL, 1.71 mL). The mixture was allowed to stir at 55 °C after which it was cooled to room temperature and extracted twice with EtOAc (~10 mL), water (~10 mL) and saturated aqueous $NaHCO_3$. The combined organic extracts were dried over anhydrous Na_2SO_4(s) and then concentrated to give the title compound (0.15 g, 0.67 mmol, 78%).

Step 2

(S)-tert-butyl (4-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}phenyl)carbamate

In a manner similar to that described in Example 449, tert-butyl 4-ethynylphenylcarbamate (0.096 g, 0.443 mmol) and 5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were reacted to give the title compound as a solid (63 mg, 0.13 mmol, 45%).

Example 456

(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(2-thienylcarbonyl)amino]phenyl}ethynyl)nicotinamide.

Step 1

N-(3-ethynylphenyl)thiophene-2-carboxamide

A dry 25mL flask was charged with thiophene-2-carbonyl chloride and THF (5 mL) was added. 3-Ethynyl-phenylamine (0.905 g, 3.59 mmol) was added to the THF solution of the acid chloride followed by NEt_3, and the mixture was allowed to stir at 55 °C. The reaction mixture was then allowed to cool to room temperature and extracted with EtOAc (~10 mL), 1M HCl (~10 mL), followed by brine (~10 mL). The combined organic extracts were combined and dried over anhydrous Na_2SO_4(s) and the concentrated. The crude residue was purified by chromatography (silica gel, gradient elution EtOAc/Hexanes 0 to 50%). The product containing fractions were concentrated to give the title compound as a tan solid (0.33 mg, 1.45 mmol, 85%).

Step 2

(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(2-thienylcarbonyl)amino]phenyl}ethynyl)nicotinamide.

In a manner similar to that described in Example 449, thiophene-2-carboxylic acid (3-ethynyl-phenyl)-amide (0.100 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (100 mg, 0.295 mmol) were reacted to give the title compound as a solid (44 mg, .092 mmol, 31%).

Example 457

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

Step 1
2,5-Dimethyl-2H-pyrazole-3-carboxylic acid (3-ethynyl-phenyl)-amide

A dry 25mL flask was charged with 2,5-dimethyl-2H-pyrazole-3-carbonyl chloride (0.135 g, 0.854 mmol) and THF (5 mL) was added. 3-Ethynyl-phenylamine (0.100 g, 0.854 mmol) was added to the THF solution of the acid chloride followed by NEt_3, and the mixture was allowed to stir at 55 °C. The reaction mixture was then allowed to cool to room temperature. The reaction was extracted twice with EtOAc (~5mL) and water (~10 mL) followed by saturated aqueous $NaHCO_3$(~10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (s) and then concentrated. The crude residue was purified by chromatography (silica gel, gradient elution EtOAc/Hexanes 0 to 60%). The product containing fractions were concentrated to give the title compound as a tan solid (147 mg. 72%).

Step 2
(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide.

In a manner similar to that described in Example 449, 2,5-Dimethyl-2H-pyrazole-3-carboxylic acid (3-ethynyl-phenyl)-amide (0.0354 g, 0.222 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (0.050 g, 0.148 mmol) were reacted to give the title compound as a white solid (47 mg, 64%).

Example 458
N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(3-methylthienyl-2-carbonyl)amino]phenyl}ethynyl)nicotinamide

Step 1
N-(3-ethynylphenyl)-3-methylthiophene-2-carboxamide

A dry 25mL flask was charged with 3-methylthiophene-2-carboxylic acid (0.201 g, 1.41 mmol) followed by thionyl chloride (10 mL). The reaction was heated to 50 °C for 2 h after which the reaction was cooled to room temperature and concentrated to afford the crude acid chloride. The crude acid chloride was dissolved into 10 mL of THF and 3-ethynyl-phenylamine (0.165 g, 1.41 mmol) was added to the solution followed by NEt_3, and the mixture was allowed to stir at 55 °C for 4 hours. The reaction mixture was allowed to cool to room temperature and then

partitioned between EtOAc and water. The organic layer was then washed once with of 1M HCl (~10 mL) and then twice with of saturated aqueous$NaHCO_3$ (~10 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4(s) and then concentrated to give the title compound as a tan solid (265 mg, 1.10 mmol, 78%).

Step 2
(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(3-methylthienyl-2-carbonyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described in Example 449, N-(3-ethynylphenyl)-3-methylthiophene-2-carboxamide (0.213 g, 0.885 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (0.200 g, 0.590 mmol) were reacted to give the title compound as a solid (274 mg, 93%).

Example 459

(S)-tert-butyl (3-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}phenyl)carbamate.

Step 1
tert-butyl 3-ethynylphenylcarbamate

A dry 25mL flask was charged with 3-ethynyl-phenylamine (0.100 g, 0.855 mmol) and THF (5 mL) was added. Di-tert-butyl dicarbonate (0.242 g, 1.11 mmol) was added to the THF solution followed by NEt_3 (0.23mL, 1.71 mmol). The mixture was allowed to stir at 55 °C after which it was cooled to room temperature and extracted twice with EtOAc (~10 mL), water (~10 mL) and saturated aqueous $NaHCO_3$. The combined organic extracts were dried over anhydrous Na_2SO_4(s) and then concentrated to give the title compound (0.13 g, 0.67 mmol, 72%).

Step 2

(S)-tert-butyl (3-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}phenyl)carbamate.

In a manner similar to that described in Example 449, tert-butyl 3-ethynylphenylcarbamate (0.098 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (0.100 g, 0.295 mmol) reacted to give the title compounds as a white solid (32 mg, 23%).

Example 460

(S)-5-({3-[(2-methylbenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

Step 1

N-(3-ethynylphenyl)-2-methylbenzamide.

A dry 25 mL flask was charged with 2-methylbenzoyl chloride (0.155 g, 1.00 mmol) was cooled to room temperature, and THF (10 mL) was added. 3-Ethynyl-phenylamine (0.117 g, 1.00 mmol) was added to the THF solution of the acid chloride followed by NEt_3 (0.272 mL, 2.00 mmol), and the mixture was allowed to stir at 55 °C. The reaction mixture was then allowed to cool to room temperature and partitioned between EtOAc (10 mL) and H_2O (15 mL). The organic layer was washed with then washed once with 1M HCl (~20 mL) followed by of saturated aqueous $NaHCO_3$ (~20 mL) and of brine (~20 mL). The organic extracts were concentrated and the crude residue was purified by chromatography (silica gel, gradient elution EtOAc/hexanes 10 to 70%). The product containing fractions were concentrated to give the title compound as a tan solid (434 mg, 0.88 mmol, 88%).

Step 2
(S)-5-({3-[(2-methylbenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a 4 mL vial, N-(3-ethynylphenyl)-2-methylbenzamide (0.104 g, 0.443 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (0.100 g, 0.295 mmol) were added and dissolved into EtOAc (2 mL) The mixture was then degassed for ~20 min after which NEt_3 (0.141 mL, 1.035 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (21.0 mg, 0.030 mmol) and CuI (2.9 mg, 0.016 mmol). The reaction mixture was allowed to stir at 50 °C for 4 hours after which the reaction mixture was partitioned between EtOAc (4 mL) and water (4 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrared. The residue as purified by

chromatography (silica gel, gradient elution 25% EtOAc/Hexanes EtOAc). The product containing fractions were concentrated to give the title compound as a solid (121 mg, 83%).

Example 461

(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(3-methylfuryl-2-carbonyl)amino]phenyl}ethynyl)nicotinamide

Step 1

N-(3-ethynylphenyl)-3-methylfuran-2-carboxamide.

A dry 25 mL flask was charged with 3-methylfuran-2-carboxylic acid (0.500 g, 3.46mmol) and thionyl chloride (10 mL). The reaction was heated to 50 °C and allowed to react for 2 h. The reaction was then cooled to room temperature and concentrated affording the crude acid chloride. The acid chloride was then dissolved in THF (5 mL) and 3-ethynyl-phenylamine (0.41 g, 3.47 mmol) was added followed by NEt_3 (0.95 mL, 7 mmol). The mixture was allowed to stir at 55 °C for 3 hours and the cooled to room temperature. The reaction was then partitioned between EtOAc and water. The organic layer was then washed once with 1M HCl (5 mL) and then once with saturated aqueous $NaHCO_3$ (5 mL). The organic extracts were then concentrated to give the title compound as a light brown solid (631 mg, 2.80 mmol, 81%).

Step 2

(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(3-methylfuryl-2-carbonyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described in Example 460, N-(3-ethynylphenyl)-3-methylfuran-2-carboxamide (0.199 g, 0.885 mmol) and (S)-5-bromo-*N*-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (0.200 g, 0.590 mmol) were reacted to give the title compound as a solid (243 mg, 87%).

Example 462

(S)-tert-butyl (5-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}-1,3-thiazol-2-yl)carbamate

Step 1

tert-butyl (5-bromo-1,3-thiazol-2-yl)carbamate

The title compound was prepared by a modification of the procedure described in J. Med. Chem. 2005, 48, 1886-1900. A mixture of 2-amino-6-bromothiazole monohydrobromide (390 mg, 1.5 mmol) and $NaHCO_3$ (441 mg, 5.3 mmol) in 6.0 mL tert-butyl alcohol was heated for 1 minute at near reflux, then cooled to room temperature. To this mixture was added DMAP (18 mg, 0.15 mmol) and di-*tert*-butyl dicarbonate (1.0 M in THF, 1.65 mL) and the reaction stirred at room temperature for 16 hours. In order to drive reaction to completion, additional di-*tert*-butyl dicarbonate (1.0 M in THF, 0.5 mL) was added, the reaction heated at 50 °C for 2 hours, then di-*tert*-butyl dicarbonate (1.0 M in THF, 1.0 mL) and 100 mg $NaHCO_3$ added and continued heating at 50 °C an additional 2 hours. The mixture was filtered and rinsed with EtOAc, then the EtOAc filtrate washed with H_2O, dilute aqueous HCl, saturated $NaHCO_3$ solution, brine, dried with anhydrous anhydrous Na_2SO_4 and rotary evaporated. The brown solid was chromatographed eluting with hexane/EtOAc and the product triturated with hexane to give the title compound as a cream solid (204 mg, 49%).

Step 2

(S)-tert-butyl (5-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}-1,3-thiazol-2-yl)carbamate

A mixture of N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (73 mg, 0.21 mmol), *tert*-butyl (5-bromo-1,3-thiazol-2-yl)carbamate (74 mg, 0.27 mmol), dichlorobis(triphenylphosphine)palladium(II) (14 mg, 0.02 mmol), triphenylphosphine (2.7 mg, .004 mmol) and triethylamine (0.071 mL, 0.51 mmol) in 1.8 mL DMF at room temperature was degassed using vacuum and a H_2/N_2 (1:1) mixture and then copper(I)iodide (2 mg, 0.01 mmol) added. While stirring the mixture at room temperature, tetrabutylammonium fluoride (1.0 M in THF, 0.21 mL) was added over 2.5 minutes. After 5 minutes the reaction was heated at 60 °C for 2 hours. The reaction was partitioned between EtOAc and H_2O and the EtOAc layer washed with H_2O, aqueous HCl, saturated $NaHCO_3$ solution, brine, dried with anhydrous Na_2SO_4 and concentrated. The brown oil was chromatographed eluting with hexane/acetone and the product containing fractions were concentrated to give the title compound as a light yellow solid (17 mg, 18%).

Example 463

(S)-5-[(2-amino-1,3-thiazol-5-yl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a solution containing *tert*-butyl (5-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}-1,3-thiazol-2-yl)carbamate (16 mg, 0.032

mmol) in 2.0 mL dichloromethane at room temperature was added trifluoroacetic acid (0.099 mL, 1.3mmol). The reaction was stirred at room temperature for 17 hours, then partitioned between EtOAc and saturated $NaHCO_3$ solution. The EtOAc layer was washed with H_2O, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The resulting solid film was purified by chromatography (silica gel, $CHCl_3$/EtOAc) to give the title compound as a tan solid (9 mg, 74%).

Example 464

(S)-5-{[2-(benzoylamino)-1,3-thiazol-5-yl]ethynyl}-N-[methyl(oxo)phenyl-lambda~4~-sulfanylidene]nicotinamide

Step 1

N-(5-bromo-1,3-thiazol-2-yl)benzamide

A mixture of 2-amino-6-bromothiazole monohydrobromide (156 mg, 0.6 mmol) in 2.0 mL pyridine (degassed) at room temperature was added benzoyl chloride (0.058 mL, 0.5mmol) over 1 minute. After stirring at room temperature for 20 minutes the reaction was quenched with H_2O, and then extracted into EtOAc. The EtOAc layer was washed with H_2O, saturated $NaHCO_3$ solution, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The solid was triturated with hot 10% EtOAc/hexane to give a quantitative yield (142mg) of the title compound as a light tan solid.

Step 2

5-{[2-(benzoylamino)-1,3-thiazol-5-yl]ethynyl}-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that described in Example 462, 5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (74 mg, 0.26 mmol), N-(5-bromo-1,3-thiazol-2-yl)benzamide (74 mg, 0.26 mmol) were reacted to give the title compound as a cream solid (33 mg, 26%).

Example 465

(S)-6-amino-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide

Step 1

methyl 6-amino-5-iodonicotinate

To a solution of iodine (3.55 g, 14.0 mmol) in 100 mL absolute ethanol at room temperature was added silver sulfate (4.37 g, 14.0 mmol) and methyl 6-aminonicotinate (1.52 g, 10.0 mmol). After 42 hours the reaction was filtered to isolate a tan precipitate. The solid was heated with 20% MeOH/$CHCl_3$ then cooled to room temperature, filtered, and rinsed with MeOH and $CHCl_3$. The filtrate was evaporated, dissolved in hot MeOH, filtered to remove brownish impurities, and then crystallized from MeOH to give the title compound as a light tan solid (1.73g, 62%).

Step 2

6-amino-5-iodonicotinic acid

A solution of methyl 6-amino-5-iodonicotinate (723 mg, 2.6 mmol) and potassium hydroxide (729 mg, 13.0 mmol) in 40 mL methanol/H_2O (3:1 ratio) was heated at 50 °C. After 4 hours 10 mL THF was added and the reaction continued until 22 hours. The reaction was cooled to room temperature and concentrated HCl added until the solution was pH 4. The solution was concentrated to a volume of 15mL and the resulting precipitate filtered, rinsed with H_2O and 40% EtOAc/hexane to give the title compound as a white solid (443mg, 65%).

Step 3

(S)-6-amino-5-iodo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a solution of 6-amino-5-iodonicotinic acid (330 mg, 1.3 mmol), N, N-diisopropylethylamine (0.44 mL, 2.5 mmol), and (S)-(+)-S-methyl-S-phenylsulfoximine (291 mg, 1.9 mmol) in 7.0 mL DMF at room temperature was added BOP (608 mg, 1.4 mmol). The solution was stirred 10 minutes and then heated at 60 °C for 5 hours. The mixture was dissolved in EtOAc, washed with Na_2CO_3 solution, H_2O, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The brown oil was purified by chromatography (silica gel, hexane/acetone). The product containing fractions were purified by chromatography one additional time (silica gel, EtOAc/MeOH). To give the title compound as a white foam (354 mg, 71%).

Step 4

(S)-6-amino-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide

To a degassed solution containing (S)-6-amino-5-iodo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (345 mg, 0.86 mmol) in 6.0 mL DMF at room temperature was added triethylamine (0.36 mL, 2.6 mmol), trimethylsilylacetylene (0.24 mL, 1.7 mmol), dichlorobis(triphenylphosphine)palladium(II) (60 mg, 0.09 mmol), and copper(I)iodide (16 mg, 0.09 mmol). After stirring at room temperature for 1 hour, the reaction was partitioned between EtOAc and H_2O. The EtOAc layer was washed with saturated $NaHCO_3$, brine, dried with

anhydrous Na_2SO_4 and rotary evaporated. Then added 30 mL ethyl ether to the dark oil, filtered to remove the dark precipitate. The organic extracts were concentrated and the residue was purifed by chromatography (silica gel, ethyl ether/EtOAc) to the title compound as a tan foam (317 mg, 99%).

Example 466

(S)-6-amino-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a solution of (S)-6-amino-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-[(trimethylsilyl)ethynyl]nicotinamide (308 mg, 0.83 mmol) in 20 mL THF/methanol (1:1 ratio) at 0 °C was added K_2CO_3 (344 mg, 2.5 mmol) added. After 7 minutes the solution was decanted from the solids and partitioned between EtOAc and H_2O. The EtOAc layer was washed with brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The brown oil was purified by chromatography (silica gel, $CHCl_3$/EtOAc) to give the title compound as a white solid (193 mg, 78 %).

Example 467

6-amino-5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

A mixture of (S)-6-amino-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (60 mg, 0.2 mmol), 3-iodophenol (66 mg, 0.3 mmol), triethylamine (0.07 mL, 0.5 mmol), dichlorobis(triphenylphosphine)palladium(II) (14 mg, 0.02 mmol), triphenylphosphine (1.3 mg, .005 mmol) in 1.8 mL DMF at room temperature was degassed using a H_2/N_2 (1:1) mixture and then copper(I)iodide (2 mg, 0.01 mmol) added. The reaction was heated at 60 °C for 15 minutes and then partitioned between EtOAc and saturated $NaHCO_3$. The EtOAc layer was washed with brine, dried with anhydrous Na_2SO_4 and rotary evaporated to a brown oil. Before chromatography a different lot of product (23 mg) was added and the combined lots were purified by chromatography (silica gel, EtOAc/EtOH) to the title compound as an off-white solid (91 mg, 89%).

Example 468

(S)-6-amino-5-[(4-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

In a manner similar to that describe in Example 467, (S)-6-amino-5-ethynyl-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide and 4-iodophenol are converted to the title compound (41 mg, 62%).

Example 469

(S)-2-amino-5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

Step 1

(S)-2-amino-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a solution of 2-amino-5-bromonicotinic acid (189 mg, 0.87 mmol), N, N-diisopropylethylamine (0.30 mL, 1.7 mmol), and (S)-(+)-S-methyl-S-phenylsulfoximine (162 mg, 1.0 mmol) in 4.0 mL DMF at room temperature was added BOP (423 mg, 0.96 mmol). The solution was stirred 30 minutes, then heated at 60 °C for 30 minutes, and then cooled back to room temperature. After 19 hours, the mixture was dissolved in EtOAc, washed with Na_2CO_3 solution, H_2O, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The yellow foam was purified by chromatography (silica gel, $CHCl_3$/EtOAc) to give the title compound as a light yellow solid (260 mg, 84%).

Step 2

(S)-2-amino-5-[(3-hydroxyphenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide

To a degassed solution containing (S)-2-amino-5-bromo-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide (106 mg, 0.3 mmol) and 3-hydroxyphenylacetylene (50 mg, 0.42 mmol) in 2.0 mL EtOAc at room temperature was added triethylamine (0.13 mL, 0.9 mmol), dichlorobis(triphenylphosphine)palladium(II) (21 mg, 0.03 mmol), and copper(I)iodide (6 mg, 0.03 mmol). The reaction was stirred at 70 °C for 3.3 hours. Additional 3-hydroxyphenylacetylene was added (50 mg, 0.42 mmol) and then again at 5.3 hours (75 mg, 0.63 mmol). The reaction was cooled to room temperature, and after 23 hours additional dichlorobis(triphenylphosphine)palladium(II) (20 mg, 0.03 mmol) was added. The reaction was heated to 60 °C and 3-hydroxyphenylacetylene (120 mg, 1.0 mmol) in 0.7 mL EtOAc (degassed) added dropwise over 7 minutes. The heat was removed after 1 hour and the reaction stirred an additional 22 hours at room temperature. The reaction was dissolved in EtOAc and washed with H_2O. The EtOAc layer was extracted with 2% aqueous HCl. The combined acidic aqueous layers were washed with 30% EtOAc/hexane and then made basic with Na_2CO_3. The basic aqueous layer was extracted with EtOAc. Then the combined organic layers washed with brine, dried with anhydrous Na_2SO_4 and concentrated. The yellow oil was purified by chromatography (silica gel, $CHCl_3$/EtOAc) to give the title compound as a white solid (5 mg, 4%).

Example 470

Step 1

(S)-trimethyl{[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}silane

To a stirred pre-warmed solution of (S)-(+)-S-methyl-S-phenylsulphoximine (3 g, 18.7 mmol) in acetonitrile (2 mL) at 65 °C was added (trimethylsilyl)diethylamine (4.12 g, 21.1 mmol) dropwise via a syringe. The reaction was maintained at 65 °C and stirred for 3 hours. Additional amount of (trimethylsilyl)diethylamine (2 mL, 10.2 mmol) was added and the reaction mixture was stirred at 65 °C overnight. The reaction was then concentrated under reduced pressure and dried under vacuum to give the title compound. This material was used directly in next step of the synthesis without further purification.

Step 2

(S)-Ethyl [S-phenyl-N-(trimethylsilyl)sulfonimidoyl]acetate

To a 100 mL round bottom flask equipped with a magnetic stir-bar and a rubber septum was added a solution of 2,2,6,6-tetra-methylpiperidine (8.91 mL, 52.5 mmol) in anhydrous THF (22 mL). The solution was cooled to 0 °C and was treated with n-BuLi (18 mL, 45 mmol) (2.5 M in hexanes) via a syringe. The resulting solution was stirred for 10 min at 0 °C, cooled to -78 °C, and treated dropwise with a solution of (S)-trimethyl{[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}silane (18.7 mmol) in THF (10 mL). The reaction mixture was stirred at -78 °C for 30 min and then was treated with ethyl chloroformate (5.16 mL, 52.5 mmol) dropwise. The reaction mixture was stirred for an hour and warmed to room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (2.5 mL). The white solid which formed was collected by filtration and discarded. The filtrate was treated with additional saturated aqueous NH_4Cl solution and the resulting mixture was stored in a -20 °C fridge for 15 hours. The organic layer was collected and concentrated to give the title compound. This material was used directly in the next step of the synthesis

Step 3

(S)-Ethyl (S-phenylsulfonimidoyl)acetate

A solution of Ethyl [S-phenyl-N-(trimethylsilyl)sulfonimidoyl]acetate (18.7 mmol, obtained as crude oil from step 2) in MeOH-H_2O (10:1, 7.5 mL) was treated with cesium fluoride (0.25 g, 1.65 mmol) in one portion. The reaction mixture was heated to 50 °C and stirred for 2 hours. The reaction mixture was concentrated, the residue absorbed to silica gel and purified by chromatography (silica gel, EtOAc-Hexane, Et_3N 0.1 %). The product containing fractions were concentrated to give the title compound as a pale yellow oil (1.65g, 39 % for steps 1 - 3).

Step 4

(S)-Ethyl {N-[(5-bromopyridin-3-yl)carbonyl]-S-phenylsulfonimidoyl}acetate

To a solution of 5-bromonicotinic acid (343 mg, 1.66 mmol) in anhydrous DMF (5.5 mL) was added N,N-diisopropylethylamine (0.58 mL, 3.32 mmol) and ethyl (S-phenylsulfonimidoyl)acetate (415 mg, 1.83 mmol) followed by the final addition of (benzotriazol-1-yloxy)-tris(dimethylamino)-phophonium hexafluorophophate (0.81 g, 1.83 mmol). The reaction mixture was stirred at room temperature for 20 min, and then partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was separated and washed once with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and the residue purified by chromatography (silica gel, gradient elution (5:1 Hexane/EtOAc to 3:1 Hexane/EtOAc). The product containing fractions were concentrated to give the title compound as a white solid (230 mg, 34 %).

Step 5

(S)-Ethyl [N-({5-[(3-hydroxyphenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate

A solution ethyl {N-[(5-bromopyridin-3-yl)carbonyl]-S-phenylsulfonimidoyl}acetate (216 mg, 0.52 mmol) and 3-hydroxyphenylacetylene (0.052 mL, 0.79 mmol) in anhydrous DMF (3 mL) was treated with triethylamine (0.22 mL, 1.58 mmol). The reaction mixture was degassed (alternating vacuum and argon) and $PdCl_2(Ph_3P)_2$ (36.9 mg, 0.052 mmol) and triphenylphosphine (3.4 mg, 0.013 mmol) were added. The reaction mixture was degassed (alternating vacuum and argon) and placed under an atmosphere of 1:3 Argon/hydrogen atmosphere. Copper(1^+) iodide was added and the reaction mixture was heated at 60 °C for 50 min. The brown reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was collected and washed further with saturated aqueous $NaHCO_3$ (1X), brine (1X), and dried over anhydrous Na_2SO_4. The residue was purified by chromatography (silica gel, 50:1 $CHCl_3$:MeOH). The product containing fractions were concentrated to give the title compound as a light yellow solid (220 mg, 94 %).

Example 471

(S)-N-[(2-{[2-(diethylamino)ethyl]amino}-2-oxoethyl)(oxo)phenyl-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide

(S)-Ethyl [N-({5-[(3-hydroxyphenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate (73 mg, 0.16 mmol) in anhydrous MeOH (1.5 mL) was added N,N-diethylethylenediamine (0.12 mL, 0.84 mmol) dropwise. The reaction mixture was heated at 30 °C for 4 hours. The reaction mixture was evaporated and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed once with brine, dried (anhydrous

Na_2SO_4), concentrated. The residue was purified by chromatography (silica gel, 50:1 $CHCl_3$: MeOH to 10:1 $CHCl_3$:MeOH). The product containing fractions were concentrated to give the title compound as a foamy solid (50 mg, 59 %).

Example 472

(S)-N-[{2-[(2-hydroxyethyl)(methyl)amino]-2-oxoethyl}(oxo)phenyl-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide

In a manner similar to that described for Example 471, (S)-Ethyl [N-({5-[(3-hydroxyphenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate (65 mg, 0.14 mmol) and 2-(methylamino)ethanol (0.1 mL, 1.2 mmol) were reacted to give the title as clear oil (42 mg, 61 %).

Example 473

5-[(3-hydroxyphenyl)ethynyl]-N-{[2-(methylamino)-2-oxoethyl](oxo)phenyl-λ^6-sulfanylidene}nicotinamide

In a manner similar to that described for Example 471, (S)-Ethyl [N-({5-[(3-hydroxyphenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate (50 mg, 0.11 mmol) and methylamine (2.0 M solution in MeOH, 0.5 mL, 1.0 mmol) were reacted to give the title compound as colorless oil (43 mg, 90 %).

Example 474

N-[{2-[(2-hydroxyethyl)amino]-2-oxoethyl}(oxo)phenyl-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide

In a manner similar to that described for Example 471, (S)-Ethyl [N-({5-[(3-hydroxyphenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate (75 mg, 0.17 mmol) and ethanolamine (0.05 mL, 0.84 mmol) were reacted to give the title compound as colorless oil (63 mg, 81 %).

Example 475

N-[{2-[(2-amino-2-oxoethyl)amino]-2-oxoethyl}(oxo)phenyl-λ^6-sulfanylidene]-5-[(3-hydroxyphenyl)ethynyl]nicotinamide

In a manner similar to that described for Example 471, (S)-Ethyl [N-({5-[(3-hydroxyphenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate (75 mg, 0.17

mmol) and glycinamide hydrochloride (95 mg, 0.84 mmol) were reacted to give the title compound as colorless oil (40 mg, 50 %).

Example 476

(S)-5-[(2-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

Step 1

N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide

In a manner similar to that described in Example 457, 2,5-dimethyl-2H-pyrazole-3-carbonyl chloride (0.135 g, 0.854 mmol) was and 2-ethynyl-phenylamine (0.100 g, 0.854 mmol) were reacted to give the title compound as a tan solid (0.101 mg, 53 %).

Step 2

(S)-5-[(2-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 460 (step 2) N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (0.0354 g, 0.222) and (S)-5-bromo-*N*-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide (0.050 g, 0.148 mmol) reacted to give the title compound as a white solid (0.025 g, 34 %).

Example 477

(S)-5-({2-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

Step 1

3-Methyl-furan-2-carboxylic acid (2-ethynyl-phenyl)-amide

In a manner similar to that described in Example 458 (step 1), 3-methylthiophene-2-carboxylic acid (0.100 g, 0.794 mmol) and 2-ethynyl-phenylamine (0.093 g, 0.794 mmol) were reacted to give the title compound as a tan solid (0.110 g, 56 %).

Step 2

(S)-5-({2-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described for Example 460(step 2), (S)-5-bromo-*N*-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide (0.050 g, 0.148 mmol) and 3-methyl-furan-2-carboxylic acid (2-ethynyl-phenyl)-amide (0.050 g, 0.222 mmol) were reacted to give the title compound (0.031 g, 43%).

Example 478

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)amino]carbonyl}phenyl)ethynyl]-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

Step 1

N-(2,5-Dimethyl-2H-pyrazol-3-yl)-3-ethynyl-benzamide

3-Ethynylbenzoic acid (0.1 g, 0.685 mmol) was added to a dry 50 mL round bottom flask and dissolved in DMF (6.85 mL). To the resulting solution was added 1,3-dimethyl-1H-pyrazol-5-amine (0.076 g, 0.685 mmol), followed by BOP (0.393 g, 0.890 mmol), and 0.238 mL of DIPEA (1.37 mmol). This reaction mixture was heated to 50 °C for 3 h. After allowing the reaction to cool to room temperature it was taken up in EtOAc (15 mL) and extracted with brine (3 x 15 mL). The EtOAc layer was then washed with saturated aqueous $NaHCO_3$ (2 x 15 mL). The organics were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude residue was purified via column chromatography (silica gel, gradient eluant mixture of EtOAc in Hexanes: 0% to 100% EtOAc) affording N-(1,3-dimethyl-1H-pyrazol-5-yl)-3-ethynylbenzamide (0.128 g, 78%).

Step 2

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)amino]carbonyl}phenyl)ethynyl]-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 460 (step 2), (S)-5-bromo-*N*-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide (0.141 g, 0.418 mmol) and N-(1,3-dimethyl-1H-pyrazol-5-yl)-3-ethynylbenzamide (0.1g, 0.418mmol) were reacted to give the title compound (0.126 g, 61%)

Example 479

(S)-5-({3-[(methoxyamino)carbonyl]phenyl}ethynyl)-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

Step 1

3-Ethynyl-N-methoxy-benzamide

In a manner similar to that described for Example 478 (step 1), 3-ethynylbenzoic acid (0.1 g, 0.685 mmol) and O-methylhydroxylamine hydrogen chloride (0.057 g, 0.685 mmol) were reacted to give the title compound (0.128 g, 61 %).

Step 2

(S)-5-({3-[(methoxyamino)carbonyl]phenyl}ethynyl)-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 460 (step 2), (S)-5-bromo-*N*-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide (0.100 g, 0.295 mmol) and 3-Ethynyl-N-methoxy-benzamide (0.106 g, 0.442 mmol) were reacted to give the title compound yield (0.126 g, 86 %)

Example 480

Methyl 3-{4-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]-amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}-propanoate

Step 1

5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)-ethynyl]nicotinic acid

In a 50 mL round bottom flask, N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (0.888 g, 3.71 mmol) and 5-bromo nicotinic acid (0.50 g, 2.47 mmol) were dissolved in DMF (15 mL) The mixture was then degassed by bubbling $N_{2(g)}$ through it for ~20 min. The mixture was then treated sequentially with NEt_3 (1.37 mL, 9.90 mmol), $Pd(PPh_3)_2Cl_2$ (0.173g, 0.247 mmol) and CuI (0.094g, 4.95 mmol). The reaction mixture was allowed to stir at 50 °C for 4 h. The reaction mixture was diluted with EtOAc (25 mL) causing a pale yellow precipitate to form. The white precipitate was filtered off giving the title compound (0.105 g, 12 %).

Step 2

Methyl 3-[4-(methylthio)phenyl]propanoate

In a 100 mL round bottom flask, 3-(4-(methylthio)phenyl)propanoic acid (1.00 g, 5.10 mmol) was dissolved in DMF (17 mL) under $N_{2(g)}$. CDI (1.24g, 7.65 mmol) was then added to the reaction mixture and the resulting mixture was allowed to stir at room temperature for ~45 min. MeOH (6 mL) was then added in dropwise fashion to the reaction. The reaction was allowed to stir for an additional 1 h, after which time it was extracted with EtOAc (3 x 50 mL) and brine(3 x

50 mL). The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was purified by column chromatography (silica gel, gradient elution mixture: 10% EtOAc in Hexanes to 100% EtOAc) to give the title compound (0.771 g, 72%).

Step 3

Methyl 3-[4-(methylsulfinyl)phenyl]propanoate

In a 250 mL round bottom flask, methyl 3-(4-(methylthio)phenyl)propanoate (0.50 g, 2.38 mmol) was dissolved in MeOH under a $N_{2(g)}$. The resulting solution was cooled to 0 °C, then 0.5 M $NaIO_4$ (4.76 mL, 2.38 mmol) was added dropwise to the cooled solution causing the formation of a white precipitate. The reaction was allowed to warm to room temperature. When HPLC indicated complete consumption of starting thioether, the reaction was filtered and the filtrate was concentrated. The resulting residue was taken up in $CHCl_3$ (25 mL) then extracted with brine. The brine layer was subsequently extracted with $CHCl_3$ (2 x 25 mL). The combined organic extracts were then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated. The resulting sulfoxide was then purified by passing through a plug of silica using EtOAc/Hexanes as eluant affording methyl 3-(4-(methylsulfinyl)phenyl)propanoate (0.436 g, 81%).

Step 4

Methyl 3-{4-[S-methyl-N-(trifluoroacetyl)sulfonimidoyl]phenyl}-propanoate

In a 100 mL round bottom flask, methyl 3-(4-(methylsulfinyl)phenyl)propanoate (0.4 g, 1.77 mmol) was added to CH_2Cl_2 (18 mL). Subsequently the reaction was treated with MgO (0.285 g, 7.08 mmol), trifluoroacetamide (0.400 g, 3.54 mmol), $PhI(OAc)_4$ (0.884 g, 2.66 mmol), and $Rh_2(OAc)_4$ (19.55 mg, 0.0443mmol). The suspension was stirred overnight then filtered through celite. The filtrate was the concentrated. The resulting residue was purified via column chromatography (silica gel, gradient eluant mixture: 20% EtOAc in hexanes to 100% EtOAc) to give the title compound (0.294 g, 69%).

Step 5:

Methyl 3-[4-(S-methylsulfonimidoyl)phenyl]propanoate

Methyl 3-{4-[S-methyl-N-(trifluoroacetyl)sulfonimidoyl]phenyl}propanoate (0.200 g, 0.653 mmol) was dissolved in MeOH (3 mL). K_2CO_3 (0.450 g, 3.27 mmol) was added to the solution, and the resulting suspension was allowed to stir for 5 minutes. The suspension was filtered and the filtrate was concentrated. The residue was dissolved in EtOAc and dried over anhydrous anhydrous $Na_2SO_{4(s)}$ to give the title compound (0.147 g, 93%).

Step 6

Methyl 3-{4-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]-amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}-propanoate

A solution of 5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)-ethynyl]nicotinic acid (0.149 g, 0.414 mmol) in DMF (4 mL) was treated with methyl 3-(4-(S-methylsulfonimidoyl)phenyl)propanoate (0.100 g, 0.414 mmol), followed by BOP (0.238 g, 0.539 mmol) and DIPEA (0.144 mL, 0.830 mmol). The reaction mixture was heated to 50 °C for 3 h. After allowing the reaction to cool to room temperature it was taken up in EtOAc (10 mL) and extracted with brine (3 x 10 mL). The EtOAc layer was then washed with saturated aqueous Na_2CO_3 (2 x 10 mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated. The crude residue was purified via column chromatography (silica gel, gradient elution, EtOAc in Hexanes: 0% to 100% EtOAc) affording the title compound (0.108 g, 45%).

Example 481

3-{4-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}propanoic acid

A solution of Methyl 3-{4-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}propanoate (0.075 g, 0.129 mmol) in THF (3 mL) was cooled to 0°C and slowly treated with 0.5M NaOH (1.29 mL, 0.643mmol). The reaction mixture was allowed to slowly come to room temperature. Once the reaction was done by TLC, the reaction was acidified with acetic acid and then extracted with EtOAc (20 mL) and H_2O (20 mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated to give the title compound (0.052 g, 71%).

Example 482

N-[(4-{[3-(dimethylamino)propyl]amino}phenyl)(methyl)oxido-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

Step 1: tert-Butyl [4-(methylthio)phenyl]carbamate

4-Methylsulfanyl-phenylamine (0.5 g, 3.59 mmol) was dissolved in THF (12 mL) The resulting solution was treated with di-tert butyl dicarbonate (1.02 g, 4.67 mmol) and then with TEA (1.5 mL, 10.78 mmol). The reaction was heated at 50 °C for 3 h and then allowed to cool to room temperature. The cool reaction mixture was taken up in EtOAc (20 mL) and extracted with H_2O (20 mL). The organic layer was further washed with a saturated aqueous solution of $NaHCO_3$

(20 mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude mixture was purified via column chromatography (gradient eluant mixture of EtOAc in Hexanes: 0% to 100% EtOAc) to the tilte compound (0.652 g, 76%).

Step 2: tert-Butyl [4-(methylsulfinyl)phenyl]carbamate

In a manner similar to that described in Example 480 (step 3), tert-Butyl [4-(methylthio)phenyl]carbamate (0.650 g, 2.72 mmol) was converted to the title compound (0.347 g, 50%).

Step 3: tert-butyl {4-[S-methyl-N-(trifluoroacetyl)sulfonimidoyl]phenyl}-carbamate

In a manner similar to that described in Example 480 (step 4), tert-Butyl [4-(methylsulfinyl)phenyl]carbamate (0.300 g, 1.18 mmol) was converted to the title compound (0.224 g, 52%).

Step 4: tert-Butyl [4-(S-methylsulfonimidoyl)phenyl]carbamate

In a manner similar to that described in Example 480 (step 5), tert-butyl {4-[S-methyl-N-(trifluoroacetyl)sulfonimidoyl]phenyl}-carbamate (0.224 g, 0.612 mmol) was converted to the title compound (0.150 g, 91%).

Step 5: tert-butyl (4-{N-[(5-bromopyridin-3-yl)carbonyl]-S-methylsulfonimidoyl}phenyl)carbamate

In a manner similar to that described in Example 480 (step 6), tert-Butyl [4-(S-methylsulfonimidoyl)phenyl]carbamate (0.141 g, 0.522 mmol) and 5-bromonicotinic acid (0.104 g, 0.522 mmol), were converted to the title compound (0.177 g, 75%).

Step 6:

N-[(4-{[tertbutyloxycarbonyl]amino}phenyl)(methyl)oxido-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

In a manner similar to that described in Example 460, tert-butyl (4-{N-[(5-bromopyridin-3-yl)carbonyl]-S-methylsulfonimidoyl}phenyl)carbamate (0.158 g, 0.349 mmol) and 2,5-dimethyl-2H-pyrazole-3-carboxylic acid (3-ethynyl-phenyl)-amide (0.125 g, 0.0524 mmol) were reacted to give the title compound (0.108 g, 51%).

Step 7: N-[(4-{amino}phenyl)(methyl)oxido-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

The BOC protected N-[(4-{amino}phenyl)(methyl)oxido-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide (0.108 g, 0.177 mmol) was dissolved in $CHCl_3$ (3.5 mL) and the resulting solution was cooled to 0°C. The resulting reaction mixture was then treated slowly with CF_3COOH (1 mL) and allowed to stir while warming to rt. The reaction mixture was stirred at room temperature for 4 hours and then was diluted with $CHCl_3$ (5 mL). The organic mixture was extracted with H_2O (5 mL), then with a saturated aqueous solution of $NaHCO_3$ (2 x 5 mL) and then with brine (5 mL). The organic layer was then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* give the title compound (0.086 g, 95%).

Step 8:

N-[(4-{[3-(dimethylamino)propyl]amino}phenyl)(methyl)oxido-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

N-[(4-{amino}phenyl)(methyl)oxido-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide (0.085 g, 0.168 mmol) was dissolved in dioxane (1.7 mL) then treated with (3-Chloro-propyl)-diethyl-amine (0.047g, 0.252mmol) and TEA (0.070 mL, 0.504 mmol). The reaction mixture was then heated to 100°C for 48 h then cooled to room temperature. The cooled mixture was dissolved in EtOAc (5 mL) and then extracted with water (3 x 5 mL) and with brine (5 mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude mixture was purified via column chromatography (gradient eluant mixture of MeOH in EtOAc: 0% to 20% MeOH) to give the title compound (4 mg, 3.5%).

Example 483

Methyl 3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)phenyl]propanoate

In a manner similar to that described in Example 480 (step 6), Methyl 3-(4-(S-methylsulfonimidoyl)phenyl)propanoate (0.25 g, 1.037 mmol) and 5-((3-(3-methylfuran-2-carboxamido)phenyl)ethynyl)nicotinic acid (0.326 g, 0.943 mmol) reacted to give the title compound (0.508 g, 86%).

Example 484:

3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)phenyl]propanoic acid

In a manner similar to that described in Example 481, Methyl 3-(4-(S-methyl-N-(5-((3-(3-methylfuran-2-carboxamido)phenyl)ethynyl)-nicotinoyl)-sulfonimidoyl)phenyl)propanoate (0.4 g, 0.703mmol) was converted to the title compound (0.350 g, 89%).

Example 485

5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-N-{methyl[4-(3-morpholin-4-yl-3-oxopropyl)phenyl]oxido-λ^4-4-sulfanylidene}nicotinamide

3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)phenyl]propanoic acid (0.050 g, 0.090 mmol) was dissolved in DMF (1 mL) then treated with BOP (0.051 g, 0.117 mmol) and TEA (0.050 mL, 0.360 mmol) and allowed to stir for 20 min. Morpholine (0.015 mL, 0.180 mmol) was then added and the reaction was allowed to stir for an additional 4 h. The resulting reaction mixture was dissolved in EtOAc (5mL) and then extracted with brine (2 x 5 mL). The organic layer was then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude mixture was then purified via column chromatography (silica gel, gradient eluant mixture of MeOH in EtOAc: 0% to 0% MeOH) give the title compound (0.023 g, 41%).

Example 486

N-[(4-{3-[(2,3-dihydroxypropyl)(methyl)amino]-3-oxopropyl}phenyl)-(methyl)oxido-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)nicotinamide

In a manner similar to that described in Example 485, 3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)-phenyl]propanoic acid (0.050 g, 0.090 mmol) and 3-methylamino-propane-1,2-diol (0.050 mL, 0.520mmol) were reacted to give the title compound (0.020 g, 35%).

Example 487:

N-[{4-[3-(3-hydroxypyrrolidin-1-yl)-3-oxopropyl]phenyl}(methyl)oxido-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)nicotinamide

In a manner similar to that described in Example 485, 3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)-phenyl]propanoic acid (0.050 g, 0.090 mmol) and pyrrolidin-3-ol (0.016 g, 0.180mmol) were reacted to give the title compound (0.015 g, 27%).

Example 488:

N-{[4-(3-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}-3-oxopropyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described in Example 485, 3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)-phenyl]propanoic acid (0.050 g, 0.090 mmol) and 2-(2-piperazin-1-yl-ethoxy)-ethanol (0.030 mL, 0.180mmol) were reacted to give the title compound (0.030 g, 47%).

Example 489:

2-hydroxyethyl 3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)phenyl]propanoate

3-[4-(S-methyl-N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)pyridin-3-yl]carbonyl}sulfonimidoyl)phenyl]propanoic acid (0.150 g, 0.270 mmol) was dissolved in DMF (2.7 mL) then treated with EDCI (0.062 g, 0.324 mmol) and DMAP (0.003 g, 0.027 mmol) and allowed to stir at 60 °C for 30 min. Ethylene glycol (3 mL) was then added and the reaction was allowed to stir for 4 hours. The reaction mixture was then cooled to room temperature and dissolved in EtOAc (10 mL) and extracted with brine (3 x 10 mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude mixture was then redisolved in EtOAc (1 mL) and triturated with Hexanes (20 mL) causing the product to precipitate out. The resulting white solid to give the title compound (0.125 g, 77%).

Example 490

N-{[4-(hydroxymethyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)nicotinamide

Step 1: tert-butyl(dimethyl){[4-(methylthio)benzyl]oxy}silane

t-Butyldimethylsilyl chloride (2.45g, 16.2 mmol) was dissolved in DMF (3.25 mL) then treated with imidazole (2.21g, 32.4 mmol). The reaction mixture was allowed to stir for 20 minutes before 4-Methylsulfanyl-phenyl)-methanol (0.5g, 3.25mmol) was added. The reaction was stirred overnight and then dissolved in EtOAc (20 mL). The organic mixture was extracted with H_2O (3 x 10 mL). The organic organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude residue was then purified purified via column chromatography (gradient eluant mixture of EtOAc in Hexanes: 0% to 100% EtOActo give the title compound (0.828g, 95%).

Step 2: tert-butyl(dimethyl){[4-(methylsulfinyl)benzyl]oxy}silane

In a manner similar to that described in Example 480 (step 3), tert-Butyl-dimethyl-(4-methylsulfanyl-benzyloxy)-silane (0.828 g, 3.08 mmol), was converted to the title compound in 82% yield (0.716 g, 82%).

Step 3: tert-Butyl(dimethyl){[4-(S- methyl-N-(trifluoroacetyl)-sulfonimidoyl)benzyl]oxy}silane

In a manner similar to that described in Example 480 (step 4), tert-butyl(dimethyl){[4-(methylsulfinyl)benzyl]oxy}silane (0.716 g, 2.52 mmol) was converted to the title compound (0.524 g, 52%).

Step 4: tert-Butyl(dimethyl){[4-(S-methylsulfonimidoyl)benzyl]oxy}silane

In a manner similar to that described in Example 480 (step 5), tert-Butyl(dimethyl){[4-(S-methyl-N-(trifluoroacetyl)-sulfonimidoyl)benzyl]oxy}silane (0.524 g, 1.32 mmol) was converted to the title compound (0.385 g, 97%).

Step 5: N-{[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)nicotinamide

In a manner similar to that described in Example 480 (step 6), tert-Butyl(dimethyl){[4-(S-methylsulfonimidoyl)benzyl]oxy}silane (0.485 g, 1.62 mmol) and 5-((3-(3-methylfuran-2-carboxamido)phenyl)ethynyl)nicotinic acid (0.561 g, 1.62 mmol) were reacted to give the title compound (0.722 g, 71%)

Step 6

N-{[4-(hydroxymethyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)nicotinamide

N-{[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)nicotinamide (0.722 g, 1.15 mmol) was dissolved in THF (2.3 mL). The resulting solution was treated with 1M solution of TBAF in THF (2.3 mL, 2.30 mmol) causing the mixture to turn black in color. The mixture was allowed to stir for 1 h, subsequently dissolved in EtOAc (10 mL) and extracted with H_2O (3 x 15 mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (gradient eluant mixture of EtOAc in Hexanes: 0% to 100% EtOAc) to afford the tilte compound in 94% yield (0.350 g, 0.682 mmol).

Example 491

N-{[4-({4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}methyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

Step 1: N-{[4-(Bromomethyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

N-{[4-(hydroxymethyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide (0.1 g, 0.195 mmol) and CBr_4 (0.097 g, 0.293 mmol) were dissolved in CH_2Cl_2 (0.485 mL) and the resulting solution was cooled to 0 °C. PPh_3 (0.858 g, 0.293 mmol) was dissolved in CH_2Cl_2 (0.250 mL) and then added dropwise to the 0 °C reaction mixture. Subsequently the reaction was allowed to warm to room temperature and stir for ~1.5 h. The reaction was then diluted with CH_2Cl_2 (5 mL) and the resulting organic mixture was washed with a saturated aqueous solution of $NaHCO_3$ (5 mL), then with brine (5 mL). The organic layer was dried anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude product was then taken on without further purification.

Step 2: N-{[4-({4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}methyl)phenyl](methyl)-oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

Crude N-{[4-(Bromomethyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide was dissolved in THF (2 mL). 2-(2-Piperazin-1-yl-ethoxy)-ethanol (0.064 g, 0.390 mmol) and TEA (0.054 mL, 0.390 mmol) were then added to the solution and the resulting reaction mixture was allowed to stir for 1h at rt. The reaction mixture, subsequently, was dissolved in EtOAc and then extracted with H_2O (2 x mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (gradient eluant mixture of MeOH in EtOAc: 0% to 20% MeOH) to afford the title compound (0.064 g, 49% overall for step 1 and 2).

Example 492

Methyl 3-{4-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}propanoate

In a manner similar to that described in Example 480 (step 6), 6-Amino-5-{3-[(2,5-dimethyl-2H-pyrazole-3-carbonyl)-amino]-phenylethynyl}-nicotinic acid (0.250 g, 0.666 mmol) and methyl 3-(4-(S-methylsulfonimidoyl)-phenyl)propanoate (0.160 g, 0.666 mmol) were reacted to give the title compound (0.167 g, 42%)

Example 493 3-{4-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]-amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}propanoic acid

In a manner similar to that described for Example 481, methyl 3-{4-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]-phenyl}propanoate (0.167 g, 0.280 mmol) was converted to the title compound (0.150 g, 89%)

Example 494:
3-[4-(N-{[6-amino-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-pyridin-3-yl]carbonyl}-S-methylsulfonimidoyl)phenyl]propanoic acid

Step 1: 6-Amino-5-{3-[(3-methyl-furan-2-carbonyl)-amino]-phenylethynyl}-nicotinic acid methyl ester

In a 4 mL vial, N-(3-ethynylphenyl)-3-methylfuran-2-carboxamide (0.607g, 2.70 mmol) and methyl 6-amino-5-iodonicotinate (0.5g, 1.80mmol) were dissolved in DMF (6 mL). The solution was degassed by bubbling $N_{2(g)}$ through it for ~30 min. To the degassed solution was added DIPEA (1.25 mL, 7.19mmol), followed by $Pd(PPh_3)_2Cl_2$ (0.126g, 0.18 mmol) and CuI (0.068 g, 0.360 mmol). The reaction mixture was allowed to stir at 50 °C for 3 h. The reaction mixture then was taken up in EtOAc (10 mL) and was extracted with brine (3 x 10 mL). The organic layers were combined and concentrated *in vacuo*. The crude mixture was purified via column chromatography (gradient eluant mixture of EtOAc in Hexanes: 25% to 100% EtOAc) to give the title compound as a white solid (0.554g, 82%).

Step 2: 6-Amino-5-{3-[(3-methyl-furan-2-carbonyl)-amino]-phenylethynyl}-nicotinic acid

Methyl 6-amino-5-((3-(3-methylfuran-2-carboxamido)phenyl)ethynyl)nicotinate (0.550 g, 1.47 mmol) was dissolved in THF (15 mL) and then treated with 1.0 M NaOH (7.33 mL, 7.33 mmol). The reaction mixture was heated to 50 °C. Once the reaction was done by TLC, the reaction was cooled to room temperature and then acidified with acetic acid. The reaction mixture was taken up in of EtOAc (~15 mL) then extracted with H_2O (2 x 15 mL). The water layer then was re-washed with EtOAc (~15 mL) and the combined organic layers were dried over anhydrous $Na_2SO_{4(s)}$. The mixture was then filtered and concentrated *in vacuo* to give the title compound (0.495 g, 1.37 mmol).

Step 3: Methyl 3-[4-(N-{[6-amino-5-({3-[(3-methyl-2-furoyl)amino]phenyl}-ethynyl)pyridin-3-yl]carbonyl}-S-methylsulfonimidoyl)phenyl]propanoate

6-Amino-5-((3-(3-methylfuran-2-carboxamido)phenyl)ethynyl)nicotinic acid (0.1 g, 0.277 mmol) was dissolved in DMF (2.8 mL). EDCI (0.64 g, 0.332 mmol) and DMAP (3.42 mg, 0.028 mmol) were then added and the reaction mixture was stirred at 60 °C for 20 minutes. Methyl 3-(4-(S-methylsulfonimidoyl)-phenyl)propanoate (0.068 g, 0.277mmol) was then added, and the reaction was allowed to stir for 3 hours at 60 °C. The mixture was cooled to room temperature then taken up in EtOAc (10 mL) and extracted with brine (3 x 10 mL). The organic layer was dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo*. The crude product was then

purified over silica purified via column chromatography (gradient eluant mixture of MeOH in EtOAc: 0% to 10% MeOH) to give the title compound (0.060 g, 37%).

Step 4

3-[4-(N-{[6-amino-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-pyridin-3-yl]carbonyl}-S-methylsulfonimidoyl)phenyl]propanoic acid

In a manner similar to that described in Example 481, methyl 3-(4-(N-(6-amino-5-((3-(3-methylfuran-2-carboxamido)phenyl)ethynyl)-nicotinoyl)-S-methylsulfonimidoyl)phenyl)propanoate (0.060 g, 0.103 mmol) was converted to the title compound in (0.040 g, 68%).

Example 495

6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

Step 1

N-(3-iodophenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide

To a solution of 3-iodoaniline (131 mg, 0.60 mmol) in 1.5 ml pyridine at room temperature was added over 2 minutes a solution of 1,3-dimethylpyrazole-5-carbonyl chloride (79 mg, 0.50 mmol) in 0.3 ml 1,2-dichloroethane. The reaction was stirred at room temperature for 30 minutes, quenched into a $NaHCO_3$ solution, and extracted into EtOAc. The EtOAc solution was washed with $NaHCO_3$ solution, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The resultant gummy solid was recrystallized from hexane/EtOAc to give the title compound as solid white needles (135 mg, 80%).

Step 2

6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

A mixture of 6-amino-5-ethynyl-N-[methyl(oxido)phenyl-λ^4-sulfanylidene]nicotinamide (42 mg, 0.14 mmol), N-(3-iodophenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (57 mg, 0.17 mmol), triethylamine (0.049 ml, 0.35 mmol), dichlorobis(triphenylphosphine)palladium(II) (8 mg, 0.011 mmol), and triphenylphosphine (1.8 mg, 0.007 mmol) in 1.2 ml DMF at room temperature was degassed using a H_2/N_2 (1:1) mixture and then copper(I)iodide (1.3 mg, 0.007 mmol) added. The reaction was stirred at room temperature for 15 minutes and then partitioned between EtOAc and saturated $NaHCO_3$/brine mixture. The EtOAc layer was washed with $NaHCO_3$/brine mixture, brine, dried with anhydrous

Na_2SO_4 and rotary evaporated. The orange oil was chromatographed eluting with hexane/acetone to give the title compound as a light tan solid (64 mg, 90%).

Example 496

Step 1

[3-(methylsulfinyl)phenyl]acetic acid

In a manner similar to that described in Example 480 (step 3), 3-(methylthio)phenylacetic acid (2.55 g, 14.0 mmol) was converted to give the title compound as a light tan solid (2.36 g, 85%).

Step 2

Methyl [3-(methylsulfinyl)phenyl]acetate

A solution of [3-(methylsulfinyl)phenyl]acetic acid (1.31 g, 6.60 mmol) and carbonyldiimidazole (1.18 g, 7.26 mmol) in 25.0 mL THF was stirred at room temperature for 15 minutes, then methanol (2.1mL, 52.8 mmol) was added. After 10 minutes the reaction was briefly warmed to near reflux temperature, then allowed to cool to room temperature. After 20 minutes, the reaction was partitioned between EtOAc and $NaHCO_3$/brine mixture. The EtOAc layer was washed with dilute brine, dilute HCl solution, brine, dried with anhydrous Na_2SO_4 and rotary evaporated to give the title compound as a yellow-orange oil (1.14 g, 82%).

Step 3

Methyl {3-[S-methyl-N-(trifluoroacetyl)sulfonimidoyl]phenyl}acetate

In a manner similar to that decribed in Example 480 (step 4), methyl [3-(methylsulfinyl)phenyl]acetate (1.18 g, 5.54 mmol), was converted to the title compound as a white solid (1.23 g, 68%).

Step 4

Methyl [3-(S-methylsulfonimidoyl)phenyl]acetate

In a manner similar that described in Example 480 (step 5), methyl {3-[S-methyl-N-(trifluoroacetyl)sulfonimidoyl]phenyl}acetate (1.29 g, 3.98 mmol) was converted to the title compound as a cloudy white oil (849 mg, 94%).

Step 5

Methyl (3-{N-[(5-bromopyridin-3-yl)carbonyl]-S-methylsulfonimidoyl}phenyl)acetate

To a solution of 5-bromonicotinic acid (648 mg, 3.21 mmol), methyl [3-(S-methylsulfonimidoyl)phenyl]acetate (802 mg, 3.53 mmol), and catalytic DMAP in 15.0 ml DMF at room temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (738 mg, 3.85 mmol). The reaction was stirred 1 hour at room temperature then added to EtOAc. The EtOAc solution was washed with dilute brine, $NaHCO_3$ solution, brine, dilute HCl/brine mixture, brine/$NaHCO_3$ solution, dried with anhydrous Na_2SO_4 and rotary evaporated. The oil was chromatographed eluting with $CHCl_3$/EtOAc to give viscous clear oil (994 mg, 75%).

Step 6

methyl {3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}acetate

In a manner similar to that described in Example 460, methyl (3-{N-[(5-bromopyridin-3-yl)carbonyl]-S-methylsulfonimidoyl}phenyl)acetate (202 mg, 0.492 mmol) and N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (153 mg, 0.64 mmol), were converted to the title compound as a light yellow solid foam (275 mg, 98%).

Example 497

{3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}acetic acid

A 50 ml THF solution of methyl {3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}acetate (216 mg, 0.38 mmol) and 0.5M NaOH (6.1 ml, 3.04 mmol) was stirred at room temperature for 2 hours. The reaction was quenched with acetic acid (0.174 ml, 3.04 mmol) and rotary evaporated to remove the THF solvent. Additional impure lots of product (22 mg) were combined and the aqueous mixture partitioned between EtOAc and $NaHCO_3$ solution. The EtOAc layer was extracted with another portion of $NaHCO_3$ solution. The combined basic aqueous layers were adjusted to pH 4 using 10% HCl and extracted with EtOAc. The combined EtOAc layers were washed with brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The off-white solid foam was chromatographed eluting with $CHCl_3$/MeOH and then recrystallized from a mixture of $CHCl_3$/EtOAc/MeCN to give white solid (144 mg, 62%).

Example 498

Step 1

3-(methylsulfinyl)benzoic acid

In a manner similar to that described in Example 480 (step 3), 3-(methylthio)benzoic acid (3.03 g, 18.0 mmol) to give the title compound as a white solid (3.11 g, 94%).

Step 2

Methyl 3-(methylsulfinyl)benzoate

In a manner similar to that described in Example 496 (step 2), 3-(methylsulfinyl)benzoic acid was converted to the title compound.

Step 3

Methyl 3-(S-methylsulfonimidoyl)benzoate

A solution of methyl 3-(methylsulfinyl)benzoate (3.23 g, 16.3 mmol), 2,2,2-trifluoroacetamide (3.69 g, 32.6 mmol), magnesium oxide (1.97 g, 48.9 mmol), rhodium(II)acetate dimer (0.18 g, 0.408 mmol), and iodobenzene diacetate (7.88 g, 24.5 mmol) in 150ml dichloromethane was stirred at room temperature. After 16 hours, the mixture was filtered past filter agent (Celite), rinsed with chloroform, and rotary evaporated. The sample was dissolved in EtOAc, washed with brine/dilute HCl, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The yellow-orange oil was dissolved in 60ml MeOH, K_2CO_3 (6.76 g, 48.9 mmol) added, and the mixture stirred at room temperature for 12 minutes. The MeOH filtrate was decanted from the solids, which were then rinsed with MeOH and EtOAc. The pH of the combined organic filtrates were adjusted to pH 2 using 4% HCl, then the aqueous layer diluted by adding H_2O. The aqueous layer was washed with 30% EtOAc in hexane, then the pH adjusted to pH 9 with saturated Na_2CO_3. The aqueous layer was extracted with $CHCl_3$, the combined $CHCl_3$ layers washed with brine, dried with anhydrous Na_2SO_4 and rotary evaporated to give the title compound as a light tan solid (2.58 g, 74%).

Step 4

Methyl 3-{N-[(5-bromopyridin-3-yl)carbonyl]-S-methylsulfonimidoyl}benzoate

In a manner similar to that described in Example 480 (step 6), 5-bromonicotinic acid and methyl 3-(S-methylsulfonimidoyl)benzoate were reacted to give the title compound.

Step 5

methyl 3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoate

In a manner similar to that described in Example 460, methyl 3-{N-[(5-bromopyridin-3-yl)carbonyl]-S-methylsulfonimidoyl}benzoate and N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide were reacted to give the title compound.

Example 499

3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoic acid

A 50 ml THF solution of methyl 3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoate (228 mg, 0.41 mmol) and 0.5M NaOH (6.6 ml, 3.28 mmol) was stirred at room temperature for 3 hours. The reaction was quenched with acetic acid (0.188 ml, 3.28 mmol) and rotary evaporated to remove the THF solvent. The aqueous solution was partitioned between EtOAc and dilute HCl/brine mixture, the EtOAc layer washed with brine, dried with anhydrous Na_2SO_4 and rotary evaporated to white solid foam. The solid was combined with impure product from another lot (14 mg) and recrystallized from EtOAc/hexane to give the title compound as a white solid (147 mg, 62%).

Example 500

5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(3-{[(2-morpholin-4-ylethyl)amino]carbonyl}phenyl)oxido-λ^4-sulfanylidene]nicotinamide

A solution of 3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoic acid (20 mg, 0.036 mmol) and 1, 1'-carbonyldiimidazole (12 mg, 0.072 mmol) in 0.8ml THF was stirred at room temperature for 35 minutes. Then 4-(2-aminoethyl)morpholine (0.009 ml, 0.072 mmol) was added, stirred 30 minutes at room temperature, and the mixture added to EtOAc. The EtOAc solution was washed with $NaHCO_3$ solution, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The clear film was chromatographed eluting with $CHCl_3$/MeOH and then chromatographed again using a preparative TLC plate (eluted with 8:2/$CHCl_3$:MeOH) to afford an off-white solid foam (19 mg, 81%).

Example 501

5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(3-{2-[(2-morpholin-4-ylethyl)amino]-2-oxoethyl}phenyl)oxido-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 500, {3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-

methylsulfonimidoyl]phenyl}acetic acid and 4-(2-aminoethyl)morpholine were reacted to give the title compound (54%).

Example 502

N-{[3-({[2-(diethylamino)ethyl]amino}carbonyl)phenyl](methyl)oxido-λ^4-sulfanylidene}-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

To a solution of 3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoic acid (52 mg, 0.096 mmol), 2-diethylaminoethylamine (0.016 ml, 0.115 mmol), and N, N-diisopropylethylamine (0.034 ml, 0.192 mmol) in 3.0 ml DMF at room temperature was added benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate (47 mg, 0.106 mmol). The reaction was stirred at room temperature for 1.5 hours, and then partitioned between EtOAc and dilute brine. The EtOAc layer was washed with saturated $NaHCO_3$ solution, dilute brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The yellow oil (combined 7 mg impure product from another lot) was chromatographed eluting with EtOAc/MeOH, then rechromatographed using a preparative TLC plate (eluted with (1:1:2.5) $CHCl_3$:EtOAc:MeOH plus NH_4OH) to give the title compound as a white solid foam (28 mg).

Example 503

{3-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}acetic acid

A solution of methyl {3-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}acetate (13 mg, 0.021 mmol) and 1.0M NaOH (0.171 ml, 0.171 mmol) in 2.0ml MeOH and 0.1ml H_2O was stirred at room temperature for 1 hour 10 minutes. The pH of the mixture was adjusted to pH 4 using 10% HCl, brine added, and the aqueous extracted with EtOAc. The combined EtOAc layers were washed with brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The white solid was triturated with hot EtOAc to give white solid (11mg, 92%).

Example 504

methyl 3-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoate

To a solution of 6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinic acid (68 mg, 0.18 mmol), methyl 3-(S-methylsulfonimidoyl)benzoate (42 mg, 0.198 mmol), and N, N-diisopropylethylamine (0.063 ml, 0.36 mmol) in 1.5ml DMF at room temperature was added benzotriazole-1-yl-oxy-tris-

(dimethylamino)-phosphoniumhexafluorophosphate (88 mg, 0.198 mmol). The reaction was heated at 60°C for 3.5 hours, then at 48°C for 16.5 hours. The mixture was partitioned between EtOAc and dilute brine. The EtOAc layer was washed with $NaHCO_3$ solution, dilute HCl, $NaHCO_3$ solution, brine, dried with anhydrous Na_2SO_4 and rotary evaporated. The dark foam was chromatographed eluting with hexane/acetone yielding light pink solid (38 mg, 37%).

Example 505

3-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoic acid

In a manner similar to that described in Example 503, methyl 3-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]benzoate was converted to the title compound.

Example 506

N-[(3-hydroxypropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

Step 1

(S)-tert-butyl(dimethyl)[3-(S-phenylsulfonimidoyl)propoxy]silane

To the sulfoximine (6.46 g, 41.62 mmol) solution in anhydrous CH_3CN (5 mL) at 70 °C was added dropwise *N,N*-diethyl-trimethylsilylamine (1.2 eq ~ 1.5 eq). The reaction mixture was heated and stirred at this temperature for one hour. It was then concentrated under reduced pressure to yield slightly brown oil (9.26 g) which was dried *in-vacuo*. The brown oil was dissolved in anhydrous THF (40 mL) and the resulting solution was cooled to -78 °C followed by dropwise addition of nBuLi (17.1 mL, 2.5 M in hexanes). The reaction mixture was stirred 10 min at -78 °C and then 20 min at 0 °C. After hexamethylphosphoramide (13.5 mL) was added, the reaction mixture was cooled back to -78 °C followed by dropwise addition of 2-bromoethoxy-tert-butyl-dimethylsilane over a few minutes. The reaction mixture was stirred at -78 °C for about an hour and allowed to warm-up to room temperature within 4 hours. The reaction mixture was then concentrated at room temperature under reduced pressure. The oily residue was taken up in ether (500 mL), which was subsequently washed with ice-water (2X300 mL), brine (1X), and dried with anhydrous Na_2SO_4 overnight. The ether layer was decanted and concentrated.

The crude oily residue was dissolved in MeOH-H_2O (16 mL, 10:1) followed by addition of CsF (1.24 g). The resulting reaction mixture was heated to 50 °C for one hour. It was then concentrated under reduced pressure and the yellow oily residue was partitioned between EtOAc (500 mL) and H_2O (300 mL). The organic layer was separated and washed subsequently with H_2O (2X), brine

(1X), and dried (Anhydrous Na2SO4). The EtOAc layer was decanted and concentrated. The title compound was isolated as clear oil (6.65 g) upon gradient column chromatography (EtOAc-Hex: from 1:25 to 1:2). The overall yield is 51 % for total of three steps.

Step 2

(S)-5-bromo-N-[(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

To the solution of (S)-tert-butyl(dimethyl)[3-(S-phenylsulfonimidoyl)propoxy]silane (1.55 g, 4.95 mmol) in DMF (15 mL) at room temperature was added *N,N*-diisopropylethylamine (1.72 mL), 3-bromonicotinic acid (1.07 g), and finally the coupling reagent, (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate (2.48 g). The reaction was stirred for 15 min and then poured into saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAC (1X), which was subsequently washed with aqueous $NaHCO_3$, brine (1X), and dried with anhydrous Na_2SO_4. The organic layer was decanted, concentrated, and the oily residue was subject to a gradient column chromatography (EtOAc-Hex: from 1:20 to 1:6) yielding the title compound as an amber oil (2.39 g, 97%).

Step 3

(S)-N-[(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

To the solution of (S)-5-bromo-N-[(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)(oxido)phenyl-λ^4-sulfanylidene]nicotinamide (1.9 g, 3.82 mmol) in anhydrous DMF (19 mL) under nitrogen atmosphere was added sequentially 3-methyl-furan-2-carboxylic acid (3-ethynyl-phenyl)-amide (1.72 g), triethylamine (2.13 mL), bis(triphenylphosphine)palladium(II) dichloride (268 mg), and triphenylphosphine (25 mg). The reaction system was placed under a N_2-H_2 (1:1) atmosphere and CuI (145 mg) was added in one portion. After the reaction mixture was stirred and heated at 60 °C for 1.5 hours, it was poured into saturated aqueous $NaHCO_3$. The aqueous was extracted with EtOAc (1X), which was subsequently washed with aqueous $NaHCO_3$ (1X), brine (1X), and dried (anhydrous Na_2SO_4). The organic layer was decanted, evaporated and wrapped with silica gel. Two times column chromatography (EtOAc-Hex: from 1:4 to 1:2; and MeOH-CH_2Cl_2: 1:100) gave the title compound as yellow foam (2.2 g, 90%).

Step 4

(S)-N-[(3-hydroxypropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

To the solution of (S)-N-[(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide (2.2 g, 3.43 mmol) in anhydrous THF (60 mL) at 0 °C was added dropwise *tert*-butylammonium fluoride (7.2 mL, 1 M in THF) and the reaction was stirred at 0 °C for 1 hour. The yellow reaction solution was then concentrated at room temperature to give a red oil. The oily residue was diluted with EtOAc, which was washed with saturated aqueous $NaHCO_3$ (2X), brine (1X), and then dried (anhydrous Na_2SO_4). The organic layer was decanted, concentrated, and the resulting oily residue was chromatographed (MeOH-CH_2Cl_2: from 1:100 to 1:50) yielding the title compound as a clear oil which turned into white foam *in-vacuo* (1.72 g, 95%).

Example 507

(S)-N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

N-[(3-hydroxypropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide (1.71 g, 3.24 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and the resulting solution was cooled to 0 °C. A solution of carbon tetrabromide (1.565 g) in CH_2Cl_2 (3 mL) was added dropwise followed by a dropwise addition of a solution of triphenylphosphine (1.24 g) in CH_2Cl_2 (3 mL). The reaction was stirred at room temperature for 1.5 hours and then partitioned between saturated aqueous $NaHCO_3$ and dichloromethane. The organic layer was separated, washed with brine (1X), dried with anhydrous Na_2SO_4, and concentrated with silica gel under reduced pressure. A gradient column chromatography (acetone-hex: from 1:10 to 1:4) rendered title compound as white solid in amount of 1.56 g (82%).

Example 508

(S)-N-[(3-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}propyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

To the solution of N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide (450 mg, 0.76 mmol) in anhydrous DMF (5 mL) was added dropwise 1-[2-(2-hydroxyethoxy)ethyl]piperazine. The resulting reaction solution was stirred and heated at 80 °C for 30 min. It was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The EtOAc layer was separated and washed with brine (1X). The aqueous $NaHCO_3$ layer was extracted with $CHCl_3$ (1X) and the extract was washed with brine (1X). The organic layers were combined and dried over anhydrous sodium sulfate. The organic solution was decanted, concentrated, and wrapped with silica gel. Column chromatography (MeOH-EtOAc from 1:10 to 1:6) rendered the title compound as white foam in amount of 500 mg (96 %).

Example 509

(S)-N-{[3-(diethylamino)propyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and diethylamine were converted to the title compound.

Example 510

(S)-N-[{3-[(2-hydroxyethyl)amino]propyl}(oxido)phenyl--λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 2-hydroxyethylamine were converted to the title compound.

Example 511

N-{[3-(3-hydroxypyrrolidin-1-yl)propyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 3-hydroxypyrrolidine were converted to the title compound.

Example 512

N-[{3-[(2,3-dihydroxypropyl)(methyl)amino]propyl}(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 3-methylamino-1,2-propanediol were converted to the title compound.

Example 513

(S)-N-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl](oxido)phenylv-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and thiomorpholine-1,1-dioxide were converted to the title compound.

Example 514

(S)-N-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl}(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 1-piperazineethanol were converted to the title compound.

Example 515

N-{[3-(3-fluoropiperidin-1-yl)propyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 3-fluoropiperidine were converted to the title compound.

Example 516

(S)-N-{[3-(3,3-difluoropiperidin-1-yl)propyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 3,3-difluoropiperidine were converted to the title compound.

Example 517

(S)-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-N-[(3-morpholin-4-ylpropyl)(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and morpholine were converted to the title compound.

Example 518

5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-N-[oxido(phenyl){3-[3-(trifluoromethyl)piperidin-1-yl]propyl}-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described for example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 3-(trifluoromethyl)piperidine were converted to the title compound.

Example 519

(S)-N-{[3-(4-hydroxypiperidin-1-yl)propyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 4-hydroxypiperidine were converted to the title compound.

Example 520

(S)-N-[{3-[(2-hydroxyethyl)(methyl)amino]propyl}(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 2-methylaminoethanol were converted to the title compound.

Example 521

5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-N-[(3-{methyl[(2S,3R,4S,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}propyl)(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 1-deoxy-1-(methylamino)-D-galactitol were converted to the title compound.

Example 522

(S)-N-[(3-azidopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for Example 508, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and sodium azide were converted to the title compound.

Example 523

(S)-N-[(3-aminopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described for example 508, (S)-N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and ammonia were converted to the title compound.

Example 524

(S)-N-[(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

In a manner similar to that described in Example 506 (step 3), (S)-5-bromo-N-[(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)(oxido)phenyl-λ^4-sulfanylidene]nicotinamide and N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide are converted to the title compound.

Example 525

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[(3-hydroxypropyl)(oxido)phenyl-lambda-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 506 (step 4), (S)-N-[(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide is converted to the title compound.

Example 526

(S)-N-[(3-bromopropyl)(oxido)phenyl-4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

In a manner similar to that described in Example 507, (S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[(3-hydroxypropyl)(oxido)phenyl-lambda-λ^4-sulfanylidene]nicotinamide is converted to the title compound.

Example 527

(S)-N-{[3-(diethylamino)propyl](oxido)phenyl-λ^4-sulfanylidene}-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

In a manner similar to that described for example 508, (S)- N-[(3-bromopropyl)(oxido)phenyl-4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and diethylamine were converted to the title compound.

Example 528

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[{3-[(2-hydroxyethyl)amino]propyl}(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described for example 508, (S)-N-[(3-bromopropyl)(oxido)phenyl-4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and hydroxyethylamine were converted to the title compound.

Example 529

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[{3-[(2-hydroxyethyl)(methyl)amino]propyl}(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described for example 508, (S)- N-[(3-bromopropyl)(oxido)phenyl-4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and 2-methylaminoethanol were converted to the title compound.

Example 530

(S)-N-{[3-(dimethylamino)propyl](oxido)phenyl-λ^4-sulfanylidene}-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

In a manner similar to that described for example 508, (S)-N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-

yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and dimethylamine were converted to the title compound.

Example 531

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[(3-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}propyl)(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described for example 508, (S)- N-[(3-bromopropyl)(oxido)phenyl-4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and 1-[2-(2-hydroxyethoxy)ethyl]piperazine were converted to the title compound.

Example 532

(S)-Ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate

Step 1

5-{3-[(3-Methyl-furan-2-carbonyl)-amino]-phenylethynyl}-nicotinic acid

In a manner similar to that described for Example 480 (step 1), 3-methyl-furan-2-carboxylic acid (3-ethynyl-phenyl)-amide and 5-bromo nicotinic acid were reacted to provide the title compound.

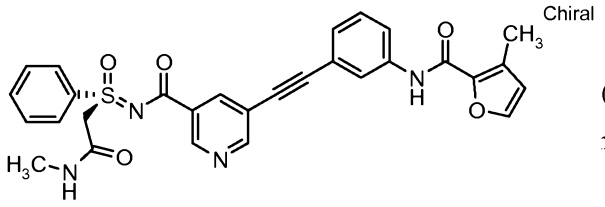
Step 2

(S)-Ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate

To a solution of ethyl (S)-(S-phenylsulfonimidoyl)acetate (139 mg, 0.61 mmol) in anhydrous DMF (3 mL) at room temperature was added 5-{3-[(3-Methyl-furan-2-carbonyl)-amino]-phenylethynyl}-nicotinic acid (233 mg), catalytic amount of 4-(dimethylamino)pyridine, and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (141 mg). The reaction mixture was stirred at room temperature for 30 min. The reaction was then poured into aqueous HCl (0.5 %) and extracted with EtOAc. After the aqueous layer was separated, solid sodium chloride was added and the resulting aqueous mixture was extracted again with EtOAc. The organic layers were combined, washed with brine (1X), saturated aqueous $NaHCO_3$ (1X), then brine (1X), and finally dried with sodium sulfate. The upper solution was decanted, concentrated, and the yellow oily residue was subject to a column chromatography (silica gel, gradient elution EtOAc-Hex from 1:5 to 1:1.5) to give the title compound as a white foam (147 mg, 43 %).

Example 533

N-{[2-(3-hydroxypyrrolidin-1-yl)-2-oxoethyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide



To the solution of (S)-[illegible] furoyl)amino]phenyl}ethynyl)[illegible] (4.03 g, 7.26 mmol) in anhydrous THF (75 [illegible]ne resulting reaction solution was heated at [illegible] under reduced pressure and the yellow oily residue was partitioned between aqueous NH_4Cl and EtOAc. The organic layer was separated and washed sequentially with brine (1X), saturated aqueous $NaHCO_3$ (1X), brine (1X), and finally dried with anhydrous sodium sulfate overnight. The clear solution was decanted and concentrated. The oily residue was subject to multiple times of column chromatography (eg. from CH_2Cl_2 to MeOH-CH_2Cl_2 1:25 or from EtOAc-Hex 3:1 to MeOH-EtOAc 1:100) the title compound as white foam (2.35 g, 54 %).

Example 534

N-[{2-[(2,3-dihydroxypropyl)(methyl)amino]-2-oxoethyl}(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

To the solution of of (S)-ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate (3.5 g, 6.3 mmol) in anhydrous THF (50 mL) was added dropwise 3-methylamino-1,2-propanediol (6.77 g) and the resulting reaction solution was heated at 75 °C for 8.5 hours. The reaction was then concentrated under reduced pressure and the yellow oily residue was partitioned between aqueous NH_4Cl and EtOAc. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (1X), brine (1X), and dried with sodium sulfate. The upper clear solution was decanted and evaporated, the resulting yellowish foamy residue was subjected to a gradient column chromatography (from EtOAc-Hex 6:1 to MeOH-EtOAc 1:50) yielding the title compound as white foam in amount of 2.56 g (66 %).

Example 535

(S)-N-{[2-(methylamino)-2-oxoethyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate and methylamine were reacted to give the title compound

Example 536

(S)-N-{[2-(4-hydroxypiperidin-1-yl)-2-oxoethyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate and 4-hydroxypiperidine were reacted to give the title compound

Example 537

(S)-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)-N-[oxido(2-oxo-2-pyrrolidin-1-ylethyl)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate and pyrrolidine were reacted to give the title compound

Example 538

N-{[2-(3-hydroxypiperidin-1-yl)-2-oxoethyl](oxido)phenyl-λ^4-sulfanylidene}-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate and 3-hydroxypiperidine were reacted to give the title compound

Example 539

(S)-Ethyl 1-[(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetyl]piperidine-3-carboxylate

In a manner similar to that described in Example 534, (S)-Ethyl (N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)acetate and ethyl nipecotate were reacted to give the title compound

Example 540

(S)-Ethyl [N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate

In a manner similar to that described in Example 532 (step 2), (S)-Ethyl (S)-(S-phenylsulfonimidoyl)acetate and 5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinic acid were reacted to give the title compound.

Example 541

(S)-N-[{2-[(2-amino-2-oxoethyl)amino]-2-oxoethyl}(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl [N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate and glycineamide were reacted to give the title compound

Example 542

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-{[2-(methylamino)-2-oxoethyl](oxido)phenyl-λ^4-sulfanylidene}nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl [N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate and methylamine were reacted to give the title compound

Example 543

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[{2-[(2-hydroxyethyl)amino]-2-oxoethyl}(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl [N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate and 2-hydroxyethylamine were reacted to give the title compound

Example 544

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[{2-[(2-hydroxyethyl)(methyl)amino]-2-oxoethyl}(oxido)phenyl-λ^4-sulfanylidene]nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl [N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate and 2-methylaminoethanol were reacted to give the title compound

Example 545

N-[{2-[(2,3-dihydroxypropyl)amino]-2-oxoethyl}(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

In a manner similar to that described in Example 534, (S)-Ethyl [N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]acetate and 3-amino-1,2-propanediol were reacted to give the title compound

Example 546

(S)-Methyl 5-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]pentanoate

Step 1

(S)-Trimethyl{[methyl(oxido)phenyl-λ^4-sulfanylidene]amino}silane

To a stirred solution of (S)-(+)-S-methyl-S-phenylsulphoximine (621 mg, 4.0 mmol) in anhydrous acetonitrile (1 mL) at 70 °C was added (trimethylsilyl)diethylamine (1.37 mL, 7.0 mmol) dropwise. The reaction was maintained at this temperature and stirred for 2 hours, at which time the TLC showed complete conversion of the starting material into a higher R_f component.

The reaction solution was concentrated under reduced pressure and dried in vacuo yielding brown oil, which was used directly in the next step without further purification.

Step 2

(S)-9,9-dimethoxy-2,2-dimethyl-4-phenyl-10-oxa-λ^4-thia-3-aza-2-silaundec-3-ene 4-oxide

The brown oil, obtained from last step, was dissolved in 4 mL anhydrous THF. After the solution was cooled to -78 °C, n-butyllithium (1.64 mL, 2.5 M solution in hexanes) was added dropwise. The resulting reaction mixture was stirred at -78 °C for 10 min, then at 0 °C for 20 min, followed by an addition of hexamethyl phosphoramide (1.32 mL). After the reaction was cooled back to -78 °C, trimethyl 4-bromo-orthobutyrate (1.1 mL) was added dropwise. The reaction was stirred and its temperature was allowed to rise to room temperature during 16 hours. The reaction mixture was then diluted with ethyl ether (250 mL) and washed with ice cold water (2X), brine (1X), and dried with anhydrous sodium sulfate. The solution was decanted and concentrated giving a brown oily residue which was used directly for next step.

Step 3

(S)-[S-(5,5,5-trimethoxypentyl)sulfonimidoyl]benzene

To the solution of the oily residue, obtained in last step, in MeOH-H_2O (10:1, 2 mL) was added cesium fluoride (91.2 mg) and the resulting reaction mixture was heated at 50 °C for 2 hours. The reaction was then concentrated and the oily residue was partitioned between cold water and EtOAc. The organic layer was separated and washed with brine (1X). After it was dried with anhydrous sodium sulfate, it was concentrated for a direct use in next step.

Step 4

(S)-Methyl 5-(S-phenylsulfonimidoyl)pentanoate

The crude oil, obtained in last step, was dissolved in MeOH-H_2O (4:0.1, 20 mL) and the resulting solution was cooled in an ice-bath. A catalytic amount of pyridinium toluene-4-sulfonate was added to the reaction and it was stirred at this temperature for 1 hour. The reaction was then concentrated at room temperature to remove most part of MeOH and the residue was diluted with EtOAc. The EtOAc was washed with saturated aqueous $NaHCO_3$ (2X), brine (1X), and dried with anhydrous sodium sulfate. The organic was decanted, concentrated under reduced pressure, and wrapped with silica gel. A gradient chromatography (Et_2O-Hex from 1:1 to Et_2O) rendered the title compound as clear oil in amount of 477 mg (47 % for total of 4 steps).

Step 5

(S)-Methyl 5-{N-[(5-bromopyridin-3-yl)carbonyl]-S-phenylsulfonimidoyl}pentanoate

To the solution of (S)-Methyl 5-(S-phenylsulfonimidoyl)pentanoate (475 mg, 1.86 mmol) in anhydrous DMF (6 mL) at room temperature under nitrogen atmosphere was added diisopropylethylamine (0.65 mL), 5-bromonicotinic acid (0.38 g), and (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate (0.81 g). The resulting reaction mixture was stirred for about 15 min at room temperature and then poured into saturated aqueous $NaHCO_3$. The aqueous was extracted with EtOAc (1X), which was then washed with saturated aqueous $NaHCO_3$ and brine (v:v 1:1, 2X), brine (1X), and dried with anhydrous sodium sulfate. The solution was decanted and concentrated with silica gel. A column chromatography (EtOAc-Hex 1:2) rendered the title compound as slightly yellow colored solid in amount of (616 mg, 75 %).

Step 6

(S)-Methyl 5-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]pentanoate

To the flame-dried 100 mL round bottom flask containing (S)-Methyl 5-{N-[(5-bromopyridin-3-yl)carbonyl]-S-phenylsulfonimidoyl}pentanoate (609 mg, 1.39 mmol), N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (0.50 g), triethylamine (0.77 mL), bis(triphenylphosphine)palladium(II) dichloride (97.3 mg), and triphenylphosphine (9.1 mg) under nitrogen/hydrogen (1:1) atmosphere at room temperature was added copper(I) iodide (52.8 mg). The resulting reaction mixture was heated and stirred at 60 °C for 1 hour. It was then diluted with EtOAc, washed sequentially with saturated aqueous $NaHCO_3$ (2X), brine (1X), and finally dried with anhydrous sodium sulfate. The solution was decanted and concentrated with silica gel. Chromatography (EtOAc-Hex from 1:2 to 3:2) yielded the title compound as white foam in amount of (712 mg, 86 %).

Example 547

N-[{5-[(2,3-dihydroxypropyl)(methyl)amino]-5-oxopentyl}(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide

To the solution of 3-methylamino-1,2-propanediol (180 mg) in anhydrous THF was added (S)-Methyl 5-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]pentanoate (100 mg, 0.17 mmol). The reaction solution was heated to 50 °C for 2 hours and then the temperature was raised to 70 °C for 17 hours. Further 3-methylamino-1,2-propanediol (100 mg) was added, and the reaction was stirred and heated at 85 °C for an additional 24 hours. The reaction mixture was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was isolated and washed with brine (1X), dried (anhydrous Na_2SO_4) and concentrated. Upon a gradient column chromatography (MeOH-EtOAc from 1:50 to 1:15) the title

compound was obtained as a clear oil (74 mg, 66 %) which gave a white foamy solid upon standing *in vacuo*.

Example 548

(S)-5-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]pentanoic acid

To the solution of (S)-Methyl 5-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]pentanoate (120 mg, 0.2 mmol) in THF (4 mL) at 0 °C was added dropwise a solution of aqueous NaOH (0.5 N, 2.0 mL). After the reaction mixture was stirred at 0 °C for 2 hours, 2 N HCl was carefully added to adjust the pH ~5 followed by a partition between aqueous NH_4Cl and EtOAc. The EtOAc layer was further washed with brine once and dried with anhydrous sodium sulfate. The organic layer was decanted, concentrated and subject to a gradient column chromatography (from EtOAc to MeOH-EtOAc 1:5) yielding the title compound as white foam in amount of (85 mg ,73 %).

Example 549

(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-{[5-(hydroxyamino)-5-oxopentyl](oxido)phenyl-λ^4-sulfanylidene}nicotinamide

At 0 °C to the solution of 5-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]pentanoic acid (50 mg, 0.086mmol) in DMF (1 mL) was added hydroxylamine hydrochloride (30 mg), 1-hydroxybenzotriazole hydrate (20 mg), (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate (57 mg), and triethylamine (84 μL). The reaction mixture was stirred at this temperature for 30 min. The reaction was then poured into aqueous NH_4Cl and extracted with EtOAc. The organic layer was isolated, washed further with brine once, and dried (anhydrous Na_2SO_4). A gradient column chromatography (MeOH-CH_2Cl_2 from 1:100 to 1:5) gave the title compound as white foam (37 mg, 71 %).

Example 550

Methyl rel-(2R,4S)-1-{3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-R-phenylsulfonimidoyl]propyl}-4-hydroxypyrrolidine-2-carboxylate

The mixture of N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide (200 mg, 0.33 mmol), L-4-hydroxyproline methyl ester hydrochloride (126 mg), and sodium bicarbonate (167 mg) in anhydrous acetonitrile (2 mL) in a seal tube was stirred and heated at 90 °C for 5 hours. After it was cooled to room temperature, the reaction was diluted with EtOAc. The organic was washed

with saturated aqueous $NaHCO_3$ (2X), brine (1X), and then dried with anhydrous sodium sulfate. The solution layer was decanted, concentrated, and the oily residual was chromatographed (EtOAc-Hex 1:1 to neat EtOAc) yielding the title compound as colorless oil in amount of 128 mg (58%).

Example 551

(S)-Methyl ({3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}amino)acetate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and glycine methyl ester were reacted to give the title compound.

Example 552

Methyl 2-({3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}amino)-3-hydroxypropanoate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and 2-amino-3-hydroxypropionic acid methyl ester were reacted to give the title compound.

Example 553

Ethyl 1-{3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}piperidine-3-carboxylate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and ethyl nipecotate were reacted to give the title compound.

Example 554

Methyl 2-({3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}amino)-3-(1H-imidazol-4-yl)propanoate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinamide and histidine methyl ester were reacted to give the title compound.

Example 555

rel-(2R,4S)-1-{3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-R-phenylsulfonimidoyl]propyl}-4-hydroxypyrrolidine-2-carboxylic acid

Methyl rel-(2R,4S)-1-{3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-R-phenylsulfonimidoyl]propyl}-4-hydroxypyrrolidine-2-carboxylate (116 mg, 0.17mmol) was dissolved in THF (3.5 mL) and the resulting solution was cooled in an ice-bath. After aqueous NaOH (0.5 N, 1.75 mL) was dropwise added, the reaction was stirred at 0 °C for 30 min. The reaction was then diluted with ice water followed by a pH adjustment to 3~4 with 2 N HCl. The reaction was further diluted with saturated brine, and then extracted with $CHCl_3$-iPrOH (5:1) (2X). The organic layers were combined, dried (anhydrous Na_2SO_4), and then filtered through a plug of cotton. The filtrate was concentrated and the residue was chromatographed (MeOH-$CHCl_3$ 1:10 to 1:4) yielding the title compound as white solid in amount of 108 mg (95%).

Example 556

({3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}amino)acetic acid

In a manner similar to that described in Example 555, methyl ({3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}amino)acetate
was converted to the title compound

Example 557

2-({3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}amino)-3-hydroxypropanoic acid

In a manner similar to that described in Example 555, methyl 2-({3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}amino)-3-hydroxypropanoate was converted to the title compound

Example 558

1-{3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}piperidine-3-carboxylic acid

In a manner similar to that described in Example 555, ethyl 1-{3-[N-({5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-phenylsulfonimidoyl]propyl}piperidine-3-carboxylate was converted to the title compound

Example 559

(S)-Methyl {[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]amino}acetate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and glycine methyl ester are converted to the title compound.

Example 560

methyl 1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]pyrrolidine-2-carboxylate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 2-carboxymethyl pyrollidine are converted to the title compound.

Example 561

methyl 1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]pyrrolidine-3-carboxylate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and 3-carboxymethyl pyrollidine are converted to the title compound.

Example 562

ethyl 1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]piperidine-3-carboxylate

In a manner similar to that described in Example 550, N-[(3-bromopropyl)(oxido)phenyl-λ^4-sulfanylidene]-5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)nicotinamide and ethyl nipecotate are converted to the title compound.

Example 563

(S)-{[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]amino}acetic acid

In a manner similar to that described in Example 555, methyl {[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]amino}acetate is converted to the title compound.

Example 564

1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]pyrrolidine-2-carboxylic acid

In a manner similar to that described in Example 555, methyl 1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]pyrrolidine-2-carboxylate is converted to the title compound.

Example 565

1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]pyrrolidine-3-carboxylic acid

In a manner similar to that described in Example 555, methyl 1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]pyrrolidine-3-carboxylate is converted to the title compound.

Example 566

1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]piperidine-3-carboxylic acid

In a manner similar to that described in Example 555, ethyl 1-[3-(N-{[5-({3-[(3-methyl-2-furoyl)amino]phenyl}ethynyl)pyridin-3-yl]carbonyl}-S-phenylsulfonimidoyl)propyl]piperidine-3-carboxylate is converted to the title compound

Example 567

methyl {3-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}acetate

Step 1

methyl 6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinate

A mixture of methyl 6-amino-5-iodonicotinate (111 mg, 0.40 mmol), N-(3-ethynylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (144 mg, 0.60mmol), triethylamine (0.167 ml, 1.2mmol), dichlorobis(triphenylphosphine)palladium(II) (23 mg, 0.032 mmol) and triphenylphosphine (5.2 mg, 0.020 mmol) in 3.2 ml DMF at room temperature was degassed using

vacuum and a balloon of H_2, then copper(I)iodide (3.8 mg, 0.020 mmol) added. The reaction was heated at 60°C for 1 hour 40 minutes, then partitioned between EtOAc and dilute brine. The EtOAc layer was dried with anhydrous Na_2SO_4 and rotary evaporated. The solid was recrystallized from EtOAc/hexane to give the title compound as a yellow-tan solid (122 mg, 78%).

Step 2

6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinic acid

A solution of methyl 6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinate (51 mg, 0.13 mmol) and KOH (37 mg, 0.65 mmol) in 4.0ml MeOH:H_2O (3:1) was heated at 65°C for 1 hour 40 minutes. The pH of the mixture was adjusted to pH 4 using 10% HCl, brine added, and the aqueous extracted with EtOAc. The combined EtOAc layers were dried with anhydrous Na_2SO_4 and rotary evaporated. The light yellow solid was triturated with hot EtOAc to give the title compound as an off-white solid (41 mg, 84%).

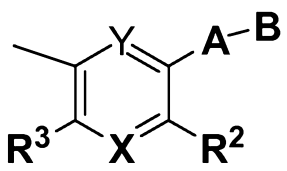
Step 3

methyl {3-[N-({6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]pyridin-3-yl}carbonyl)-S-methylsulfonimidoyl]phenyl}acetate

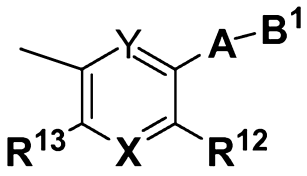
In a manner similar to that described in Example 496 (step 5), 6-amino-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]nicotinic acid and methyl {3-[S-methyl-N-(trifluoroacetyl)sulfonimidoyl]phenyl}acetate were reacted to give the title compound

The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention only. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description.

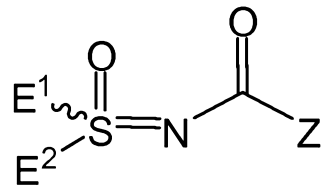
For example, the novel compounds of this invention include any compound which is a substituted aroyl sulfoximine compound which binds to the tyrosine kinase receptor wherein said substituted aryl moiety may be represented by formula IV below:



or said substituted aryl moiety may be represented by formula V below



wherein B^1, R^{12} and R^{13} are selected from the group consisting of halogen, nitro, hydroxy, hydrocarbyl, substituted hydrocarbyl, amide, thioamide, amine, thioether and cyano or said novel sulfoxime may be represented by formula VI below



wherein Z is said substituted aroyl group and E^1 and E^2 are selected from the group consisting of halogen, nitro, hydroxy, hydrocarbyl, substituted hydrocarbyl, amide, thioamide, amine, thioether and cyano.

Such modifications are intended to fall within the scope of the appended claims.

All references cited herein are hereby incorporated by reference in their entirety.

In particular, the compounds of the present invention may be prepared by methods that are analogous to the methods disclosed in such references, with one of skill in the art varying the reactants to achieve the desired compounds. Also, the compounds of the present invention may be tested by the various in-vitro and in-vivo assays disclosed in such references to demonstrate the claimed utilities.

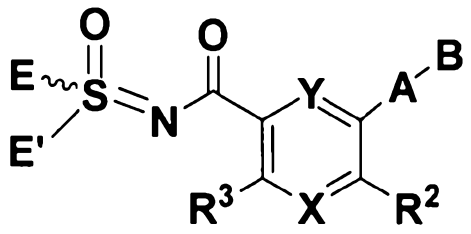
The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

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

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

The claims defining the invention are as follows:

1. A compound represented by the general formula I or a pharmaceutically acceptable salt thereof



I

wherein:

X is CR^4 or N;

Y is CR^1 or N;

$\mathbf{R^1}$ is selected from the group consisting of hydrogen, alkyl, halogen, OR^4, CN, NO_2, COR^4, $(CH_2)_aOR^4$, $(CH_2)_an(R^4)_2$, $C(O)N(R^4)_2$ and $N(R^4)_2$;

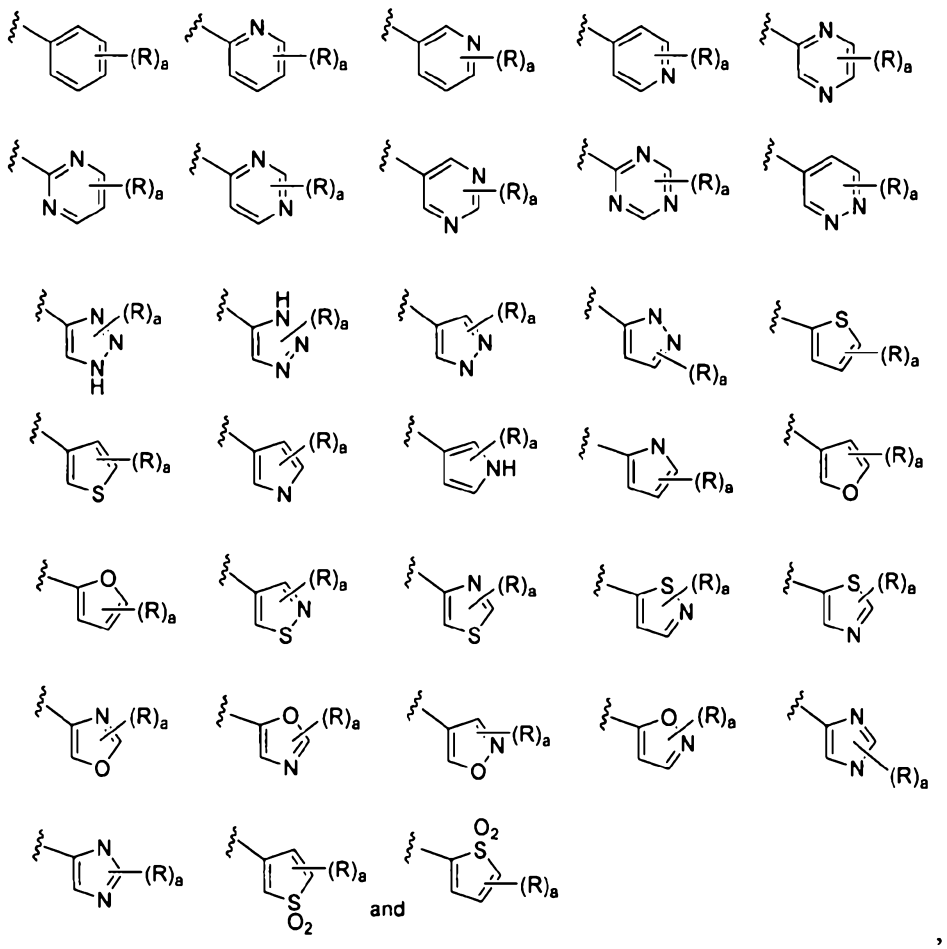
$\mathbf{R^2}$ is selected from the group consisting of hydrogen, halogen, alkyl, OR^4, CN, NO_2, $SO_2N(R^4)_2$, COR^4, $(CH_2)_aOR^4$, $(CH_2)_an(R^4)_2$, $C(O)N(R^4)_2$, $N(R^4)_2$ and $N(R^6)(CR^7R^8)_aR^{10}$;

$\mathbf{R^3}$ is selected from the group consisting of hydrogen, halogen, alkyl, OR^4, CN, NO_2, $SO_2N(R^4)_2$, COR^4, $(CH_2)_aOR^4$, $(CH_2)_an(R^4)_2$, $C(O)N(R^4)_2$, $N(R^4)_2$ and $N(R^6)(CR^7R^8)_aR^{10}$;

$\mathbf{R^4}$ is hydrogen or C_1 to C_4 alkyl;

A is $\mathbf{C\equiv C}$;

B is a carbocyclic aryl or heterocyclic aryl selected from the group consisting of:



R is selected from the group consisting of halogen, alkyl, CF_3, OCF_3, OCF_2H, CH_2CN, CN, SR^6, $OP(O)(OR^6)_2$, OCH_2O, HC=N-NH, N=CH-S, $(CR^7R^8)_aC(O)R^6$, $O(CR^7R^8)_aC(O)R^6$, $N(R^6)(CR^7R^8)_aC(O)R^6$, $C(O)(CR^7R^8)_aC(O)R^6$, $S(O)_e(CR^7R^8)_aC(O)R^6$, $(CR^7R^8)_aC(O)OR^6$, $O(CR^7R^8)_aC(O)OR^6$, $N(R^6)(CR^7R^8)_aC(O)OR^6$, $C(O)(CR^7R^8)_aC(O)OR^6$, $S(O)_e(CR^7R^8)_aC(O)OR^6$, $O(CR^7R^8)_aC(O)N(R^6)_2$, $N(R^6)(CR^7R^8)_aC(O)N(R^6)_2$, $C(O)(CR^7R^8)_aC(O)N(R^6)_2$, $S(O)_e(CR^7R^8)_aC(O)N(R^6)_2$, $(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $O(CR^7R^8)_bN(R^6)C(O)N(R^6)_2$, $N(R^6)(CR^7R^8)_bN(R^6)C(O)N(R^6)_2$, $C(O)(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $S(O)_e(CR^7R^8)_aN(R^6)C(O)N(R^6)_2$, $(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $O(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $N(R^6)(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $C(O)(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $S(O)_e(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $(CR^7R^8)_a(OR^6)$, $O(CR^7R^8)_a(OR^6)$, $N(R^6)(CR^7R^8)_a(OR^6)$, $C(O)(CR^7R^8)_a(OR^6)$, $S(O)_e(CR^7R^8)_a(OR^6)$, $(CR^7R^8)_aN(R^6)_2$, $O(CR^7R^8)_bN(R^6)_2$, $N(R^6)(CR^7R^8)_bN(R^6)_2$, $C(O)(CR^7R^8)_aN(R^6)_2$, $S(O)_e(CR^7R^8)_aN(R^6)_2$, $(CR^7R^8)_aR^6$, $O(CR^7R^8)_aR^6$, $N(R^6)(CR^7R^8)_aR^6$, $C(O)(CR^7R^8)_aR^6$ and, $S(O)_e(CR^7R^8)_aR^6$;

E is a 5 or 6 membered carbocyclic aryl or heterocyclic aryl group which may be substituted with one or more group selected from halogen, trihalomethyl, hydroxyl, SH, NO_2,

thioether, cyano, alkoxy, alkyl and amino;

E' is selected from the group consisting of alkyl, CF_3, $(CR^7R^8)_aC(O)OR^{10}$, $(CR^7R^8)_aC(O)N(R^{10})_2$, $(CR^7R^8)_aC(O)N(OR^{10})(R^{10})$, $(CR^7R^8)_a(OR^{10})$, $(CR^7R^8)_aN(R^{10})_2$, and $(CR^7R^8)_aR^{10}$;

R^7 and **R^8** are selected from the group consisting of H, halogen, hydroxyl, and alkyl or CR^7R^8 may represent a carbocyclic ring of from 3 to 6 carbons; and being optionally substituted with one or more group/atom selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethylamino and SH;

R^{10} is selected from the group consisting of hydrogen, halogen, alkyl, hydroxyl, hydroxymethyl, carbocyclic aryl, heterocyclic aryl, $(CR^7R^8)_aC(O)OR^6$, $(CR^7R^8)_aC(O)R_6$, $(CR^7R^8)_aC(O)N(R^6)_2$, $(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $(CR^7R^8)_a(OR^6)$, $(CR^7R^8)_aN(R^6)_2$ and $(CR^7R^8)_aR^6$, the aryl groups being optionally susbstituted with one or more group selected from the group consisting of halogen, trihalomethyl, hydroxyl, SH, NO_2, thioether, cyano, alkoxy, alkyl and amino;

R^6 is selected from the group consisting of hydrogen, carboalkyl, alkylamine, alkylhydroxy, and alkyloxyalkyl or R^6 is a 5 or 6 membered carbocyclic or heterocyclic group optionally substituted with one or more group/atom selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethylamino and SH;

the alkyl groups may be substituted with one or more group/atom selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethylamino and SH;

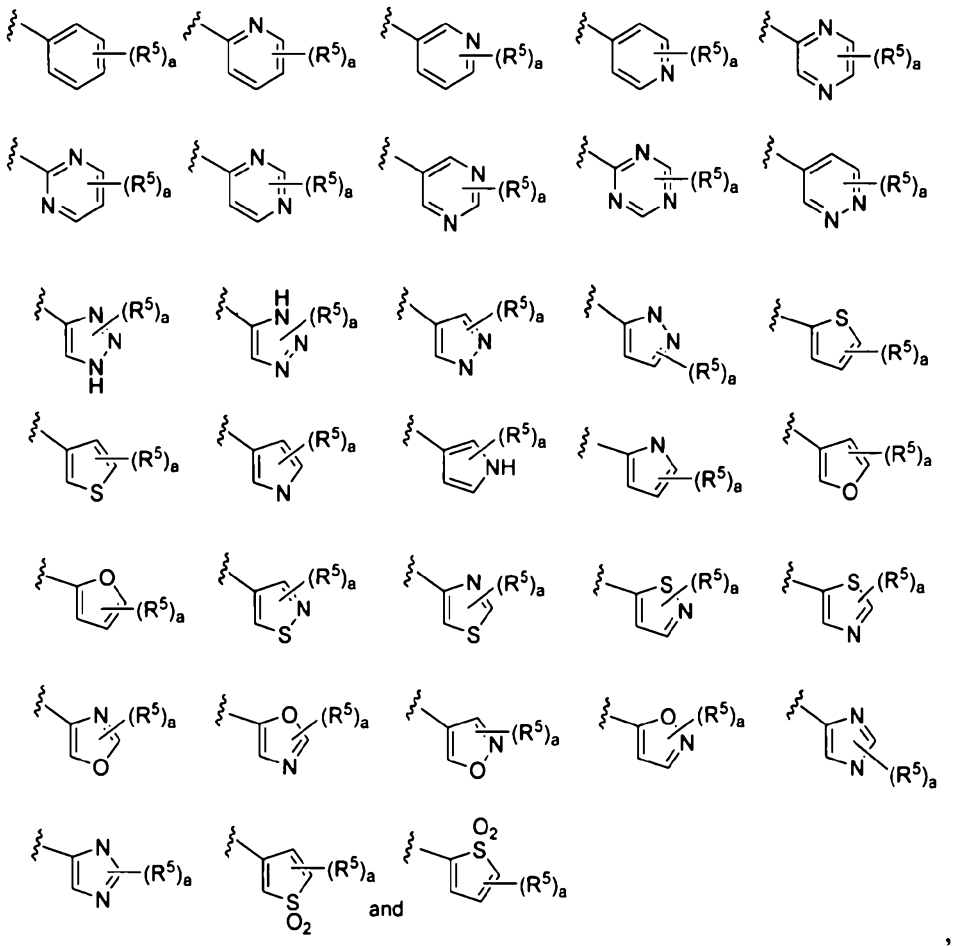
the heterocyclic aryl groups of E and R^{10} and the heterocyclic groups of R^6 contain 1 to 3 heteroatoms in the rings;

a is 0 or an integer of from 1 to 5;

b is an integer of from 2 to 5; and

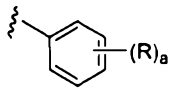
e is 0 or an integer of from 1 to 2.

2. A compound of claim 1, wherein **R^6** is selected from the group consisting of hydrogen, alkyl, di-C_{1-7} alkylamine and the carbocyclic and heterocyclic groups represented by the list below, or $N(R^6)_2$ represents a 3 to 7 membered heterocyclic group having 1 to 3 heteroatoms in the ring and being optionally substituted with one or more group/atom selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, dimethylamino and SH,



wherein $\mathbf{R^5}$ is hydrogen, halogen, $C_{1\text{-}12}$ alkyl, CF_3, hydroxyl, OR^7, $N(R^7)_2$ or NO2.

3. A compound of Claim 1 or Claim 2, wherein B is



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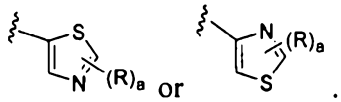
4. A compound of any one of Claim 1 or Claim 2, wherein B is



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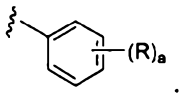
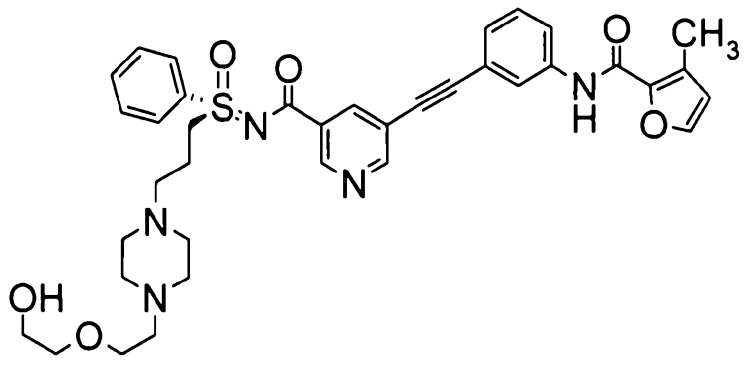
5. A compound of any one of Claims 1 to 4, wherein E is

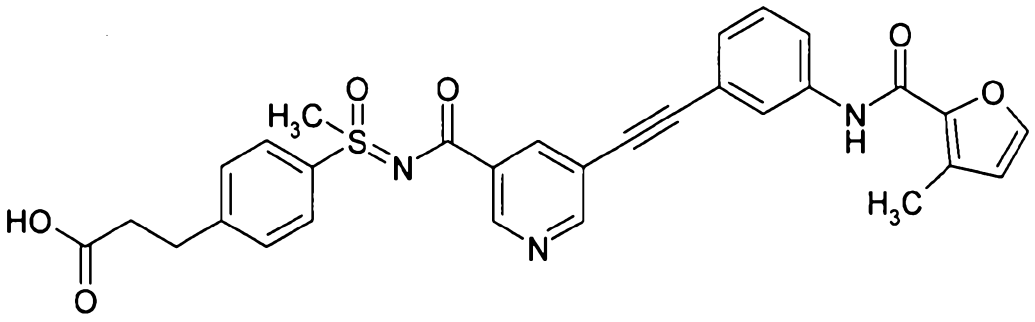


6. A compound of any one of Claims 1 to 5, wherein R is selected from the group consisting of $N(R^6)(CR^7R^8)_aC(O)R^6$, $(CR^7R^8)_aC(O)N(R^6)_2$, $(CR^7R^8)_aC(O)N(OR^6)(R^6)$, $(CR^7R^8)_a(OR^6)$, $C(O)(CR^7R^8)_aN(R^6)_2$ and $N(R^6)(CR^7R^8)_aC(O)OR^6$.

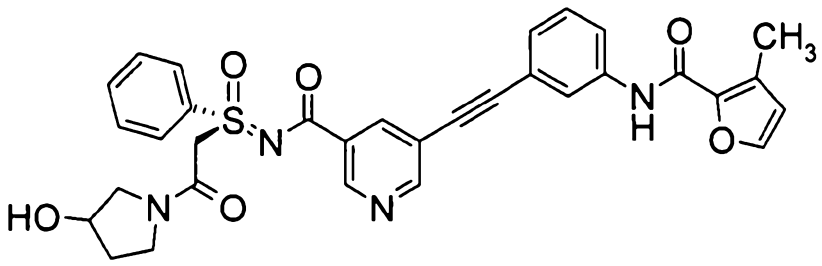
7. A compound of Claim 6 selected from the group consisting of:
(S)-5-({4-[(2-methylbenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide;
(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(2-thienylcarbonyl)amino]phenyl}ethynyl)nicotinamide;
(S)-5-[(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenyl)ethynyl]-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide;
(S)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]-5-({3-[(3-methylthienyl-2-carbonyl)amino]phenyl}ethynyl)nicotinamide;
(S)-tert-butyl (3-{[5-({[methyl(oxo)phenyl-λ^6-sulfanylidene]amino}carbonyl)pyridin-3-yl]ethynyl}phenyl)carbamate;
(S)-5-({3-[(2-methylbenzoyl)amino]phenyl}ethynyl)-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide; and
(S)-5-{[3-(acetylamino)phenyl]ethynyl}-N-[methyl(oxo)phenyl-λ^6-sulfanylidene]nicotinamide.

8. A compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:





, and



9. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 8 and a pharmaceutically acceptable carrier or excipient.

10. A method for treating a disease related to unregulated tyrosine kinase signal transduction, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 8 or a pharmaceutical composition according to claim 9.

11. The method of claim 10, wherein said disease is selected from the group consisting of cancer, a blood vessel proliferative disorder, a fibrotic disorder (including hepatic cirrhosis and atherosclerosis), a mesangial cell proliferative disorder (including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies), and a metabolic disease (including psoriasis, diabetes mellitus, wound healing, inflammation and neurodegenerative disease).

12. The method of claim 11, wherein the blood vessel proliferative disorder is selected from the group consisting of diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, arthritis and restenosis.

13. Use of a compound according to any one of Claims 1 to 8 or a pharmaceutical composition according to claim 9 in the manufacture of a medicament for the treatment of a disease related to unregulated tyrosine kinase signal transduction.

14. Use of Claim 13, wherein said disease is selected from the group consisting of cancer, a blood vessel proliferative disorder, a fibrotic disorder (including hepatic cirrhosis and atherosclerosis), a mesangial cell proliferative disorder (including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies), and a metabolic disease (including psoriasis, diabetes mellitus, wound healing, inflammation and neurodegenerative disease).

15. Use of Claim 14, wherein the blood vessel proliferative disorder is selected from the group consisting of diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, arthritis and restenosis.

16. A compound according to any one of Claims 1 to 8 or a pharmaceutical composition according to claim 9 for use in treating a disease related to unregulated tyrosine kinase signal transduction.

17. A compound according to Claim 16, wherein said disease is selected from the group consisting of cancer, a blood vessel proliferative disorder, a fibrotic disorder (including hepatic cirrhosis and atherosclerosis), a mesangial cell proliferative disorder (including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies), and a metabolic disease (including psoriasis, diabetes mellitus, wound healing, inflammation and neurodegenerative disease).

18. A compound according to Claim 17, wherein the blood vessel proliferative disorder is selected from the group consisting of diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, arthritis and restenosis.

19. A compound represented by the general formula I defined in Claim 1, substantially as hereinbefore described with reference to the Examples.