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(71) Applicant: JANSSEN PHARMACEUTICA NV
[BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventor; and

(71) Applicant : MEEGALLA, Sanath [US/US]; Welsh & McKean Rds., Spring House, Pennsylvania 19477 (US).

(72) Inventors: PLAYER, Mark R.; Welsh & McKean Rds., Spring House, Pennsylvania 19477 (US). HUANG, Hui; Welsh & McKean Rds., Spring House, Pennsylvania 19477 (US). WINTERS, Michael P.; Welsh & McKean Rds., Spring House, Pennsylvania 19477 (US).

(74) Agents: SHIRTZ, Joseph F. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

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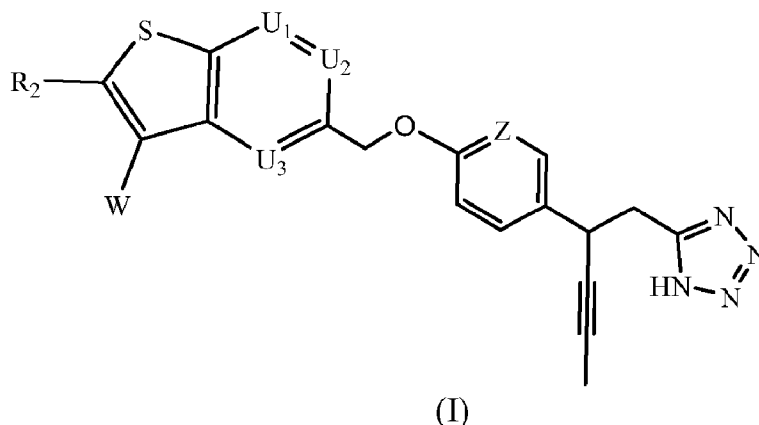
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(54) Title: SUBSTITUTED BENZOTHIOPHENYL DERIVATIVES AS GPR40 AGONISTS FOR THE TREATMENT OF TYPE II DIABETES



(57) Abstract: Disclosed are substituted benzothiophenyl derivatives, compositions and methods for treating of disorders that are affected by the modulation of the GPR40 receptor such as Type II diabetes mellitus. Such compounds are represented by Formula (I) as follows:

SUBSTITUTED BENZOTHIOPHENYL DERIVATIVES AS GPR40 AGONISTS FOR THE TREATMENT OF TYPE II DIABETES

CROSS-REFERENCE TO RELATED APPLICATIONS

This Application claims priority to United States Provisional Patent Application No. 62/320,828, filed April 11, 2016 which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds which are GPR40 agonists and are useful for the treatment of disorders that are affected by the modulation of the GPR40 receptor. The invention also relates to pharmaceutical compositions comprising one or more of such compounds, to processes to prepare such compounds and compositions, and to the use of such compounds or pharmaceutical compositions for the treatment of various diseases, syndromes and disorders, including Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, that are related to GPR40 modulation.

BACKGROUND OF THE INVENTION

According to WHO 2013 estimates, diabetes continues to present an increasing health risk to the global population, affecting 347 million individuals worldwide. There are two main types of diabetes. Type 1 diabetes, which affects ~ 10% of diabetic patients, is characterized by a depletion of pancreatic insulin supply, resulting from an autoimmune destruction of the insulin-producing beta-cells. Treatment requires the administration of exogenous insulin in order to meet energy demands. Type 2 diabetes, which affects the vast majority (~ 90%) of the diabetic population, occurs when the body cannot effectively utilize the insulin that is being produced. A number of factors may contribute to an

impaired insulin response, including decreases in insulin production, insulin secretion or insulin sensitivity. In the initial stages of Type 2 diabetes, most patients' beta cells undergo a compensatory expansion of functional mass and insulin output. As the disease progresses, this compensatory response eventually fails and pharmaceutical intervention is required in order to adequately regulate glucose levels. However, with further disease progression, the effectiveness of initially prescribed therapeutics generally declines, thus requiring additional agents to be incorporated into the treatment regimen, each of which carries its own side-effect liability or risk.

Agents that reduce hepatic glucose production, the so-called biguanides, such as metformin or phenformin, are generally preferred as the first-line of treatment for newly-diagnosed patients. Glitazones, such as rosiglitazone and pioglitazone function as insulin sensitizers (i.e., enhance insulin action) through the activation of peroxisome proliferator-activated receptor- γ (PPAR- γ). These agents can provide the benefit of enhanced insulin action in tissues such as muscle, liver and adipose, but their use is frequently accompanied by increased weight and edema. In addition, rosiglitazone has recently been linked to heart attacks and its use has subsequently been more restricted. The insulin secretagogue sulfonylureas (such as tolbutamide, chlorpropamide, glipizide or glyburide) enhance insulin secretion from functional beta cells and are often combined with biguanide or glitazone therapy. However, because their effects on stimulating insulin release are independent of glucose levels, the sulfonylureas bear the risk of inducing incidences of hypoglycemia. Weight gain is also a common side-effect from this compound class.

More recently, agents capable of inducing insulin secretion from beta cells in a glucose-dependent fashion have been developed, based upon the mechanisms of incretin peptide hormones (ex., GLP-1, GIP). Importantly, because of their glucose-dependent mechanisms of action, these agents are able to provide glucose control while avoiding the risk of hypoglycemia. The direct GLP-1 receptor agonists, Exendin-4 (Byetta[®]) and Liraglutide (Victoza[®]), which were engineered to provide enhanced metabolic stabilities in vivo, have been developed as marketed biological therapeutics. Dipeptidyl-peptidase-4 (DPP-4) inhibitors (the so-called, "gliptins" such as sitagliptin, saxagliptin, linagliptin,

vildagliptin, anagliptin or alogliptin) inhibit the metabolic degradation of endogenous incretins and thereby provide indirect increases in insulin secretion in response to elevations in circulating glucose levels.

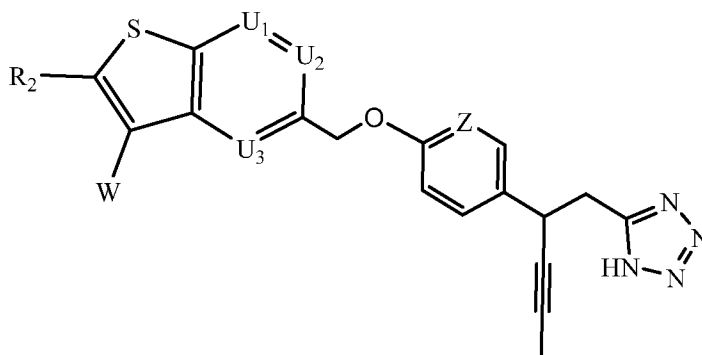
Most recently, the recognition of GPR40 as a receptor whose activation enhances glucose-dependent insulin secretion has led to the search for selective agonists for this putative therapeutic target. GPR40, also known as free fatty acid receptor 1 (FFR1), is one of a family of G-protein coupled receptors that, through receptor deorphanization studies, was shown to be endogenously activated by medium- to long-chain saturated and unsaturated fatty acids ($\sim C_{12-20}$) (Brisco, et al., **2003**, *J Biol Chem*, 278: 11303-11311; Itoh, et al., **2003**, *Nature*, 422: 173-176; Kotarsky et al., **2003**, *Biochem Biophys Res Commun*, 301: 406-410). In humans and rodents, although present in brain and enteroendocrine cells, its expression is particularly high in pancreatic beta cells. Operating primarily through $G\alpha_{q/11}$ signaling, GPR40 activation of the beta cell leads to an increase in intracellular calcium levels, which in the presence of glucose, ultimately results in augmented insulin secretion. In enteroendocrine cells, GPR40 activation by fatty acids leads to stimulation of incretin secretion (Edfalk, et al., **2008**, *Diabetes*, 57: 2280-2287). Thus, in addition to directly promoting GSIS from islet beta cells, GPR40 activation in enteroendocrine cells provides an indirect means of stimulating GSIS through the actions of released incretins.

Because of the hyperglycemic dependency of GPR40-mediated effects on insulin secretion, selective activation of this receptor provides a unique potential therapeutic mechanism by which to treat the diabetic state with minimal risk of hypoglycemic incidents. Given the relatively restricted tissue expression pattern of GPR40, selective GPR40 agonists may offer the additional advantage of providing an improved safety profile relative to the aforementioned therapeutic agents. Thus, GPR40 agonists of the present invention may provide therapeutic benefit for the treatment of diabetes (particularly Type 2 diabetes) and its associated conditions, including Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as

hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, that are related to GPR40 modulation.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I)



Formula (I)

wherein

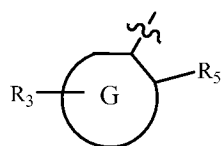
U_1 is N or C(R_1), wherein R_1 is hydrogen, fluoro, chloro, or methyl;

U_2 and U_3 are independently selected from CH or N, such that only up to one of U_1 , U_2 , and U_3 is N in any instance;

R_2 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, cyano, and C_{1-4} alkylsulfonyl;

W is selected from the group consisting of

i) hydrogen;



ii) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, pyrazinyl, and pyrimidinyl; and, when ring G is phenyl, substituents R_3

and R₅ are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, 2,2,-dimethylchroman-5-yl, or (1-ethylcarboxy-indolin-4-yl);

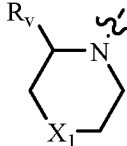
wherein R₃ is selected from the group consisting of hydrogen, chloro, C₁₋₄alkyl, 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, C₁₋₃alkylsulfonyl, C₁₋₃alkylsulfonylamino, and -OR₄;

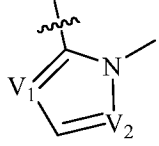
wherein R₄ is

- i) C₁₋₈alkyl optionally independently substituted with one or two C₁₋₃alkoxy or hydroxy substituents;
 - ii) 4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-ylmethyl;
 - iii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
 - iv) tetrahydro-2*H*-pyran-4-yl;
 - v) C₁₋₃alkylsulfonylpropyl;
- or
- vi) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

- iii) C₃₋₈cycloalkyl;

- iv) ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;

- v) ; wherein V₁ and V₂ are independently selected from CH or N;

and

vi) C₁₋₆alkyl;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

The present invention also provides a pharmaceutical composition comprising, consisting of and/or consisting essentially of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent and a compound of Formula (I), or a pharmaceutically acceptable salt form thereof.

Also provided are processes for making a pharmaceutical composition comprising, consisting of, and/or consisting essentially of admixing a compound of Formula (I), and a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent.

The present invention further provides methods for treating or ameliorating a disease, syndrome, or condition in a subject, including a mammal and/or human in which the disease, syndrome, or condition is affected by the agonism of GPR40, such as Type II diabetes mellitus, using a compound of Formula (I).

The present invention also is also directed to the use of any of the compounds described herein in the preparation of a medicament wherein the medicament is prepared for treating a disease or condition that is affected by the agonism of GPR40, selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, in a subject in need thereof.

The present invention is also directed to the preparation of substituted benzothiophenyl derivatives that act as selective agonists of the GPR40 receptor.

Exemplifying the invention are methods of treating a disorder modulated by GPR40 selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

In another embodiment, the present invention is directed to a compound of Formula (I) for use in the treatment of a disorder affected by the agonism of GPR40 selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema.

In another embodiment, the present invention is directed to a composition comprising a compound of Formula (I) for the treatment of a disorder affected by the agonism of GPR40 selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema.

DETAILED DESCRIPTION OF THE INVENTION

With reference to substituents, the term “independently” refers to the situation where when more than one substituent is possible, the substituents may be the same or different from each other.

The term “alkyl” whether used alone or as part of a substituent group, refers to straight and branched carbon chains having 1 to 8 carbon atoms. Therefore, designated numbers of carbon atoms (e.g., C₁₋₈) refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger alkyl-containing substituent. In substituent groups with multiple alkyl groups such as, (C₁₋₆alkyl)₂amino-, the C₁₋₆alkyl groups of the dialkylamino may be the same or different.

The term “alkoxy” refers to an -O-alkyl group, wherein the term “alkyl” is as defined above.

The terms “alkenyl” and “alkynyl” refer to straight and branched carbon chains having 2 to 8 carbon atoms, wherein an alkenyl chain contains at least one double bond and an alkynyl chain contains at least one triple bond.

The term “cycloalkyl” refers to saturated or partially saturated, monocyclic or polycyclic hydrocarbon rings of 3 to 14 carbon atoms. Examples of such rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl.

The term “heterocyclyl” refers to a nonaromatic monocyclic or bicyclic ring system having 3 to 10 ring members that include at least 1 carbon atom and from 1 to 4 heteroatoms independently selected from N, O, and S. Included within the term heterocyclyl is a nonaromatic cyclic ring of 5 to 7 members in which 1 to 2 members are N, or a nonaromatic cyclic ring of 5 to 7 members in which 0, 1 or 2 members are N and up to 2 members are O or S and at least one member must be either N, O, or S; wherein, optionally, the ring contains 0 to 1 unsaturated bonds, and, optionally, when the ring is of 6 or 7 members, it contains up to 2 unsaturated bonds. The carbon atom ring members that form a heterocycle ring may be fully saturated or partially saturated. The term “heterocyclyl” also includes two 5 membered monocyclic heterocycloalkyl groups bridged to form a bicyclic ring. Such groups are not considered to be fully aromatic and are not referred to as heteroaryl groups. When a heterocycle is bicyclic, both rings of the heterocycle are non-aromatic and at least one of the rings contains a heteroatom ring member. Examples of heterocycle groups include, and are not limited to, pyrrolinyl (including 2*H*-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl, imidazoliny,

imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, and piperazinyl. Unless otherwise noted, the heterocycle is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure.

The term “aryl” refers to an unsaturated, aromatic monocyclic or bicyclic ring of 6 to 10 carbon members. Examples of aryl rings include phenyl and naphthalenyl. The term “heteroaryl” refers to an aromatic monocyclic or bicyclic aromatic ring system having 5 to 10 ring members and which contains carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O, and S. Included within the term heteroaryl are aromatic rings of 5 or 6 members wherein the ring consists of carbon atoms and has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen, and sulfur. In the case of 5 membered rings, the heteroaryl ring preferably contains one member of nitrogen, oxygen or sulfur and, in addition, up to 3 additional nitrogens. In the case of 6 membered rings, the heteroaryl ring preferably contains from 1 to 3 nitrogen atoms. For the case wherein the 6 membered ring has 3 nitrogens, at most 2 nitrogen atoms are adjacent. Examples of heteroaryl groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl and quinazolinyl. Unless otherwise noted, the heteroaryl is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure.

The term “halogen” or “halo” refers to fluorine, chlorine, bromine and iodine atoms.

The term “carboxy” refers to the group $-C(=O)OH$.

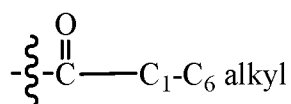
The term “formyl” refers to the group $-C(=O)H$.

The term “oxo” or “oxido” refers to the group $(=O)$.

Whenever the term “alkyl” or “aryl” or either of their prefix roots appear in a name of a substituent (e.g., arylalkyl, alkylamino) the name is to be interpreted as including those limitations given above for “alkyl” and “aryl.” Designated numbers of carbon atoms

(e.g., C₁-C₆) refer independently to the number of carbon atoms in an alkyl moiety, an aryl moiety, or in the alkyl portion of a larger substituent in which alkyl appears as its prefix root. For alkyl and alkoxy substituents, the designated number of carbon atoms includes all of the independent members included within a given range specified. For example C₁₋₆ alkyl would include methyl, ethyl, propyl, butyl, pentyl and hexyl individually as well as sub-combinations thereof (e.g., C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₂₋₆, C₃₋₆, C₄₋₆, C₅₋₆, C₂₋₅, etc.).

In general, under standard nomenclature rules used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. Thus, for example, a “C₁-C₆ alkylcarbonyl” substituent refers to a group of the formula:



The term “R” at a stereocenter designates that the stereocenter is purely of the *R*-configuration as defined in the art; likewise, the term “S” means that the stereocenter is purely of the *S*-configuration. As used herein, the terms “*R” or “*S” at a stereocenter are used to designate that the stereocenter is of pure but unknown configuration. As used herein, the term “RS” refers to a stereocenter that exists as a mixture of the *R*- and *S*-configurations. Similarly, the terms “*RS” or “*SR” refer to a stereocenter that exists as a mixture of the *R*- and *S*-configurations and is of unknown configuration relative to another stereocenter within the molecule.

Compounds containing one stereocenter drawn without a stereo bond designation are a mixture of two enantiomers. Compounds containing two stereocenters both drawn without stereo bond designations are a mixture of four diastereomers. Compounds with two stereocenters both labeled “RS” and drawn with stereo bond designations are a two-component mixture with relative stereochemistry as drawn. Compounds with two stereocenters both labeled “*RS” and drawn with stereo bond designations are a two-component mixture with relative stereochemistry unknown. Unlabeled stereocenters drawn without stereo bond designations are a mixture of the *R*- and *S*-configurations. For

unlabeled stereocenters drawn with stereo bond designations, the absolute stereochemistry is as depicted.

Unless otherwise noted, it is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The term “subject” refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term “therapeutically effective amount” refers to an amount of an active compound or pharmaceutical agent, including a compound of the present invention, which elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation or partial alleviation of the symptoms of the disease, syndrome, condition, or disorder being treated.

The term “composition” refers to a product that includes the specified ingredients in therapeutically effective amounts, as well as any product that results, directly, or indirectly, from combinations of the specified ingredients in the specified amounts.

The term “GPR40 agonist” is intended to encompass a compound that interacts with GPR40 to substantially increase its downstream signaling, thereby resulting in physiologic effects such as, but not limited to, insulin secretion in the pancreas.

The term “GPR40 receptor-modulated” is used to refer to the condition of being affected by the modulation of the GPR40 receptor, including but not limited to, the state of being mediated by the GPR40 receptor, for the treatment of a disease or condition such as Type II diabetes or impaired glucose tolerance.

As used herein, unless otherwise noted, the term “disorder modulated by the GPR40 receptor” shall mean any disease, disorder or condition characterized in that at least one of its characteristic symptoms is alleviated or eliminated upon treatment with a GPR40

receptor agonist. Suitable examples include, but are not limited to Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema; more preferably, Type II diabetes mellitus and impaired glucose tolerance.

As used herein unless otherwise noted, the term “cardiovascular risk factors” shall mean any cardiovascular disease, disorder or condition in which obesity or diabetes (preferably, Type II diabetes) has a role in the initiation or exacerbation of said disorder or condition. Suitable examples include, but are not limited to, hypertension, atherosclerosis, diabetic nephropathy, and cardiac fibrosis.

As used herein, unless otherwise noted, the term “affect” or “affected” (when referring to a disease, syndrome, condition or disorder that is affected by agonism of GPR40) includes a reduction in the frequency and / or severity of one or more symptoms or manifestations of said disease, syndrome, condition or disorder; and / or include the prevention of the development of one or more symptoms or manifestations of said disease, syndrome, condition or disorder or the development of the disease, condition, syndrome or disorder.

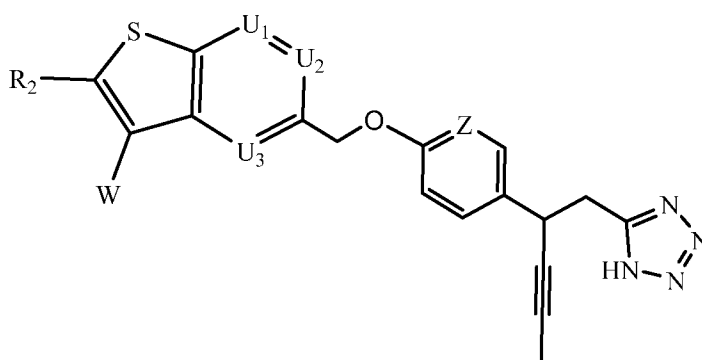
The compounds of the instant invention are useful in methods for treating or ameliorating a disease, a syndrome, a condition or a disorder that is affected by the agonism of GPR40 receptor. Such methods comprise, consist of and/or consist essentially of administering to a subject, including an animal, a mammal, and a human in need of such treatment, amelioration and / or prevention, a therapeutically effective amount of a compound of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt thereof.

In particular, the compounds of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt form thereof are useful for treating or ameliorating diseases, syndromes, conditions, or disorders such as Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance,

metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema.

More particularly, the compounds of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt form thereof, are useful for treating or ameliorating Type II diabetes mellitus or impaired glucose tolerance, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt form thereof as herein defined.

Embodiments of the present invention include a compound of Formula (I)

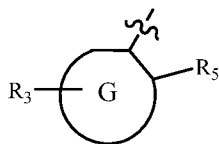


Formula (I)

wherein

- U_1 is N or C(R_1), wherein R_1 is hydrogen, fluoro, or chloro;
- U_2 and U_3 are independently selected from CH or N, such that only up to one of U_1 , U_2 , and U_3 is N in any instance;
- U_2 is independently selected from CH or N; and U_3 is CH, such that only one of U_1 and U_2 is N in any instance;
- R_2 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, and cyano;
- R_2 is selected from the group consisting of hydrogen, chloro, fluoro, bromo, trifluoromethyl, and cyano;

- f) R_2 is selected from the group consisting of hydrogen, chloro, fluoro, bromo, iodo, methyl, methanesulfonyl, trifluoromethyl, and cyano;
- g) W is selected from the group consisting of



- i) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R_3 and R_5 are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

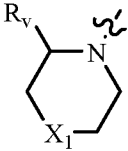
wherein R_3 is selected from the group consisting of hydrogen, chloro, C_{1-4} alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and $-OR_4$;

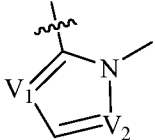
wherein R_4 is

- i) C_{1-8} alkyl independently substituted with one or two C_{1-3} alkoxy or hydroxy substituents;
- ii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
- iii) C_{1-3} alkylsulfonylpropyl;
- or
- iv) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R_5 is methyl, bromo, chloro, or trifluoromethyl;

- ii) C_{5-8} cycloalkyl;

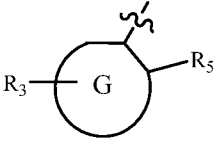
- iii)  ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;

- iv)  ; wherein V₁ and V₂ are independently selected from CH or N;

and

- v) C₁₋₆alkyl;

- h) W is selected from the group consisting of

- i)  ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R₃ and R₅ are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

wherein R₃ is selected from the group consisting of hydrogen, chloro, C₁₋₄alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and -OR₄;

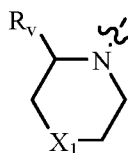
wherein R₄ is

- i) C₁₋₆alkyl independently substituted with one or two C₁₋₃alkoxy substituents;
- ii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
- iii) C₁₋₃alkylsulfonylpropyl;

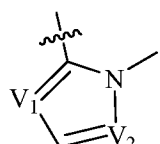
or

iv) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

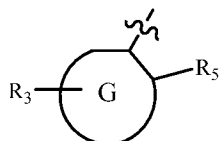
wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

ii)  ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;

and

iii)  ; wherein V₁ is independently selected from CH or N, and V₂ is CH;

i) W is selected from the group consisting of

i)  ; wherein ring G is selected from the group consisting of phenyl and pyridyl; and, when ring G is phenyl, substituents R₃ and R₅ are optionally taken together with the atoms to which they are attached to form (1-ethylcarboxy-indolin-4-yl);

wherein R₃ is selected from the group consisting of hydrogen, and -OR₄;

wherein R₄ is

- i) C₁₋₆alkyl independently substituted with one or two C₁₋₃alkoxy substituents;
- ii) C₁₋₃alkylsulfonylpropyl;

or

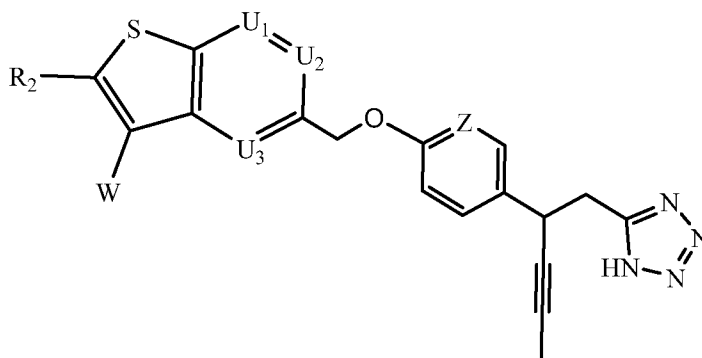
iii) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

- j) W is selected from the group consisting of 2-methylphenyl, 2-bromophenyl, 2-chloro-5-methylpyridin-4-yl, 2-methyl-4-(4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxyphenyl, 2-methyl-4-(3-methyl-3-hydroxybutoxy)phenyl, 2-methyl-4-(2-methoxyethoxy)phenyl, 2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl, 2-methyl-3-(2-methoxyethoxy)phenyl, 2-methylpyridin-3-yl, 2-methyl-4-(3-methyl-1,1-dioxidothietan-3-yl)methoxyphenyl, 2-trifluoromethylphenyl, 2-methyl-4-(methylsulfonyl)phenyl, 2-methyl-5-(2-methoxyethoxy)phenyl, 2-methyl-4-(3-methanesulfonylpropyloxy)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yloxy)phenyl, 2,6-dimethylphenyl, 2-(2-methoxyethoxy)-4-methylpyridin-5-yl, 1-methyl-1*H*-pyrazol-5-yl, 1-methyl-1*H*-1,2,4-triazol-5-yl, 4-methylpyrimidin-5-yl, 5-(2-methoxyethoxy)-3-methylpyridin-2-yl, dihydrobenzo[b][1,4]dioxin-5-yl, 1-(ethylcarboxy)-indolin-4-yl, 2-methyl-5-(methanesulfonylamino)phenyl, 2,2,-dimethylchroman-5-yl, 2-methyl-4-(2,3-dihydroxy-propyloxy)phenyl, 2-chlorophenyl, 5-(2-methoxyethoxy)-2-methylpyridin-3-yl, cyclopropyl, cyclohexyl, cyclopentyl, isopropyl, 2-methylpiperidin-1-yl, 2-methyl-4-methoxyphenyl, *n*-propyl, hydrogen, and *n*-butyl;

and any combination of embodiments a) through j) above, provided that it is understood that combinations in which different embodiments of the same substituent would be combined are excluded; or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

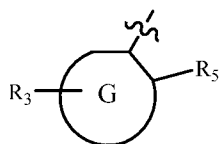
wherein

U_1 is N or C(R_1), wherein R_1 is hydrogen, fluoro, or chloro;

U_2 and U_3 are independently selected from CH or N, such that only up to one of U_1 , U_2 , and U_3 is N in any instance;

R_2 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, and cyano;

W is selected from the group consisting of



- i) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R_3 and R_5 are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

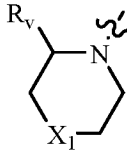
wherein R_3 is selected from the group consisting of hydrogen, chloro, C_{1-4} alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and -OR₄;

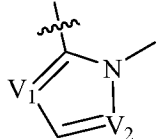
wherein R_4 is

- vii) C₁₋₈alkyl independently substituted with one or two C₁₋₃alkoxy or hydroxy substituents;
- viii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
- ix) C₁₋₃alkylsulfonylpropyl;
- or
- x) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

- ii) C₅₋₈cycloalkyl;

- iii)  ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;

- iv)  ; wherein V₁ and V₂ are independently selected from CH or N;

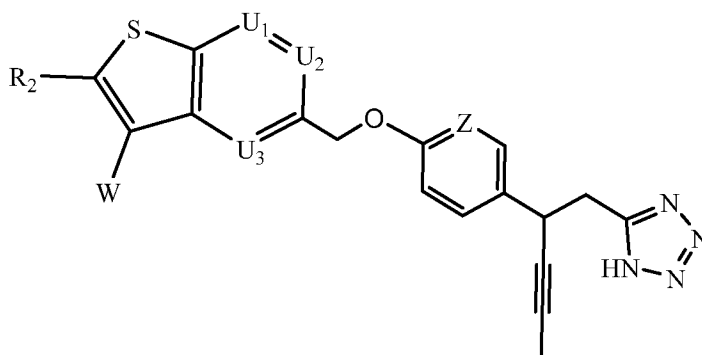
and

- v) C₁₋₆alkyl;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

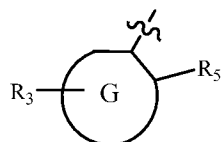
U₁ is N or C(R₁), wherein R₁ is hydrogen, fluoro, or chloro;

U₂ is independently selected from CH or N;

U₃ is CH, such that only one of U₁ and U₂ is N in any instance;

R₂ is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, and cyano;

W is selected from the group consisting of



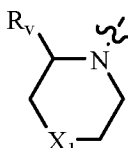
- i) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R₃ and R₅ are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

wherein R_3 is selected from the group consisting of hydrogen, chloro, C_{1-4} alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and $-OR_4$;

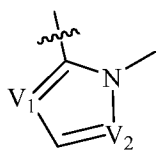
wherein R_4 is

- v) C_{1-6} alkyl independently substituted with one or two C_{1-3} alkoxy substituents;
 - vi) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
 - vii) C_{1-3} alkylsulfonylpropyl;
- or
- viii) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R_5 is methyl, bromo, chloro, or trifluoromethyl;

- ii)  ; wherein X_1 is selected from the group consisting of CH_2 , O, S, NH, and $N(C_{1-4}alkyl)$; and wherein R_v is hydrogen or methyl;

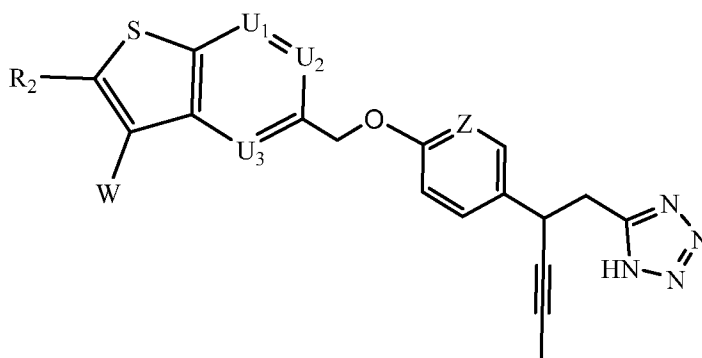
and

- iii)  ; wherein V_1 is independently selected from CH or N, and V_2 is CH;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

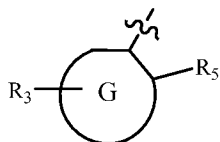
U_1 is N or C(R_1), wherein R_1 is hydrogen, fluoro, or chloro;

U_2 is independently selected from CH or N;

U_3 is CH, such that only one of U_1 and U_2 is N in any instance;

R_2 is selected from the group consisting of hydrogen, chloro, fluoro, bromo, trifluoromethyl, and cyano;

W is selected from the group consisting of



- i) ; wherein ring G is selected from the group consisting of phenyl and pyridyl; and, when ring G is phenyl, substituents R_3 and R_5 are optionally taken together with the atoms to which they are attached to form (1-ethylcarboxy-indolin-4-yl);

wherein R_3 is selected from the group consisting of hydrogen, and $-OR_4$;

wherein R_4 is

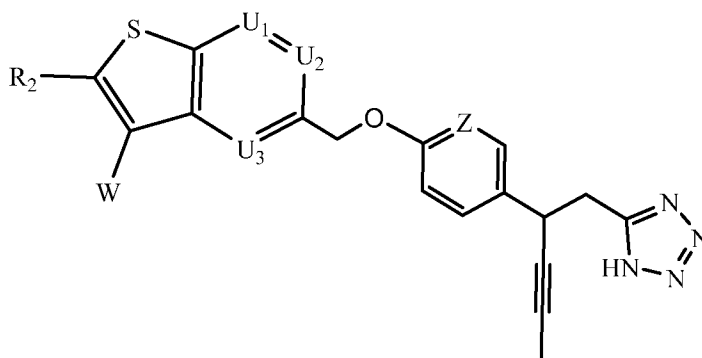
- i) C₁₋₆alkyl independently substituted with one or two C₁₋₃alkoxy substituents;
 - ii) C₁₋₃alkylsulfonylpropyl;
- or
- iii) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

U₁ is N or C(R₁), wherein R₁ is hydrogen, methyl, fluoro, or chloro;

U₂ is independently selected from CH or N;

U₃ is CH or N, such that only one of U₁ and U₂ is N in any instance;

R₂ is selected from the group consisting of hydrogen, chloro, fluoro, bromo, iodo, methyl, methanesulfonyl, trifluoromethyl, and cyano;

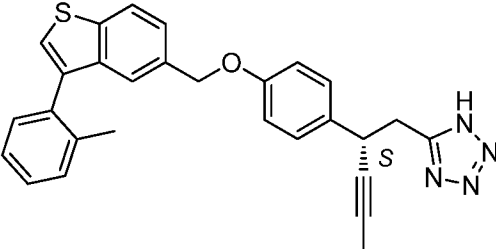
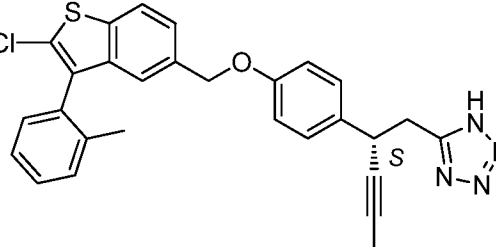
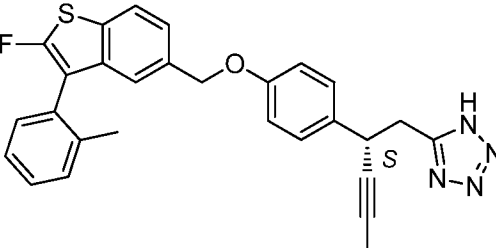
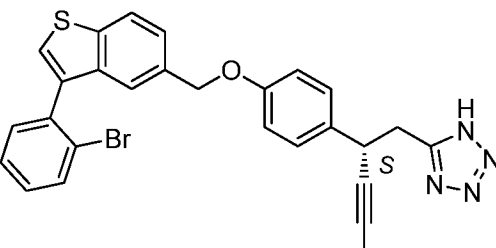
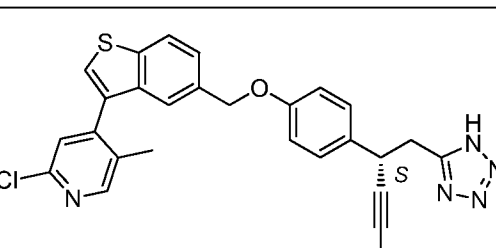
W is selected from the group consisting of 2-methylphenyl, 2-bromophenyl, 2-chloro-5-methylpyridin-4-yl, 2-methyl-4-(4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxyphenyl, 2-methyl-4-(3-methyl-3-hydroxybutoxy)phenyl, 2-methyl-4-(2-methoxyethoxy)phenyl, 2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl, 2-methyl-3-(2-methoxyethoxy)phenyl, 2-methylpyridin-3-yl, 2-methyl-4-(3-methyl-1,1-dioxidothietan-3-yl)methoxyphenyl, 2-trifluoromethylphenyl, 2-methyl-4-(methanesulfonyl)phenyl, 2-methyl-5-(2-methoxyethoxy)phenyl, 2-methyl-4-(3-methanesulfonylpropyloxy)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yloxy)phenyl, 2,6-dimethylphenyl, 2-(2-methoxyethoxy)-4-methylpyridin-5-yl, 1-methyl-1*H*-pyrazol-5-yl, 1-methyl-1*H*-1,2,4-triazol-5-yl, 4-methylpyrimidin-5-yl, 5-(2-methoxyethoxy)-3-methylpyridin-2-yl, dihydrobenzo[*b*][1,4]dioxin-5-yl, 1-(ethylcarboxy)-indolin-4-yl, 2-methyl-5-(methanesulfonylamino)phenyl, 2,2,-dimethylchroman-5-yl, 2-methyl-4-(2,3-dihydroxypropyloxy)phenyl, 2-chlorophenyl, 5-(2-methoxyethoxy)-2-methylpyridin-3-yl, cyclopropyl, cyclohexyl, cyclopentyl, isopropyl, 2-methylpiperidin-1-yl, 2-methyl-4-methoxyphenyl, *n*-propyl, hydrogen, and *n*-butyl;

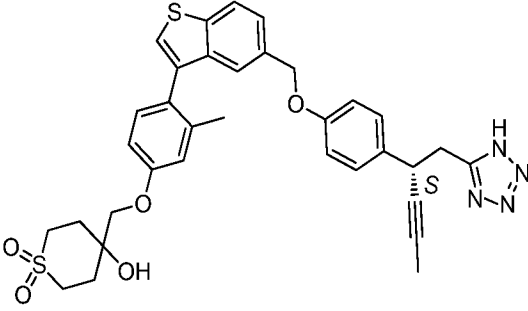
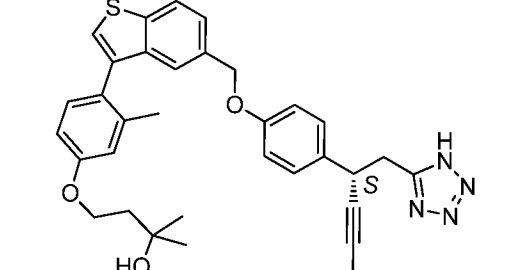
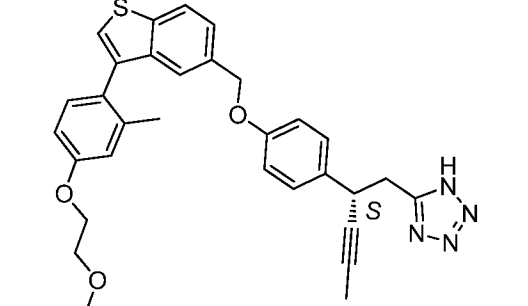
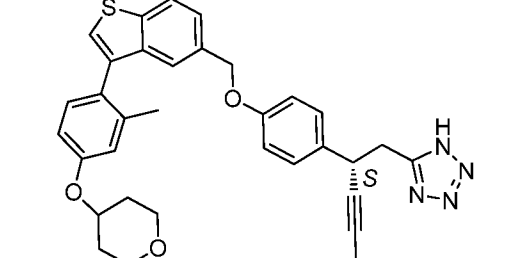
Z is CH or N;

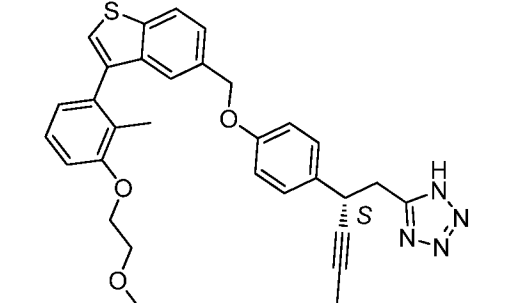
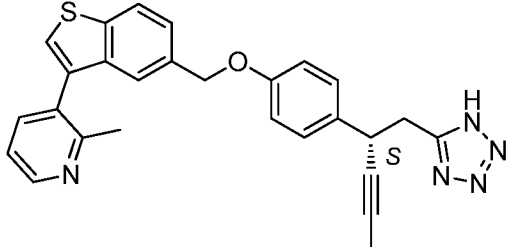
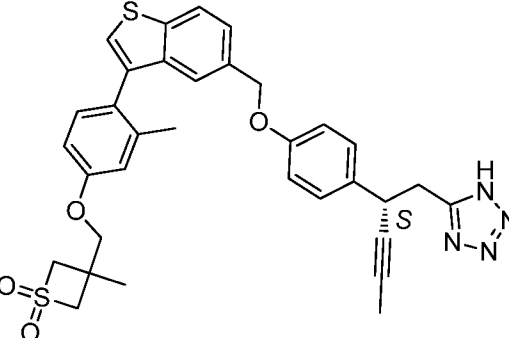
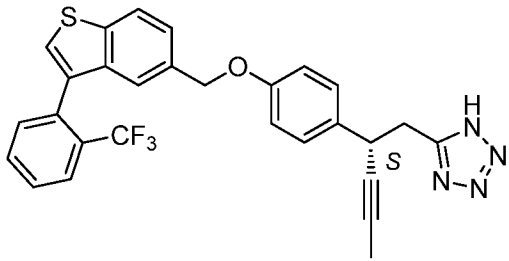
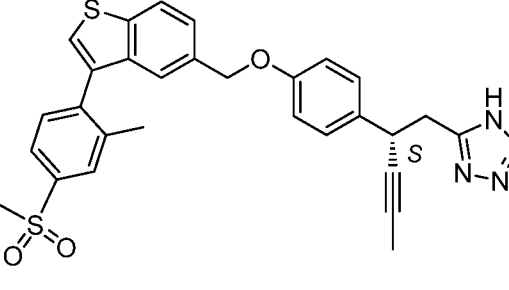
or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

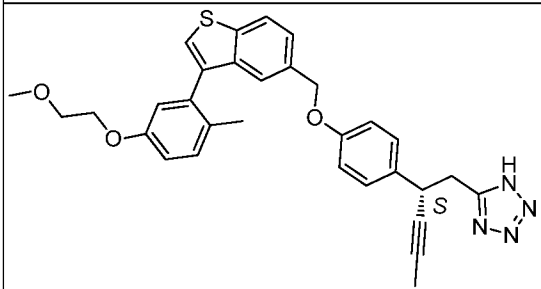
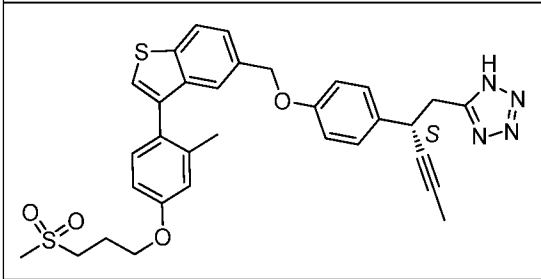
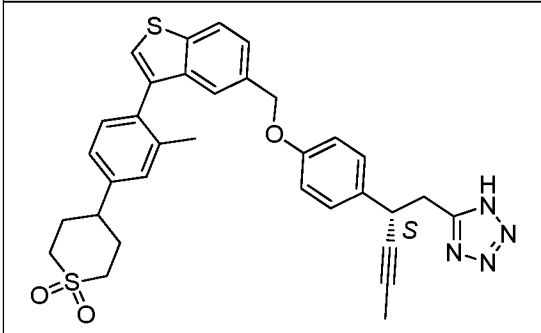
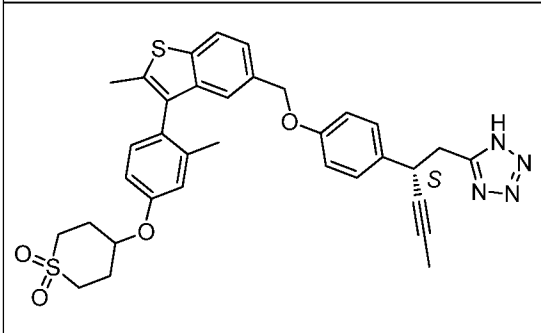
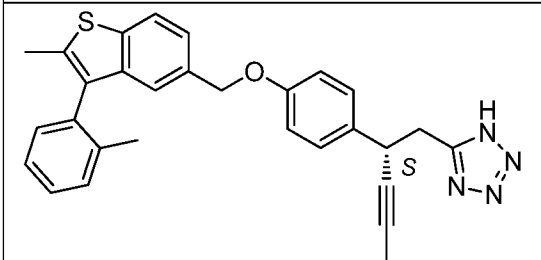
Additional embodiments of the present invention include compounds of Formula (I) as herein defined, or an enantiomer, diastereomer, solvate, or a pharmaceutically acceptable salt form thereof, as exemplified in the listing in Table 1, below.

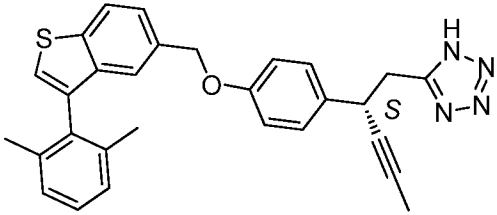
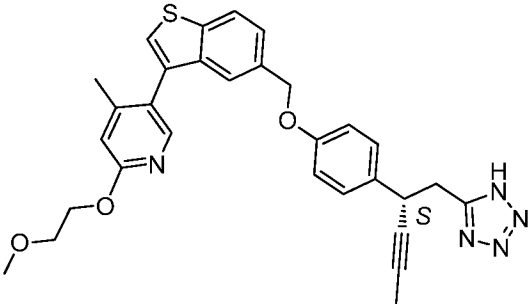
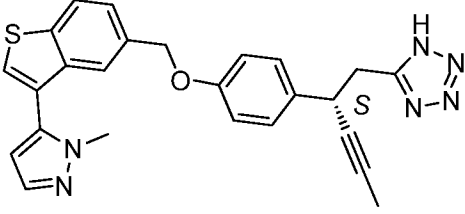
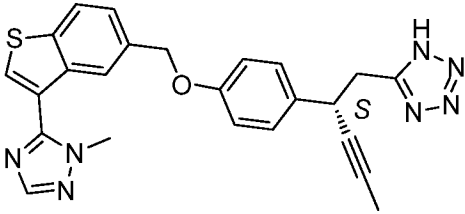
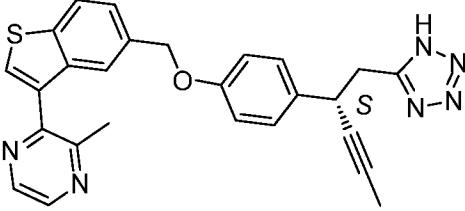
Table 1.

Structure	Cpd No.	Cpd Name
	1	(2 <i>S</i>)-5-(2-(4-((3-(2-Methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	2	5-((2 <i>S</i>)-2-(4-((2-Chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1 <i>H</i> -tetrazole
	3	5-((2 <i>S</i>)-2-(4-((2-Fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1 <i>H</i> -tetrazole
	4	(2 <i>S</i>)-5-(2-(4-((3-(2-Bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	5	(2 <i>S</i>)-4-(5-((4-(1-(1 <i>H</i> -tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-chloro-5-methylpyridine

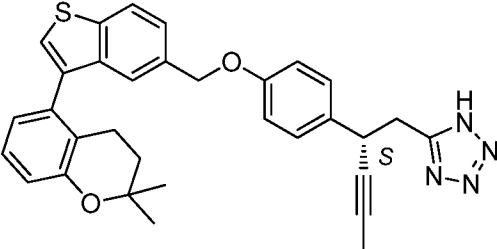
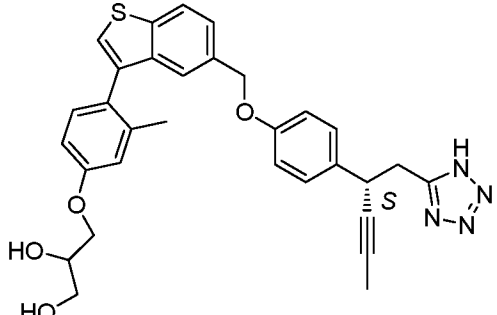
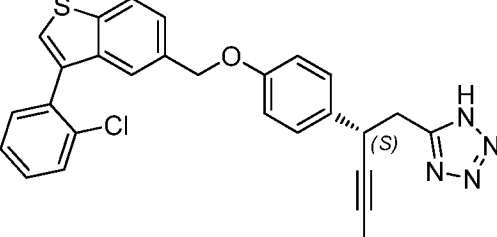
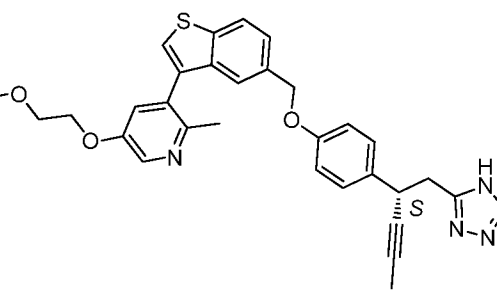
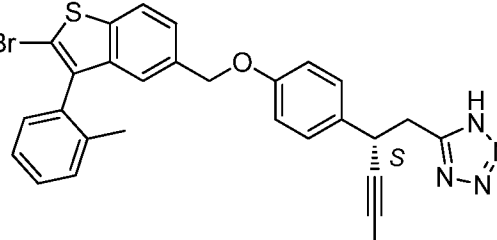
Structure	Cpd No.	Cpd Name
	6	(2 <i>S</i>)-4-((4-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)methyl)-4-hydroxytetrahydro-2 <i>H</i> -thiopyran 1,1-dioxide
	7	(2 <i>S</i>)-4-(4-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol
	8	(2 <i>S</i>)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	9	(2 <i>S</i>)-5-(2-(4-((3-(2-Methyl-4-((tetrahydro-2 <i>H</i> -pyran-4-yl)oxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole

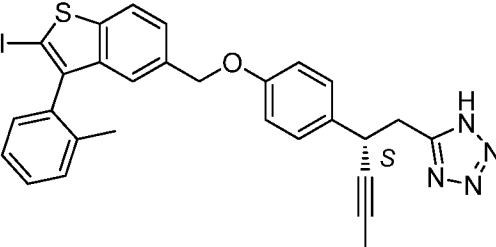
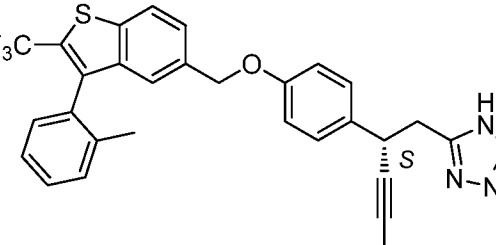
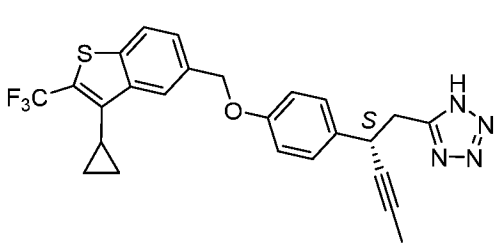
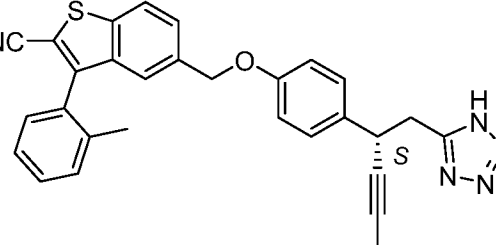
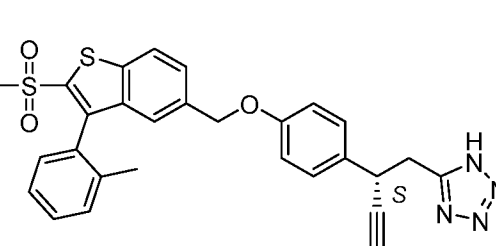
Structure	Cpd No.	Cpd Name
	10	(2 <i>S</i>)-5-(2-(4-((3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	11	(2 <i>S</i>)-3-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-methylpyridine
	12	(2 <i>S</i>)-3-((4-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)methyl)-3-methylthietane 1,1-dioxide
	13	(2 <i>S</i>)-5-(2-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	14	(2 <i>S</i>)-5-(2-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole

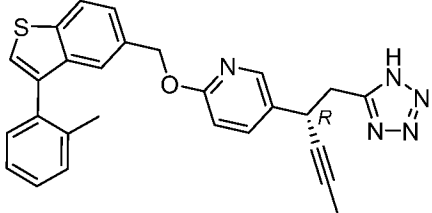
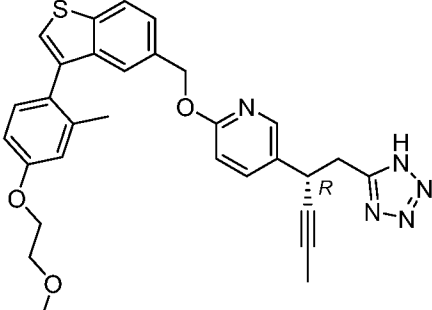
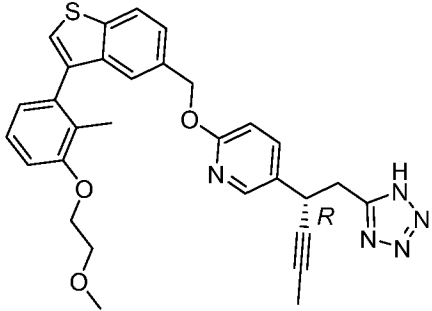
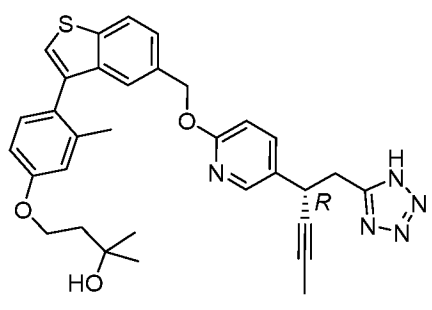
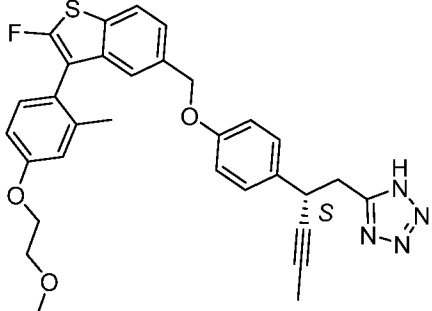
Structure	Cpd No.	Cpd Name
	15	(2 <i>S</i>)-5-(2-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	16	(2 <i>S</i>)-5-(2-(4-((3-(2-Methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	17	(2 <i>S</i>)-4-(4-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenyl)tetrahydro-2 <i>H</i> -thiopyran 1,1-dioxide
	18	4-(4-(5-((4-((2 <i>S</i>)-1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-2-methylbenzo[b]thiophen-3-yl)-3-methylphenoxy)tetrahydro-2 <i>H</i> -thiopyran 1,1-dioxide
	19	5-((2 <i>S</i>)-2-(4-((2-Methyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1 <i>H</i> -tetrazole

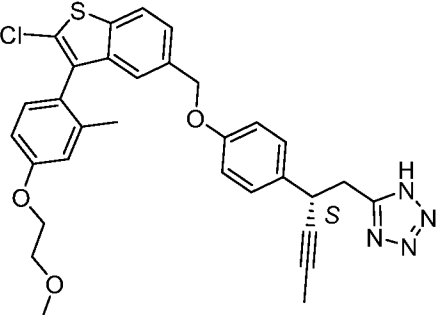
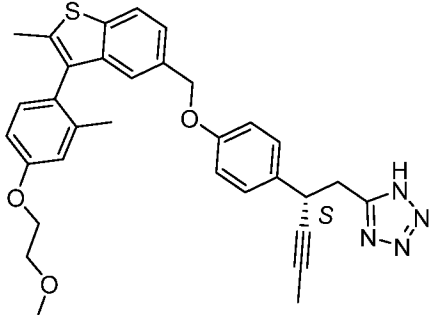
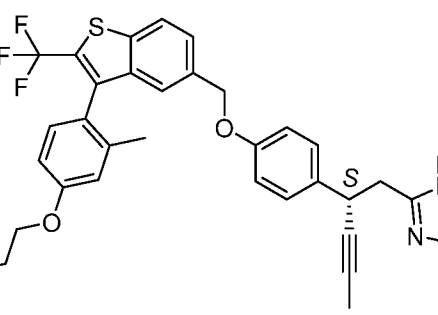
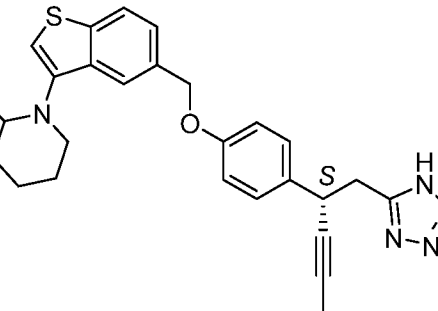
Structure	Cpd No.	Cpd Name
	20	(2 <i>S</i>)-5-(2-(4-((3-(2,6-Dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	21	(2 <i>S</i>)-5-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-(2-methoxyethoxy)-4-methylpyridine
	22	(2 <i>S</i>)-5-(2-(4-((3-(1-Methyl-1 <i>H</i> -pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	23	(2 <i>S</i>)-5-(2-(4-((3-(1-Methyl-1 <i>H</i> -1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	24	(2 <i>S</i>)-2-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylpyrazine

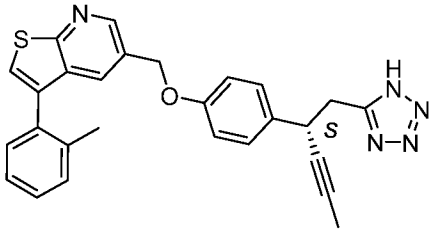
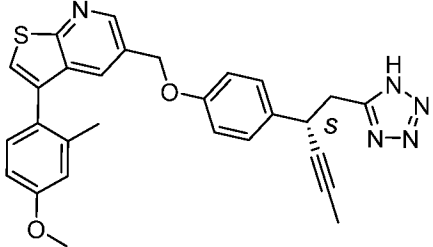
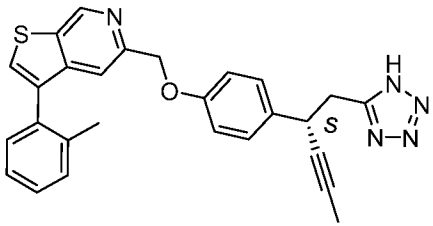
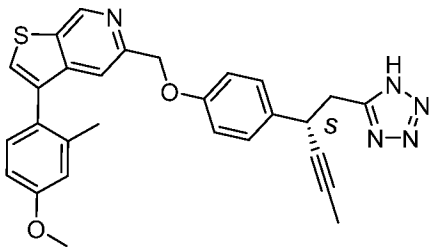
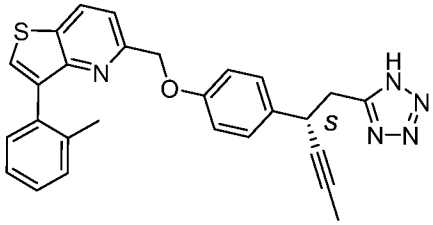
Structure	Cpd No.	Cpd Name
	25	(2 <i>S</i>)-5-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-4-methylpyrimidine
	26	(2 <i>S</i>)-2-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-5-(2-methoxyethoxy)-3-methylpyridine
	27	(2 <i>S</i>)-5-(2-(4-((3-(2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	28	(2 <i>S</i>)-1-(4-(5-((4-(1-(1 <i>H</i> -tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)indolin-1-yl)propan-1-one
	29	(2 <i>S</i>)- <i>N</i> -(3-(5-((4-(1-(1 <i>H</i> -tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-4-methylphenyl)methanesulfonamide

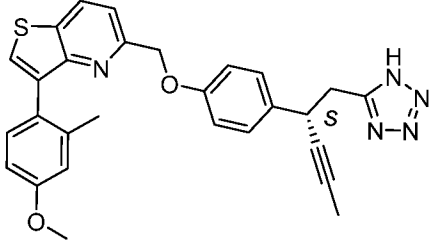
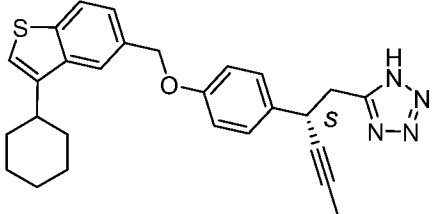
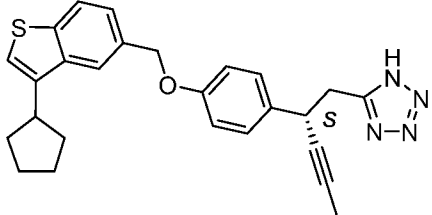
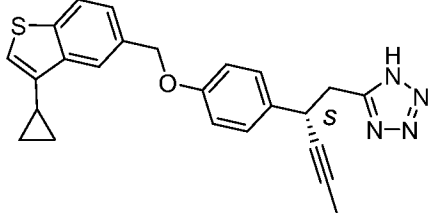
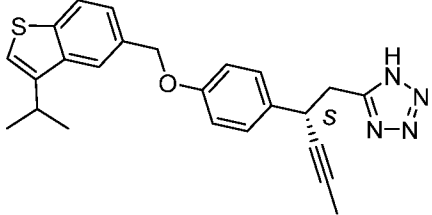
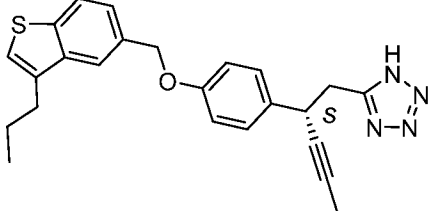
Structure	Cpd No.	Cpd Name
	30	(2 <i>S</i>)-5-(2-(4-((3-(2,2-dimethylchroman-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	31	3-(4-(5-((4-((2 <i>S</i>)-1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[<i>b</i>]thiophen-3-yl)-3-methylphenoxy)propane-1,2-diol
	32	(2 <i>S</i>)-5-(2-(4-((3-(2-Chlorophenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	33	(2 <i>S</i>)-3-(5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[<i>b</i>]thiophen-3-yl)-5-(2-methoxyethoxy)-2-methylpyridine
	34	5-((2 <i>S</i>)-2-(4-((2-Bromo-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1 <i>H</i> -tetrazole

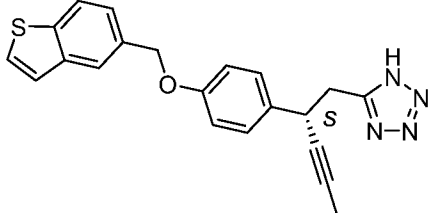
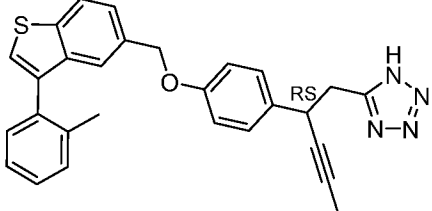
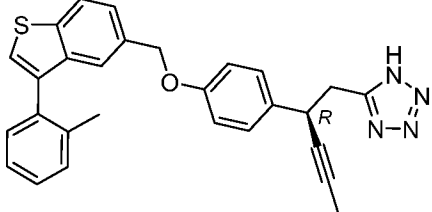
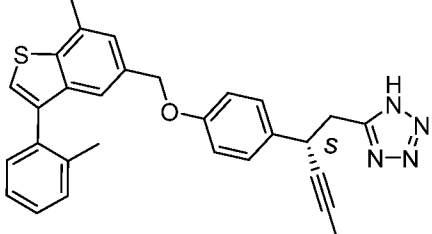
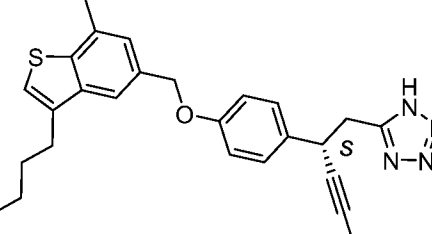
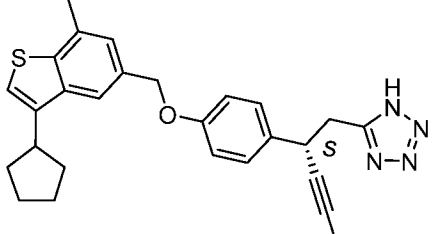
Structure	Cpd No.	Cpd Name
	35	5-((2 <i>S</i>)-2-(4-((2-Iodo-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1 <i>H</i> -tetrazole
	36	5-((2 <i>S</i>)-2-(4-((2-Trifluoromethyl-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1 <i>H</i> -tetrazole
	37	(2 <i>S</i>)-5-(2-(4-((3-Cyclopropyl-2-(trifluoromethyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	38	5-((2 <i>S</i>)-2-(4-((2-Cyano-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	39	(2 <i>S</i>)-5-(2-(4-((2-(Methylsulfonyl)-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole

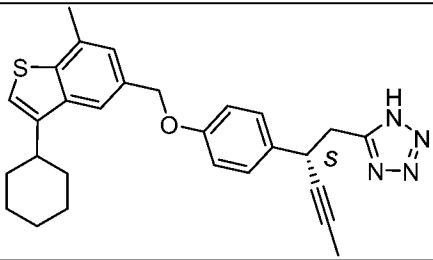
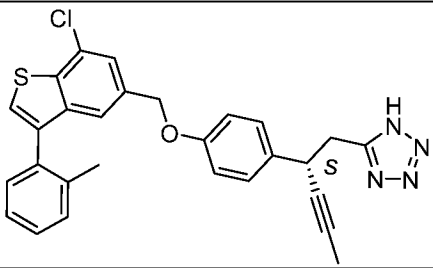
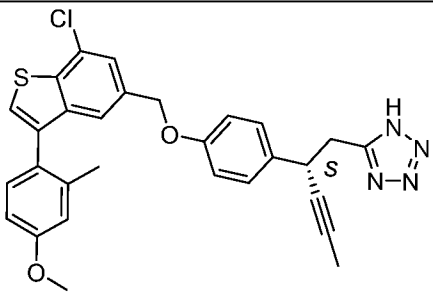
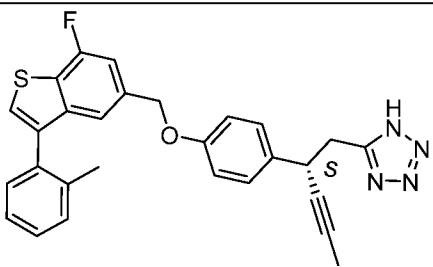
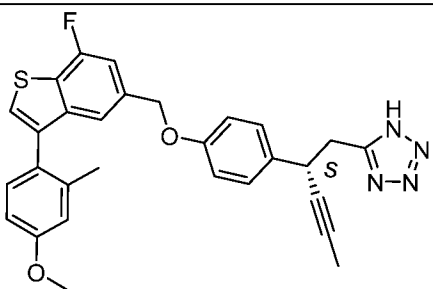
Structure	Cpd No.	Cpd Name
	40	(2 <i>R</i>)-5-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)pyridine
	41	(2 <i>R</i>)-5-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)pyridine
	42	(2 <i>R</i>)-5-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)pyridine
	43	(2 <i>R</i>)-4-(4-(5-(((5-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)pyridin-2-yl)oxy)methyl)-benzo[<i>b</i>]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol
	44	(2 <i>S</i>)-5-(2-(4-((2-Fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole

Structure	Cpd No.	Cpd Name
	45	(2 <i>S</i>)-5-(2-(4-((2-Chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	46	(2 <i>S</i>)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	47	5-((2 <i>S</i>)-2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	48	1-(5-((4-((2 <i>S</i>)-1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-methylpiperidine

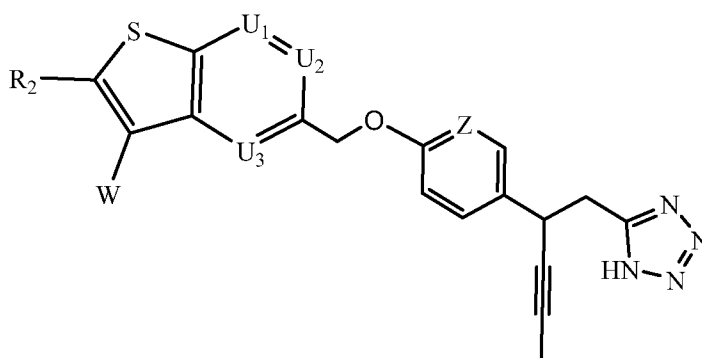
Structure	Cpd No.	Cpd Name
	49	(2 <i>S</i>)-5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3- <i>b</i>]pyridine
	50	(2 <i>S</i>)-5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3- <i>b</i>]pyridine
	51	(2 <i>S</i>)-5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3- <i>c</i>]pyridine
	52	(2 <i>S</i>)-5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3- <i>c</i>]pyridine
	53	(2 <i>S</i>)-5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[3,2- <i>b</i>]pyridine

Structure	Cpd No.	Cpd Name
	54	(2 <i>S</i>)-5-((4-(1-(1 <i>H</i> -Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[3,2- <i>b</i>]pyridine
	55	(2 <i>S</i>)-5-(2-(4-((3-Cyclohexylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	56	(2 <i>S</i>)-5-(2-(4-((3-Cyclopentylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	57	(2 <i>S</i>)-5-(2-(4-((3-Cyclopropylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	58	(2 <i>S</i>)-5-(2-(4-((3-Isopropylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	59	(2 <i>S</i>)-5-(2-(4-((3-Propylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole

Structure	Cpd No.	Cpd Name
	60	(2 <i>S</i>)-5-(2-(4-(Benzo[<i>b</i>]thiophen-5-ylmethoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	61	(2 <i>RS</i>)-5-(2-(4-((3-(2-Methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	62	(2 <i>R</i>)-5-(2-(4-((3-(2-Methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	63	(2 <i>S</i>)-5-(2-(4-((7-Methyl-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	64	(2 <i>S</i>)-5-(2-(4-((3-Butyl-7-methylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	65	(2 <i>S</i>)-5-(2-(4-((3-Cyclopentyl-7-methylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole

Structure	Cpd No.	Cpd Name
	66	(2 <i>S</i>)-5-(2-(4-((3-Cyclohexyl-7-methylbenzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	67	(2 <i>S</i>)-5-(2-(4-((7-Chloro-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	68	(2 <i>S</i>)-5-(2-(4-((7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	69	(2 <i>S</i>)-5-(2-(4-((7-Fluoro-3-(2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole
	70	(2 <i>S</i>)-5-(2-(4-((7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[<i>b</i>]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1 <i>H</i> -tetrazole

In a further embodiment, the invention is directed to a compound of Formula (I)



Formula (I)

selected from the group consisting of

- Cpd 1**, (2*S*)-5-(2-(4-((3-(2-Methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 2**, 5-((2*S*)-2-(4-((2-Chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- Cpd 3**, 5-((2*S*)-2-(4-((2-Fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- Cpd 4**, (2*S*)-5-(2-(4-((3-(2-Bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 5**, (2*S*)-4-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-chloro-5-methylpyridine;
- Cpd 6**, (2*S*)-4-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)methyl)-4-hydroxytetrahydro-2*H*-thiopyran 1,1-dioxide;
- Cpd 7**, (2*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol;
- Cpd 8**, (2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 9**, (2*S*)-5-(2-(4-((3-(2-Methyl-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

- Cpd 10**, (2*S*)-5-(2-(4-((3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 11**, (2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-methylpyridine;
- Cpd 12**, (2*S*)-3-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)methyl)-3-methylthietane 1,1-dioxide;
- Cpd 13**, (2*S*)-5-(2-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 14**, (2*S*)-5-(2-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 15**, (2*S*)-5-(2-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 16**, (2*S*)-5-(2-(4-((3-(2-Methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 17**, (2*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenyl)tetrahydro-2*H*-thiopyran 1,1-dioxide;
- Cpd 18**, 4-(4-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-2-methylbenzo[*b*]thiophen-3-yl)-3-methylphenoxy)tetrahydro-2*H*-thiopyran 1,1-dioxide;
- Cpd 19**, 5-((2*S*)-2-(4-((2-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- Cpd 20**, (2*S*)-5-(2-(4-((3-(2,6-Dimethylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 21**, (2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-(2-methoxyethoxy)-4-methylpyridine;

- Cpd 22**, (2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 23**, (2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 24**, (2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylpyrazine;
- Cpd 25**, (2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-4-methylpyrimidine;
- Cpd 26**, (2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)-methyl)benzo[*b*]thiophen-3-yl)-5-(2-methoxyethoxy)-3-methylpyridine;
- Cpd 27**, (2*S*)-5-(2-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 28**, (2*S*)-1-(4-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one;
- Cpd 29**, (2*S*)-*N*-(3-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-4-methylphenyl)methanesulfonamide;
- Cpd 30**, (2*S*)-5-(2-(4-((3-(2,2-dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 31**, 3-(4-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)propane-1,2-diol;
- Cpd 32**, (2*S*)-5-(2-(4-((3-(2-Chlorophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 33**, (2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-5-(2-methoxyethoxy)-2-methylpyridine;
- Cpd 34**, 5-((2*S*)-2-(4-((2-Bromo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- Cpd 35**, 5-((2*S*)-2-(4-((2-Iodo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;

- Cpd 36**, 5-((2*S*)-2-(4-((2-Trifluoromethyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- Cpd 37**, (2*S*)-5-(2-(4-((3-Cyclopropyl-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 38**, 5-((2*S*)-2-(4-((2-Cyano-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 39**, (2*S*)-5-(2-(4-((2-(Methylsulfonyl)-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 40**, (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridine;
- Cpd 41**, (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridine;
- Cpd 42**, (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridine;
- Cpd 43**, (2*R*)-4-(4-(5-(((5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)pyridin-2-yl)oxy)methyl)-benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol;
- Cpd 44**, (2*S*)-5-(2-(4-((2-Fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 45**, (2*S*)-5-(2-(4-((2-Chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 46**, (2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 47**, 5-((2*S*)-2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 48**, 1-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-methylpiperidine;
- Cpd 49**, (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*b*]pyridine;

- Cpd 50**, (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*b*]pyridine;
- Cpd 51**, (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*c*]pyridine;
- Cpd 52**, (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*c*]pyridine;
- Cpd 53**, (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[3,2-*b*]pyridine;
- Cpd 54**, (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[3,2-*b*]pyridine;
- Cpd 55**, (2*S*)-5-(2-(4-((3-Cyclohexylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 56**, (2*S*)-5-(2-(4-((3-Cyclopentylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 57**, (2*S*)-5-(2-(4-((3-Cyclopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 58**, (2*S*)-5-(2-(4-((3-Isopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 59**, (2*S*)-5-(2-(4-((3-Propylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 60**, (2*S*)-5-(2-(4-(Benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 61**, (2*RS*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 62**, (2*R*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 63**, (2*S*)-5-(2-(4-((7-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

- Cpd 64**, (2*S*)-5-(2-(4-((3-Butyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 65**, (2*S*)-5-(2-(4-((3-Cyclopentyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 66**, (2*S*)-5-(2-(4-((3-Cyclohexyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 67**, (2*S*)-5-(2-(4-((7-Chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 68**, (2*S*)-5-(2-(4-((7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 69**, (2*S*)-5-(2-(4-((7-Fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- Cpd 70**, (2*S*)-5-(2-(4-((7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole

or a pharmaceutically acceptable salt form thereof.

For use in medicine, salts of compounds of Formula (I) refer to non-toxic “pharmaceutically acceptable salts.” Other salts may, however, be useful in the preparation of compounds of Formula (I) or of their pharmaceutically acceptable salt forms thereof. Suitable pharmaceutically acceptable salts of compounds of Formula (I) include acid addition salts that can, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as, hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of Formula (I) carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts such as, sodium or potassium salts; alkaline earth metal salts such as, calcium or magnesium salts; and salts formed with suitable organic ligands such as, quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts

include acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoate, tosylate, triethiodide, and valerate.

Representative acids and bases that may be used in the preparation of pharmaceutically acceptable salts include acids including acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-gluconic acid, L-glutamic acid, α -oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (\pm)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (\pm)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebaic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid; and bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-

hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine, tromethamine, and zinc hydroxide.

Embodiments of the present invention include prodrugs of compounds of Formula (I). In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treating or preventing embodiments of the present invention, the term “administering” encompasses the treatment or prevention of the various diseases, conditions, syndromes and disorders described with the compound specifically disclosed or with a compound that may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to a patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in “Design of Prodrugs”, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to embodiments of this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention. The skilled artisan will understand that the term compound as used herein, is meant to include solvated compounds of Formula (I).

Where the processes for the preparation of the compounds according to certain embodiments of the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as, preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as, the formation of diastereomeric pairs by salt formation with an optically active acid such as,

(-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

One embodiment of the present invention is directed to a composition, including a pharmaceutical composition, comprising, consisting of, and/or consisting essentially of the (+)-enantiomer of a compound of Formula (I) wherein said composition is substantially free from the (-)-isomer of said compound. In the present context, substantially free means less than about 25 %, preferably less than about 10 %, more preferably less than about 5 %, even more preferably less than about 2 % and even more preferably less than about 1 % of the (-)-isomer calculated as

$$\% (+) - \text{enantiomer} = \frac{(\text{mass} (+) - \text{enantiomer})}{(\text{mass} (+) - \text{enantiomer}) + (\text{mass} (-) - \text{enantiomer})} \times 100$$

Another embodiment of the present invention is a composition, including a pharmaceutical composition, comprising, consisting of, and consisting essentially of the (-)-enantiomer of a compound of Formula (I) wherein said composition is substantially free from the (+)-isomer of said compound. In the present context, substantially free from means less than about 25 %, preferably less than about 10 %, more preferably less than about 5 %, even more preferably less than about 2 % and even more preferably less than about 1 % of the (+)-isomer calculated as

$$\% (-) - \text{enantiomer} = \frac{(\text{mass} (-) - \text{enantiomer})}{(\text{mass} (+) - \text{enantiomer}) + (\text{mass} (-) - \text{enantiomer})} \times 100$$

During any of the processes for preparation of the compounds of the various embodiments of the present invention, it may be necessary and/or desirable to protect

sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups such as those described in *Protective Groups in Organic Chemistry, Second Edition*, J.F.W. McOmie, Plenum Press, 1973; T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis, Third Edition*, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Even though the compounds of embodiments of the present invention (including their pharmaceutically acceptable salts and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient and/or a pharmaceutically acceptable diluent selected with regard to the intended route of administration and standard pharmaceutical or veterinary practice. Thus, particular embodiments of the present invention are directed to pharmaceutical and veterinary compositions comprising compounds of Formula (I) and at least one pharmaceutically acceptable carrier, pharmaceutically acceptable excipient, and/or pharmaceutically acceptable diluent.

By way of example, in the pharmaceutical compositions of embodiments of the present invention, the compounds of Formula (I) may be admixed with any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilizing agent(s), and combinations thereof.

Solid oral dosage forms such as, tablets or capsules, containing the compounds of the present invention may be administered in at least one dosage form at a time, as appropriate. It is also possible to administer the compounds in sustained release formulations.

Additional oral forms in which the present inventive compounds may be administered include elixirs, solutions, syrups, and suspensions; each optionally containing flavoring agents and coloring agents.

Alternatively, compounds of Formula (I) can be administered by inhalation

(intratracheal or intranasal) or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream comprising, consisting of, and/or consisting essentially of an aqueous emulsion of polyethylene glycols or liquid paraffin. They can also be incorporated, at a concentration of between about 1 % and about 10 % by weight of the cream, into an ointment comprising, consisting of, and/or consisting essentially of a wax or soft paraffin base together with any stabilizers and preservatives as may be required. An alternative means of administration includes transdermal administration by using a skin or transdermal patch.

The pharmaceutical compositions of the present invention (as well as the compounds of the present invention alone) can also be injected parenterally, for example, intracavernosally, intravenously, intramuscularly, subcutaneously, intradermally, or intrathecally. In this case, the compositions will also include at least one of a suitable carrier, a suitable excipient, and a suitable diluent.

For parenteral administration, the pharmaceutical compositions of the present invention are best used in the form of a sterile aqueous solution that may contain other substances, for example, enough salts and monosaccharides to make the solution isotonic with blood.

For buccal or sublingual administration, the pharmaceutical compositions of the present invention may be administered in the form of tablets or lozenges, which can be formulated in a conventional manner.

By way of further example, pharmaceutical compositions containing at least one of the compounds of Formula (I) as the active ingredient can be prepared by mixing the compound(s) with a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, and/or a pharmaceutically acceptable excipient according to conventional pharmaceutical compounding techniques. The carrier, excipient, and diluent may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral, etc.). Thus, for liquid oral preparations such as, suspensions, syrups, elixirs and solutions, suitable carriers, excipients and diluents include water, glycols, oils, alcohols,

flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations such as, powders, capsules, and tablets, suitable carriers, excipients and diluents include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations also may be optionally coated with substances such as, sugars, or be enterically coated so as to modulate the major site of absorption and disintegration. For parenteral administration, the carrier, excipient and diluent will usually include sterile water, and other ingredients may be added to increase solubility and preservation of the composition. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives such as, solubilizers and preservatives.

A therapeutically effective amount of a compound of Formula (I) or a pharmaceutical composition thereof includes a dose range from about 0.1 mg to about 3000 mg, or any particular amount or range therein, in particular from about 1 mg to about 1000 mg, or any particular amount or range therein, or, more particularly, from about 10 mg to about 500 mg, or any particular amount or range therein, of active ingredient in a regimen of about 1 to about 4 times per day for an average (70 kg) human; although, it is apparent to one skilled in the art that the therapeutically effective amount for a compound of Formula (I) will vary as will the diseases, syndromes, conditions, and disorders being treated.

For oral administration, a pharmaceutical composition is preferably provided in the form of tablets containing about 1.0, about 10, about 50, about 100, about 150, about 200, about 250, and about 500 milligrams of a compound of Formula (I).

Advantageously, a compound of Formula (I) may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three and four times daily.

Optimal dosages of a compound of Formula (I) to be administered may be readily determined and will vary with the particular compound used, the mode of administration, the strength of the preparation and the advancement of the disease, syndrome, condition or disorder. In addition, factors associated with the particular subject being treated, including

subject gender, age, weight, diet and time of administration, will result in the need to adjust the dose to achieve an appropriate therapeutic level and desired therapeutic effect. The above dosages are thus exemplary of the average case. There can be, of course, individual instances wherein higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of Formula (I) may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever use of a compound of Formula (I) is required for a subject in need thereof.

One embodiment of the present invention is directed to a pharmaceutical composition comprising 3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid (compound 97) and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.

Another embodiment of the present invention is directed to a pharmaceutical composition comprising (3*S*)-3-[4-[[3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid (compound 2) and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.

As GPR40 agonists, the compounds of Formula (I) are useful in methods for treating or preventing a disease, a syndrome, a condition or a disorder in a subject, including an animal, a mammal and a human in which the disease, the syndrome, the condition or the disorder is affected by the modulation, including agonism, of the GPR40 receptor. Such methods comprise, consist of and/or consist essentially of administering to a subject, including an animal, a mammal, and a human, in need of such treatment or prevention, a therapeutically effective amount of a compound, salt or solvate of Formula (I).

In another embodiment, the present invention is directed to a compound of Formula (I) for use in the treatment of a disorder affected by the agonism of GPR40 receptor selected from the group consisting of Type 2 diabetes mellitus, obesity, obesity related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cholesterol/lipids, osteoporosis, inflammation and eczema; preferably, Type II diabetes mellitus, metabolic syndrome, and impaired glucose tolerance; more preferably, Type II diabetes mellitus or impaired glucose tolerance.

In another embodiment, the present invention is directed to a compound of Formula (I) for use in the treatment of Type 2 diabetes mellitus.

GENERAL SYNTHETIC METHODS

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and illustrated in the schemes and examples that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions described in the schemes and examples. The various starting materials used in the schemes and examples are commercially available or may be prepared by methods well within the skill of persons versed in the art. The variables are as defined herein.

Abbreviations used in the instant specification, particularly the schemes and examples, are as follows:

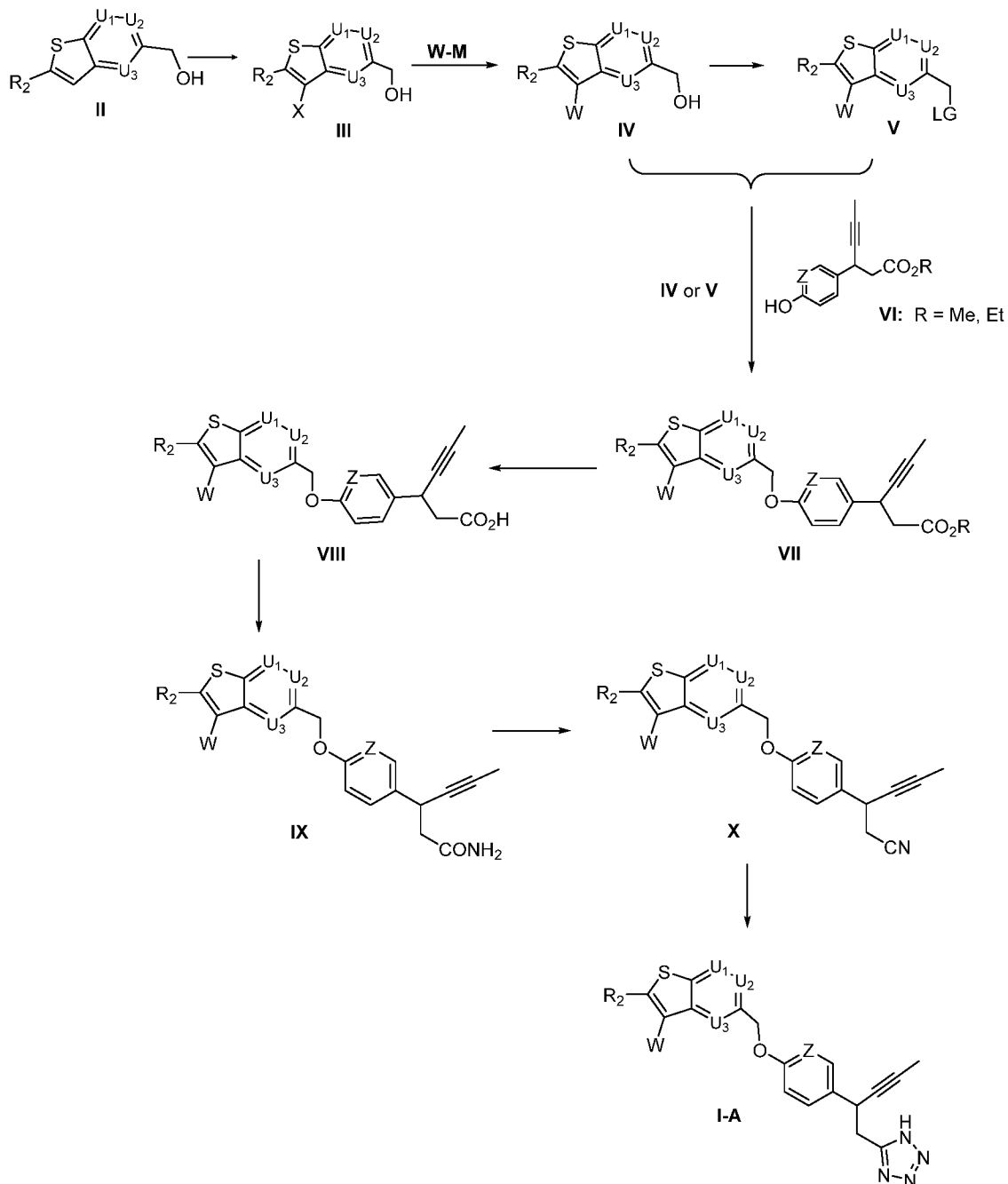
ADDP	azodicarboxylic acid dipiperidide
aq	aqueous
Boc	<i>tert</i> -butoxycarbonyl
DBAD	di- <i>tert</i> -butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane

DEA	diethylamine
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	dimethylformamide
DMSO	methyl sulfoxide
eq.	equivalents
Et	ethyl
EtOAc	ethyl acetate
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'- tetramethyluronium hexafluorophosphate
HBTU	2-(1 <i>H</i> -Benzotriazole-1-yl)-1,1,3,3- tetramethyluronium hexafluorophosphate)
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
LAH	lithium aluminum hydride
LC/MS	high pressure liquid chromatography with mass spectrometry
mCPBA	3-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methyl alcohol
mg	milligram
MOM	methoxymethyl

MsCl	methanesulfonyl chloride
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NMP	N-methyl-2-pyrrolidone
$\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex)
$\text{Pd}_2(\text{dba})_3$	tris(dibenzylideneacetone)dipalladium(0)
rt	room temperature
Ru-Phos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
satd.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBSCl	<i>tert</i> -butyldimethylsilyl chloride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
wt.	weight

Scheme A illustrates a method for the preparation of certain compounds of Formula (I) of the present invention.

Scheme A



Certain compounds of Formula **(I-A)** may be synthesized as outlined by the general synthetic route illustrated in Scheme A. 5-Hydroxymethylbenzothiophene **II** may be treated with a halogenating reagent such as NBS, NIS in a suitable solvent such as DCM,

DCE, CCl₄, THF, dioxane, DMF and the like, or, with Br₂ in HOAc, at a temperature preferably in the range of from about 0 and 50 °C to provide a 3-halogenated benzothiophene of formula **III** wherein X is bromo or iodo. The halogenated benzothiophene of formula **III** may be reacted with a compound of formula **W-M** wherein W is as defined herein, under suitable coupling conditions, to yield the corresponding coupling product of formula **IV**. A compound of formula **W-M** is chosen wherein W may be substituted aryl groups such as (R₃)(R₅)-G, heteroaryl groups as defined above or alkyl or cycloalkyl groups and M may be (a) a boronic acid to form a compound of formula W-B(OH)₂; (b) a suitably selected boronic ester such as pinacolatoboryl, neopentylglycolatoboryl, or the like; (c) a suitably selected trialkylstannyl such as tri(*n*-butyl)tin, or the like; (d) a suitably selected trialkylsilyl such as triallylsilyl, or the like; (e) a suitably selected aryldialkylsilyl such as 2-(hydroxymethyl)phenyldimethylsilyl, or the like; or (f) a suitably selected organo zinc reagent such as W-ZnX wherein X is a halogen such as chloro, bromo, or iodo.

For example, a compound of formula **W-M**, wherein M is preferably -B(OH)₂ or a suitably selected boronic ester, may be reacted with a compound of formula **III** under Suzuki coupling conditions, more particularly in the presence of a suitably selected palladium catalyst selected from palladium (II) acetate, palladium (II) chloride, *bis*(acetonitrile)-dichloro-palladium(II), allylpalladium (II) chloride dimer, *tris*(dibenzylideneacetone) dipalladium (0) (Pd₂(dba)₃), 2-(di-*tert*-butylphosphino)biphenyl, dichloro-*bis*(di-*tert*-butylphenylphosphine)-palladium (II), [1,1'-*bis*-(diphenylphosphino)-ferrocene]-palladium (II) dichloride dichloromethane adduct (PdCl₂(dppf)DCM), *tetrakis*(triphenylphosphine) palladium(0) (Pd(PPh₃)₄), (1,1'-*bis*(di-*tert*-butylphosphino)ferrocene) palladium (II) chloride, and the like; optionally in the presence of a suitably selected ligand such as triphenylphosphine, tri-*o*-tolylphosphine, tributylphosphine, tri(*tert*-butyl)-phosphine, tricyclohexylphosphine, 1,1'-*bis*(diphenylphosphino)-ferrocene, 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl, S-Phos, Ru-Phos, *bis*[2-(diphenyl-phosphino)phenyl] ether, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, tris(2-furyl)phosphine, 1-butyl-3-

methylimidazolium hexafluorophosphate, or the like; in the presence of a suitably selected inorganic base such as cesium carbonate, potassium carbonate, sodium carbonate, cesium fluoride, potassium fluoride, tetrabutylammonium fluoride, potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydroxide, sodium bicarbonate; or potassium phosphate; preferably, sodium carbonate; in a suitably selected solvent such as ethanol, THF, DMF, toluene, benzene, DME, H₂O, 1,4-dioxane, and the like, or a combination thereof; at a temperature ranging from about rt to about 180 °C.

A compound of formula **IV** may be reacted under Mitsunobu conditions (for a review, see: Mitsunobu, O. *Synthesis* (1981), 1-28) with compounds of formula **VI** in the presence of triphenylphosphine, tri-*n*-butylphosphine, tri-*tert*-butylphosphine, or a resin-bound triphenylphosphine equivalent such as PS-PPh₃; and an azido coupling reagent such as DIAD, ADDP, DBAD, DEAD, or the like; in an organic solvent such as THF, MeCN, toluene, N,N-DMA, or the like; at a temperature preferably in the range of from about 25 to 100 °C, to yield a compound of formula **VII**.

Alternatively, the alcoholic function of a compound of formula **IV** may be converted to a suitable leaving group (LG) such as chloro, bromo, iodo, tosylate, mesylate, nosylate, or the like, (March, J. *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 2nd ed.; McGraw-Hill Co.: New York, 1977; pp 326) to form a compound of formula **V**, which may then react with a compound of formula **VI** in the presence of a suitable base to provide a compound of formula **VII**. For example, treatment of a compound of formula **IV** with a halogenating agent such as oxalyl chloride, oxalyl bromide, thionyl chloride, thionyl bromide, Ph₃PBr₂, PBr₃, or the like; or with a sulfonyl halide such as tosyl chloride, mesyl chloride, nosyl chloride, or the like; in the presence of a base such as K₂CO₃, Cs₂CO₃, KOH, NaH, or the like; in a solvent such as NMP, DMF, THF, or the like; at a temperature preferably in the range of from about 25 to 150 °C may provide a compound of formula **V**. Reaction of a compound of formula **V** with a compound of formula **VI** in the presence of a suitable base such as K₂CO₃, Cs₂CO₃, KOH, NaH, or the like, in a solvent such as NMP, DMF, THF, or the like; at a temperature

preferably in the range of from about 25 to 150 °C; may provide a compound of formula **VII**.

One skilled in the art will recognize that for the preparation of certain compounds of the present invention, the order in which the above transformations are carried out to provide compounds of formula **VII** may be reversed. For example, a compound of formula **VI** may be reacted with a compound of formula **III** or a derivative thereof, and subsequently reacted with a compound of formula **W-M** to provide a compound of formula **VII**.

Hydrolysis of the ester functionality of a compound of formula **VII** may be effected under a variety of conditions to provide a compound of formula **VIII** (such as described in T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999). For example, treatment of a compound of formula **VII** with a base such as NaOH, LiOH, KOH, CsOH, or the like; in a solvent such as THF, EtOH, MeOH, a dioxane and water mixture, or the like, or mixtures thereof; at a temperature in the range of from about 25 to 100 °C; may provide a compound of formula **VIII**. The preferred method for this transformation includes the treatment of a compound of formula **VII** with an aqueous base such as NaOH or LiOH; in a solvent mixture such as THF/MeOH; at about room temperature.

A carboxylic acid of formula **VIII** may be converted to its corresponding nitrile of formula **X** following conventional methods available in the scientific literature. A preferred method for this transformation includes conversion of an acid of formula **VIII** to its corresponding primary amide of formula **IX**, followed by the dehydration of the latter to the corresponding nitrile of formula **X**. The conversion of an acid of formula **VIII** to the corresponding primary amide of formula **IX** includes, but is not limited to, reaction with ammonia or an ammonia equivalent under suitable coupling conditions, in the presence of one or more suitable catalysts or activators. A preferred method for this transformation is reaction of a carboxylic acid with ammonium chloride, in the presence of a coupling agent such as HBTU, HATU, or the like; in a solvent such as THF, DCM, DMF, or the like; at a temperature in the range of from about -20 to 50 °C. Alternatively, in a two-stage process,

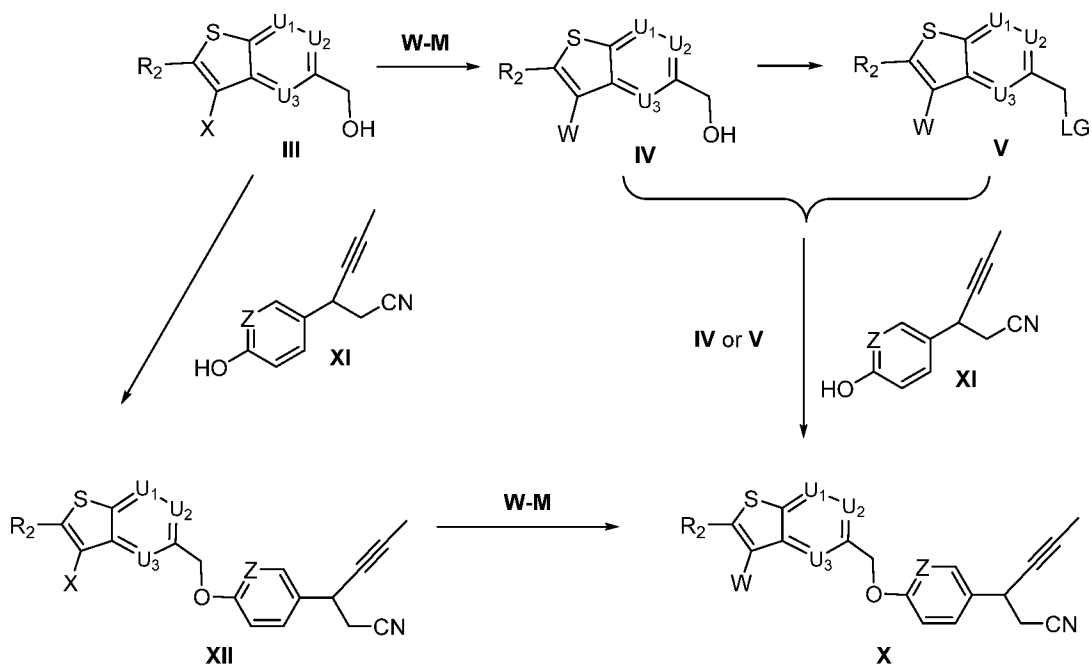
a carboxylic acid of formula **VIII** may be converted to its corresponding acid chloride by treatment with oxalyl chloride, thionyl chloride, or the like, followed by treatment with ammonia, to provide the corresponding amide of formula **IX**. One of ordinary skill in the art will recognize that there are a variety of reagents and reaction conditions available for the dehydration of the primary amides to corresponding nitriles. A preferred method for this transformation includes treatment of a compound of formula **IX** with triflic anhydride as a dehydrating reagent, in the presence of a base, such as TEA, DIEA, or the like; in a solvent such as DCM, DCE, or the like; at a temperature in the range of from about -20 to 50 °C, preferably at a temperature in the range of from about 0 °C to 5 °C. The addition of azide ion to the nitrile is a convenient way to obtain a desired tetrazole of Formula **I-A** from a compound of formula **X**.

It is understood that the chemical literature is replete with methods and protocols to perform this transformation. The addition of a silyl azide, such as Me₃SiN₃, in the presence of a suitable catalyst such as Bu₂SnO; in a solvent such as toluene or xylene; at an elevated temperature, preferably in the range of from about 70 to 130 °C; is a preferred method for carrying out this conversion. It should be understood that certain compounds of formulas **W-M**, **IV**, **V**, or **VII**, **W** may contain functionalities that may optionally bear a suitable functional protecting group (**P**) (see *Protective Groups in Organic Chemistry*, J.F.W. McOmie, Ed.; Plenum Press: 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999). In such cases where the R₃ substituent contains one or more amino groups, suitable protecting groups such as Boc, Cbz, or the like, may be incorporated, which may subsequently be removed under appropriate conditions known to those skilled in the art. For example, Boc-protected amines may be deprotected under acidic conditions using reagents such as HCl, TFA, and the like. Likewise, Cbz-protected amines may be deprotected under acidic conditions or hydrogenolysis. In the case where an R₃ substituent contains one or more carboxyl groups, suitable protecting groups such as methyl, ethyl and *t*-butyl esters, or the like, may be incorporated, which may subsequently be removed under acidic conditions using HCl, TFA, or the like. In the case where R₃ is substituted with one or more hydroxy

groups, suitable protecting groups such as MOM, THP, *t*-butyl ethers, acetonides (for 1,2-dihydroxylated substituents), or the like, may be incorporated, and subsequently removed under acidic conditions such as HCl, TFA, or the like. The unmasked functionalities generated by deprotection may be subjected to further chemical transformations according to methods known in the art, to provide additional derivatives of Formula **I-A**.

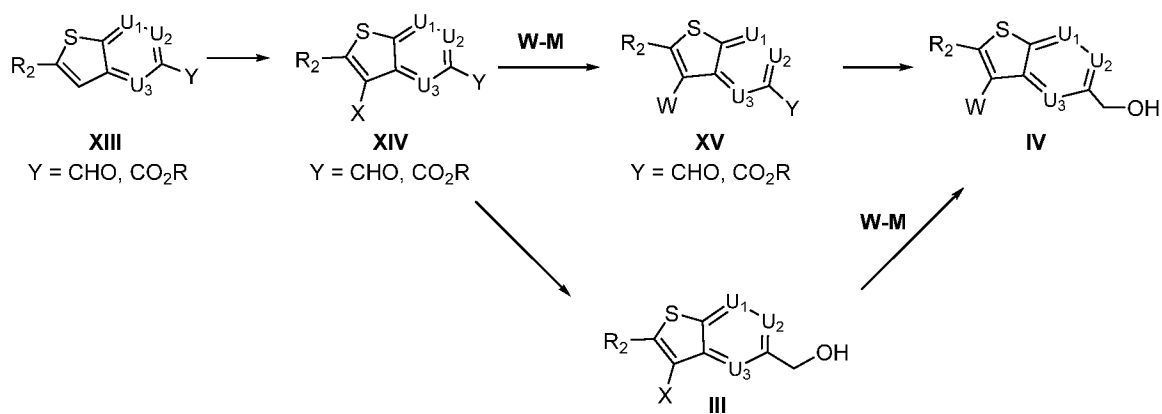
Compounds of formula **X** may be obtained by an alternate route, as illustrated in general Scheme B, by the incorporation of a hydroxyarylpropionitrile of formula **XI** in place of a hydroxyarylpropionic ester of formula **VI**. Thus, compounds of formula **X** may be obtained directly by suitable reaction with a compound of formulas **IV** or **V**, using methods described in Scheme A. Alternatively, incorporation of a hydroxyarylpropionitrile of formula **XI** may precede the incorporation of a compound of formula **W-M**. Thus, reaction of a hydroxyarylpropionitrile of formula **XI** with a compound of formula **III** under Mitsunobu conditions, as described above, may provide a compound of formula **XII**. These, in turn, may be reacted with a compound of formula **W-M** to provide a compound of formula **X**.

Scheme B



In certain cases, a compound of formula IV of the present invention may be prepared from an alternative starting material, wherein either an aldehyde or an ester functionality may serve as a precursor for the hydroxymethyl group, as illustrated in Scheme C.

Scheme C

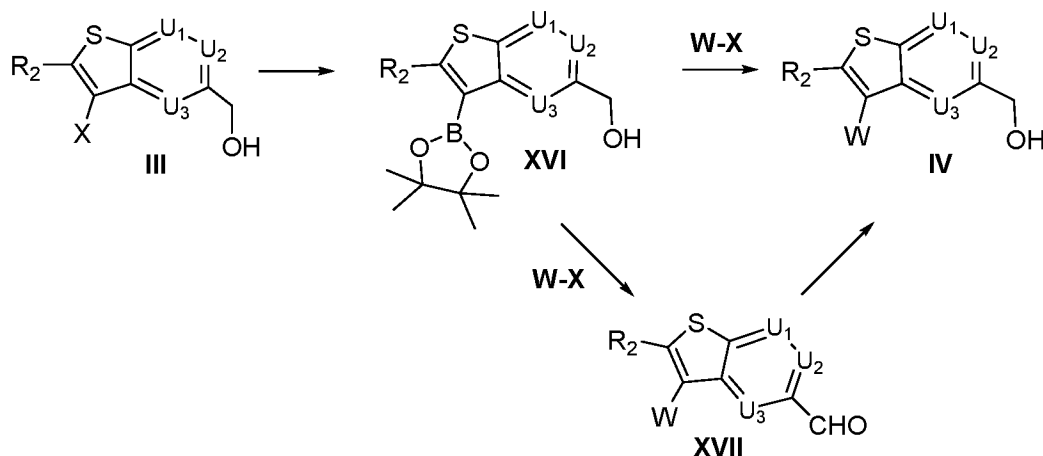


In such cases, a compound of formula XIII may be halogenated to provide a compound of

formula **XIV**, which in turn may be converted to a compound of formula **XV** via a coupling reaction with a compound of formula **W-M**, using the methods outlined in Scheme A. The ester or aldehyde functionality of a compound of formula **XV** may be reduced upon treatment with a suitably selected reducing agent (as described in Larock, R. C. *Comprehensive Organic Transformations. A Guide to Functional Group Preparations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 61), such as NaBH₄, LAH, B₂H₆, DIBAL-H, NaCNBH₃, AlH₃, LiAlH(O-t-Bu)₃, KBH(O-i-Pr)₃, or the like; preferably NaBH₄ or B₂H₆, in a solvent such as THF, ether, dioxane, MeOH, EtOH, or the like; at a temperature preferably in the range of from about 0 to 75 °C; to provide the corresponding benzylic alcohol of formula **IV**. In certain cases, the order of these transformations may be reversed, such that the reduction of a compound of formula **XIV** to afford a compound of formula **III** precedes the coupling reaction with a compound of formula **W-M**.

In certain cases, a compound of formula **IV** of the present invention may be prepared by an alternative cross-coupling strategy, as illustrated in Scheme D.

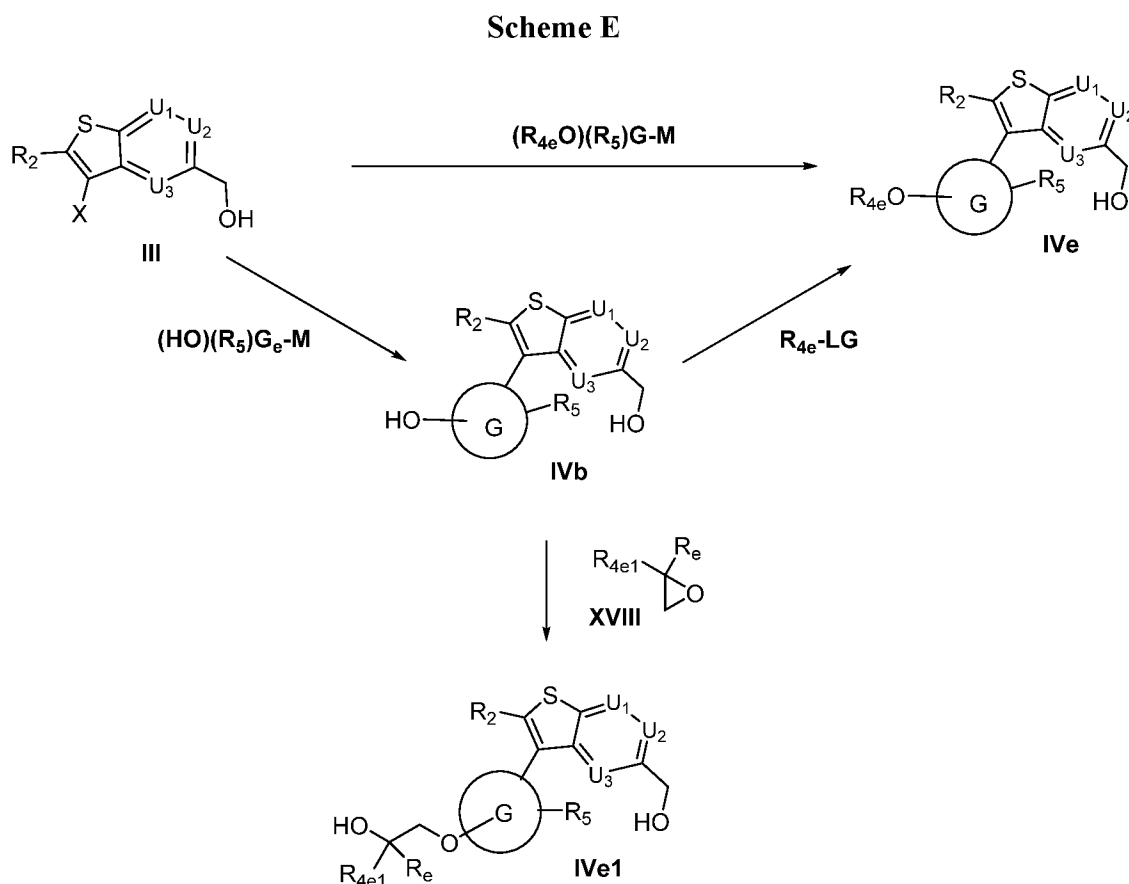
Scheme D



Under Suzuki coupling conditions as previously described in Scheme A, a compound of formula **III** may be reacted with bis(pinacolato)diboron to provide the corresponding boronate of formula **XVI**. A compound of formula **XVI** may, in turn, be reacted with an aromatic halide of formula **W-X**, wherein W is substituted aryl or heteroaryl and X is as

defined in Scheme A, to provide a compound of formula **IV** directly. In certain cases, this coupling reaction may afford the corresponding aldehydic compound of formula **XVII**, which upon treatment with a suitable reducing agent, using methods described in Scheme C, may provide an alcohol of formula **IV**.

Certain compounds of formula **IV** of the present invention in which W is $(R_3)(R_5)G$ and R_3 is $-OR_{4e}$ may be prepared as illustrated in Scheme E. As defined herein, R_{4e} is R_4 wherein the hydroxy-substituted R_4 substituents are suitably protected with a conventional hydroxy protecting group.



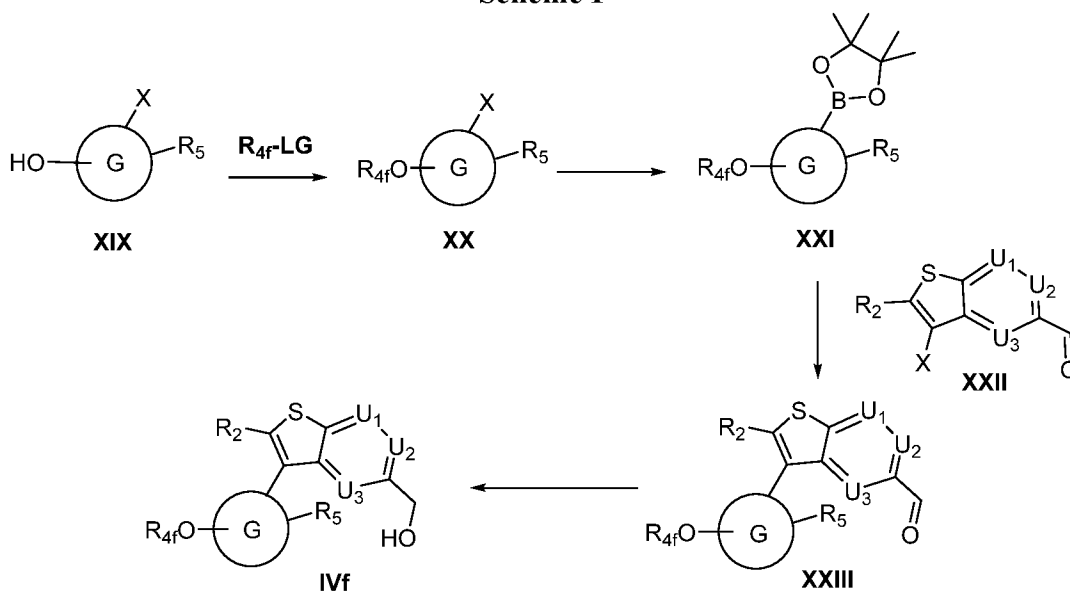
Treatment of a compound of formula **III** with a compound of formula $(R_{4e}O)(R_5)G-M$, where G is phenyl or pyridyl, R_5 is methyl and M is as defined in Scheme A, under coupling conditions previously described may provide a compound of formula **IVe** directly. Alternatively, a compound of formula **III** may be reacted with a compound of formula $(HO)(R_5)G_e-M$ wherein G_e is phenyl or pyridyl, and M is preferably a boronic

acid or boronic ester, under suitable coupling conditions as previously described, to provide the corresponding coupling product of formula **IVb**. Alkylation of a compound of formula **IVb** with a compound of formula **R_{4e}-LG**, where LG is a suitable leaving group as previously described, in the presence of a base such as K₂CO₃, Cs₂CO₃, KOH, NaH, or the like; in a solvent such as NMP, DMF, THF, or the like; at a temperature preferably in the range of from about 25 to 150 °C; may provide a compound of formula **IVe**.

Alternatively, a compound of formula **IVb** may be alkylated by reaction with an epoxide of formula **XVIII**, wherein R_e is hydrogen and R_{4e1} is defined as C₁₋₆alkyl, C₃₋₇cycloalkyl, or C₁₋₃alkoxy(C₁₋₈)alkyl, to provide a compound of formula **IVe1**. Similarly, a compound of formula **IVb** may be alkylated by reaction with an epoxide of formula **XVIII**, wherein R_e and R_{4e1} may be taken together to form a spirofused 1,1-dioxido-tetrahydro-2*H*-thiopyran-4-yl, to provide additional compounds of formula **IVe1**. The reaction with an epoxide of formula **XVIII** is preferably carried out in the presence of a base such as K₂CO₃, Cs₂CO₃, KOH, or the like; in a solvent such as NMP, DMF, THF, or the like; at a temperature preferably in the range of from about 25 to 125 °C.

Alternatively, certain compounds of formula **IV** of the present invention in which W is (R₃)(R₅)G, G is phenyl or pyridyl, R₃ is -OR_{4f} and R₅ is Me or CF₃ may be prepared as illustrated in Scheme F. As defined herein, R_{4f} is R₄ wherein the hydroxy-substituted R₄ substituents are suitably protected with a conventional hydroxy protecting group.

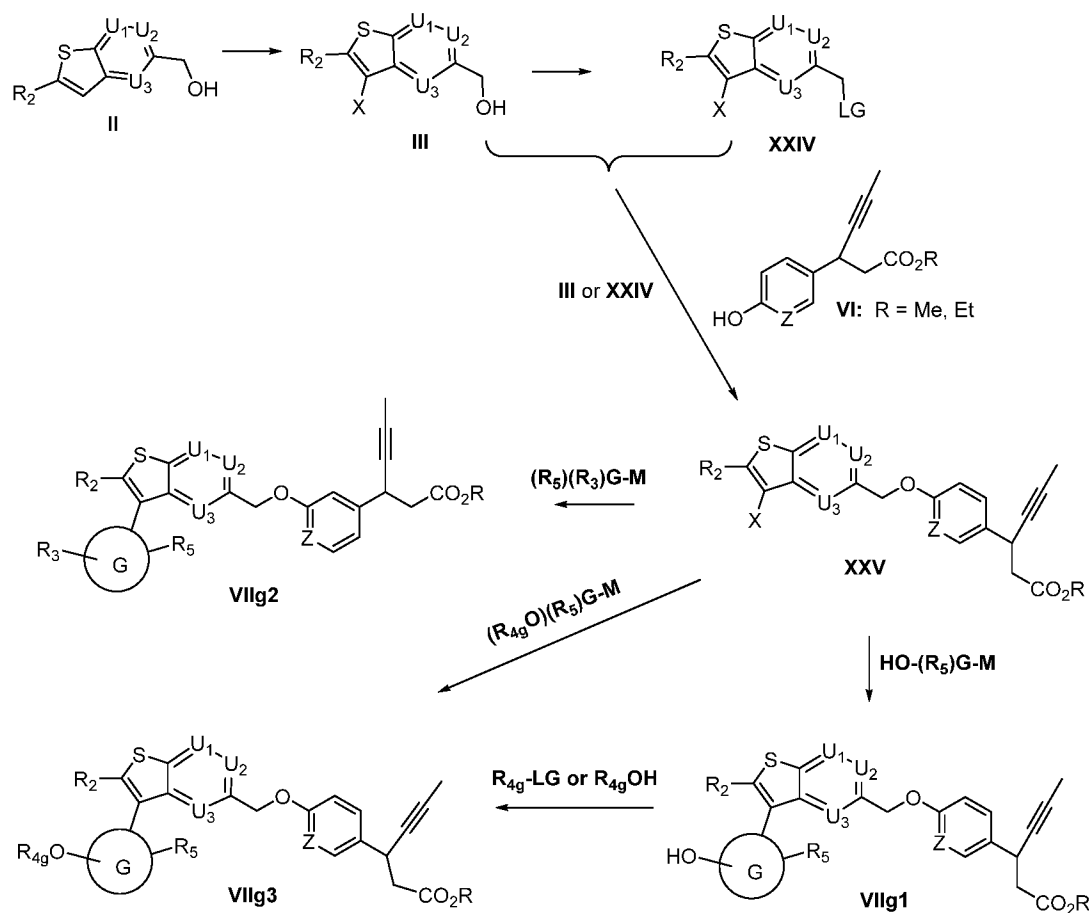
Scheme F



Alkylation of a phenolic compound of formula **XIX** with a compound of formula $\text{R}_{4f}\text{-LG}$, where LG is a suitable leaving group as previously described, in the presence of a base such as K_2CO_3 , Cs_2CO_3 , KOH , NaH , or the like; in a solvent such as NMP, DMF, THF, or the like; at a temperature preferably in the range of from about $25\text{ }^\circ\text{C}$ to $150\text{ }^\circ\text{C}$; may provide a compound of formula **XX**. Treatment of a compound of formula **XX** with bis(pinacolato)diboron under Suzuki coupling conditions, as defined in Scheme A, may provide the corresponding borolane of formula **XXI**. A borolane of formula **XXI** may be reacted with a benzothiophene aldehyde of formula **XXII** under Suzuki coupling conditions, as defined in Scheme A, to provide an arylated benzothiophene aldehyde of formula **XXIII**, which in turn may be reduced upon treatment with a suitably selected reducing agent, as described in Scheme C, to provide the corresponding benzylic alcohol of formula **IVf**.

Certain compounds of formula **VII** of the present invention in which W is $(\text{R}_3)(\text{R}_5)\text{G}$, G is phenyl, pyrazolyl or pyridyl and R_3 is $-\text{OH}$, CF_3 or $-\text{OR}_4$ may be prepared as illustrated in Scheme G.

Scheme G

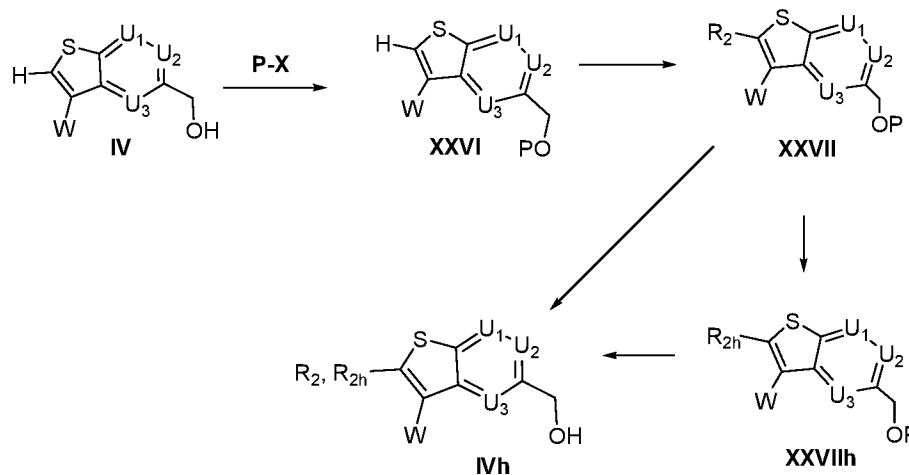


A compound of formula **III** may be reacted with a compound of formula **VI** directly under Mitsunobu conditions, as defined in Scheme A to provide a compound of formula **XXV**. Alternatively, a compound of formula **III** may be converted to a compound of formula **XXIV**, wherein LG is a suitable leaving group as previously described, and reacted with a phenol of formula **VI** in the presence of a suitable base as previously described to provide a compound of formula **XXV**. Reaction of a compound of formula **XXV** with a compound of formula **(R₅)(R₃)G-M**, using the methods described in Scheme A, provides a compound of formula **VIIg2**. In instances wherein R₃ is hydroxy, this reaction provides a compound of formula **VIIg1**. A compound of formula **VIIg1** may be reacted under Mitsunobu conditions as previously described with a compound of formula **R₄OH**, or may be reacted with a compound of formula **R₄-LG** in the presence of a suitable base as previously

described, to provide a compound of formula **VIIg3**. Alternatively, a compound of formula **XXV** may be reacted with a compound of formula **(R₄O)(R₅)G-M** to provide a compound of formula **VIIg3** directly.

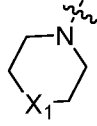
Certain compounds of formula **IV** in which R₂ is chloro, bromo, fluoro, iodo, trifluoromethyl, cyano, or methanesulfonyl may be prepared by the general route illustrated in Scheme H.

Scheme H

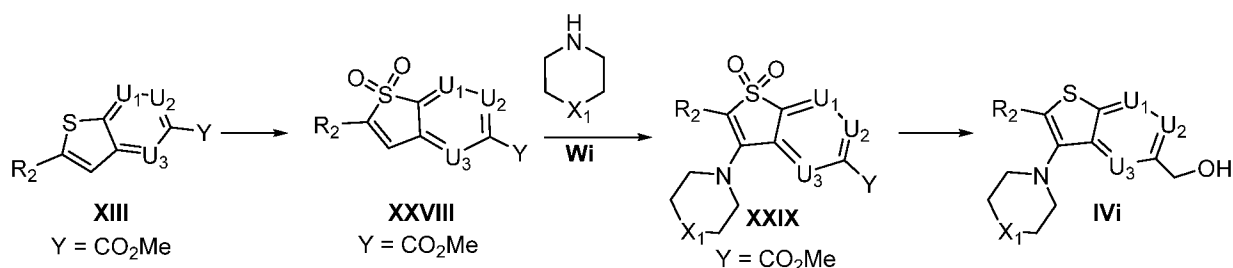


Protection of the hydroxy functionality of a compound of formula **IV** with a suitable protecting group, preferably a silyl protecting group such as *tert*-butyldimethylsilyl, may provide a compound of formula **XXVI**. Lithiation of a compound of formula **XXVI**, using an alkyl lithium reagent such as *n*-BuLi, or a lithium amide such as LDA, in an ethereal solvent such as THF, at a temperature at less than 0 °C, preferably at about -78 °C, followed by treatment with a suitable electrophile, such as iodomethane, NCS, NBS, I₂, N-fluoro-N-(phenylsulfonyl)benzenesulfonamide, or triisopropoxyborane, may provide a compound of formula **XXVII**, wherein R₂ is Me, Cl, Br, I, F and B(OH)₂, respectively. Deprotection of a compound of formula **XXVII** provides the corresponding compound of formula **IVg**. In some instances, using methods known in the art, a compound of formula **XXVII** may be further transposed to a compound of formula **XXVIIIh**. For example, a compound of formula **XXVII**, wherein R₂ is bromo, may be converted to a compound of

formula **XXVIIIh**, where R_{2h} is CN, CF_3 or SO_2Me . Similarly, a compound of formula **XXVII**, wherein R_2 is $B(OH)_2$ may also be converted to a compound of formula **XXVIIIh**, where R_{2h} is CF_3 .

Certain compounds of formula **IV** wherein W is  may be prepared by the general route illustrated in Scheme I.

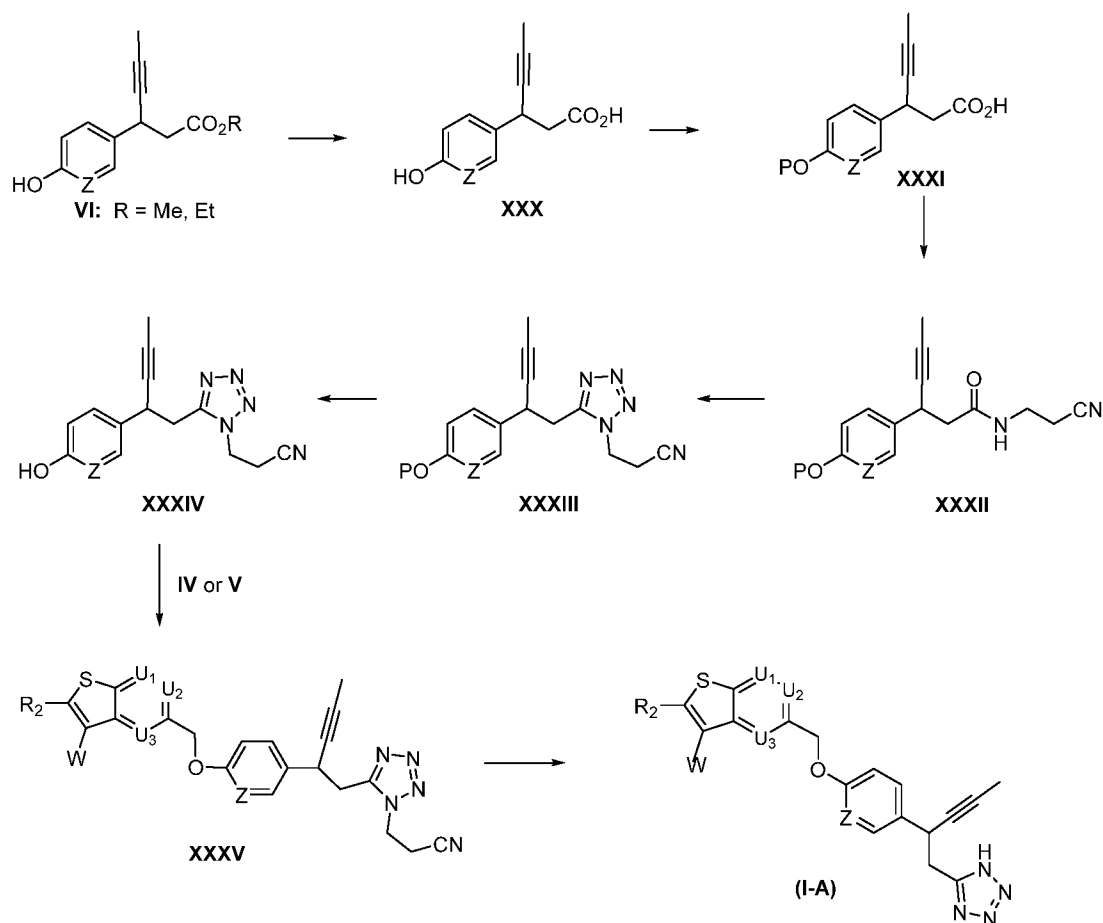
Scheme I



Oxidation of a compound of formula **XIII**, using methods well known in the art, may provide a compound of formula **XXVIII**. Preferably, this oxidation is carried out with aqueous hydrogen peroxide in a suitable co-solvent such as DCM or the like, in the presence of an acid, such as TFA, at ambient temperature. Reaction of a compound of formula **XXVIII** with a secondary amine of formula **Wi**, in a solvent such as toluene or the like, at an elevated temperature, preferably at about 120 °C, may provide a compound of formula **XXIX**. Dual reduction of the sulfone and ester functionalities of a compound of formula **XXIX** may be effected using a suitable reducing agent as described in Scheme C, to provide a compound of formula **IVi**. Preferably, this reduction is carried out using DIBAL-H, in a solvent or solvent combination selected from THF or DCM, or the like, at a reaction temperature in the range of from about -20 to 40 °C, preferably in the range of from about 0 °C to rt.

Certain compounds of Formula **I-A** may be synthesized as outlined by the general synthetic route illustrated in Scheme J.

Scheme J

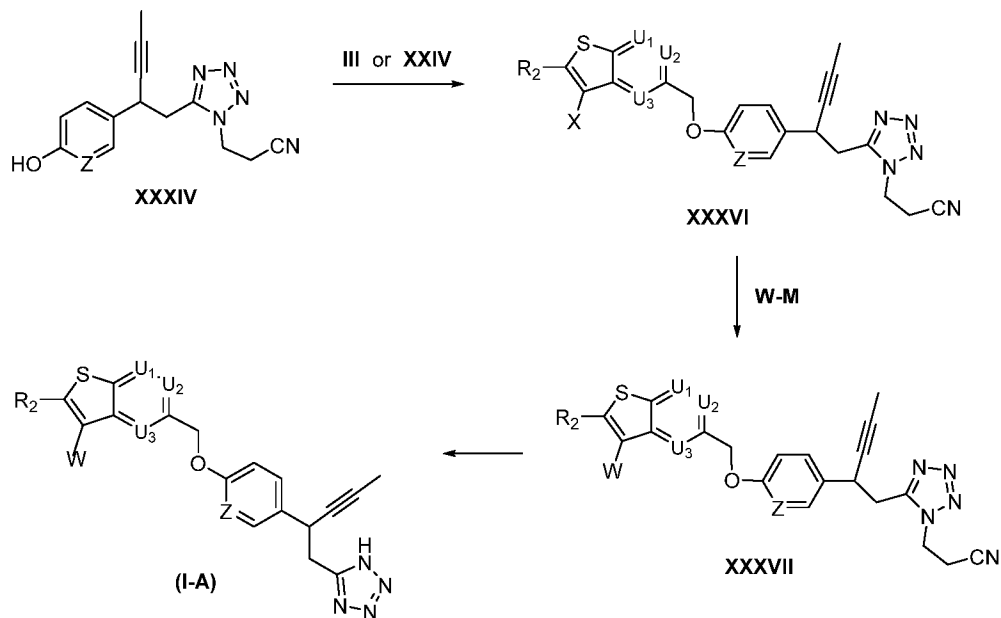


Hydrolysis of a hydroxyphenylpropanoate of formula **VI** may provide the corresponding hydroxyphenylpropionic acid or formula **XXX**. Protection of the phenolic hydroxy group with a suitable protecting group as defined in Scheme A, preferably with a 4-methoxybenzyl group, may provide a compound of formula **XXXI**. Coupling of a compound of formula **XXXI** with a suitably protected amine, such as 2-cyanoethylamine, may be effected under a variety of conditions known in the art to provide compounds of formula **XXXII**. For example, this transformation may be conveniently carried out using HATU as the coupling agent in the presence of a suitable base, such as DIEA, in a suitable reaction solvent, such as DMF at a temperature in the range of from about 0 to 100 °C,

preferably at ambient temperature. A compound of formula **XXXII** may be converted to the corresponding tetrazole compound of formula **XXXIII** in a two-stage process by way of the *in situ*-generated iminochloride. For example, treatment of a compound of formula **XXXII** with a chlorinating agent such as PCl_5 in the presence of an amine such as pyridine, in a suitable solvent such as DCM at a temperature of about 40 °C provides the corresponding imidoyl chloride, which upon treatment with a silyl azide, such as trimethylsilyl azide, provides a compound of formula **XXXIII**. Deprotection of the phenolic protecting group of a compound of formula **XXXIII** provides compound **XXXIV**. When a 4-methoxybenzyl protecting group has been used, its removal may be conveniently carried out upon treatment with TFA in a solvent such as DCM, or the like, at a concentration of about 25 to 50 % (v/v). Treatment of a compound of formulas **IV** or **V** with a compound of formula **XXXIV**, using the methods described in Scheme A for its reaction with a compound of formula **VI**, may provide a compound of formula **XXXV**. Treatment of a compound of formula **XXXV** with an aqueous solution of a metal hydroxide, such as NaOH or LiOH, in a protic co-solvent such as MeOH, EtOH, i-PrOH, or the like, along with an ethereal co-solvent such as THF or dioxane, may provide the corresponding tetrazole of formula **I-A**.

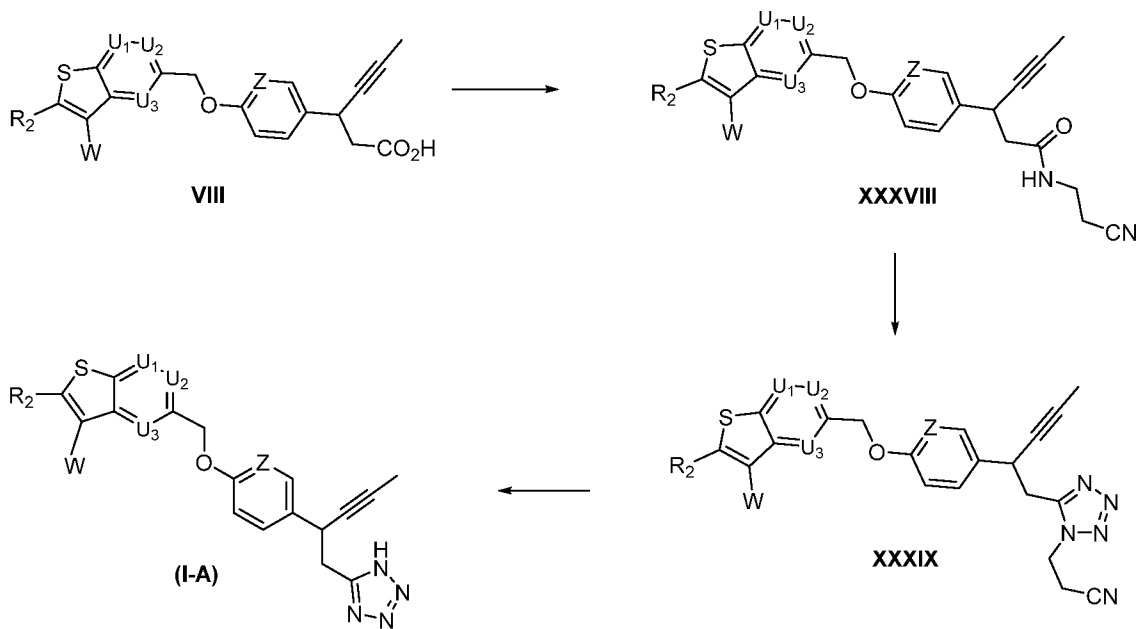
In a related manner, certain compounds of Formula **I-A** may be synthesized as outlined by the general synthetic route illustrated in Scheme K. Reaction of a compound of formula **XXXIV** with a compound of formula **III** or **XXIV**, using methods described in Scheme G, may provide a compound of formula **XXXVI**. A compound of formula **XXXVI**, in turn, may be cross-coupled with a compound of formula **W-M**, as described in Scheme A, to provide a compound of formula **XXXVII**. Reaction of a compound of formula **XXXVII** with a metal hydroxide solution, as described in Scheme J, may provide a compound of formula **I-A**.

Scheme K



Certain compounds of formula **I-A** may be prepared as illustrated in general Scheme L.

Scheme L



Using methods similar to those described in Scheme J, a carboxylate of formula **VIII** may be converted to an amide of formula **XXXVIII**, which in turn, may be converted to a protected tetrazole of formula **XXXIX**. Deprotection of the tetrazole of formula **XXXIX**, as described in Scheme J, may provide the corresponding tetrazole of formula **I-A**.

Specific Examples

General Procedure A: A mixture of an arylbromide or aryl iodide (1 mmol), an arylboronic acid, aryl dioxaborolane or bis(pinacolato)diboron (1.5 mmol), a palladium catalyst (0.1 mmol) and K_2CO_3 (2-3 mmol) was placed in a reaction vessel which was then thoroughly purged with argon. Dioxane (3 mL) and water (1.5 mL) were added, and the mixture was stirred at 80 - 95 °C for 1 to 4 h. After cooling to rt, the mixture was poured into EtOAc/H₂O (1:1, 10 mL) and the aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (EtOAc/heptanes) afforded the desired biaryl product.

General Procedure B: To a mixture of the alcohol (0.2 mmol) and the phenol (0.3 mmol) in dry THF (1 mL) was added a mixture of the phosphine (Ph_3P , Bu_3P or *t*- Bu_3P ; 0.3 mmol) and the azidodicarboxylate (DEAD, DIAD, DBAD or ADDP; 0.3 mmol), and the resultant solution was stirred under argon for 1- 16 h. The mixture was then either worked up by an extractive process (ex., quenching with satd. aq. NH_4Cl and extraction with EtOAc) or concentrated directly under reduced pressure and the resultant residue was purified by silica gel chromatography (EtOAc/heptanes) or EtOAc/petroleum ether to afford the desired phenolic ether.

General Procedure C: To a solution of the ester (0.16 mmol) in THF (1 mL) and MeOH (0.5 mL) was added the hydroxide base (1N LiOH (aq) or 1N NaOH (aq)) (1 mL) and the resultant mixture was stirred at rt for 1 - 3 h, or until hydrolysis was complete. The reaction was then acidified to pH 3-4 with either 1-2N HCl or 2M citric acid and poured

into a 1:1 mixture of EtOAc/H₂O (10 mL). The aqueous layer was extracted with EtOAc (5 mL X 2) and the combined organic extract was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was dissolved in DCM (1 mL) and the product was precipitated with heptanes to afford the pure carboxylic acid.

General Procedure D: To an ice-cooled solution of the benzylic alcohol (0.22 mmol) in DCM (5 mL) was added thionyl chloride (0.45 mmol) in drop-wise fashion. After stirring at 0 – 5 °C for 2 h, the reaction was quenched by the addition of water (~ 10 mL) followed by DCM (50 mL). After partitioning the two phases, the organic layer was successively washed with water, satd. NaHCO₃ and brine, then dried (Na₂SO₄), filtered and concentrated to afford the corresponding benzylic chloride which was used without further purification.

General Procedure E: A mixture of the benzylic chloride (0.11 mmol), the phenol (0.14 mmol) and Cs₂CO₃ (0.17 mmol) in MeCN (2 mL) was stirred at rt for 16 h. EtOAc (50 mL) was then added and the organic layer was successively washed with water and brine, dried (Na₂SO₄), filtered and concentrated to afford the crude corresponding benzylic phenyl ether, which was purified by silica gel chromatography (EtOAc/heptanes).

General Procedure F: To an ice-cooled solution of the benzothiophenyl aldehyde (1.02 mmol) in THF (4 mL) and MeOH (0.5 mL) was added NaBH₄ (2.09 mmol) in a portion-wise fashion. After stirring for 30 min, the reaction was quenched by the addition of satd. NH₄Cl (10 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (EtOAc/petroleum ether) afforded the corresponding benzylic alcohol.

General Procedure G: To a cooled (0 °C) solution of the arylalkanoic acid (1 mmol) and DMF (10 μL) in DCM (25 mL) was added either thionyl chloride (3 mmol) or oxalyl

chloride (2 mmol) in drop-wise fashion. After stirring at 0 °C for 1 h, the reaction was quenched by the addition of satd. aq. NaHCO₃ (3 mL) and the resulting mixture was extracted with DCM (3 x 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude arylalkanoyl chloride, which was used directly without further purification.

General Procedure Ha: To a cold (0 °C) solution of the crude arylalkanoyl chloride (6 mmol) in THF (1 mL) was added aq. NH₄OH (28 – 30 %, w/w; 5 mL) in drop-wise fashion. Alternatively, the reaction solution could be prepared by a drop-wise addition of a solution of the arylalkanoyl chloride in THF to cold aq. NH₄OH (inverse addition). After stirring at 0 °C for 1 h, the resulting mixture was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to afford the corresponding crude arylalkanoyl amide, which was used directly without further purification.

General Procedure Hb: To a solution of the crude arylalkanoyl chloride (2.2 mmol) in diethyl ether (100 mL) was bubbled ammonia gas at rt for 10 min. The mixture was then concentrated under reduced pressure to afford the corresponding arylalkanoyl amide, which was used directly without further purification.

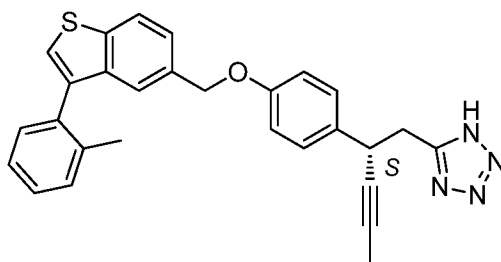
General Procedure I: To a cold (0 °C) solution of the arylalkanoyl amide (1 mmol) and TEA (3 mmol) in DCM (4 mL) was added trifluoroacetic anhydride (1 mmol) in drop-wise fashion. After stirring at 0 °C for 0.5 h, the reaction was quenched by the addition of sat'd aq. NaHCO₃ (3 mL) and the resulting mixture was extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure and the residue thus obtained was purified by silica gel chromatography (EtOAc/petroleum ether) to afford the corresponding arylalkylnitrile.

General Procedure J: A mixture of the nitrile (0.32 mmol), azidotrimethylsilane (3 eq.) and Bis(tri-n-butyltin)oxide (0.2 eq.) in toluene (2 mL) was stirred overnight at 110 °C in a

sealed tube. The reaction was then quenched by the addition of water (10 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue thus obtained was purified by reverse-phase flash chromatography using Flash Spherical C18 columns (120g, 20-35 μm , 100 \AA ; Agela Technologies), eluting with a gradient of MeCN/ H_2O (0.05% NH_4HCO_3) (Workup 1). Alternatively, the crude reaction was concentrated under reduced pressure and the residue was directly purified by silica gel chromatography eluting with DCM/MeOH or EtOAc/petroleum ether mixtures (Workup 2).

Example 1

(2*S*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 1



(A) To an ice-cooled solution of 5-hydroxymethylbenzothiophene (1.45 g; 8.83 mmol) in THF (15 mL) was added NBS (1.73 g; 9.71 mmol) under an argon atmosphere. The resulting solution was allowed to warm to rt, with stirring continued for another 3 h. The reaction was then concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 0-20% EtOAc in heptanes to afford 3-bromo-5-hydroxymethylbenzothiophene (968 mg, 45%) as a white solid. ^1H NMR (CDCl_3) δ : 7.78 - 7.88 (m, 2H), 7.46 (s, 1H), 7.43 (d, $J = 9.6$ Hz, 1H), 4.86 (d, $J = 5.8$ Hz, 2H), 1.84 (t, $J = 5.8$ Hz, 1H).

(B) 5-Hydroxymethyl-3-(2-methylphenyl)benzo[*b*]thiophene was prepared from 3-bromo-5-hydroxymethylbenzothiophene and 2-methylphenylboronic acid following

General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst. LC/MS: mass calcd. for C₁₆H₁₄OS: 254.35, found 277.1 [M+Na]⁺.

(C) (3*S*)-Methyl 3-(4-((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-hydroxymethyl-3-(2-methylphenyl)benzo[b]-thiophene and (3*S*)-methyl 3-(4-hydroxyphenyl)hex-4-ynoate (prepared as described in WO 2005086661) following General Procedure B using PPh₃ and DBAD. LC/MS: mass calcd. for C₂₉H₂₆O₃S: 454.59, found 455.1 [M]⁺, 477.0 [M+Na]⁺.

(D) (3*S*)-3-[4-[[3-(2-Methylphenyl)benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid was prepared from (3*S*)-methyl 3-(4-((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base 2N HCl for reaction acidification. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J* = 9.09 Hz, 1H), 7.41 - 7.50 (m, 2H), 7.27 - 7.38 (m, 7H), 6.89 (d, *J* = 8.59 Hz, 2H), 5.08 (s, 2H), 3.97 - 4.10 (m, 1H), 2.78(dd, *J* = 8.59, 15.66 Hz, 1H), 2.69(dd, *J* = 6.57, 15.66 Hz, 1H), 2.15 (s, 3H), 1.82 (d, *J* = 2.02 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₄O₃S: 440.56, found 463.1 [M+Na]⁺.

(E) (3*S*)-Methyl 3-(4-((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-[4-[[3-(2-methylphenyl)benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid following General Procedure G.

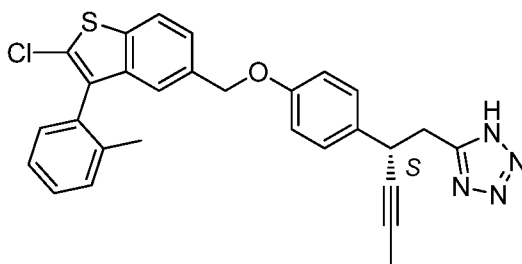
(F) (3*S*)-3-(4-((3-(2-Methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-[4-[[3-(2-methylphenyl)benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoyl chloride following General Procedure Hb. LC/MS: mass calcd. for C₂₈H₂₅NO₂S: 439.16, found: 440.1 [M+H]⁺.

(G) (3*S*)-3-(4-((3-(2-Methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-[4-[[3-(2-methylphenyl)benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid following General Procedure I. LC/MS: mass calcd. for C₂₈H₂₃NOS: 421.15, found: 444.1 [M+Na]⁺.

(H) (2*S*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd 1) was prepared from (3*S*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following the General Procedure J, using Workup 2. ¹H NMR (DMSO-*d*₆) δ 8.08 (d, *J* = 8.1 Hz, 1H), 7.72 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.41 (s, 1H), 7.37 (d, *J* = 4.0 Hz, 2H), 7.19 - 7.35 (m, 4H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.17 (s, 2H), 4.06 - 4.13 (m, 1H), 3.23 (d, *J* = 8.1 Hz, 2H), 2.08 (s, 3H), 1.74 (d, *J* = 2.5 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₄N₄OS: 464.17, found: 465.1 [M+H]⁺.

Example 2

5-((2*S*)-2-(4-((2-Chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole, Cpd 2



(A) To a solution of 5-Hydroxymethyl-3-(2-methylphenyl)benzo[*b*]thiophene (from Example 1B) (2.54 g, 9.99 mmol), TBSCl (1.8g, 11.94 mmol) and DMAP (122 mg, 1 mmol) in DCM (50 mL) was added TEA (2.02 g, 20 mmol) and the resultant solution was stirred at rt for 2 h. Water (100 mL) was then added and the mixture was extracted with DCM (3 x 50 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-5% EtOAc/petroleum ether) afforded *tert*-butyldimethyl-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)silane (3.5 g, 95%) as colorless oil. LC/MS: mass calcd. for C₂₂H₂₈OSSi: 368.16, found: 391.1 [M+Na]⁺.

(B) To a cooled (-78 °C) solution of *tert*-butyldimethyl-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)silane (300 mg, 0.81 mmol) in anhydrous

THF (4 mL), maintained under a nitrogen atmosphere was added n-BuLi (2.5 M in hexanes; 0.65 mL, 1.625 mmol) in drop-wise fashion. After stirring at -78 °C for 10 min, a solution of NCS (163 mg, 1.22 mmol) in THF (2 mL) was added in drop-wise fashion and the mixture was stirred for an additional 0.5 h. The reaction was then quenched by the addition of aq. NH₄Cl (15 mL) and the resultant mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-5% EtOAc/petroleum ether) afforded *tert*-butyl-((2-chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane (250 mg, 76 %) as yellow oil. LC/MS: mass calcd. for C₂₂H₂₇ClOSSi: 402.12, found: 371.1 [M-OTBS]⁺.

(C) To a solution of *tert*-butyl-((2-chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane (250 mg, 0.62 mmol) in THF (10 mL) was added TBAF (1M in THF; 0.75 mL, 0.75 mmol) and the resultant solution was stirred at rt for 0.5 h. Water (15 mL) was then added and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-15% EtOAc/petroleum ether) afforded (2-chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol (130 mg, 73 %) as yellow oil. LC/MS: mass calcd. for C₁₆H₁₃ClOS: 288.04, found: 271.1 [M-OH]⁺.

(D) 2-Chloro-5-(chloromethyl)-3-(2-methylphenyl)benzo[b]thiophene was prepared from (2-chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

(E) (3*S*)-3-(4-Hydroxyphenyl)hex-4-ynoic acid was prepared from (3*S*)-3-(4-hydroxyphenyl)hex-4-ynoic acid (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05592) following General Procedure G, using thionyl chloride with DMF as the chlorinating agent.

(F) (3*S*)-3-(4-Hydroxyphenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-hydroxyphenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for C₁₂H₁₃NO₂: 203.24, found: 204.0 [M+H]⁺.

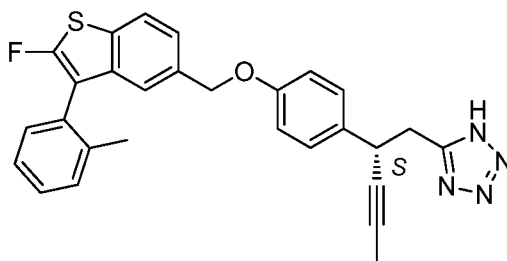
(G) (3*S*)-3-(4-Hydroxyphenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-hydroxyphenyl)hex-4-ynamide following General Procedure I. ¹H NMR (DMSO-*d*₆) δ 9.40 (s, 1H), 7.14 - 7.33 (m, 2H), 6.60 - 6.85 (m, 2H), 3.91 - 4.15 (m, 1H), 2.74 - 3.00 (m, 2H), 1.85 (d, *J* = 2.4 Hz, 3H).

(H) (3*S*)-3-(4-((2-Chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from 2-chloro-5-(chloromethyl)-3-(2-methylphenyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-yne nitrile following General Procedure E, at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₂₈H₂₂ClNOS: 455.11, found: 478.2 [M+Na]⁺.

(I) 5-((2*S*)-2-(4-((2-Chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole (Cpd **2**) was prepared from (3*S*)-3-(4-((2-chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (45 – 95%). ¹H NMR (DMSO-*d*₆) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.21 - 7.52 (m, 8H), 6.88 - 6.94 (m, 2H), 5.13 (s, 2H), 4.10 - 4.18 (m, 1H), 3.23 (d, *J* = 7.8 Hz, 2H), 2.02 (s, 3H), 1.74 (d, *J* = 2.1 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₃ClN₄OS: 498.13, found: 499.0 [M+H]⁺.

Example 3

5-((2*S*)-2-(4-((2-Fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole, Cpd **3**



(A) To a cooled (-78 °C) solution of *tert*-butyldimethyl((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane (from Example 2A; 1.0 g, 2.71 mmol) in THF (25 mL) was added *n*-BuLi (2.5 M in hexanes; 0.65 mL, 1.625 mmol) in drop-wise fashion. After stirring for 10 min, a solution of *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (1027 mg, 3.257 mmol) in THF (5 mL) was added in drop-wise fashion and stirring was continued at -78 °C for 30 min. The reaction was then quenched by the addition of aq. NH₄Cl (15 mL) and the resultant mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-5% EtOAc/petroleum ether) afforded *tert*-butyldimethyl-((2-fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane (800 mg, 76 %) as a yellow oil. LC/MS: mass calcd. for C₂₂H₂₇FOSSi: 386.15, found: 254.9 [M-OTBS]⁺.

(B) (2-Fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol was prepared from *tert*-butyldimethyl-((2-fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane following the procedure described in Example 2C. LC/MS: mass calcd. for C₁₆H₁₃FOS: 272.07, found: 254.9 [M-OH]⁺.

(C) 2-Fluoro-5-(chloromethyl)-3-(2-methylphenyl)benzo[b]thiophene was prepared from (2-fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

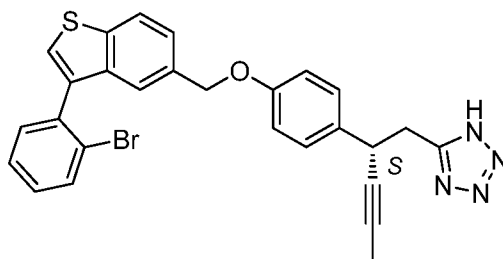
(D) (3*S*)-3-(4-((2-Fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 2-fluoro-5-(fluoromethyl)-3-(2-methylphenyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from

Example 2G) following General Procedure E, at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₂₈H₂₂ClNOS: 439.14, found: 457.0 [M+NH₄]⁺.

(E) 5-((2*S*)-2-(4-((2-Fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole (Cpd 3) was prepared from (3*S*)-3-(4-((2-fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (45 – 95%). ¹H NMR (DMSO-*d*₆) δ 8.01(d, *J* = 8.4 Hz, 1H), 7.30 - 7.50 (m, 6H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.13 (s, 2H), 4.07 - 4.10 (m, 1H), 3.23 (d, *J* = 7.8 Hz, 2H), 2.11 (s, 3H), 1.74 (d, *J* = 2.1 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₃FN₄OS: 482.16, found: 483.0 [M+H]⁺.

Example 4

(2*S*)-5-(2-(4-((3-(2-Bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 4



(A) To a cooled (15 °C) solution of benzo[b]thiophene-5-carbaldehyde (6.9 g, 52.54 mmol) in HOAc (80 mL) was added a solution of bromine (10.5 g, 65.7 mmol) in HOAc (20 mL) in drop-wise fashion. After stirring at 15 °C for 2 h, water (500 mL) was added, whereupon the solid product precipitated from the mixture. The precipitate was collected by filtration and dried under vacuum to provide 3-bromobenzo[b]thiophene-5-carbaldehyde (7.8 g, 38 % yield) as a yellow solid. ¹H NMR (CDCl₃) δ 10.17 (s, 1H), 8.32 (s, 1H), 7.93 - 7.98 (m, 2H), 7.78 (s, 1H).

- (B) 3-(2-Bromophenyl)benzo[b]thiophene-5-carbaldehyde was prepared from 3-bromobenzo[b]thiophene-5-carbaldehyde and 2-bromophenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₅H₉BrOS: 317.20, found: 317.0 [M]⁺, 319.0 [M+2]⁺.
- (C) (3-(2-Bromophenyl)benzo[b]thiophen-5-yl)methanol was prepared from 3-(2-bromophenyl)benzo[b]thiophene-5-carbaldehyde following General Procedure F. LC/MS: mass calcd. for C₁₅H₁₁BrOS: 319.22, found: 319.0 [M]⁺, 321.0 [M+2]⁺.
- (D) 3-(2-Bromophenyl)-5-(chloromethyl)benzo[b]thiophene was prepared from (3-(2-bromophenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.
- (E) (3*S*)-Ethyl 3-(4-((3-(2-bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 3-(2-bromophenyl)-5-(chloromethyl)benzo[b]thiophene and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E, at a reaction temperature of 50 °C for 2 h. LC/MS: mass calcd. for C₂₉H₂₅BrO₃S: 533.48, found: 533.1 [M]⁺, 535.1 [M+H]⁺.
- (F) (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2-bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base, EtOH in place of MeOH and 2N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 8.08 (d, *J* = 8.1 Hz, 1H), 7.80 - 7.85 (m, 2H), 7.40 - 7.56 (m, 5H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.16 (s, 2H), 3.89 - 3.94 (m, 1H), 2.58 (d, *J* = 7.5 Hz, 2H), 1.77 (s, 3H). LC/MS: mass calcd. for C₂₇H₂₁BrO₃S: 505.42, found: 505.0 [M]⁻, 507.0, [M+2]⁻.
- (G) (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

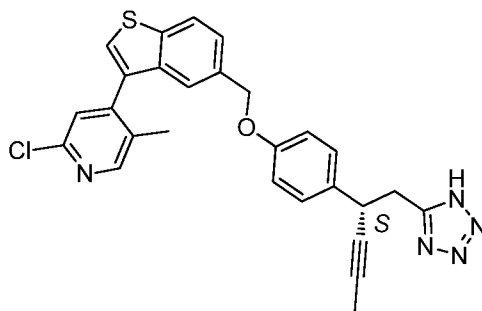
(H) (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha (inverse addition), and used directly without further characterization.

(I) (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₇H₂₀BrNOS: 485.05, found: 508.0, 509.9 [M+Na]⁺, [M+Na+2]⁺.

(J) (2*S*)-5-(2-(4-((3-(2-Bromophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd 4) was prepared from (3*S*)-3-(4-((3-(2-Bromophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (20 – 50%). ¹H NMR (CD₃OD) δ 7.96 (d, *J* = 8.7 Hz, 1H), 7.75 - 7.78 (m, 1H), 7.56 (s, 1H), 7.33 - 7.50 (m, 5H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.14 (s, 2H), 4.03 - 4.08 (m, 1H), 3.25 - 3.28 (m, 2H), 1.78 (s, 3H). LC/MS: mass calcd. for C₂₇H₂₁BrN₄OS: 428.06, found: 528.8, 530.8 [M+H]⁺, [M+H+2]⁺.

Example 5

(2*S*)-4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-chloro-5-methylpyridine, Cpd 5



(A) (3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-5-yl)methanol was prepared from 3-bromo-5-hydroxymethylbenzothiophene (from Example 1A) and bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and KOAc in place of K₂CO₃. LC/MS: mass calcd. for C₁₅H₁₉BO₃S: 290.19, found: 273.1[M-OH]⁺.

(B) (3-(2-Chloro-5-methylpyridin-4-yl)benzo[b]thiophen-5-yl)methanol was prepared from 4-bromo-2-chloro-5-methylpyridine and (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-5-yl)methanol following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₅H₁₂ClNOS: 289.78, found: 290.0 [M]⁺, 292.0 [M+2]⁺.

(C) (3*S*)-Ethyl 3-(4-((3-(2-chloro-5-methylpyridin-4-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3-(2-chloro-5-methylpyridin-4-yl)benzo[b]thiophen-5-yl)methanol and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure B, using Bu₃P and ADDP at a reaction temperature of 60 °C in toluene overnight. LC/MS: mass calcd. for C₂₉H₂₆ClNO₃S: 504.04, found: 504.1 [M]⁺, 506.1 [M+2]⁺.

(D) (3*S*)-3-(4-((3-(2-Chloro-5-methylpyridin-4-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared (3*S*)-ethyl 3-(4-((3-(2-chloro-5-methylpyridin-4-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using NaOH as base, MeOH as solvent and a reaction temperature of 60 °C for 2 h. For workup, the reaction mixture was filtered and concentrated, then purified directly by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.5% NH₄HCO₃) gradient (65 – 75%). ¹H NMR (CD₃OD) δ 8.31 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.41 (s, 1H), 7.36 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.16 (s, 2H), 3.90 - 3.98 (m, 1H), 2.48 - 2.63 (m, 2H), 2.05 (s, 3H), 1.76 (s, 3H). LC/MS: mass calcd. for C₂₇H₂₂ClNO₃S: 475.99, found: 476.1 [M]⁺, 478.1 [M+2]⁺.

(E) (3*S*)-3-(4-((3-(2-Chloro-5-methylpyridin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2-chloro-5-methylpyridin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

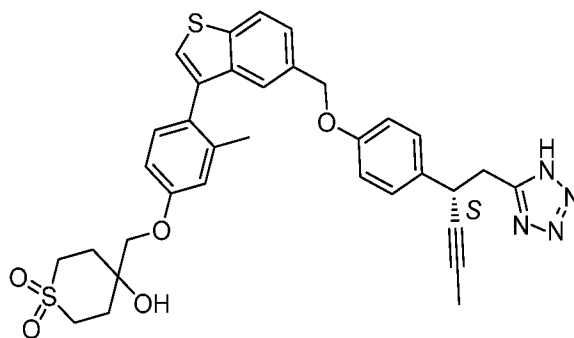
(F) (3*S*)-3-(4-((3-(2-Chloro-5-methylpyridin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2-chloro-5-methylpyridin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for C₂₇H₂₃ClN₂O₂S: 474.12, found: 475.0 [M+H]⁺.

(G) (3*S*)-3-(4-((3-(2-Chloro-5-methylpyridin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(2-chloro-5-methylpyridin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₇H₂₁ClN₂OS: 456.11, found: 457.2 [M+H]⁺.

(H) (2*S*)-4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-chloro-5-methylpyridine (Cpd 5) was prepared from (3*S*)-3-(4-((3-(2-chloro-5-methylpyridin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 8.31 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.35 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.15 (s, 2H), 3.97 - 4.06 (m, 1H), 3.17 - 3.29 (m, 2H), 2.06 (s, 3H), 1.75 (s, 3H). LC/MS: mass calcd. for C₂₇H₂₂ClN₅OS: 499.12, found: 500.0 [M+H]⁺.

Example 6

(2*S*)-4-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)methyl)-4-hydroxytetrahydro-2*H*-thiopyran 1,1-dioxide, Cpd 6



(A) 5-Hydroxymethyl-3-(4-hydroxy-2-methylphenyl)benzo[b]thiophene was prepared from 3-bromo-5-hydroxymethylbenzothiophene (from Example 1A) and 4-hydroxy-2-methylphenylboronic acid following General Procedure A, using PdCl₂(dppf) CH₂Cl₂ as the palladium catalyst. LC/MS: mass calcd. for C₁₆H₁₄O₂S: 270.35, found 293.0 [M+Na]⁺.

(B) A mixture of 5-hydroxymethyl-3-(4-hydroxy-2-methylphenyl)benzo[b]thiophene (162 mg; 0.6 mmol), 1-oxa-6-thiaspiro[2.5]octane 6,6-dioxide (107 mg; 0.66 mmol) and K₂CO₃ (138 mg; 1 mmol) in DMF (1.5 mL) was stirred at 90 °C for 6 h. After cooling to rt, the reaction was partitioned between EtOAc and aq NH₄Cl and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5-80% EtOAc in heptanes to afford 4-hydroxy-4-((4-(5-(hydroxymethyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)methyl)tetrahydro-2H-thiopyran 1,1-dioxide (245 mg, 94%). LC/MS: mass calcd. for C₂₂H₂₄O₅S₂: 432.56, found 455.0 [M+Na]⁺.

(C) (3*S*)-Methyl 3-(4-((3-(4-((4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 4-hydroxy-4-((4-(5-(hydroxymethyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide and (3*S*)-methyl 3-(4-hydroxyphenyl)hex-4-ynoate (prepared as described in WO 2005086661) following General Procedure B using PPh₃ and DBAD. MS: mass calcd. for C₃₅H₃₆O₇S₂: 632.8, found 633.2 [M]⁺, 655.2 [M+Na]⁺.

(D) (3*S*)-3-[4-[[3-[4-[(4-Hydroxy-1,1-dioxothian-4-yl)methoxy]-2-methylphenyl]-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid was prepared from (3*S*)-methyl 3-(4-((3-(4-((4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base and 2N HCl for reaction acidification. ¹H NMR (CDCl₃) δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.37 - 7.49 (m, 2H), 7.27 - 7.32 (m, 3H), 7.22 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 3H), 6.82 (dd, *J* = 8.1, 2.5 Hz, 1H), 5.09 (s, 2H), 3.98 - 4.10 (m, 1H), 3.93 (s, 2H), 3.42 - 3.59 (m, 2H), 2.92 - 3.02 (m, 2H), 2.80 (dd, *J* = 15.7, 8.1 Hz, 1H), 2.70 (dd, *J* = 15.7, 7.1 Hz, 1H), 2.13 (s, 3H), 1.83 (d, *J* = 2.53 Hz, 3H). LC/MS: mass calcd. for C₃₄H₃₄O₇S₂: 618.8, found 619.0 [M]⁺.

(E) A solution of (3*S*)-3-[4-[[3-[4-[(4-hydroxy-1,1-dioxothian-4-yl)methoxy]-2-methylphenyl]-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid (30 mg, 0.048 mmol), HATU (55 mg, 0.145 mmol), NH₄Cl (26 mg, 0.49 mmol) and DIEA (19 mg, 0.15 mmol) in DMF (2 mL) was stirred at rt for 1 h. The reaction was then quenched by the addition of satd. aq NH₄Cl (5 mL) and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to afford (3*S*)-3-[4-[[3-[4-[(4-hydroxy-1,1-dioxothian-4-yl)methoxy]-2-methylphenyl]-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide (20 mg, 67%) as a light yellow oil, which was used directly without purification. LC/MS: mass calcd. for C₃₄H₃₅NO₆S₂: 617.19, found 618.0 [M+H]⁺.

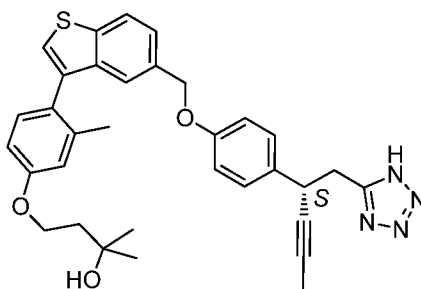
(F) (3*S*)-3-[4-[[3-[4-[(4-hydroxy-1,1-dioxothian-4-yl)methoxy]-2-methylphenyl]-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynenitrile was prepared from (3*S*)-3-[4-[[3-[4-[(4-hydroxy-1,1-dioxothian-4-yl)methoxy]-2-methylphenyl]-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₃₄H₃₃NO₅S₂: 599.18, found 617.1 [M+NH₄]⁺.

(G) (2*S*)-4-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)methyl)-4-hydroxytetrahydro-2*H*-thiopyran 1,1-dioxide (Cpd **6**) was prepared from (3*S*)-3-[4-[[3-[4-

[(4-hydroxy-1,1-dioxothian-4-yl)methoxy]-2-methylphenyl]-benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH₄HCO₃) gradient (30 – 85%). ¹H NMR (CDCl₃) δ 7.92 (d, *J* = 8.7 Hz, 1H), 7.41 - 7.43 (m, 2H), 7.20 - 7.27 (m, 4H), 6.79 - 6.89 (m, 4H), 5.07 (s, 2H), 4.05 - 4.09 (m, 1H), 3.94 (s, 2H), 3.49 - 3.52 (m, 2H), 3.36 - 3.39 (m, 2H), 2.87 - 3.11 (m, 2H), 2.22 - 2.30 (m, 4H), 2.12 (s, 3H), 1.85 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₃₄H₃₄N₄O₅S₂: 642.20, found 643.0 [M+H]⁺.

Example 7

(2*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol, Cpd 7



(A) 3-Bromo-5-(chloromethyl)benzo[b]-thiophene was prepared from 3-bromo-5-hydroxymethylbenzothiophene (from Example 1A) following General Procedure D.

(B) A mixture of 3-bromo-5-(chloromethyl)-1-benzothiophene (200 mg, 0.76 mmol), (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (180 mg, 0.77 mmol) (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) and K₂CO₃ (420 mg, 1.29 mmol) in MeCN (20 mL) was stirred overnight at 50 °C. The reaction was then quenched by the addition of satd. aq. NH₄Cl (40 mL) and the resulting solution was extracted with ethyl acetate (3 x 40 mL) and the combined organic extracts were concentrated under reduced pressure. The resultant residue was purified by silica gel

chromatography (0-20% EtOAc/ petroleum ether) to provide (3*S*)-ethyl 3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate as a colorless oil (300 mg, 86 % yield). LC/MS: mass calcd. for C₂₃H₂₁BrO₃S: 457.38, found: 459.0 [M+H]⁺.

(C) (3*S*)-Ethyl 3-(4-((3-(4-hydroxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3*S*)-ethyl 3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate and 4-hydroxy-2-methylphenylboronic acid following General Procedure A using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₃₀H₂₈O₄S: 484.61, found: 485.2 [M+H]⁺.

(D) (3*S*)-Ethyl 3-(4-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 3-(4-((3-(4-hydroxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate and 3-methylbutane-1,3-diol following General Procedure B using PPh₃ and ADDP. LC/MS: mass calcd. for C₃₅H₃₈O₅S: 570.74, found: 571.2 [M+H]⁺.

(E) (3*S*)-3-(4-((3-(4-(3-Hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (CD₃OD) δ 7.96 (m, 1H), 7.48 (m, 1H), 7.38 (s, 2H), 7.22 - 7.28 (m, 2H), 7.13 - 7.16 (m, 1H), 6.81 - 6.95 (m, 4H), 5.16 (s, 2H), 4.19 - 4.22 (m, 2H), 3.39 - 4.01 (m, 1H), 2.62 - 2.67 (m, 2H), 2.01 - 2.08 (m, 5H), 1.82 (s, 3H), 1.38 (s, 6H). LC/MS: mass calcd. for C₃₃H₃₄O₅S: 542.69, found: 543.2 [M+H]⁺.

(F) (3*S*)-3-(4-((3-(4-(3-Hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoamide was prepared by the HATU-mediated coupling of (3*S*)-3-(4-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid and NH₄Cl following the procedure described in Example 6E. LC/MS: mass calcd. for C₃₃H₃₅NO₄S: 541.23, found: 542.1 [M+H]⁺.

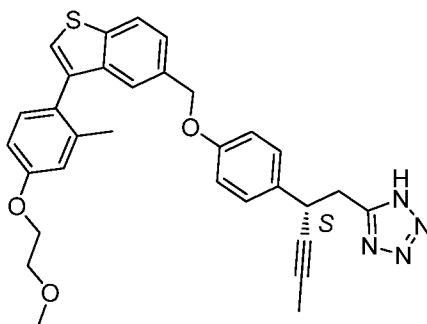
(G) (3*S*)-3-(4-((3-(4-(3-Trifluoroacetoxy-3-methylbutoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoamide following General Procedure I. LC/MS: mass calcd. for C₃₅H₃₂F₃NO₄S: 619.20, found 506.0 [M-CF₃COO]⁺.

(H) (3*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-yl 2,2,2-trifluoroacetate was prepared from (3*S*)-3-(4-((3-(4-(3-Trifluoroacetoxy-3-methylbutoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. LC/MS: mass calcd. for C₃₅H₃₃F₃N₄O₄S: 662.22, found 549.1 [M-CF₃COO]⁺.

(I) A solution of (3*S*)-4-(4-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-yl 2,2,2-trifluoroacetate (10 mg, 0.015 mmol), LiOH (20 mg, 0.48 mmol), THF (2 mL) and water (1 mL) was stirred at rt overnight. The mixture was concentrated under reduced pressure and then diluted with water (5 mL). The pH of the solution was adjusted to 4~5 with 1 M HCl and the solids that formed were collected by filtration and dried to afford (2*S*)-4-(4-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol (Cpd 7) (2.7 mg, 33 %) as a white solid. ¹H NMR (CD₃OD + D₂O) δ 7.90 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.34 (d, *J* = 5.1 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.80 - 6.84 (m, 4H), 5.09 (s, 2H), 4.16 (t, *J* = 6.6 Hz, 2H), 4.02 (br. s, 1H), 3.07 - 3.15 (m, 2H), 1.95 - 2.00 (m, 5H), 1.71 (s, 3H), 1.28 (s, 6H). LC/MS: mass calcd. for C₃₃H₃₄N₄O₃S: 566.24, found: 567.1 [M+H]⁺.

Example 8

(2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 8



(A) A mixture of 4-bromo-3-methylphenol (5 g, 26.7 mmol), 1-bromo-2-methoxyethane (4.4 g, 31.7 mmol) and K_2CO_3 (15 g, 108.5 mmol) in MeCN (100 mL) was stirred overnight at 80 °C. After cooling to rt, the reaction was filtered and the filtrate was concentrated under reduced pressure to afford 1-bromo-4-(2-methoxyethoxy)-2-methylbenzene as a yellow oil. 1H NMR ($CDCl_3$) δ 7.38 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 6.63 (dd, J = 8.4, 2.8 Hz, 1H), 4.06 (t, J = 4.8 Hz, 2H), 3.72 (t, J = 4.8 Hz, 2H), 3.43 (s, 3H), 2.34 (s, 3H).

(B) 2-(4-(2-Methoxyethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared from 1-bromo-4-(2-methoxyethoxy)-2-methylbenzene and bis(pinacolato)diboron following General Procedure A, using $PdCl_2(dppf) \cdot CH_2Cl_2$ as the palladium catalyst and Cs_2CO_3 in place of K_2CO_3 . LC/MS: mass calcd. for $C_{16}H_{25}BO_4$: 292.18, found: 293.2 $[M+H]^+$.

(C) 3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophene-5-carbaldehyde was prepared from 2-(4-(2-methoxyethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3-bromobenzo[b]thiophene-5-carbaldehyde (from Example 4A) following General Procedure A, using $PdCl_2(dppf) \cdot CH_2Cl_2$ as the palladium catalyst and Cs_2CO_3 in place of K_2CO_3 . 1H NMR ($CDCl_3$) δ 10.02 (s, 1H), 8.02 - 8.04 (m, 1H), 7.88 - 7.90 (m, 2H), 7.37 (s, 1H), 7.20 - 7.26 (m, 1H), 6.83 - 6.94 (m, 2H), 4.19 - 4.21 (m, 2H), 3.37 - 3.82 (m, 2H), 3.49 (s, 3H), 2.14 (s, 3H).

(D) (3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol was prepared from 3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophene-5-carbaldehyde

following General Procedure F. LC/MS: mass calcd. for $C_{19}H_{20}O_3S$: 328.43, found: 311.0 $[M-OH]^+$.

(E) 5-(Chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophene was prepared from (3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D. LC/MS: mass calcd. for $C_{19}H_{19}ClO_2S$: 346.87, found: 347.1 $[M]^+$.

(F) (3*S*)-Ethyl 3-(4-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-(chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophene and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E. LC/MS: mass calcd. for $C_{33}H_{34}O_5S$: 542.69, found: 543.2 $[M+H]^+$.

(G) (3*S*)-3-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. 1H NMR (DMSO- d_6) δ 8.06 (d, $J = 8.4$ Hz, 1H), 7.65 (s, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.41 (s, 1H), 7.23 - 7.25 (m, 2H), 7.16 (d, $J = 8.0$ Hz, 1H), 6.86 - 6.96 (m, 4H), 5.17 (s, 2H), 4.13 - 4.16 (m, 2H), 3.90 - 3.95 (m, 1H), 3.68 - 3.70 (m, 2H), 3.33 (s, 3H), 2.54 - 2.58 (m, 2H), 2.05 (s, 3H), 1.76 (s, 3H). LC/MS: mass calcd. for $C_{31}H_{30}O_5S$: 514.63, found: 515.2 $[M+H]^+$.

(H) (3*S*)-3-(4-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

(I) (3*S*)-3-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(4-(2-

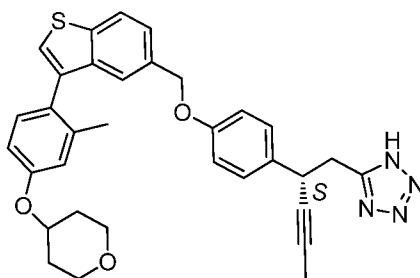
methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for $C_{31}H_{31}NO_4S$: 513.20, found: 514.3 $[M+H]^+$.

(J) (3*S*)-3-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $C_{31}H_{29}NO_3S$: 495.19, found: 513.1 $[M+NH_4]^+$.

(K) (2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, (Cpd **8**) was prepared from (3*S*)-3-(4-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. 1H NMR (CD_3OD) δ 7.92 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 8.4$ Hz, 1H), 6.84 – 6.91 (m, 4H), 5.12 (s, 2H), 4.15 – 4.17 (m, 2H), 4.02 – 4.07 (m, 1H), 3.76 – 3.78 (m, 2H), 3.45 (s, 3H), 3.25 (d, $J = 7.6$ Hz, 2H), 2.05 (s, 3H), 1.77 (s, 3H). LC/MS: mass calcd. for $C_{31}H_{30}N_4O_3S$: 538.20, found: 539.1 $[M+H]^+$.

Example 9

(2*S*)-5-(2-(4-((3-(2-Methyl-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **9**



(A) 4-(4-Bromo-3-methylphenoxy)-tetrahydro-2*H*-pyran was prepared from 4-bromo-3-methylphenol and oxan-4-ol following General Procedure B using PPh_3 and DBAD at a reaction temperature of 50 °C overnight. 1H NMR ($CDCl_3$) δ 7.41 (d, $J = 8.6$ Hz, 1H),

6.81 (d, $J = 3.0$ Hz, 1H), 6.62 (dd, $J = 8.7, 3.0$ Hz, 1H), 4.39-4.47 (m, 1H), 3.93 – 4.00 (m, 2H), 3.53 - 3.60 (m, 2H), 2.35 (s, 3H), 1.95 – 2.03 (m, 2H), 1.70 – 1.82 (m, 2H); LC/MS: Calcd. for $C_{12}H_{15}BrO_2$: 271.2, found: 271.0 $[M]^+$, 273.0 $[M+2]^+$.

(B) 4,4,5,5-Tetramethyl-2-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)-1,3,2-dioxaborolane was prepared from 4-(4-bromo-3-methylphenoxy)-tetrahydro-2*H*-pyran and bis(pinacolato)diboron following General Procedure A, using $PdCl_2(dppf)CH_2Cl_2$ as the palladium catalyst, KOAc in place of K_2CO_3 and a reaction temperature of 70 °C overnight. LC/MS: mass calcd. for $C_{18}H_{27}BO_4$: 318.2, found: 319.2 $[M]^+$.

(C) 3-(2-Methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[b]thiophene-5-carbaldehyde was prepared from 3-bromobenzo[b]thiophene-5-carbaldehyde (from Example 4A) and 4,4,5,5-tetramethyl-2-[2-methyl-4-(oxan-4-yloxy)phenyl]-1,3,2-dioxaborolane following General Procedure A using $PdCl_2(dppf)CH_2Cl_2$ as the palladium catalyst and Cs_2CO_3 in place of K_2CO_3 . LC/MS: mass calcd. for $C_{21}H_{20}O_3S$: 352.45, found: 353.1 $[M+H]^+$.

(D) (3-(2-Methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[b]thiophen-5-yl)methanol was prepared from 3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[b]thiophene-5-carbaldehyde following General Procedure F. LC/MS: mass calcd. for $C_{21}H_{22}O_3S$: 354.46, found: 355.1 $[M+H]^+$.

(E) 4-(4-(5-(Chloromethyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-tetrahydro-2*H*-pyran was prepared from (3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

(F) (3*S*)-Ethyl 3-(4-((3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 4-(4-(5-(chloromethyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-tetrahydro-2*H*-pyran and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E using DMF as

solvent at a reaction temperature of 60 °C for 1 h. LC/MS: mass calcd. for C₃₅H₃₆O₅S: 568.72, found: 569.2 [M]⁺.

(G) (3*S*)-3-(4-((3-(2-Methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)ethyl 3-(4-((3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 12.35 (br. s, 1H), 8.00 - 8.04 (m, 1H), 7.65 (s, 1H), 7.42 - 7.49 (m, 2H), 7.23 - 7.26 (m, 2H), 7.14 - 7.17 (m, 1H), 6.98 - 6.99 (m, 1H), 6.90 - 6.93 (m, 3H), 5.17 (s, 2H), 4.60 - 4.66 (m, 1H), 3.84 - 3.95 (m, 3H), 3.47 - 3.55 (m, 2H), 2.56 - 2.59 (m, 2H), 1.99 - 2.05 (m, 5H), 1.76 (s, 3H), 1.56 - 1.68 (m, 2H). LC/MS: mass calcd. for C₃₃H₃₂O₅S: 540.67, found: 541.2 [M+H]⁺.

(H) (3*S*)-3-(4-((3-(2-Methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yloxy)methyl)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

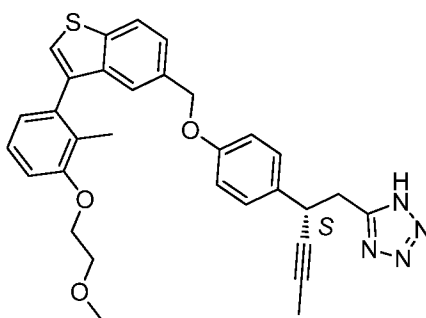
(I) (3*S*)-3-(4-((3-(2-Methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yloxy)methyl)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yloxy)methyl)phenyl)hex-4-ynoyl chloride following General Procedure Ha and was used directly without characterization.

(J) (3*S*)-3-(4-((3-(2-Methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yloxy)methyl)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yloxy)methyl)phenyl)hex-4-ynamide following General Procedure I and was used directly without characterization.

(K) (2*S*)-5-(2-(4-((3-(2-Methyl-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, (Cpd **9**) was prepared from (3*S*)-3-(4-((3-(2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl)benzo[*b*]thiophen-5-yloxy)methyl)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.78 (d, *J* = 8.8 Hz, 1H), 7.30 - 7.33 (m, 5H), 7.02 - 7.14 (m, 2H), 6.78 - 6.95 (m, 3H), 5.01 (s, 2H), 4.62 - 4.64 (m, 1H), 4.10 - 4.15 (m, 1H), 3.96 - 4.02 (m, 2H), 3.60 - 3.67 (m, 2H), 3.30 - 3.33 (m, 2H), 2.05 - 2.16 (m, 2H), 1.94 (s, 3H), 1.68 - 1.86 (m, 5H). LC/MS: mass calcd. for C₃₃H₃₂N₄O₃S: 564.22, found: 565.3 [M+H]⁺.

Example 10

(2*S*)-5-(2-(4-((3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **10**



(A) 1-Bromo-3-(2-methoxyethoxy)-2-methylbenzene was prepared from 3-bromo-2-methylphenol and 1-bromo-2-methoxyethane following the procedure described in Example 8A. GC/MS: mass calcd. for C₁₀H₁₃BrO₂: 244.01, found: 244.0 [M]⁺, 246.0 [M+2]⁺.

(B) 2-[3-(2-Methoxyethoxy)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared from 1-bromo-3-(2-methoxyethoxy)-2-methylbenzene and bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst, KOAc in place of K₂CO₃ and DMSO as solvent at a reaction temperature of 90 °C overnight. ¹H NMR (CDCl₃) δ 7.35 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.13

(t, $J = 7.5$ Hz, 1H), 6.91 – 6.93 (m, 1H), 4.09 – 4.12 (m, 2H), 3.75 – 3.78 (m, 2H), 3.46 (s, 3H), 2.44 (s, 3H), 1.34 (s, 12H).

(C) Ethyl (3*S*)-3-[4-([3-[3-(methoxymethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoate was prepared from 2-[3-(2-methoxyethoxy)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and ethyl (3*S*)-3-[4-[(3-bromo-1-benzothiophen-5-yl)methoxy]phenyl]hex-4-ynoate (from Example 22C) following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₃₃H₃₄O₅S: 542.69, found: 543.2 [M+H]⁺.

(D) (3*S*)-3-[4-([3-[3-(2-Methoxyethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoic acid was prepared from ethyl (3*S*)-3-[4-([3-[3-(methoxymethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.06 (d, $J = 8.1$ Hz, 1H), 7.67 (s, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.39 - 7.40 (m, 1H), 7.21 – 7.28 (m, 3H), 7.04 – 7.07 (m, 1H), 6.85 – 6.90 (m, 3H), 5.15 (s, 2H), 4.15 – 4.18 (m, 2H), 3.89 – 3.95 (m, 1H), 3.71 – 3.74 (m, 2H), 3.35 (s, 3H), 2.36 – 2.44 (m, 2H), 1.92 (s, 3H), 1.75 (s, 3H). LC/MS: mass calcd. for C₃₁H₃₀O₅S: 514.63, found: 515.2 [M+H]⁺, 537.2 [M+Na]⁺.

(E) (3*S*)-3-(4-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-[4-([3-[3-(2-methoxyethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

(F) (3*S*)-3-(4-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha and was used directly without characterization.

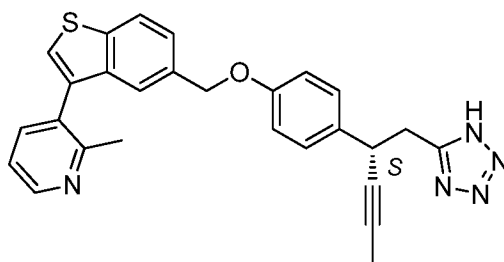
(G) (3*S*)-3-(4-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(3-(2-

methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I and was used directly without characterization.

(H) (2*S*)-5-(2-(4-((3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **10**) was prepared from (3*S*)-3-(4-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.50 - 7.54 (m, 1H), 7.36 - 7.38 (m, 2H), 7.18 - 7.29 (m, 3H), 6.99 - 7.06 (m, 1H), 6.88 - 6.92 (m, 3H), 5.13 (s, 2H), 4.17 - 4.25 (m, 2H), 4.07 - 4.10 (m, 1H), 3.79 - 3.84 (m, 2H), 3.47 (s, 3H), 3.26 (d, *J* = 7.7 Hz, 2H), 1.97 (s, 3H), 1.79 (s, 3H). LC/MS: mass calcd. for C₃₁H₃₀N₄O₃S: 538.20, found: 539.3 [M+H]⁺.

Example 11

(2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-methylpyridine, Cpd **11**



(A) (3*S*)-Ethyl 3-(4-((3-(2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3*S*)-ethyl 3-(4-((3-bromobenzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (from Example 7B) and (2-methylpyridin-3-yl)boronic acid following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₂₉H₂₇NO₃S: 469.59, found: 470.2 [M+H]⁺.

(B) (3*S*)-3-(4-((3-(2-Methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2-methylpyridin-3-yl)benzo[b]thiophen-

5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base, EtOH in place of MeOH and 2N HCl for reaction acidification. ^1H NMR (DMSO- d_6) δ 12.24 (s, 1H), 8.56 (dd, $J = 1.6, 4.8$ Hz, 1H), 8.11 (d, $J = 8.4$ Hz, 1H), 7.85 (s, 1H), 7.68 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.44 (s, 1H), 7.34 - 7.38 (m, 1H), 7.24 (d, $J = 8.4$ Hz, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 5.18 (s, 2H), 3.90 - 3.92 (m, 1H), 2.56 (d, $J = 7.6$ Hz, 2H), 2.29 (s, 3H), 1.77 (s, 3H). LC/MS: mass calcd. for $\text{C}_{27}\text{H}_{23}\text{NO}_3\text{S}$: 441.54, found: 442.1 $[\text{M}+\text{H}]^+$.

(C) (3*S*)-3-(4-((3-(2-Methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

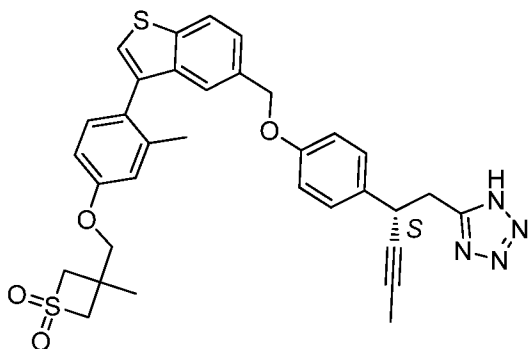
(D) (3*S*)-3-(4-((3-(2-Methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha (inverse addition). LC/MS: mass calcd. for $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$: 440.16, found: 441.1 $[\text{M}+\text{H}]^+$.

(E) (3*S*)-3-(4-((3-(2-Methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $\text{C}_{27}\text{H}_{22}\text{N}_2\text{OS}$: 422.15, found: 423.2 $[\text{M}+\text{H}]^+$.

(F) (2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-methylpyridine (Cpd 11) was prepared from (3*S*)-3-(4-((3-(2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ^1H NMR (CD_3OD) δ 8.73 - 8.75 (m, 1H), 8.34 - 8.37 (m, 1H), 8.06 (d, $J = 8.1$ Hz, 1H), 7.84 - 7.91 (m, 2H), 7.52 - 7.58 (m, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 5.19 (s, 2H), 4.04 - 4.10 (m, 1H), 3.22 - 3.23 (m, 2H), 2.54 (s, 3H), 1.79 (s, 3H). LC/MS: mass calcd. for $\text{C}_{27}\text{H}_{23}\text{N}_5\text{OS}$: 465.16, found: 466.2 $[\text{M}+\text{H}]^+$.

Example 12

(2*S*)-3-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)methyl)-3-methylthietane 1,1-dioxide, Cpd **12**



(A) To an ice-cooled solution of 4-bromo-3-methylphenol (300 mg, 1.60 mmol), (3-methylthietan-3-yl)methanol (300 mg, 2.54 mmol) and (n-Bu)₃P (810 mg, 4.02 mmol) in toluene (10 mL) was added ADDP (1020 mg, 4.07 mmol). Upon completion of addition, the reaction mixture was warmed to 60 °C and stirred for 2 h. The reaction was treated with satd. aq. NH₄Cl (50 mL), extracted with EtOAc (2 x 50 mL) and the combined organic extracts were concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-2% EtOAc/petroleum ether) afforded 3-((4-bromo-3-methylphenoxy)methyl)-3-methylthietane (0.67 g, crude) as a white solid. ¹H NMR (CDCl₃) δ 7.36 - 7.42 (m, 1H), 6.84 - 6.85 (m, 1H), 6.63 - 6.67 (m, 1H), 3.90 (s, 2H), 3.18 (d, *J* = 6.3 Hz, 2H), 2.95 (d, *J* = 6.3 Hz, 2H), 2.37 (s, 3H), 1.46 (s, 3H).

(B) To a solution of 3-((4-bromo-3-methylphenoxy)methyl)-3-methylthietane (570 mg, 1.37 mmol) and Na₂WO₄·2H₂O (110 mg, 0.35 mmol) in MeOH (50 mL) was added 30% H₂O₂ (1.92 g, 16.94 mmol) in drop-wise fashion, and the resulting mixture was stirred at rt for 2 h. The mixture was then concentrated under reduced pressure and purified directly by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford 3-(4-bromo-3-methylphenoxy)methyl)-3-methylthietane-1,1-dioxide (412 mg, 94% yield) as a colorless oil. ¹H NMR (CDCl₃) δ 7.41 - 7.44 (m, 1H), 6.82 - 6.83 (m, 1H), 6.61 - 6.65 (m, 1H), 4.20 - 4.25 (m, 2H), 3.97 (s, 2H), 3.83 - 3.88 (m, 2H), 2.37 (s, 3H), 1.60 (s, 3H).

(C) 3-Methyl-3-[3-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)methyl]-thietane-1,1-dioxide was prepared from 3-(4-bromo-3-methylphenoxy)methyl-3-methyl-thietane-1,1-dioxide and bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst, dioxane as solvent and Cs₂CO₃ in place of K₂CO₃ at a reaction temperature of 80 °C overnight. ¹H NMR (CDCl₃) δ 7.44 - 7.46 (m, 1H), 6.85 - 6.86 (m, 1H), 6.64 - 6.67 (m, 1H), 4.23 - 4.29 (m, 2H), 3.99 (s, 2H), 3.85 - 3.90 (m, 2H), 2.37 (s, 3H), 1.63 (s, 3H), 1.35 (s, 12H).

(D) 3-{2-Methyl-4-[(3-methyl-1,1-dioxo-thietan-3-yl)methoxy]phenyl}-1-benzothiophene-5-carbaldehyde was prepared from 3-methyl-3-[3-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)methyl]-thietane-1,1-dioxide and 3-bromobenzo[b]thiophene-5-carbaldehyde (from Example 4A) following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃ at a reaction temperature of 80 °C overnight. ¹H NMR (CDCl₃) δ 7.44 - 7.46 (m, 1H), 6.85 - 6.86 (m, 1H), 6.64 - 6.67 (m, 1H), 4.23 - 4.29 (m, 2H), 3.99 (s, 2H), 3.85 - 3.90 (m, 2H), 2.37 (s, 3H), 1.63 (s, 3H), 1.35 (s, 12H).

(E) 3-{4-[5-(Hydroxymethyl)-1-benzothiophen-3-yl]-3-methylphenoxy)methyl}-3-methyl-thietane-1,1-dione was prepared from 3-{2-methyl-4-[(3-methyl-1,1-dioxo-thietan-3-yl)methoxy]phenyl}-1-benzothiophene-5-carbaldehyde following General Procedure F. LC/MS: mass calcd. for C₂₁H₂₂O₄S₂: 402.53, found: 403.1 [M+H]⁺.

(F) 3-{4-[5-(Chloromethyl)-1-benzothiophen-3-yl]-3-methylphenoxy)methyl}-3-methyl-thietane-1,1-dione was prepared from 3-{4-[5-(hydroxymethyl)-1-benzothiophen-3-yl]-3-methylphenoxy)methyl}-3-methyl-thietane-1,1-dione following General Procedure D. LC/MS: mass calcd. for C₂₁H₂₁ClO₃S₂: 420.97; found: 421.1 [M]⁺.

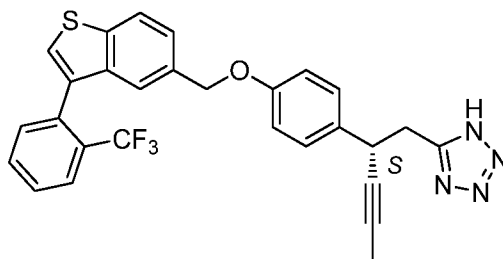
(G) (3*S*)-3-(4-((3-(2-Methyl-4-((3-methyl-1,1-dioxidothietan-3-yl)methoxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 3-{4-[5-(chloromethyl)-1-benzothiophen-3-yl]-3-methylphenoxy)methyl}-3-methyl-thietane-1,1-dione and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G)

following General Procedure E, at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₃₃H₃₁NO₄S₂: 569.17, found: 587.0 [M+NH₄]⁺.

(H) (2*S*)-3-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)methyl)-3-methylthietane 1,1-dioxide (Cpd **12**) was prepared from (3*S*)-3-(4-((3-(2-methyl-4-((3-methyl-1,1-dioxidothietan-3-yl)methoxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.90 (d, *J* = 8.4Hz, 1H), 7.35 - 7.42 (m, 3H), 7.12 - 7.19 (m, 3H), 6.84 - 6.94 (m, 4H), 5.08 (s, 2H), 4.22 - 4.27 (m, 2H), 4.08 (s, 2H), 3.99 - 4.05 (m, 1H), 3.84 - 3.89 (m, 2H), 3.21 - 3.24 (m, 2H), 2.03 (s, 3H), 1.74 (d, *J* = 2.4 Hz, 3H), 1.57 (s, 3H). LC/MS: mass calcd. for C₃₃H₃₂N₄O₄S₂: 612.19, found: 613.0 [M+H]⁺.

Example 13

(2*S*)-5-(2-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **13**



(A) (3*S*)-Ethyl 3-(4-((3-(2-(trifluoromethyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 2-(trifluoromethyl)phenylboronic acid and (3*S*)-ethyl 3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (from Example 7B) following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₃₀H₂₅F₃O₃S: 522.58, found: 523.1 [M+H]⁺.

(B) (3*S*)-3-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2-(trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base, EtOH in place of MeOH, 2N HCl for reaction acidification and a reaction temperature of 30 °C overnight. ¹H NMR (DMSO-*d*₆) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.69 - 7.82 (m, 3H), 7.48 - 7.51 (m, 2H), 7.43 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.13 (s, 2H), 3.91 - 3.93 (m, 1H), 2.58 - 2.67 (m, 2H), 1.77 (s, 3H). LC/MS: mass calcd. for C₂₈H₂₁F₃O₃S: 494.52, found: 493.1 [M-H]⁻.

(C) (3*S*)-3-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

(D) (3*S*)-3-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2-(trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha (inverse addition). LC/MS: mass calcd. for C₂₈H₂₂F₃NO₂S: 493.13, found: 494.2 [M+H]⁺.

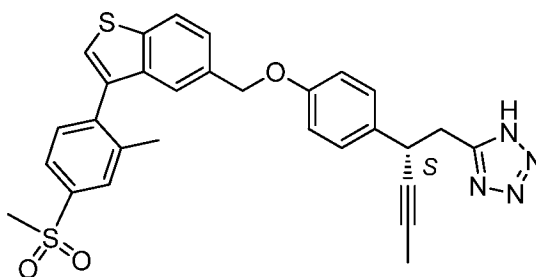
(E) (3*S*)-3-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-(2-(trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₈H₂₀F₃NOS: 475.12, found: 498.1 [M+Na]⁺.

(F) (2*S*)-5-(2-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **13**) was prepared from (3*S*)-3-(4-((3-(2-(trifluoromethyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. Additional purification of the product

was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (20 – 50%). ¹H NMR (CD₃OD) δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.61 - 7.75 (m, 2H), 7.36 - 7.52 (m, 4H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.12 (s, 2H), 4.03 - 4.09 (m, 1H), 3.25 - 3.28 (m, 2H), 1.78 (s, 3H). LC/MS: mass calcd. for C₂₈H₂₁F₃N₄OS: 518.14, found: 519.2 [M+H]⁺.

Example 14

(2*S*)-5-(2-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 14



(A) 3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[*b*]thiophene-5-carbaldehyde was prepared from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-5-yl)methanol (from Example 5A) and 1-bromo-4-methanesulfonyl-2-methylbenzene following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst, Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₇H₁₄O₃S₂: 330.42, found: 331.1 [M+H]⁺.

(B) (3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[*b*]thiophen-5-yl)methanol was prepared from 3-(2-methyl-4-(methylsulfonyl)phenyl)benzo[*b*]thiophene-5-carbaldehyde and NaBH₄, following General Procedure F. LC/MS: mass calcd. for C₁₇H₁₆O₃S₂: 332.44, found: 314.9 [M-OH]⁺.

(C) (3*S*)-Ethyl 3-(4-((3-(2-methyl-4-(methylsulfonyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3-(2-methyl-5-

(methylsulfonyl)phenyl)benzo[b]-thiophen-5-yl)methanol and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure B, using Bu₃P and ADDP at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₃₁H₃₀O₅S₂: 546.70, found: 547.2 [M]⁺.

(D) (3*S*)-3-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2-methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 12.23 (br. s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 7.85 - 7.87 (m, 2H), 7.51 - 7.57 (m, 2H), 7.45 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.17 (s, 2H), 3.90 - 3.95 (m, 1H), 3.29 (s, 3H), 2.54 - 2.59 (m, 2H), 2.21 (s, 3H), 1.76 (s, 3H). LC/MS: mass calcd. for C₂₉H₂₆O₅S₂: 518.64, found: 519.0 [M]⁺.

(E) (3*S*)-3-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

(F) (3*S*)-3-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2-methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for C₂₉H₂₇NO₄S₂: 517.14, found: 518.0 [M+H]⁺.

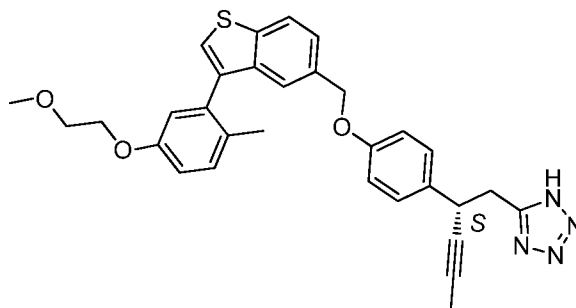
(G) (3*S*)-3-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-(2-methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following

General Procedure I. LC/MS: mass calcd. for $C_{29}H_{25}NO_3S_2$: 499.13, found: 517.0 $[M+NH_4]^+$.

(H) (2*S*)-5-(2-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **14**) was prepared from (3*S*)-3-(4-((3-(2-methyl-4-(methylsulfonyl)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. 1H NMR (CD_3OD) δ 7.95 (t, $J = 8.1$ Hz, 2H), 7.84 (d, $J = 8.1$ Hz, 1H), 7.55 (s, 1H), 7.48 (t, $J = 8.4$ Hz, 2H), 7.35 (s, 1H), 7.18 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.12 (s, 2H), 4.02 - 4.08 (m, 1H), 3.21 - 3.28 (m, 2H), 3.16 (s, 3H), 2.17 (s, 3H), 1.75 (s, 3H). LC/MS: mass calcd. for $C_{29}H_{26}N_4O_3S_2$: 542.15, found: 543.0 $[M+H]^+$.

Example 15

(2*S*)-5-(2-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **15**



(A) 2-Bromo-4-(2-methoxyethoxy)-1-methylbenzene was prepared from 3-bromo-4-methylphenol and 1-bromo-2-methoxyethane following the procedure described in Example 8A. GC/MS: mass calcd. for $C_{10}H_{13}BrO_2$: 244.01, found: 244.1 $[M]^+$, 246.1 $[M+2]^+$.

(B) 2-[5-(2-Methoxyethoxy)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared from 2-bromo-4-(2-methoxyethoxy)-1-methylbenzene and

bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst, KOAc in place of K₂CO₃ and DMSO as solvent. ¹H NMR (CDCl₃) δ 7.31 - 7.32 (m, 1H), 7.05 - 7.10 (m, 1H), 6.88 - 6.93 (m, 1H), 4.11 - 4.14 (m, 2H), 3.72 - 3.75 (m, 2H), 3.44 (s, 3H), 2.46 (s, 3H), 1.33 (s, 12H).

(C) Ethyl (3*S*)-3-[4-([3-[5-(2-methoxyethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoate was prepared from ethyl (3*S*)-3-[4-[(3-bromo-1-benzothiophen-5-yl)methoxy]phenyl]hex-4-ynoate and 2-[5-(2-methoxyethoxy)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. ¹H NMR (CDCl₃) δ 7.80 - 7.90 (m, 1H), 7.45 - 7.58 (m, 2H), 7.30 - 7.35 (m, 2H), 7.13 - 7.20 (m, 2H), 6.86 - 6.90 (m, 4H), 5.08 (s, 2H), 4.05 - 4.13 (m, 4H), 3.73 - 3.76 (m, 2H), 3.44 (s, 3H), 2.63 - 2.71 (m, 2H), 2.06 (s, 3H), 1.81 (s, 3H), 1.15 - 1.25 (m, 3H).

(D) (3*S*)-3-[4-([3-[5-(2-Methoxyethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoic acid was prepared from ethyl (3*S*)-3-[4-([3-[5-(2-methoxyethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH, a reaction temperature of 30 °C overnight and 1N HCl for reaction acidification. Additional product purification was carried out by silica gel chromatography [EtOAc/ petroleum ether (1:1)]. ¹H NMR (DMSO-*d*₆) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.71 (s, 1H), 7.45 - 7.49 (m, 2H), 7.23 - 7.28 (m, 3H), 6.90 - 6.96 (m, 3H), 6.82 (d, *J* = 2.8 Hz, 1H), 5.18 (s, 2H), 4.07 - 4.09 (m, 2H), 3.90 - 3.94 (m, 1H), 3.64 (t, *J* = 4.4 Hz, 2H), 3.29 (s, 3H), 2.56 (d, *J* = 8.4 Hz, 2H), 1.99 (s, 3H), 1.76 (s, 3H). LC/MS: mass calcd for C₃₁H₃₀O₅S: 514.63, found 515.2 [M+H]⁺, 537.2 [M+Na]⁺.

(E) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-[4-([3-[5-(2-methoxyethoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)phenyl]hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

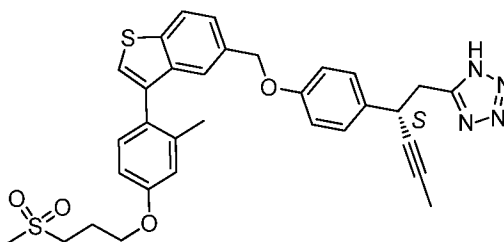
(F) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for C₃₁H₃₁NO₄S: 513.20, found: 514.1 [M+H]⁺.

(G) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₃₁H₂₉NO₃S: 495.19, found: 513.1 [M+NH₄]⁺.

(H) (2*S*)-5-(2-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **15**) was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.40 - 7.44 (m, 3H), 7.17 - 7.22 (m, 3H), 6.80 - 6.92 (m, 4H), 5.11 (s, 2H), 4.00 - 4.08 (m, 3H), 3.69 - 3.72 (m, 2H), 3.38 (s, 3H), 3.21 - 3.29 (m, 2H), 1.98 (s, 3H), 1.75 (s, 3H). LC/MS: mass calcd. for C₃₁H₃₀N₄O₃S: 538.20, found: 539.1 [M+H]⁺.

Example 16

(2*S*)-5-(2-(4-((3-(2-Methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **16**



(A) To a solution of 3-methylthiopropanol (1.6 g; 15.07 mmol) and tosyl chloride (3.16 g; 16.57 mmol) in DCM (10 mL) was added pyridine (1.46 mL; 18.08 mmol) in drop-wise

fashion, and the resultant mixture was stirred at rt for 1 h. The mixture was then concentrated under reduced pressure and the residue thus obtained was purified by silica gel chromatography eluting with 0 – 50% EtOAc in hexanes to afford 3-(methylthio)propyl 4-methylbenzenesulfonate (3.6 g; 92%) as a colorless oil. LC/MS: mass calcd. for $C_{11}H_{16}O_3S_2$: 260.38, found 283.1 $[M+Na]^+$.

(B) To an ice-cooled solution of 3-(methylthio)propyl 4-methylbenzenesulfonate (3.6 g; 13.8 mmol) in MeOH (70 mL) was added a suspension of monopersulfate compound (17 g; 27.4 mmol) in water (70 mL) in a portion-wise fashion. Upon completion of the addition, the mixture was allowed to warm to rt, and stirring was continued for 20 h. The reaction was partially concentrated to remove the MeOH and the mixture was further diluted with water and extracted with EtOAc (2x). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 – 67% EtOAc in hexanes to afford 3-(methylsulfonyl)propyl 4-methylbenzene-sulfonate (3.72 g, 92%) as a white solid. LC/MS: mass calcd. for $C_{11}H_{16}O_5S_2$: 292.38, found 315.1 $[M+Na]^+$.

(C) A mixture of 5-hydroxymethyl-3-(4-hydroxy-2-methylphenyl)benzo[b]thiophene (from Example 6A) (108 mg; 0.4 mmol), 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate (292 mg; 1.0 mmol) and K_2CO_3 (82 mg; 0.6 mmol) in DMF (1.0 mL) was stirred at 90 °C for 6 h. After cooling to rt, the reaction was partitioned between EtOAc and aq NH_4Cl and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5-60% EtOAc in heptanes to afford 5-hydroxymethyl-3-(2-methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[b]thiophene (87 mg, 56%). LC/MS: mass calcd. for $C_{20}H_{20}O_4S_2$: 390.52, found 413.1 $[M+Na]^+$.

(D) (3*S*)-Methyl 3-(4-((3-(2-methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-hydroxymethyl-3-(2-methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[b]thiophene and (3*S*)-methyl 3-(4-

hydroxyphenyl)hex-4-ynoate (prepared as described in WO 2005086661) following General Procedure B using PPh_3 and DBAD. LC/MS: mass calcd. for $\text{C}_{33}\text{H}_{34}\text{O}_6\text{S}_2$: 590.76, found 591.0 $[\text{M}]^+$, 613.0 $[\text{M}+\text{Na}]^+$.

(E) (3*S*)-3-[4-[[3-[2-Methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid was prepared from (3*S*)-methyl 3-(4-((3-(2-methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base and 2N HCl for reaction acidification. ^1H NMR (CDCl_3) δ 7.92 (d, $J = 9.1$ Hz, 1H), 7.40 - 7.48 (m, 2H), 7.27 - 7.32 (m, 3H), 7.20 (d, $J = 8.1$ Hz, 1H), 6.83 - 6.95 (m, 3H), 6.80 (dd, $J = 8.6, 2.5$ Hz, 1H), 5.08 (s, 2H), 4.17 (t, $J = 5.6$ Hz, 2H), 3.98 - 4.09 (m, 1H), 3.25 - 3.35 (m, 2H), 2.98 (s, 3H), 2.79 (dd, $J = 15.7, 8.1$ Hz, 1H), 2.69 (dd, $J = 15.7, 7.1$ Hz, 1H), 2.12 (s, 3H), 1.82 (d, $J = 2.5$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{32}\text{H}_{32}\text{O}_6\text{S}_2$: 576.73, found 577.0 $[\text{M}]^+$.

(F) (3*S*)-3-[4-[[3-[2-Methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoyl chloride was prepared from (3*S*)-3-[4-[[3-[2-methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid following General Procedure G, using thionyl chloride as the chlorinating agent.

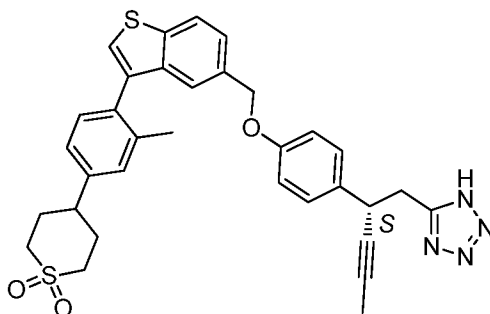
(G) (3*S*)-3-[4-[[3-[2-Methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide was prepared from (3*S*)-3-[4-[[3-[2-methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for $\text{C}_{32}\text{H}_{33}\text{NO}_5\text{S}_2$: 575.18, found: 576.0 $[\text{M}+\text{H}]^+$.

(H) (3*S*)-3-[4-[[3-[2-Methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynenitrile was prepared from (3*S*)-3-[4-[[3-[2-methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $\text{C}_{32}\text{H}_{31}\text{NO}_4\text{S}_2$: 557.72, found: 575.1 $[\text{M}+\text{NH}_4]^+$.

(I) (2*S*)-5-(2-(4-((3-(2-Methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **16**) was prepared from (3*S*)-3-[4-[[3-[2-methyl-4-(3-methylsulfonylpropoxy)phenyl]benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-yne nitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH₄CO₃) gradient (30 – 85%). ¹H NMR (CD₃OD) δ 7.92 (d, *J* = 8.4Hz, 1H), 7.43 (d, *J* = 8.0Hz, 1H), 7.36 - 7.37 (m, 2H), 7.13 - 7.19 (m, 3H), 6.91 - 6.92 (m, 1H), 6.83 - 6.87 (m, 3H), 4.03 - 4.05 (m, 1H), 3.12 - 3.37 (m, 4H), 3.02 (s, 3H), 2.28 - 2.30 (m, 2H), 2.04 (s, 3H), 1.74 (d, *J* = 2.4Hz, 3H). LC/MS: mass calcd. for C₃₂H₃₂N₄O₄S₂: 600.19, found: 601.3 [M+H]⁺.

Example 17

(2*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenyl)tetrahydro-2*H*-thiopyran 1,1-dioxide, Cpd **17**



(A) 4-(4-Bromo-3-methylphenyl)-3,6-dihydro-2*H*-thiopyran was prepared from 2-bromo-5-iodotoluene and 2-(3,6-dihydro-2*H*-thiopyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst. LC/MS: mass calcd. for C₁₂H₁₃BrS: 269.21, found 269.0 [M]⁺.

(B) To an ice-cooled solution of 4-(4-bromo-3-methylphenyl)-3,6-dihydro-2*H*-thiopyran (1.12 g; 4.16 mmol) in DCM (15 mL) was added a solution of mCPBA (1.865 g; 8.32 mmol) in DCM (15 mL) in drop-wise fashion. After stirring at 0 °C for 0.5 h, the reaction mixture was poured into a mixture of DCM (30 mL) and satd. aq. Na₂CO₃ (60 mL). The aqueous layer was extracted with DCM and the combined organic extracts were washed with satd. aq. Na₂CO₃, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography eluting with 5 - 40% EtOAc in DCM to afford 4-(4-bromo-3-methylphenyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide (815 mg, 65%). MS: mass calcd. for C₁₂H₁₃BrO₂S: 301.20, found 323.0 [M+Na]⁺, 325.0 [M+2+Na]⁺.

(C) 4-(3-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide was prepared from 4-(4-bromo-3-methylphenyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide and bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and KOAc in place of K₂CO₃. LC/MS: mass calcd. for C₁₈H₂₅BO₄S: 348.27, found 349.2 [M+H]⁺.

(D) 4-(4-(5-(Hydroxymethyl)benzo[b]thiophen-3-yl)-3-methylphenyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide was prepared from 4-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide and 3-bromo-5-hydroxymethylbenzothiophene (from Example 1A) following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst. LC/MS: mass calcd. for C₂₁H₂₀O₃S₂: 384.52, found 407.0 [M+Na]⁺.

(E) A mixture of 4-(4-(5-(hydroxymethyl)benzo[b]thiophen-3-yl)-3-methylphenyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide (from Example 6) (192 mg; 0.5 mmol) and 10% Pd/C (80 mg) in EtOH (6 mL) was prepared under an inert N₂ atmosphere and warmed to 45 - 50 °C. A solution of ammonium formate (472 mg, 7.5 mmol) in water (1 mL) was added and the mixture was stirred for 5 h. After cooling to rt, the mixture was diluted with EtOAc (10 mL), filtered and concentrated under reduced pressure. The residue was treated with a mixture of EtOAc/water (2/20 mL), followed by heptanes (30 mL), and the resulting

solid product was filtered and washed successively with water and heptanes to afford pure 4-(4-(5-(hydroxymethyl)benzo[b]thiophen-3-yl)-3-methylphenyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (136 mg, 70%). LC/MS: mass calcd. for C₂₁H₂₂O₃S₂: 386.54, found 409.0 [M+Na]⁺.

(F) (3*S*)-Methyl 3-(4-((3-(4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 4-(4-(5-(hydroxymethyl)benzo[b]thiophen-3-yl)-3-methylphenyl)tetrahydro-2*H*-thiopyran 1,1-dioxide and (3*S*)-methyl 3-(4-hydroxyphenyl)hex-4-ynoate (prepared as described in WO 2005086661) following General Procedure B using PPh₃ and DBAD. LC/MS: mass calcd. for C₃₄H₃₄O₅S₂: 486.77, found 587.3 [M]⁺; 609.2 [M+Na]⁺.

(G) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)-2-methylphenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid was prepared from (3*S*)-methyl 3-(4-((3-(4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using NaOH as base and 2M citric acid for reaction acidification. ¹H NMR (CDCl₃) δ 7.92 (d, *J* = 8.6 Hz, 1H), 7.42 - 7.48 (m, 2H), 7.22 - 7.32 (m, 4H), 7.19 (s, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 9.1 Hz, 2H), 5.08 (s, 2H), 4.00 - 4.08 (m, 1H), 3.14 - 3.23 (m, 4H), 2.74 - 2.87 (m, 2H), 2.64 - 2.73 (m, 1H), 2.40 - 2.57 (m, 2H), 2.29 (d, *J* = 14.7 Hz, 2H), 2.14 (s, 3H), 1.82 (d, *J* = 2.5 Hz, 3H). LC/MS: mass calcd. for C₃₃H₃₂O₅S₂: 572.75, found 595.3 [M+Na]⁺.

(H) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)-2-methylphenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoyl chloride was prepared from (3*S*)-3-[4-[[3-[4-(1,1-dioxothian-4-yl)-2-methylphenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid following General Procedure G, using thionyl chloride as the chlorinating agent.

(I) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)-2-methylphenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide was prepared from (3*S*)-3-[4-[[3-[4-(1,1-dioxothian-4-yl)-2-methylphenyl]benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoyl chloride

following General Procedure Ha. LC/MS: mass calcd. for $C_{33}H_{33}NO_4S_2$: 571.19, found: 572.0 $[M+H]^+$.

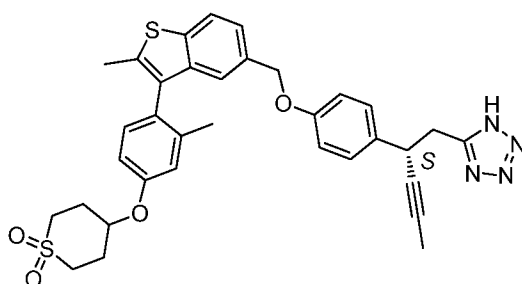
(J) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)-2-methylphenyl]benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynenitrile was prepared from (3*S*)-3-[4-[[3-[4-(1,1-dioxothian-4-yl)-2-methylphenyl]benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $C_{33}H_{31}NO_3S_2$: 553.18, found: 571.1 $[M+NH_4]^+$.

(K) (2*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (Cpd 17) was prepared from (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)-2-methylphenyl]benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH_4CO_3) gradient (30 – 85%). 1H NMR (CD_3OD) δ 7.91 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H), 7.14 - 7.23 (m, 5H), 6.81 (d, J = 8.7 Hz, 2H), 5.08 (s, 2H), 3.99 - 4.02 (m, 1H), 3.34 - 3.37 (m, 2H), 3.05 - 3.21 (m, 4H), 2.91 - 2.95 (m, 1H), 2.21 - 2.36 (m, 4H), 2.05 (s, 3H), 1.72 (d, J = 2.4 Hz, 3H). LC/MS: mass calcd. for $C_{33}H_{32}N_4O_3S_2$: 596.19, found: 597.3 $[M+H]^+$.

Example 18

4-(4-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-2-methylbenzo[*b*]thiophen-3-yl)-3-methylphenoxy)tetrahydro-2*H*-thiopyran 1,1-dioxide,

Cpd 18



(A) Methyl 3-(4-hydroxy-2-methylphenyl)-2-methylbenzo[b]thiophene-5-carboxylate was prepared from methyl 3-bromo-2-methylbenzo[b]thiophene-5-carboxylate and (4-hydroxy-2-methylphenyl)boronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst. MS: mass calcd. for C₁₈H₁₆O₃S: 312.39, found 313.2 [M+H]⁺, 335.1 [M+Na]⁺.

(B) Methyl 3-(4-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy)-2-methylphenyl)-2-methylbenzo[b]thiophene-5-carboxylate was prepared from methyl 3-(4-hydroxy-2-methylphenyl)-2-methylbenzo[b]thiophene-5-carboxylate and 4-hydroxytetrahydro-2*H*-thiopyran 1,1-dioxide following General Procedure B using PPh₃ and DBAD. MS: mass calcd. for C₂₃H₂₄O₅S₂: 444.57, found 445.0 [M]⁺, 467.1 [M+Na]⁺.

(C) To an ice-cooled solution of methyl 3-(4-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy)-2-methylphenyl)-2-methylbenzo[b]thiophene-5-carboxylate (290 mg; 0.65 mmol) in dry DCM (3 mL) under argon was added DIBAL-H (1M in DCM, 2 mL; 2 mmol). After stirring for 0.5 h, the mixture was poured into a vigorously stirring mixture of sodium potassium tartrate (1M in water, 8 mL) and DCM (5 mL) and stirring was continued for 1 h. The two phases were separated, and the aqueous phase was extracted with DCM (10 mL x 2). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford 4-(4-(5-(hydroxymethyl)-2-methylbenzo[b]thiophen-3-yl)-3-methylphenoxy)tetrahydro-2*H*-thiopyran 1,1-dioxide (265 mg, 98%). LC/MS: mass calcd. for C₂₂H₂₄O₄S₂: 416.56, found 399.1 [M-OH]⁺, 439.0 [M+Na]⁺.

(D) 4-(4-(5-(Chloromethyl)-2-methylbenzo[b]thiophen-3-yl)-3-methylphenoxy)-tetrahydro-2*H*-thiopyran 1,1-dioxide was prepared from 4-(4-(5-(hydroxymethyl)-2-methylbenzo[b]thiophen-3-yl)-3-methylphenoxy)tetrahydro-2*H*-thiopyran 1,1-dioxide following General Procedure D. ¹H NMR (CDCl₃) δ 7.78 (d, *J* = 8.6 Hz, 1H), 7.29 - 7.34 (m, 1H), 7.14 (s, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.85 (dd, *J* = 8.1,

2.5 Hz, 1H), 4.72 (br. s., 1H), 4.61 (s, 2H), 3.42 - 3.55 (m, 2H), 2.99 (d, $J = 13.1$ Hz, 2H), 2.50 - 2.60 (m, 2H), 2.36 - 2.48 (m, 2H), 2.34 (s, 3H), 2.04 (s, 3H).

(E) (3*S*)-Methyl 3-(4-((3-(4-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy)-2-methylphenyl)-2-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 4-(4-(5-(chloromethyl)-2-methylbenzo[*b*]thiophen-3-yl)-3-methylphenoxy)-tetrahydro-2*H*-thiopyran 1,1-dioxide and (3*S*)-methyl 3-(4-hydroxyphenyl)hex-4-ynoate (prepared as described in WO 2005086661) following General Procedure E. ^1H NMR (CDCl_3) δ 7.80 (d, $J = 8.6$ Hz, 1H), 7.36 (d, $J = 8.6$ Hz, 1H), 7.22 - 7.28 (m, 2H), 7.17 (s, 1H), 7.11 (d, $J = 8.6$ Hz, 1H), 6.80 - 6.93 (m, 4H), 5.02 (s, 2H), 4.71 (br. s., 1H), 3.99 - 4.08 (m, 1H), 3.65 (s, 3H), 3.43 - 3.54 (m, 2H), 2.93 - 3.03 (m, 2H), 2.70 - 2.79 (m, 1H), 2.59 - 2.68 (m, 1H), 2.49 - 2.59 (m, 2H), 2.36 - 2.47 (m, 2H), 2.34 (s, 3H), 2.02 (s, 3H), 1.82 (d, $J = 2.5$ Hz, 3H).

(F) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid was prepared from (3*S*)-methyl 3-(4-((3-(4-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy)-2-methylphenyl)-2-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using NaOH as base and 2M citric acid for reaction acidification. ^1H NMR (CDCl_3) δ 7.79 (d, $J = 8.1$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 7.11 (d, $J = 8.1$ Hz, 1H), 6.80 - 6.93 (m, 5H), 5.02 (s, 2H), 4.71 (br. s., 1H), 3.99 - 4.08 (m, 1H), 3.42 - 3.55 (m, 2H), 2.93 - 3.04 (m, 2H), 2.73 - 2.83 (m, 1H), 2.63 - 2.73 (m, 1H), 2.48 - 2.59 (m, 2H), 2.35 - 2.46 (m, 2H), 2.34 (s, 3H), 2.02 (s, 3H), 1.82 (d, $J = 2.53$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{34}\text{H}_{34}\text{O}_6\text{S}_2$: 602.77, found 603.1 [M] $^+$, 625.2 [$\text{M}+\text{Na}$] $^+$.

(G) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynoyl chloride was prepared from (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[*b*]thiophen-5-yl]methoxy]phenyl]hex-4-ynoic acid following General Procedure G, using thionyl chloride as the chlorinating agent.

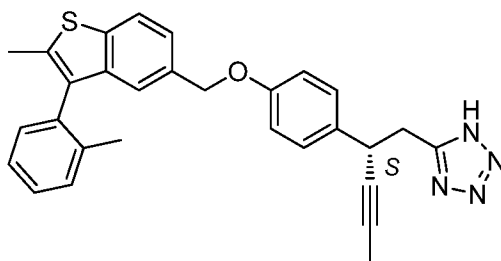
(H) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide was prepared from (3*S*)-3-[4-[[3-[4-(1,1-dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for C₃₄H₃₅NO₅S₂: 601.20, found: 602.0 [M+H]⁺.

(I) (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-yne nitrile was prepared from (3*S*)-3-[4-[[3-[4-(1,1-Dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₃₄H₃₃NO₄S₂: 583.18, found: 601.1 [M+NH₄]⁺.

(J) 4-(4-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-2-methylbenzo[b]thiophen-3-yl)-3-methylphenoxy)tetrahydro-2*H*-thiopyran 1,1-dioxide (Cpd **18**) was prepared from (3*S*)-3-[4-[[3-[4-(1,1-dioxothian-4-yl)oxy-2-methyl-phenyl]-2-methyl-benzo[b]thiophen-5-yl]methoxy]phenyl]hex-4-yne nitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH₄CO₃) gradient (30 – 85%). ¹H NMR (CD₃OD) δ 7.77 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.91 - 7.08 (m, 4H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 2H), 4.75 - 4.77 (m, 1H), 3.99 - 4.02 (m, 1H), 3.02 - 3.36 (m, 6H), 2.34 - 2.42 (m, 4H), 2.29 (s, 3H), 1.93 (s, 3H), 1.73 (d, *J* = 1.5 Hz, 3H). LC/MS: mass calcd. for C₃₄H₃₄N₄O₄S₂: 626.20, found: 627.3 [M+H]⁺.

Example 19

5-((2*S*)-2-(4-((2-Methyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole, Cpd **19**



(A) Methyl 2-methyl-3-(2-methylphenyl)benzo[*b*]thiophene-5-carboxylate was prepared from methyl 3-bromo-2-methylbenzo[*b*]thiophene-5-carboxylate and 2-methylphenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst. LC/MS: mass calcd. for C₁₈H₁₆O₂S: 296.09, found: 297.1 [M+H]⁺.

(B) To a solution of methyl 2-methyl-3-(2-methylphenyl)benzo[*b*]thiophene-5-carboxylate (300 mg, 1.01 mmol) in THF (10 mL) cooled in an ice-water bath was added LiAlH₄ (1 M in THF, 2.02 mL) drop-wise under argon. The mixture was stirred at 0 °C for 1 h before warming up to rt. satd. NH₄Cl solution was added to quench the reaction. The mixture was extracted with EtOAc (2 x 50 mL). The organic layer was washed with brine, then dried over Na₂SO₄, filtered and concentrated to afford (2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol, which was used in the next step without further purification. LC/MS: mass calcd. for C₁₇H₁₆O₂S: 268.09, found: 251.1 [M-OH]⁺.

(C) 5-(Chloromethyl)-2-methyl-3-(2-methylphenyl)benzo[*b*]thiophene was prepared from (2-methyl 3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol following General Procedure D.

(D) Ethyl (3*S*)-3-(4-((2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-(chloromethyl)-2-methyl-3-(2-methylphenyl)benzo[*b*]thiophene and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E, at a reaction temperature of 50 °C for 6 h. LC/MS: mass calcd. for C₃₁H₃₀O₃S: 482.19, found: 483.2 [M+H]⁺.

(E) (3*S*)-3-(4-((2-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from ethyl (3*S*)-3-(4-((2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using EtOH in place of MeOH, and 1N aq NaOH as the base. LC/MS: mass calcd. for C₂₉H₂₆O₃S: 454.16, found: 477.1 [M+Na]⁺.

(F) (3*S*)-3-(4-((2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G.

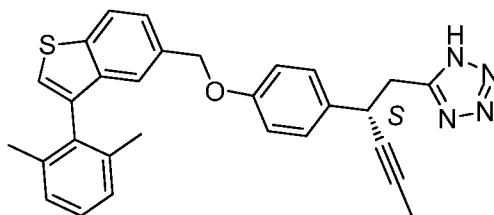
(G) (3*S*)-3-(4-((2-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Hb. LC/MS: mass calcd. for C₂₉H₂₇NO₂S: 453.18, found: 454.2 [M+H]⁺.

(H) (3*S*)-3-(4-((2-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yenenitrile was prepared from (3*S*)-3-(4-((2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₉H₂₅NOS: 435.17, found: 458.1 [M+Na]⁺.

(I) (2*S*)-5-(2-(4-((2-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **19**) was prepared from (3*S*)-3-(4-((2-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yenenitrile following General Procedure J, using preparative HPLC for product purification: Phenomenex C18 5μm column, 30 x 100 mm, 40%-100% MeCN/H₂O (0.1% TFA v/v) over 18 min. ¹H NMR (CDCl₃) δ 7.80 (d, *J* = 8.6 Hz, 1H), 7.32 - 7.40 (m, 3H), 7.25 - 7.32 (m, 1H), 7.14 - 7.24 (m, 4H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.01 (s, 2H), 4.05 (t, *J* = 5.6 Hz, 1H), 3.30 - 3.47 (m, 2H), 2.34 (s, 3H), 2.05 (s, 3H), 1.84 (d, *J* = 2.5 Hz, 3H). LC/MS: mass calcd. for C₂₉H₂₆N₄OS: 478.18, found: 501.1 [M+Na]⁺.

Example 20

(2*S*)-5-(2-(4-((3-(2,6-Dimethylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **20**



(A) 5-Hydroxymethyl-3-(2,6-dimethylphenyl)benzo[*b*]thiophene was prepared from 3-bromo-5-hydroxymethylbenzothiophene (from Example 1A) and 2,6-dimethylphenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₇H₁₆OS: 268.37, found 251.0 [M-17]⁺.

(B) 5-Chloromethyl-3-(2,6-dimethylphenyl)benzo[*b*]thiophene was prepared from 5-hydroxymethyl-3-(2,6-dimethylphenyl)benzo[*b*]thiophene following General Procedure D.

(C) (3*S*)-Methyl 3-(4-((3-(2,6-dimethylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-chloromethyl-3-(2,6-dimethylphenyl)benzo[*b*]thiophene and (3*S*)-methyl 3-(4-hydroxyphenyl)hex-4-ynoate (prepared as described in WO 2005086661) following General Procedure E using DMF as solvent and stirring over night at 40 °C. LC/MS: mass calcd. for C₃₀H₂₈O₃S: 468.61, found 469.0 [M]⁺.

(D) (3*S*)-3-(4-((3-(2,6-Dimethylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-methyl 3-(4-((3-(2,6-dimethylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 8.08 (d, *J* = 8.3 Hz, 1H), 7.63 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.12 - 7.36 (m, 6H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.14

(s, 2H), 3.85 - 4.03 (m, 1H), 2.31 - 2.44 (m, 2H), 1.93 (s, 6H), 1.76 (d, $J = 2.3$ Hz, 3H)
LC/MS: mass calcd. for $C_{29}H_{26}O_3S$: 454.58, found 453.1 [M-H]⁻.

(E) (3*S*)-3-(4-((3-(2,6-Dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2,6-dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using thionyl chloride as the chlorinating agent.

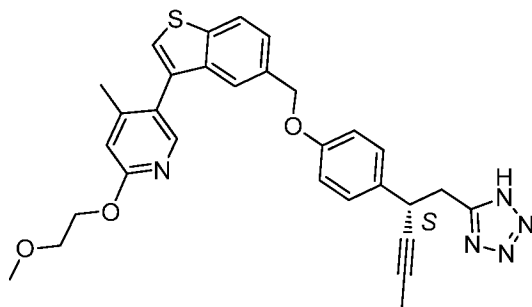
(F) (3*S*)-3-(4-((3-(2,6-Dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2,6-dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for $C_{29}H_{27}NO_2S$: 453.18, found 454.0 [M+H]⁺.

(G) (3*S*)-3-(4-((3-(2,6-Dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(2,6-dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $C_{29}H_{25}NOS$: 435.17, found 453.0 [M+NH₄]⁺.

(H) (2*S*)-5-(2-(4-((3-(2,6-Dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **20**) was prepared from (3*S*)-3-(4-((3-(2,6-dimethylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH₄HCO₃) gradient (35 – 85%). ¹H NMR (CDCl₃) δ 7.92 (d, $J = 8.4$ Hz, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.14 - 7.25 (m, 7H), 6.86 (d, $J = 7.2$ Hz, 2H), 5.02 (s, 2H), 4.03 - 4.05 (m, 1H), 3.32 - 3.34 (m, 2H), 1.99 (s, 6H), 1.80 (s, 3H). LC/MS: mass calcd. for $C_{29}H_{26}N_4OS$: 478.18, found 479.2[M+H]⁺.

Example 21

(2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-2-(2-methoxyethoxy)-4-methylpyridine, Cpd **21**



(A) To a solution of 2-methoxyethan-1-ol (1.82 g, 24 mmol) in anhydrous THF (20 mL) was added NaH (60 % wt in mineral oil; 960 mg, 24 mmol) in portions. After stirring at rt for 30 min, the mixture was cooled to 0 °C and a solution of 2,5-dibromo-4-methylpyridine (2 g, 8 mmol) in THF (10 mL) was added in drop-wise fashion. The resultant mixture was then heated at 80 °C overnight. The reaction was then quenched by the addition of satd. aq. NH₄Cl (100 mL) and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford 5-bromo-2-(2-methoxyethoxy)-4-methylpyridine (1.2 g, 61% yield) as a light yellow oil. LC/MS: mass calcd. for C₉H₁₂BrNO₂: 246.10, found: 246.0 [M]⁺, 248.0 [M+2]⁺.

(B) 2-(2-Methoxyethoxy)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was prepared from 5-bromo-2-(2-methoxyethoxy)-4-methylpyridine and bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst, KOAc in place of K₂CO₃ and DMSO as reaction solvent at a reaction temperature of 85 °C overnight. LC/MS: mass calcd. for C₁₅H₂₄BNO₄: 293.17, found: 294.1 [M+H]⁺.

(C) (3*S*)-Ethyl 3-(4-((3-(6-(2-methoxyethoxy)-4-methylpyridin-3-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 2-(2-methoxyethoxy)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine and (3*S*)-ethyl 3-(4-((3-

bromobenzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (from Example 7B) following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₃₂H₃₃NO₅S: 543.67, found: 544.2 [M+H]⁺.

(D) (3*S*)-3-(4-((3-(6-(2-Methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(6-(2-methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 12.23 (br. s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 8.02 (s, 1H), 7.77 (s, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.48 (s, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.87 (s, 1H), 5.18 (s, 2H), 4.41 - 4.44 (m, 2H), 3.89 - 3.94 (m, 1H), 3.66 (t, *J* = 4.8 Hz, 2H), 3.33 (s, 3H), 2.58 (d, *J* = 7.5 Hz, 2H), 2.04 (s, 3H), 1.76 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₃₀H₂₉NO₅S: 515.62, found: 516.2 [M+H]⁺.

(E) (3*S*)-3-(4-((3-(6-(2-Methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(6-(2-methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

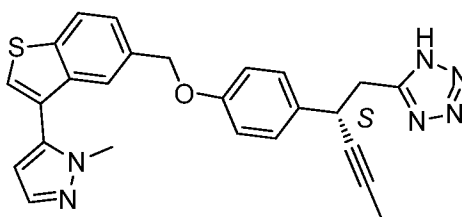
(F) (3*S*)-3-(4-((3-(6-(2-Methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(6-(2-methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha, and used directly without further characterization.

(G) (3*S*)-3-(4-((3-(6-(2-Methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(6-(2-methoxyethoxy)-4-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I, and used directly without further characterization.

(H) (2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-(2-methoxyethoxy)-4-methylpyridine (Cpd **21**) was prepared from (3*S*)-3-(4-((3-(6-(2-methoxyethoxy)-4-methylpyridin-3-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.98 - 7.80 (m, 2H), 7.55 (s, 1H), 7.51 (d, *J* = 1.2 Hz, 1H), 7.49 (d, *J* = 1.2 Hz, 1H), 7.23 - 7.25 (m, 2H), 6.92 - 6.94 (m, 2H), 6.86 (s, 1H), 5.18 (s, 2H), 4.49 (dd, *J* = 3.6, 4.8 Hz, 2H), 4.05 - 4.10 (m, 1H), 3.80 (dd, *J* = 3.2, 6.0 Hz, 2H), 3.46 (s, 3H), 3.27 - 3.33 (m, 2H), 2.09 (s, 3H), 1.80 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₃₀H₂₉N₅O₃S: 539.20, found 540.3 [M+H]⁺.

Example 22

(2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **22**



(A) (3*S*)-Ethyl 3-(4-((3-(1-methyl-1*H*-pyrazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3*S*)-ethyl 3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (from Example 7B) and 1-methyl-1*H*-pyrazol-5-ylboronic acid following General Procedure A using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₂₇H₂₆N₂O₃S: 458.17, found: 459.2 [M+H]⁺.

(B) (3*S*)-3-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(1-methyl-1*H*-pyrazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General

Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ^1H NMR (DMSO- d_6) δ 12.20 (br. s, 1H), 8.11 (d, $J = 8.4$ Hz, 1H), 8.06 (s, 1H), 7.74 (s, 1H), 7.59 - 7.60 (m, 1H), 7.53 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.26 (d, $J = 8.6$ Hz, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 6.49 (d, $J = 1.8$ Hz, 1H), 5.23 (s, 2H), 3.91 - 3.96 (m, 1H), 3.78 (s, 3H), 2.58 (d, $J = 7.6$ Hz, 2H), 1.77 (s, 3H). LC/MS: mass calcd. for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$: 430.13, found: 431.1 $[\text{M}+\text{H}]^+$.

(C) (3*S*)-3-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

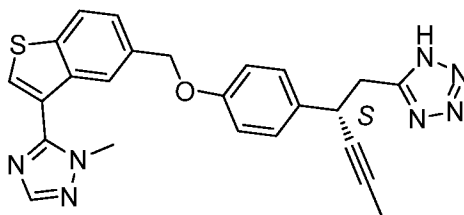
(D) (3*S*)-3-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha (inverse addition). LC/MS: mass calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$: 429.15, found 430.2 $[\text{M}+\text{H}]^+$.

(E) (3*S*)-3-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{OS}$: 411.14, found 412.0 $[\text{M}+\text{H}]^+$.

(F) (2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **22**) was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-pyrazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. ^1H NMR (CD_3OD) δ 8.02 (d, $J = 8.4$ Hz, 1H), 7.83 (s, 1H), 7.64 - 7.69 (m, 2H), 7.53 - 7.56 (m, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 6.94 - 6.97 (m, 2H), 6.48 (s, 1H), 5.23 (s, 2H), 4.06 - 4.10 (m, 1H), 3.78 (s, 3H), 3.27 - 3.32 (m, 2H), 1.80 (s, 3H). LC/MS: mass calcd. for $\text{C}_{25}\text{H}_{22}\text{N}_6\text{OS}$: 454.16, found 455.1 $[\text{M}+\text{H}]^+$.

Example 23

(2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **23**



(A) (3-(2-Methyl-2*H*-1,2,4-triazol-3-yl)benzo[*b*]thiophen-5-yl)methanol was prepared from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-5-yl)methanol (from Example 5A) and 5-bromo-1-methyl-1*H*-1,2,4-triazole following General Procedure A using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃, at a reaction temperature of 80 °C overnight. LC/MS: mass calcd. for C₁₂H₁₁N₃OS: 245.06, found: 246.0 [M+H]⁺.

(B) 5-(5-(Chloromethyl)benzo[*b*]thiophen-3-yl)-1-methyl-1*H*-1,2,4-triazole was prepared from (3-(2-methyl-2*H*-1,2,4-triazol-3-yl)benzo[*b*]thiophen-5-yl)methanol following General Procedure D.

(C) (3*S*)-Ethyl 3-(4-((3-(2-methyl-2*H*-1,2,4-triazol-3-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-(5-(chloromethyl)benzo[*b*]thiophen-3-yl)-1-methyl-1*H*-1,2,4-triazole and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E, at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₂₆H₂₅N₃O₃S: 459.16, found: 460.2 [M+H]⁺.

(D) (3*S*)-3-(4-((3-(2-Methyl-2*H*-1,2,4-triazol-3-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2-methyl-2*H*-1,2,4-triazol-3-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction

acidification. ^1H NMR (DMSO- d_6) δ 8.42 (s, 1H), 8.31 (s, 1H), 8.13 - 8.15 (m, 2H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.26 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 5.23 (s, 2H), 4.00 (s, 3H), 3.92 - 3.96 (m, 1H), 2.50 - 2.56 (m, 2H), 1.77 (d, $J = 2.0$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$: 431.13, found: 432.1 $[\text{M}+\text{H}]^+$.

(E) (3*S*)-3-(4-((3-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

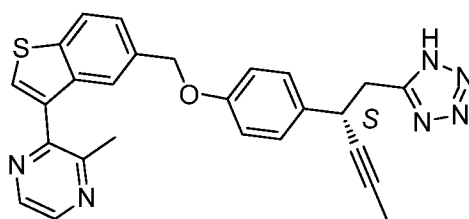
(F) (3*S*)-3-(4-((3-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha (inverse addition). LC/MS: mass calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$: 430.15, found 431.0 $[\text{M}+\text{H}]^+$.

(G) (3*S*)-3-(4-((3-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{OS}$: 412.14, found 413.2 $[\text{M}+\text{H}]^+$.

(H) (2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **23**) was prepared from (3*S*)-3-(4-((3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. ^1H NMR (CD_3OD) δ 8.14 - 8.19 (m, 2H), 8.04 - 8.06 (m, 2H), 7.58 - 7.60 (m, 1H), 7.23 - 7.26 (m, 2H), 6.95 - 6.99 (m, 2H), 5.24 (s, 2H), 4.06 - 4.10 (m, 1H), 3.98 (s, 3H), 3.27 - 3.32 (m, 2H), 1.81 (s, 3H). LC/MS: mass calcd. for $\text{C}_{24}\text{H}_{21}\text{N}_7\text{OS}$: 455.15, found 456.0 $[\text{M}+\text{H}]^+$.

Example 24

(2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylpyrazine, Cpd **24**



- (A) (3-(3-Methylpyrazin-2-yl)benzo[b]thiophen-5-yl)methanol was prepared from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-5-yl)methanol (from Example 5A) and 2-bromo-3-methylpyrazine following General Procedure A using $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ as the palladium catalyst and Cs_2CO_3 in place of K_2CO_3 . LC/MS: mass calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS}$: 256.07, found: 257.0 $[\text{M}+\text{H}]^+$.
- (B) 2-(5-(Chloromethyl)benzo[b]thiophen-3-yl)-3-methylpyrazine was prepared from (3-(3-methylpyrazin-2-yl)benzo[b]thiophen-5-yl)methanol following General Procedure D.
- (C) (3*S*)-Ethyl 3-(4-((3-(3-methylpyrazin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 2-(5-(chloromethyl)benzo[b]thiophen-3-yl)-3-methylpyrazine and (3*S*)-ethyl 3-(4-(hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E, at a reaction temperature of 90 °C for 1 h. LC/MS: mass calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$: 470.17, found: 471.3 $[\text{M}+\text{H}]^+$.
- (D) (3*S*)-3-(4-((3-(3-Methylpyrazin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(3-methylpyrazin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ^1H NMR ($\text{DMSO}-d_6$) δ 12.21 (br. s, 1H), 8.62 (dd, $J = 2.4, 12.0$ Hz, 2H), 8.10 - 8.14 (m, 2H), 7.79 (d, $J = 0.9$ Hz, 1H), 7.52 (dd, $J = 1.5, 8.1$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 2H), 6.93 (d, $J = 8.7$ Hz, 2H), 5.17 (s, 2H), 3.92 - 3.93 (m, 1H), 2.58 (d, $J = 7.5$ Hz, 2H), 2.52 (s, 3H), 1.77 (d, $J = 2.4$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$: 442.13, found: 411.0 $[\text{M}-\text{H}]^-$.

(E) (3*S*)-3-(4-((3-(3-Methylpyrazin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(3-methylpyrazin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

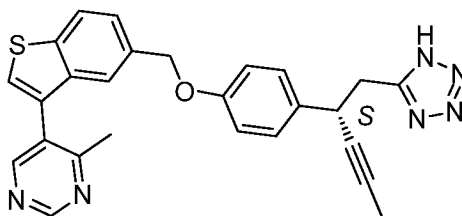
(F) (3*S*)-3-(4-((3-(3-Methylpyrazin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(3-methylpyrazin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha (inverse addition). LC/MS: mass calcd. for C₂₆H₂₃N₃O₂S: 441.15, found 442.2[M+H]⁺.

(G) (3*S*)-3-(4-((3-(3-Methylpyrazin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(3-methylpyrazin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₆H₂₁N₃OS: 423.14, found 424.1 [M+H]⁺.

(H) (2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylpyrazine (Cpd **24**) was prepared from (3*S*)-3-(4-((3-(3-methylpyrazin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 8.58 - 8.60 (m, 2H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 7.69 (s, 1H), 7.53 - 7.56 (m, 1H), 7.22 - 7.26 (m, 2H), 6.93 - 6.95 (m, 2H), 5.19 (s, 2H), 4.05 - 4.10 (m, 1H), 3.27 - 3.30 (m, 2H), 2.53 (s, 3H), 1.80 (s, 3H). LC/MS: mass calcd. for C₂₆H₂₂N₆OS: 466.16, found 467.1 [M+H]⁺.

Example 25

(2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-4-methylpyrimidine, Cpd **25**



(A) (3-(4-Methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methanol was prepared from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-5-yl)methanol (from Example 5A) and 5-bromo-4-methylpyrimidine following General Procedure A using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₄H₁₂N₂OS: 256.07, found: 257.0 [M+H]⁺.

(B) (3*S*)-Ethyl 3-(4-((3-(4-methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3-(4-methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methanol and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure B, using Bu₃P and ADDP at a reaction temperature of 60 °C in toluene overnight. LC/MS: mass calcd. for C₂₈H₂₆N₂O₃S: 470.17, found: 471.2 [M+H]⁺.

(C) (3*S*)-3-(4-((3-(4-Methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(4-methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 12.21 (br. s, 1H), 9.14 (s, 1H), 8.68 (s, 1H), 8.11 - 8.14 (m, 1H), 7.98 (s, 1H), 7.53 (d, *J* = 5.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.19 (s, 2H), 3.92 - 3.96 (m, 1H), 2.51 - 2.73 (m, 2H), 2.31 (s, 3H), 1.76 (s, 3H). LC/MS: mass calcd. for C₂₆H₂₂N₂O₃S: 442.14, found: 443.2 [M+H]⁺.

(D) (3*S*)-3-(4-((3-(4-Methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(4-

methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

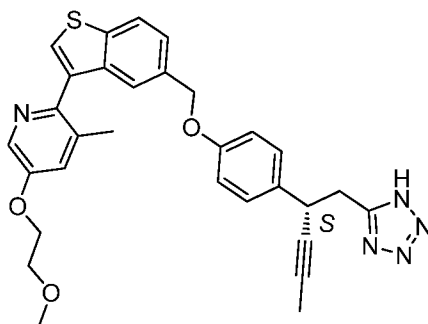
(E) (3*S*)-3-(4-((3-(4-Methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(4-methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for C₂₆H₂₃N₃O₂S: 441.15, found 442.0 [M+H]⁺.

(F) (3*S*)-3-(4-((3-(4-Methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(4-methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₆H₂₁N₃OS: 423.14, found 424.0 [M+H]⁺.

(G) (2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-4-methylpyrimidine (Cpd **25**) was prepared from (3*S*)-3-(4-((3-(4-methylpyrimidin-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 9.05 (s, 1H), 8.62 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.71 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.42 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.15 (s, 2H), 3.99 - 4.10 (m, 1H), 3.21 - 3.28 (m, 2H), 2.31 (s, 3H), 1.75 (s, 3H). LC/MS: mass calcd. for C₂₆H₂₂N₆OS: 466.16, found 467.0 [M+H]⁺.

Example 26

(2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-5-(2-methoxyethoxy)-3-methylpyridine, Cpd **26**



(A) A mixture of 6-bromo-5-methylpyridin-3-ol (1 g, 5.32 mmol), 1-bromo-2-methoxyethane (730 mg, 5.25 mmol) and K_2CO_3 (1.5 g, 10.87 mmol) in MeCN (20 mL) was stirred at rt overnight, after which the reaction was quenched by the addition of water (100 mL). The resulting solution was extracted with EtOAc (2 x 100 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-15% EtOAc/petroleum ether) to afford 2-bromo-5-(2-methoxyethoxy)-3-methylpyridine (500 mg, 38 %) as colorless oil. LC/MS: mass calcd. for $C_9H_{12}BrNO_2$: 246.10, found: 246.0 $[M]^+$, 248.0 $[M+2]^+$.

(B) (3-(5-(2-Methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methanol was prepared from 2-bromo-5-(2-methoxyethoxy)-3-methylpyridine and (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-5-yl)methanol (from Example 5A) following General Procedure A, using $PdCl_2(dppf) \cdot CH_2Cl_2$ as the palladium catalyst, Cs_2CO_3 in place of K_2CO_3 . LC/MS: mass calcd. for $C_{18}H_{19}NO_3S$: 329.41, found: 330.0 $[M+H]^+$.

(C) (3*S*)-Ethyl 3-(4-((3-(5-(2-methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3-(5-(2-methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methanol and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure B, using Bu_3P and ADDP at a

reaction temperature of 50 °C in toluene for 2 h. LC/MS: mass calcd. for C₃₂H₃₃NO₅S: 543.67, found: 544.3 [M+H]⁺.

(D) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(5-(2-methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 12.23 (br. s, 1H), 8.27 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.86 (s, 1H), 7.69 (s, 1H), 7.43 - 7.52 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.15 (s, 2H), 4.23 - 4.28 (m, 2H), 3.91 - 3.96 (m, 1H), 3.72 (d, *J* = 4.5 Hz, 2H), 3.33 (s, 3H), 2.58 (d, *J* = 7.5 Hz, 2H), 2.24 (s, 3H), 1.77 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₃₀H₂₉NO₅S: 515.62, found: 516.2 [M+H]⁺.

(E) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

(F) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha, and was used directly without characterization.

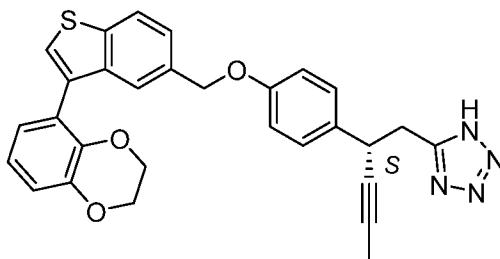
(G) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-3-methylpyridin-2-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₃₀H₂₈N₂O₃S: 496.18, found: 496.8[M+H]⁺.

(H) (2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-5-(2-methoxyethoxy)-3-methylpyridine, (Cpd

26) was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-3-methylpyridin-2-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CDCl₃) δ 8.34 (s, 1H), 7.88 - 7.90 (m, 1H), 7.50 (s, 1H), 7.35 - 7.49 (m, 3H), 6.91 - 6.93 (m, 2H), 6.63 - 6.74 (m, 2H), 5.18 (s, 2H), 4.30 (s, 2H), 3.73 - 3.91 (m, 3H), 3.54 (d, *J* = 2.4 Hz, 3H), 3.14 - 3.18 (m, 1H), 2.91 - 2.98 (m, 1H), 2.29 (s, 3H), 1.84 (s, 3H). LC/MS: mass calcd. for C₃₀H₂₉N₅O₃S: 539.20, found: 540.1 [M+H]⁺.

Example 27

(2*S*)-5-(2-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **27**



(A) (3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methanol was prepared from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-5-yl)methanol (from Example 5A) and 5-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine following General Procedure A using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₇H₁₄O₃S: 298.07, found: 281.0 [M-OH]⁺.

(B) (3*S*)-Ethyl 3-(4-((3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methanol and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure B, using Bu₃P and ADDP at a reaction temperature of 60 °C in toluene overnight. LC/MS: mass calcd. for C₃₁H₂₈O₅S: 512.17, found: 535.1 [M+Na]⁺.

(C) (3*S*)-3-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 12.22 (br. s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.89 - 6.95 (m, 5H), 5.22 (s, 2H), 4.20 - 4.28 (m, 2H), 4.05 - 4.12 (s, 2H), 3.90 - 3.95 (m, 1H), 2.59 (d, *J* = 7.6 Hz, 2H), 1.77 (s, 3H). LC/MS: mass calcd. for C₂₉H₂₄O₅S: 484.13, found: 485.2 [M+H]⁺, 507.2 [M+Na]⁺.

(D) (3*S*)-3-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

(E) (3*S*)-3-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha (inverse addition). LC/MS: mass calcd. for C₂₉H₂₅NO₄S: 483.15, found 484.0 [M+H]⁺.

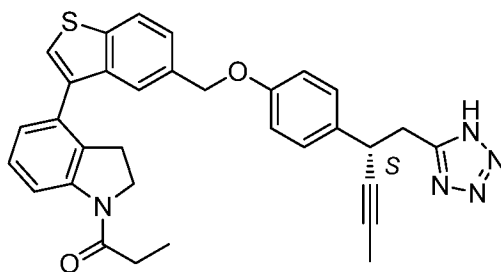
(F) (3*S*)-3-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I, and used directly without further characterization.

(G) (2*S*)-5-(2-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **27**) was prepared from (3*S*)-3-(4-((3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 1. ¹H NMR (CD₃OD) δ 7.90 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.48 (s, 1H), 7.37 - 7.44 (m, 1H), 7.17 - 7.25 (m,

2H), 6.85 - 6.92 (m, 5H), 5.17 (s, 2H), 4.13 - 4.22 (m, 2H), 3.94 - 4.11 (m, 3H), 3.21 (dd, $J = 7.8, 2.5$ Hz, 2H), 1.75 (d, $J = 2.3$ Hz, 3H). LC/MS: mass calcd. for $C_{29}H_{24}N_4O_3S$: 508.16, found 509.0 $[M+H]^+$.

Example 28

(2*S*)-1-(4-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one, Cpd 28



(A) To a solution of 4-bromoindoline (200 mg, 1.01 mmol) in DCM (5 mL) was added propionyl chloride (99 mg, 1.07 mmol) and triethylamine (204 mg, 2.02 mmol). The resulting solution was stirred at rt for 2 h. The reaction mixture was poured into of satd. aq NH_4Cl (50 mL) and the resulting mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to afford 1-(4-bromoindolin-1-yl)propan-1-one (240 mg, 93.3%), as a white solid. LC/MS: mass calcd. for $C_{11}H_{12}BrNO$: 253.01, found: 253.9, 255.9 $[M+H, M+H+2]^+$.

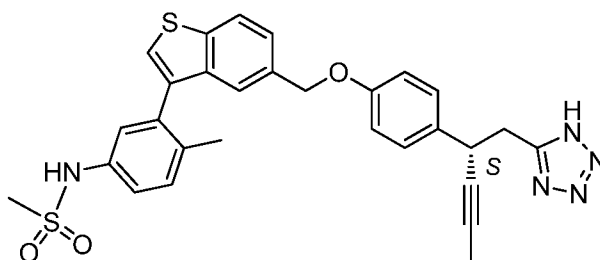
(B) 1-(4-(5-(Hydroxymethyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one was prepared from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-5-yl)methanol (from Example 5A) and 1-(4-bromoindolin-1-yl)propan-1-one following General Procedure A, using $PdCl_2(dppf) \cdot CH_2Cl_2$ as the palladium catalyst and Cs_2CO_3 as the base. LC/MS: mass calcd. for $C_{20}H_{19}NO_2S$: 337.11, found: 338.05 $[M+H]^+$.

- (C) 1-(4-(5-(Chloromethyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one was prepared from 1-(4-(5-(hydroxymethyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one following General Procedure D. LC/MS: mass calcd. for C₂₀H₁₈ClNOS: 355.08, found: 356.0 [M+H]⁺.
- (D) Ethyl (3*S*)-3-(4-((3-(1-propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 1-(4-(5-(chloromethyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E, at a reaction temperature of 60 °C. LC/MS: mass calcd. for C₃₄H₃₃NO₄S: 551.21, found: 552.2 [M+H]⁺.
- (E) (3*S*)-3-(4-((3-(1-Propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from ethyl (3*S*)-3-(4-((3-(1-propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. LC/MS: mass calcd. for C₃₂H₂₉NO₄S: 523.18, found: 524.3 [M+H]⁺.
- (F) (3*S*)-3-(4-((3-(1-Propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(1-propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G.
- (G) (3*S*)-3-(4-((3-(1-Propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(1-propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure H_a. LC/MS: mass calcd. for C₃₂H₃₀N₂O₃S: 522.20, found: 523.2 [M+H]⁺.
- (H) (3*S*)-3-(4-((3-(1-Propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(1-propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₃₂H₂₈N₂O₂S: 504.19, found: 505.0 [M+H]⁺.

(I) (2*S*)-1-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one was prepared from (3*S*)-3-(4-((3-(1-propionylindolin-4-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH₄HCO₃) gradient (35 – 85%). ¹H NMR (CDCl₃) δ 8.32 (d, *J* = 7.8Hz, 1H), 7.93 (d, *J* = 8.1Hz, 1H), 7.21 - 7.56 (m, 6H), 7.06 - 7.09 (m, 1H), 6.89 - 6.91 (m, 2H), 5.14 - 5.21 (m, 2H), 3.98 - 4.07 (m, 3H), 3.31 - 3.35 (m, 2H), 2.96 - 3.05 (m, 2H), 2.47 - 2.50 (m, 2H), 1.87 (s, 3H), 1.26 - 1.29 (m, 3H). LC/MS: mass calcd. for C₃₂H₂₉N₅O₂S: 547.20, found: 548.0 [M+H]⁺.

Example 29

(2*S*)-N-(3-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-4-methylphenyl)methanesulfonamide, Cpd **29**



(A) (3-(5-Amino-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol was prepared from 3-bromo-4-methylaniline and (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-5-yl)methanol (from Example 5A) following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₆H₁₅NOS: 269.36, found: 270.1 [M+H]⁺.

(B) (3*S*)-Ethyl 3-(4-((3-(5-amino-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3-(5-amino-2-methylphenyl)benzo[b]thiophen-5-yl)methanol and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure B, using Bu₃P and ADDP at a reaction temperature of 60 °C for 1 h. LC/MS: mass calcd. for C₃₀H₂₉NO₃S: 483.62, found: 484.0 [M]⁺.

(C) To an ice-cooled solution of (3*S*)-ethyl 3-(4-((3-(5-amino-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (200 mg, 0.41 mmol) and pyridine (0.07 mL, 0.83 mmol) in DCM (2 mL) was added MsCl (0.05 mL, 0.62 mmol) and the resultant solution was stirred overnight at rt. Water (5 mL) was added and the mixture was extracted with DCM (5 mL). The organic extracts were washed with 1N HCl (3 x 5 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-20% EtOAc/petroleum ether) to afford (3*S*)-ethyl 3-(4-((3-(2-methyl-5-(methylsulfonamido)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate as a light yellow oil (200 mg, 78% yield). LC/MS: mass calcd. for C₃₁H₃₁NO₅S₂: 561.71, found: 562.1 [M]⁺.

(D) (3*S*)-3-(4-((3-(2-Methyl-5-(methylsulfonamido)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2-methyl-5-(methylsulfonamido)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.44 - 7.49 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.23 - 7.30 (m, 3H), 7.17 (d, *J* = 1.6 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.16 (s, 2H), 3.90 - 3.94 (m, 1 H), 2.67 (s, 3H), 2.56 - 2.61 (m, 2H), 2.34 (s, 3H), 1.79 (s, 3H). LC/MS: mass calcd. for C₂₉H₂₇NO₅S₂: 533.66, found: 550.9 [M+NH₃]⁺.

(E) (3*S*)-3-(4-((3-(2-Methyl-5-(methylsulfonamido)phenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared by the HATU-mediated coupling of (3*S*)-3-(4-((3-(2-methyl-5-(methylsulfonamido)phenyl)benzo[b]thiophen-5-

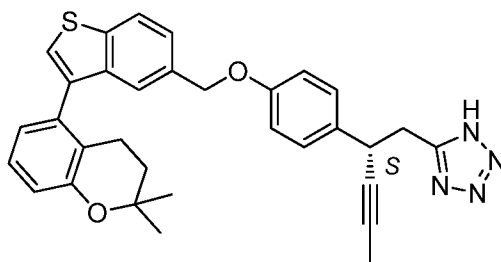
yl)methoxy)phenyl)hex-4-ynoic acid and NH_4Cl , following the procedure described in Example 6E. LC/MS: mass calcd. for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2$: 532.15, found: 533.2 $[\text{M}+\text{H}]^+$.

(F) (3*S*)-3-(4-((3-(2-Methyl-5-(methylsulfonamido)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(2-methyl-5-(methylsulfonamido)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I, and was used directly without further characterization.

(G) (2*S*)-N-(3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-4-methylphenyl)methanesulfonamide (Cpd **29**) was prepared from (3*S*)-3-(4-((3-(2-methyl-5-(methylsulfonamido)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ^1H NMR (CD_3OD) δ 7.94 (d, $J = 8.0$ Hz, 1H), 7.60 (s, 1H), 7.53 (d, $J = 1.6$ Hz, 1H), 7.44 - 7.46 (m, 2H), 7.26 - 7.28 (m, 1H) 7.17 - 7.20 (m, 3H), 6.84 - 6.86 (m, 2H), 5.12 (s, 2H), 4.02 - 4.06 (m, 1H), 3.12 - 3.24 (m, 2H), 2.52 (s, 3H), 2.36 (s, 3H), 1.74 (d, $J = 2.4$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{29}\text{H}_{27}\text{N}_5\text{O}_3\text{S}_2$: 557.16, found: 558.2 $[\text{M}+\text{H}]^+$.

Example 30

(2*S*)-5-(2-(4-((3-(2,2-Dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **30**



(A) To a solution of 1,3-cyclohexanedione (1.12 g, 9.99 mmol) and 1,2-ethanediammoniumacetate (1.8 g, 9.99 mmol) in MeOH (30 mL) was added 3-methylbut-

2-enal (0.84 g, 9.99 mmol) in drop-wise fashion, and the resulting mixture was stirred at rt for 2 h. Water (30 mL) was added and the mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-30% EtOAc/petroleum ether) to afford 2,2-dimethyl-7,8-dihydro-2*H*-chromen-5(6*H*)-one (1 g, 56 %) as a yellow liquid. LC/MS: mass calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_2$: 178.10, found 179.2 $[\text{M}+\text{H}]^+$.

(B) A mixture of 2,2-dimethyl-7,8-dihydro-2*H*-chromen-5(6*H*)-one (1 g, 5.6 mmol) and DDQ (2.55 g, 11.23 mmol) in 1,4-dioxane (20 mL) was stirred at 110 °C for 24 h. After cooling to rt, the reaction solution was filtered through diatomaceous earth and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-10% EtOAc/petroleum ether) afforded 2,2-dimethyl-2*H*-chromen-5-ol (300 mg, 30 %) as a red solid. LC/MS: mass calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_2$: 176.08, found 177.2 $[\text{M}+\text{H}]^+$.

(C) A solution of 2,2-dimethyl-2*H*-chromen-5-ol (300 mg, 1.7 mmol) in MeOH (10 mL) was hydrogenated (3 atm) over Pd/C (10 %, wt. %; 100 mg) for 2 h. The reaction was filtered and the filtrate was concentrated under reduced pressure to afford 2,2-dimethylchroman-5-ol (280 mg, 92 %) as a yellow oil. LC/MS: mass calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_2$: 178.10, found 179.2 $[\text{M}+\text{H}]^+$.

(D) To an ice-cooled solution of 2,2-dimethylchroman-5-ol (280 mg, 1.57 mmol) and TEA (476 mg, 1.88 mmol) in DCM (10 mL) was added trifluoromethanesulfonic anhydride (530 mg, 1.879 mmol) in portion-wise fashion. After stirring for 1 h at rt, water (20 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford 2,2-dimethylchroman-5-yl trifluoromethanesulfonate (310 mg, 64 %) as a white solid. ^1H NMR (CDCl_3) δ 7.14 (t, $J = 8.1$ Hz, 1H), 6.78 - 6.82 (m, 2H), 2.81 (t, $J = 6.6$ Hz, 2H), 1.83, (t, $J = 6.6$ Hz, 2H), 1.36 (s, 6H).

(E) (3-(2,2-Dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methanol was prepared from 2,2-dimethylchroman-5-yl trifluoromethanesulfonate and (3-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)benzo[b]thiophen-5-yl)methanol (from Example 5A) following General Procedure A, using PdCl₂(dppf)CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₂₀H₂₀O₂S: 324.12, found 307.1 [M-OH]⁺.

(F) 5-(5-(Chloromethyl)benzo[b]thiophen-3-yl)-2,2-dimethylchroman was prepared from (3-(2,2-dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

(G) (3*S*)-Ethyl 3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-(5-(chloromethyl)benzo[b]thiophen-3-yl)-2,2-dimethylchroman and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E at a reaction temperature of 40 °C. LC/MS: mass calcd. for C₃₄H₃₄O₄S: 538.22, found: 556.2 [M+NH₄]⁺.

(H) (3*S*)-3-(4-((3-(2,2-Dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (CD₃OD) δ 7.91 - 7.95 (m, 1H), 7.37 - 7.45(m, 3H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.15 (t, *J* = 8.1 Hz, 1H), 6.78 - 6.88 (m, 4H), 5.12 (s, 2H), 3.92 - 4.02 (m, 1H), 2.58 - 2.62 (m, 2H), 2.40 (t, *J* = 6.6 Hz, 2H), 1.79 (s, 3H), 1.63 (t, *J* = 6.6 Hz, 2H), 1.30 (s, 6H). LC/MS: mass calcd. for C₃₂H₃₀O₄S: 510.19, found: 528.1 [M+NH₄]⁺.

(I) (3*S*)-3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

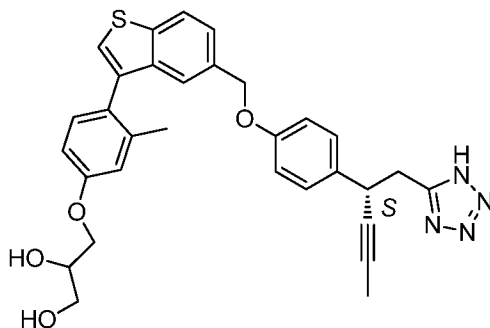
(J) (3*S*)-3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for C₃₂H₃₁NO₃S: 509.20, found 510.0 [M+H]⁺.

(K) (3*S*)-3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₃₂H₂₉NO₂S: 491.19, found 492.0 [M+H]⁺, 509.1 [M+NH₄]⁺.

(L) (2*S*)-5-(2-(4-((3-(2,2-dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **30**) was prepared from (3*S*)-3-(4-((3-(2,2-dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.93 (d, *J* = 8.1 Hz, 1H), 7.41 - 7.45 (m, 3H), 7.15 - 7.20 (m, 3H), 6.78 - 6.86 (m, 4H), 5.11 (s, 2H), 4.03 (br. s, 1H), 3.14 - 3.19 (m, 2H), 2.38 - 2.42 (m, 2H), 1.74 (s, 3H), 1.63 (t, *J* = 6.9 Hz, 2H) 1.30 (s, 6H). LC/MS: mass calcd. for C₃₂H₃₀N₄O₂S: 534.21, found 535.0 [M+H]⁺.

Example 31

3-(4-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)propane-1,2-diol, Cpd **31**



(A) 4-((4-Bromo-3-methylphenoxy)methyl)-2,2-dimethyl-1,3-dioxolane was prepared from 4-bromo-3-methylphenol and (2,2-dimethyl-1,3-dioxolan-4-yl)methanol following General Procedure B using PPh₃ and ADDP in toluene (in place of THF) at 60 °C. ¹H NMR (CDCl₃) δ 7.38 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 2.8 Hz, 1H), 6.62 (dd, *J* = 3.2, 8.8 Hz, 1H), 4.42 - 4.48 (m, 1H), 4.13 - 4.17 (m, 1H), 3.99 - 4.02 (m, 1H), 3.86 - 3.91 (m, 2H), 2.35 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H).

(B) 2-(4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared from 4-((4-bromo-3-methylphenoxy)methyl)-2,2-dimethyl-1,3-dioxolane and bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃ and a reaction temperature of 85 °C overnight. ¹H NMR (CDCl₃) δ 7.70 (d, *J* = 8.0 Hz, 1H), 6.69 - 6.72 (m, 2H), 4.45 - 4.48 (m, 1H), 4.14 - 4.18 (m, 1H), 4.05 - 4.08 (m, 1H), 3.87 - 3.96 (m, 2H), 2.51 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H), 1.32 (s, 12H).

(C) 3-(4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)benzo[b]thiophene-5-carbaldehyde was prepared from 2-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3-bromobenzo[b]thiophene-5-carbaldehyde (from Example 4A) following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. ¹H NMR: (CDCl₃) δ 10.02 (s, 1H), 8.02 - 8.04 (m, 1H), 7.89 - 7.90 (m, 2H), 7.37 (s, 1H), 7.20 - 7.26 (m, 1H), 6.82 - 7.00 (m, 2H), 4.50 - 4.53 (m, 1H), 4.14 - 4.24 (m, 2H), 3.93 - 4.08 (m, 2H), 2.15 (s, 3H), 1.48 - 1.50 (m, 3H), 1.42 - 1.43 (m, 3H).

(D) (3-(4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol was prepared from 3-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)benzo[b]thiophene-5-carbaldehyde following General Procedure F. LC/MS: mass calcd. for C₂₂H₂₄O₄S: 384.49, found: 367.1 [M-OH]⁺.

(E) 4-((4-(5-(Chloromethyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)methyl)-2,2-dimethyl-1,3-dioxolane was prepared from (3-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

(F) (3*S*)-Ethyl 3-(4-((3-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 4-((4-(5-(chloromethyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)methyl)-2,2-dimethyl-1,3-dioxolane and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator,

Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure E. LC/MS: mass calcd. for C₃₆H₃₈O₆S: 598.75, found: 599.2 [M+H]⁺.

(G) A solution of (3*S*)-ethyl 3-(4-((3-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (200 mg, 0.33 mmol) in THF (4 mL) was treated with 2N HCl (4 mL) and the resulting solution was stirred at 60 °C for 30 min. Water (10 mL) was then added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-50% EtOAc/petroleum ether) afforded (3*S*)-ethyl 3-(4-((3-(4-(2,3-dihydroxypropoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (140 mg, 75% yield) as a colorless oil. LC/MS: mass calcd. for C₃₃H₃₄O₆S: 558.68, found: 559.2 [M+H]⁺.

(H) (3*S*)-3-(4-((3-(4-(2,3-Dihydroxypropoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(4-(2,3-dihydroxypropoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.23 - 7.25 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.86 - 6.95 (m, 4H), 5.17 (s, 2H), 4.98 - 5.02 (m, 1H), 4.06 - 4.07 (m, 1H), 4.03 - 4.07 (m, 1H), 3.82 - 3.93 (m, 3H), 3.46 - 3.47 (m, 2H), 2.63 - 2.67 (m, 2H), 2.06 (s, 3H), 1.76 (s, 3H). LC/MS: mass calcd. for C₃₁H₃₀O₆S: 530.63, found: 529.2[M-H]⁻.

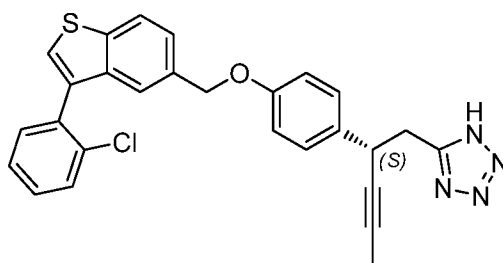
(I) (3*S*)-3-(4-((3-(4-(2,3-Dihydroxypropoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared by the HATU-mediated coupling of (3*S*)-3-(4-((3-(4-(2,3-dihydroxypropoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid and NH₄Cl following the procedure described in Example 6E. LC/MS: mass calcd. for C₃₁H₃₁NO₅S: 529.19, found: 530.2 [M+H]⁺.

(J) (3*S*)-3-(4-((3-(4-(2,3-Dihydroxypropoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared along with 3-(4-(5-((4-((3*S*)-1-cyanopent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-hydroxypropyl 2,2,2-trifluoroacetate and 3-(4-(5-((4-((3*S*)-1-cyanopent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)propane-1,2-diyl bis(2,2,2-trifluoroacetate) from (3*S*)-3-(4-((3-(4-(2,3-dihydroxypropoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I and the mixture was used in the subsequent reaction.

(K) 3-(4-(5-((4-((2*S*)-1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)propane-1,2-diol (Cpd **31**) was prepared from the mixture of (3*S*)-3-(4-((3-(4-(2,3-dihydroxypropoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile, 3-(4-(5-((4-((3*S*)-1-cyanopent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-hydroxypropyl 2,2,2-trifluoroacetate and 3-(4-(5-((4-((3*S*)-1-cyanopent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-3-methylphenoxy)propane-1,2-diyl bis(2,2,2-trifluoroacetate) following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.34 - 7.51 (m, 3H), 7.10 - 7.27 (m, 3H), 6.82 - 6.98 (m, 4H), 5.11 (s, 2H), 3.94 - 4.19 (m, 4H), 3.61 - 3.80 (m, 2H), 3.12 - 3.29 (m, 2H), 2.06 (s, 3H), 1.77 (d, *J* = 2.3 Hz, 3H). LC/MS: mass calcd. for C₃₁H₃₃N₄O₄S: 554.20, found: 555.25 [M+H]⁺.

Example 32

(2*S*)-5-(2-(4-((3-(2-Chlorophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **32**



(A) 5-Hydroxymethyl-3-(2-chlorophenyl)benzo[b]thiophene was prepared from 3-bromo-5-hydroxymethylbenzothiophene (from Example 1A) and 2-chlorophenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₁₅H₁₁ClOS: 274.02, found 257.1 [M-OH]⁺.

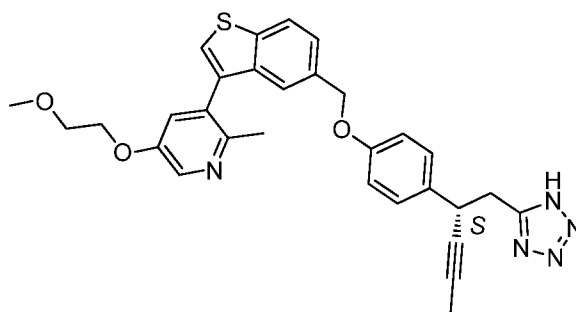
(B) 5-(Chloromethyl)-3-(2-chlorophenyl)benzo[b]thiophene was prepared from 5-hydroxymethyl-3-(2-chlorophenyl)benzo[b]thiophene following General Procedure D.

(C) (3*S*)-3-(4-((3-(2-Chlorophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 5-(chloromethyl)-3-(2-chlorophenyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, using DMF as solvent and K₂CO₃ in place of Cs₂CO₃ at a reaction temperature of 60 °C for 3 h. LC/MS: mass calcd. for C₂₇H₂₀ClNOS: 441.09, found: 441.9 [M+H]⁺.

(D) (2*S*)-5-(2-(4-((3-(2-Chlorophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **32**) was prepared from (3*S*)-3-(4-((3-(2-chlorophenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 1. ¹H NMR (DMSO-*d*₆) δ 8.06 - 8.12 (m, 1H), 7.85 (s, 1H), 7.61 - 7.69 (m, 1H), 7.44 - 7.54 (m, 5H), 7.19 - 7.25 (m, 2H), 6.87 - 6.97 (m, 2H), 5.16 (s, 2H), 4.02 - 4.18 (m, 1H), 3.20 (d, *J* = 7.7 Hz, 2H), 1.73 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₂₇H₂₁ClN₄OS: 484.11, found: 485.0 [M+H]⁺.

Example 33

(2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-5-(2-methoxyethoxy)-2-methylpyridine, Cpd **33**



- (A) 3-Bromo-5-(2-methoxyethoxy)-2-methylpyridine was prepared from 5-bromo-6-methylpyridin-3-ol and 1-bromo-2-methoxyethane following the procedure described in Example 26A. LC/MS: mass calcd. for C₉H₁₂BrNO₂: 246.10, found: 246.0[M]⁺, 248.0 [M+2]⁺.
- (B) 5-(2-Methoxyethoxy)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was prepared from 3-bromo-5-(2-methoxyethoxy)-2-methylpyridine and bis(pinacolato)diboron following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst, KOAc in place of K₂CO₃ and DMSO as reaction solvent at a reaction temperature of 85 °C overnight. LC/MS: mass calcd. for C₁₅H₂₄BNO₄: 293.17, found: 294.1 [M+H]⁺.
- (C) (3*S*)-Ethyl 3-(4-((3-(5-(2-methoxyethoxy)-2-methylpyridin-3-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-(2-methoxyethoxy)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine and (3*S*)-ethyl-3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate (from Example 7B following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ in place of K₂CO₃. LC/MS: mass calcd. for C₃₂H₃₃NO₅S: 543.67, found: 544.2 [M+H]⁺.
- (D) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylpyridin-3-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*S*)-ethyl 3-(4-((3-(5-(2-

methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. ^1H NMR (DMSO- d_6) δ 8.28 (d, J = 3.0 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.48 - 7.52 (m, 2H), 7.30 (d, J = 2.7 Hz, 1H), 7.24 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 5.18 (s, 2H), 4.17 - 4.20 (m, 2H), 3.90 - 3.94 (m, 1H), 3.65 - 3.68 (m, 2H), 3.32 (s, 3H), 2.54 - 2.57 (m, 2H), 2.20 (s, 3H), 1.76 (d, J = 2.4 Hz, 3H). LC/MS: mass calcd. for $\text{C}_{30}\text{H}_{29}\text{NO}_5\text{S}$: 515.62, found: 516.2 $[\text{M}+\text{H}]^+$.

(E) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G, using oxalyl chloride as the chlorinating agent.

(F) (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Ha. LC/MS: mass calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_4\text{S}$: 514.19, found: 515.0 $[\text{M}+\text{H}]^+$.

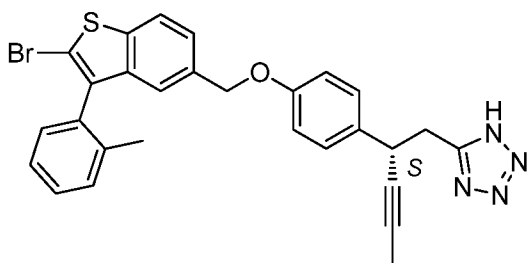
(G) (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-(5-(2-Methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_3\text{S}$: 496.18, found: 497.0 $[\text{M}+\text{H}]^+$.

(H) (2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[b]thiophen-3-yl)-5-(2-methoxyethoxy)-2-methylpyridine (Cpd **33**) was prepared from (3*S*)-3-(4-((3-(5-(2-methoxyethoxy)-2-methylpyridin-3-yl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. ^1H NMR (CD_3OD) δ 8.20 (s, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.34 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 6.87 (d, J =

8.4 Hz, 2H), 5.14 (s, 2H), 4.16 - 4.19 (m, 2H), 4.00 - 4.05 (m, 1H), 3.71 - 3.74 (m, 2H), 3.38 (s, 3H), 3.21 - 3.27 (m, 2H), 2.20 (s, 3H), 1.75 (s, 3H). LC/MS: mass calcd. for $C_{30}H_{29}N_5O_3S$: 539.20, found: 540.1 $[M+H]^+$.

Example 34

5-((2*S*)-2-(4-((2-Bromo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole, Cpd **34**



(A) To an ice-cooled solution of *tert*-butyldimethyl-((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane (400 mg, 0.27 mmol; from Example 2A) in DMF (10 mL) was added NBS (193 mg, 1.08 mmol) and the resultant mixture was stirred at 0 °C for 2 h. Water (30 mL) was then added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue that was obtained was purified by silica gel chromatography (0-30% EtOAc/petroleum ether) to afford (2-bromo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol (200 mg, 55 %) as a colorless oil. LC/MS: mass calcd. for $C_{16}H_{13}BrOS$: 331.99, found: 315.0, 317.0 $[M-OH]^+$, $[M+2-OH]^+$.

(B) 2-Bromo-5-(chloromethyl)-3-(2-methylphenyl)benzo[b]thiophene was prepared from (2-bromo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

(C) (3*S*)-3-(4-((2-Bromo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 2-bromo-5-(chloromethyl)-3-(2-methylphenyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, at a reaction temperature of 60 °C overnight.

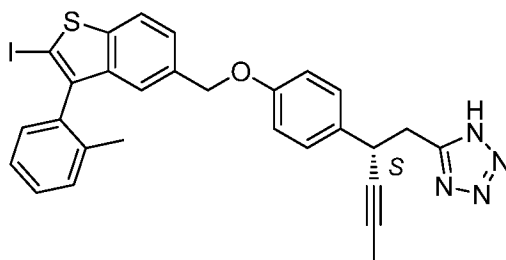
LC/MS: mass calcd. for C₂₈H₂₂BrNOS: 499.06, found: 516.9, 518.9 [M+NH₄]⁺, [M+2+NH₄]⁺.

(D) 5-((2*S*)-2-(4-((2-Bromo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole (Cpd **34**) was prepared from (3*S*)-3-(4-((2-bromo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.31 - 7.37 (m, 3H), 7.14 - 7.21 (m, 4H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.09 (s, 2H), 4.05 (br. s, 1H), 3.25 (d, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 1.77 (s, 3H).

LC/MS: mass calcd. for C₂₈H₂₃BrN₄OS: 542.08, found: 542.9, 544.9 [M+H]⁺, [M+2+H]⁺.

Example 35

5-((2*S*)-2-(4-((2-Iodo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole, Cpd **35**



(A) To a cooled (-78 °C) solution of *tert*-butyldimethyl-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)silane (400 mg, 0.27 mmol; from Example 2A) in THF (15 mL), maintained under an inert nitrogen atmosphere, was added LDA (2M in THF; 0.54 mL, 1.08 mmol) and the resultant mixture was stirred at -78 °C for 0.5 h. A solution of iodine (415 mg, 1.64 mmol) in THF was then added and the resultant mixture was stirred at -78 °C for 2 h. The reaction was then quenched by the addition of satd. aq NaCl (30 mL) and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄), concentrated under reduced pressure and the residue that was obtained was purified by silica gel chromatography (0-10% EtOAc/petroleum

ether) to afford *tert*-butyl((2-iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane (360 mg, 67 %) as a yellow oil. LC/MS: mass calcd. for $C_{22}H_{27}IOSSi$: 494.06, found: 362.8 $[M-OTBS]^+$.

(B) (2-Iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol was prepared from *tert*-butyldimethyl-((2-iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane following the procedure described in Example 2C. LC/MS: mass calcd. for $C_{16}H_{13}IOS$: 379.97, found: 362.7 $[M-OH]^+$.

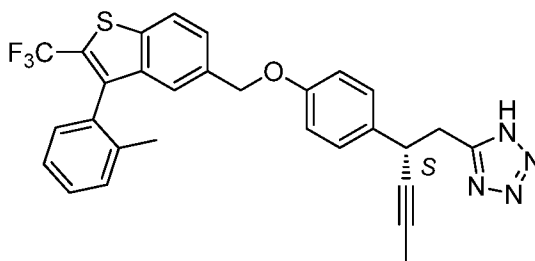
(C) 2-Iodo-5-(chloromethyl)-3-(2-methylphenyl)benzo[b]thiophene was prepared from (2-iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

(D) (3*S*)-3-(4-((2-Iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 2-iodo-5-(chloromethyl)-3-(2-methylphenyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, using K_2CO_3 in place of Cs_2CO_3 and a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for $C_{28}H_{22}INOS$: 547.05, found: 564.9 $[M+NH_4]^+$.

(E) 5-((2*S*)-2-(4-((2-Iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole (Cpd **35**) was prepared from (3*S*)-3-(4-((2-iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. 1H NMR (CD_3OD) δ 7.84 (d, $J = 8.4$ Hz, 1H), 7.27 - 7.45 (m, 4H), 7.16 - 7.20 (m, 3H), 7.08 (d, $J = 7.2$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 5.04 (s, 2H), 4.04 (br. s, 1H), 3.24 (d, $J = 7.2$ Hz, 2H), 1.96 (s, 3H), 1.77 (s, 3H). LC/MS: mass calcd. for $C_{28}H_{23}IN_4OS$: 590.06, found: 590.9 $[M+H]^+$.

Example 36

5-((2*S*)-2-(4-((2-Trifluoromethyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole, Cpd **36**



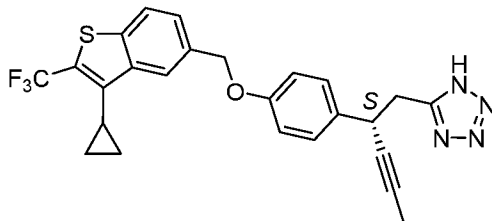
(A) To a cooled (-78 °C) solution of *tert*-butyldimethyl-((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane (300 mg, 0.814 mmol; from Example 2A) in THF (8 mL), maintained under an inert nitrogen atmosphere, was added *n*-BuLi (2.5M in hexanes; 0.65 mL, 1.63 mmol) in drop-wise fashion and the resultant mixture was stirred at -78 °C for 10 min. A solution of triisopropoxyborane (612 mg, 3.26 mmol) in THF (2 mL) was then added in drop-wise fashion and the resultant mixture was stirred at -78 °C for 30 min, then at rt for 1 h. The reaction was then quenched by the addition of water (10 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to afford 5-((*tert*-butyldimethylsilyloxy)methyl)-3-(2-methylphenyl)benzo[b]thiophen-2-ylboronic acid (250 mg, 74 %) as colorless oil. LC/MS: mass calcd. for C₂₂H₂₉BO₃SSi: 412.17, found: 411.1 [M-H]⁻.

(B) To an ice-cooled mixture of 5-((*tert*-butyldimethylsilyloxy)methyl)-3-(2-methylphenyl)benzo[b]thiophen-2-ylboronic acid (250 mg, 0.606 mmol), sodium trifluoromethanesulfinate (284 mg, 1.820 mmol), copper(I) chloride (60 mg, 0.606 mmol), DCM (5 mL), MeOH (5 mL) and water (4 mL) was added 2-hydroperoxy-2-methylpropane (273 mg, 3.029 mmol) in drop-wise fashion. After stirring at rt overnight, water (15 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), concentrated under reduced pressure and the residue that was obtained was purified by silica gel chromatography (0-5% EtOAc/petroleum ether) to afford *tert*-butyldimethyl((2-trifluoromethyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane (200 mg, 75 %) as a colorless oil. LC/MS: mass calcd. for C₂₃H₂₇F₃OSSi: 436.15, found: 305.1 [M-OTBS]⁺.

- (C) (3-(2-Methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methanol was prepared from *tert*-butyldimethyl((2-trifluoromethyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)silane following the procedure described in Example 2C. LC/MS: mass calcd. for C₁₇H₁₃F₃OS: 322.06, found: 305.1 [M-OH]⁺.
- (D) 5-(Chloromethyl)-3-(2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophene was prepared from (3-(2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.
- (E) (3*S*)-3-(4-((3-(2-Methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 5-(chloromethyl)-3-(2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₂₉H₂₂F₃NOS: 489.14, found: 507.0[M+NH₄]⁺.
- (F) 5-((2*S*)-2-(4-((2-Trifluoromethyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole (Cpd **36**) was prepared from (3*S*)-3-(4-((3-(2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH₄HCO₃) gradient (45 – 85%). ¹H NMR (DMSO-*d*₆) δ 8.02 - 8.25 (m, 1H), 7.66 - 7.69 (m, 1H), 7.33 - 7.51 (m, 3H), 7.20 - 7.25 (m, 4H), 6.86 - 6.94 (m, 2H), 5.12 - 5.16 (m, 2H), 4.08 - 4.09 (m, 1H), 3.21 (d, *J* = 7.8 Hz, 2H), 1.92 - 2.02 (m, 3H), 1.73 (d, *J* = 1.5 Hz, 3H). LC/MS: mass calcd. for C₂₉H₂₃F₃N₄OS: 532.15, found: 533.0 [M+H]⁺.

Example 37

(2*S*)-5-(2-(4-((3-Cyclopropyl-2-(trifluoromethyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 37



(A) To a solution of (3*S*)-3-(4-hydroxyphenyl)hex-4-ynoic acid (200 mg, 0.98 mmol) in THF (6 mL) was added tetrabutylammonium hydroxide (40% in water, 1.45 mL, 2.23 mmol) and H₂O (0.9 mL). After stirring at rt for 5 min, NaI (40 mg, 0.267 mmol) was added, followed by addition of a solution of 1-(chloromethyl)-4-methoxybenzene (0.12 mL, 0.89 mmol) in THF (4 mL) and stirring was continued for 18 h. The reaction was quenched by addition of 1N HCl and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to afford (3*S*)-3-(4-((4-methoxybenzyl)oxy)phenyl)hex-4-ynoic acid, which was used directly without further purification. LC/MS: mass calcd. for C₂₀H₂₀O₄: 324.14, found: 347.1 [M+Na]⁺.

(B) To a solution of (3*S*)-3-(4-((4-methoxybenzyl)oxy)phenyl)hex-4-ynoic acid (300 mg, 0.93 mmol) in DMF (4 mL) was added 3-aminopropionitrile (130 mg, 1.85 mmol), HATU (527 mg, 1.39 mmol), and DIEA (0.478 mL, 2.78 mmol) and the resulting mixture was stirred at rt for 2 h. EtOAc (50 mL) was then added, and the organic phase was washed successively with satd. aq NaHCO₃, 1N HCl and brine (3 x 50 mL). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure and the residue thus obtained was purified by silica gel chromatography (20-80% EtAOc/heptanes) to afford (3*S*)-*N*-(2-cyanoethyl)-3-(4-((4-methoxybenzyl)oxy)phenyl)hex-4-ynamide (200 mg, 57%) as a white solid. LC/MS: mass calcd. for C₂₃H₂₄N₂O₃: 376.18, found: 377.2 [M+H]⁺.

(C) To the suspension of (3*S*)-*N*-(2-cyanoethyl)-3-(4-((4-methoxybenzyl)oxy)phenyl)hex-4-ynamide (200 mg, 0.53 mmol) in DCM (10 mL) was

added pyridine (0.256 mL, 3.19 mmol) and PCl_5 (166 mg, 0.80 mmol) and the resultant mixture was stirred at 40 °C for 3h. After cooling to rt, TMSN_3 (0.282 mL, 2.13 mmol) was added and the mixture was stirred at rt overnight. The reaction was quenched by the careful addition of satd. aq NaHCO_3 (20 mL) was added slowly and after stirring for 15 min, the mixture was diluted with DCM (200 mL). The organic phase was then washed successively with 0.1N HCl and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-50% EtOAc/heptanes) to afford (2*S*)-3-(5-(2-(4-((4-methoxybenzyl)oxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (147 mg, 69%) as a yellow solid. LC/MS: mass calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_2$: 401.19, found: 402.1 $[\text{M}+\text{H}]^+$.

(D) To a solution of (2*S*)-3-(5-(2-(4-((4-methoxybenzyl)oxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (147 mg, 0.366 mmol) in DCM (2 mL) was added TFA (1 mL) and the mixture was stirred at rt for 6 h. The reaction was then concentrated under reduced pressure, and the residue was re-dissolved in EtOAc (20 mL). The solution was washed successively with satd. aq NaHCO_3 and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-60% EtOAc/heptanes) to afford (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (43 mg, 42%) as a colorless oil. ^1H NMR (CDCl_3) δ 7.06 (d, $J = 8.6$ Hz, 2H), 6.75 - 6.81 (m, 2H), 4.03 - 4.16 (m, 3H), 3.39 (dd, $J = 14.1, 7.1$ Hz, 1H), 3.21 (dd, $J = 14.4, 7.8$ Hz, 1H), 2.76 - 2.87 (m, 1H), 2.64 - 2.75 (m, 1H), 1.84 (d, $J = 2.0$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_5\text{O}$: 281.13, found: 282.1 $[\text{M}+\text{H}]^+$.

(E) Methyl 3-cyclopropylbenzo[*b*]thiophene-5-carboxylate was prepared from methyl 3-bromobenzo[*b*]thiophene-5-carboxylate and cyclopropylboronic acid following General Procedure A, using $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ as the palladium catalyst. LC/MS: mass calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_2\text{S}$: 232.06, found: 233.1 $[\text{M}+\text{H}]^+$.

(F) To a solution of methyl 3-cyclopropylbenzo[*b*]thiophene-5-carboxylate (200 mg, 0.861 mmol) in AcOH (3 mL) was added Br_2 (88.8 μL , 1.72 mmol) in DCM (3 mL) and the mixture was stirred at rt for 20 min. Water (50 mL) was added, followed by 5% aq

Na₂S₂O₃ solution (10 mL). The mixture was then extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed successively with satd. aq NaHCO₃ and brine, then dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography (0-10% EtOAc/heptane) afforded methyl 2-bromo-3-cyclopropylbenzo[*b*]thiophene-5-carboxylate (222 mg, 83%) as an off-white solid. ¹H NMR (CDCl₃) δ 8.58 (d, *J*=1.0 Hz, 1H), 7.96 (dd, *J*=8.6, 1.5 Hz, 1H), 7.70 (d, *J*=8.1 Hz, 1H), 3.97 (s, 3H), 1.82 (tt, *J*=8.5, 5.4 Hz, 1H), 1.09-1.15 (m, 2H), 0.82-0.88 (m, 2H).

(G) To a solution of methyl 2-bromo-3-cyclopropylbenzo[*b*]thiophene-5-carboxylate (200 mg, 0.643 mmol), NaI (193 mg, 1.29 mmol) and CuI (245 mg, 1.29 mmol) in DMF (5 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.409 mL, 3.21 mmol) in a drop-wise fashion under argon and the mixture was stirred at 105 °C for 2 d. After cooling to rt, the mixture was filtered through a pad of diatomaceous earth, which was further washed with EtOAc. The combined filtrate was washed successively with water and brine and the organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-10% EtOAc/heptanes) to afford methyl 3-cyclopropyl-2-iodobenzo[*b*]thiophene-5-carboxylate as the major product (200 mg, 87%). ¹H NMR (CDCl₃) δ 8.65 (d, *J*=1.5 Hz, 1H), 7.95 (dd, *J*=8.6, 1.5 Hz, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 3.97 (s, 3H), 1.78-1.90 (m, 1H), 1.14-1.21 (m, 2H), 0.79-0.86 (m, 2H).

(H) To a solution of methyl 3-cyclopropyl-2-iodobenzo[*b*]thiophene-5-carboxylate (200 mg, 0.558 mmol) and CuI (213 mg, 1.12 mmol) in DMF (4 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.355 mL, 2.79 mmol) in a drop-wise fashion under argon and the mixture was stirred at 150 °C (sealed tube) in a microwave reactor for 1 h. After cooling to rt, the mixture was filtered through a pad of diatomaceous earth, which was further washed with EtOAc. The combined filtrate was washed successively with water and brine and the organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-10% EtOAc/heptanes) to afford methyl 3-cyclopropyl-2-(trifluoromethyl)benzo[*b*]thiophene-5-

carboxylate (128 mg, 76%). $^1\text{H NMR}$ (CDCl_3) δ 8.77 (d, $J=1.5$ Hz, 1H), 8.10 (dd, $J=8.6$, 1.5 Hz, 1H), 7.88 (d, $J=8.6$ Hz, 1H), 3.99 (s, 3H), 2.01 (ddt, $J=7.2$, 3.7, 1.6 Hz, 1H), 1.15-1.22 (m, 2H), 0.86-0.92 (m, 2H).

(I) To an ice-cooled solution of methyl 3-cyclopropyl-2-(trifluoromethyl)benzo[*b*]thiophene-5-carboxylate (128 mg, 0.426 mmol) in THF (5 mL) was added LiAlH_4 (1 M in THF, 0.639 mL) in drop-wise fashion under argon and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of satd. aq NH_4Cl solution and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, then dried (Na_2SO_4) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-30% EtOAc/heptane) to give 3-cyclopropyl-2-(trifluoromethyl)benzo[*b*]thiophen-5-yl)methanol (72 mg, 62%) as a white solid. $^1\text{H NMR}$ (CDCl_3) δ 8.07 (s, 1H), 7.81 (d, $J=8.1$ Hz, 1H), 7.46 (dd, $J=8.6$, 1.5 Hz, 1H), 4.85 (s, 2H), 1.92-2.02 (m, 1H), 1.82 (br. s, 1H), 1.09-1.15 (m, 2H), 0.83-0.89 (m, 2H).

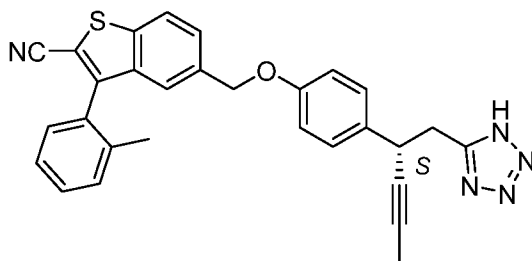
(J) (2*S*)-3-(5-(2-(4-((3-Cyclopropyl-2-(trifluoromethyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile was prepared from 3-cyclopropyl-2-(trifluoromethyl)benzo[*b*]thiophen-5-yl)methanol and (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Step D) following General Procedure B, using ADDP and Bu_3P at a reaction temperature of 60 °C for 3 h. LC/MS: mass calcd. for $\text{C}_{28}\text{H}_{24}\text{F}_3\text{N}_5\text{OS}$: 535.17, found: 536.2 $[\text{M}+\text{H}]^+$.

(K) To a solution of (2*S*)-3-(5-(2-(4-((3-cyclopropyl-2-(trifluoromethyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (60 mg, 0.112 mmol) in THF (1 mL) and *i*-PrOH (0.5 mL) was added 1N NaOH (1 mL) and the mixture was stirred at rt for 1 h. The organic solvent was evaporated and the aqueous solution was acidified with 2M aq citric acid and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resultant residue was purified by silica gel chromatography (20-100% EtOAc/heptane) to afford (2*S*)-5-(2-(4-((3-cyclopropyl-2-

(trifluoromethyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (43 mg, 80%) as a white solid. ¹H NMR (CDCl₃) δ 8.09 (s, 1H), 7.81 (d, *J*=8.1 Hz, 1H), 7.48 (dd, *J*=8.1, 1.5 Hz, 1H), 7.27 (d, *J*=7.8 Hz, 2H), 6.93 (d, *J*=7.8 Hz, 2H), 5.14 (s, 2H), 4.08-4.18 (m, 1H), 3.37-3.51 (m, 2H), 1.91-2.01 (m, 1H), 1.82 (d, *J*=2.5 Hz, 3H), 1.05-1.14 (m, 2H), 0.77-0.87 (m, 2H). LC/MS: mass calcd. for C₂₅H₂₁F₃N₄OS: 482.14, found: 505.2 [M+Na]⁺.

Example 38

5-((2*S*)-2-(4-((2-Cyano-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **38**



(A) To an ice-cooled solution of *tert*-butyldimethyl-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)silane (6 g, 16.28 mmol; from Example 2A) in DMF (50 mL) was added NBS (2.9 g, 16.3 mmol) and the resultant mixture was stirred at 0 °C for 2 h. Water (100 mL) was then added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), concentrated under reduced pressure and the residue that was obtained was purified by silica gel chromatography (0-30% EtOAc/petroleum ether) to afford ((2-bromo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)(*tert*-butyl)dimethylsilane (4 g, 55 %) as a colorless oil. LC/MS: mass calcd. for C₁₆H₁₃BrOS: 331.99, found: 315.0, 317.0 [M-OTBS]⁺, [M+2-OTBS]⁺.

(B) A mixture of ((2-bromo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)(*tert*-butyl)dimethylsilane (200 mg, 0.447 mmol), zinc cyanide (105 mg, 0.894 mmol) and

Pd(PPh₃)₄ (50 mg, 0.043 mmol) in DMF (10 mL) was placed under an inert atmosphere of nitrogen in a sealed tube and heated for 16 h at 100 °C. After cooling to rt, water (30 mL) was added, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated. The resultant residue was purified by silica gel chromatography (0-20% EtOAc/petroleum ether) to afford 5-((*tert*-butyldimethylsilyloxy)-methyl)-3-(2-methylphenyl)benzo[b]thiophene-2-carbonitrile (150 mg, 48 %) as a yellow oil. LC/MS: mass calcd. for C₂₃H₂₇NOSSi: 393.16, found: 394.0 [M+H]⁺.

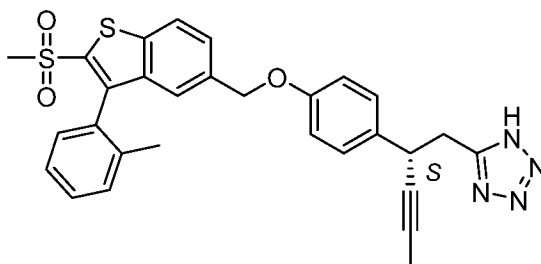
(C) 5-(Hydroxymethyl)-3-(2-methylphenyl)benzo[b]thiophene-2-carbonitrile was prepared from 5-((*tert*-butyldimethylsilyloxy)-methyl)-3-(2-methylphenyl)benzo[b]thiophene-2-carbonitrile following the procedure described in Example 2C. LC/MS: mass calcd. for C₁₇H₁₃NOS: 279.07, found: 262.0 [M-OH]⁺.

(D) 5-((4-((2*S*)-1-(1-(2-Cyanoethyl)-1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)benzo[b]thiophene-2-carbonitrile was prepared from 5-(hydroxymethyl)-3-(2-methylphenyl)benzo[b]thiophene-2-carbonitrile and (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 37D) following General Procedure B, using ADDP and Bu₃P at a reaction temperature of 60 °C. LC/MS: mass calcd. for C₃₂H₂₆N₆OS: 542.19, found: 543.0 [M+H]⁺.

(E) 5-((2*S*)-2-(4-((2-Cyano-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **38**) was prepared from 5-((4-((2*S*)-1-(1-(2-cyanoethyl)-1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)benzo[b]thiophene-2-carbonitrile following the procedure described in Example 37K, using EtOH in place of *i*-PrOH and 1N HCl for reaction acidification. ¹H NMR (CD₃OD) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.33 - 7.47 (m, 4H), 7.23 - 7.26 (m, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.17 (s, 2H), 4.02 (br. s, 1H), 3.22 (d, *J* = 7.8 Hz, 2H), 2.05 (s, 3H), 1.75 (s, 3H). LC/MS: mass calcd. for C₂₉H₂₃N₅OS: 489.16, found: 490.0 [M+H]⁺.

Example 39

(2*S*)-5-(2-(4-((2-(Methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **39**



(A) A mixture of ((2-bromo-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)(*tert*-butyl)dimethylsilane (500 mg, 1.12 mmol) (from Example 38A), sodium methanesulfinate (350 mg, 3.43 mmol), copper (I) trifluoromethanesulfonate benzene complex (110 mg, 0.22 mmol) and *N,N'*-dimethylethylenediamine (40 mg, 0.45 mmol) in DMSO (15 mL) was placed under an inert atmosphere of nitrogen in a sealed tube and heated for 16 h at 120 °C. After cooling to rt, water (20 mL) was added, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resultant residue was purified by silica gel chromatography (0-30% EtOAc/petroleum ether) to afford *tert*-butyldimethyl((2-(methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)silane (80 mg, 16%) as a yellow oil. LC/MS: mass calcd. for $\text{C}_{23}\text{H}_{30}\text{O}_3\text{S}_2\text{Si}$: 446.14, found: 446.9 $[\text{M}+\text{H}]^+$.

(B) (2-(Methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol was prepared from *tert*-butyldimethyl((2-(methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)silane following the procedure described in Example 2C. LC/MS: mass calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{S}_2$: 332.05, found: 332.9 $[\text{M}+\text{H}]^+$.

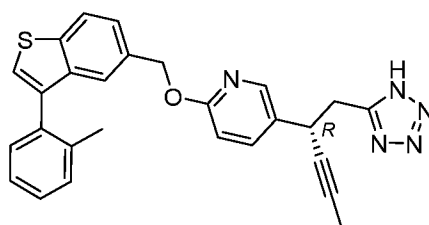
(C) 5-(Chloromethyl)-2-(methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophene was prepared from (2-(methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol following General Procedure D.

(D) (3*S*)-3-(4-((2-(Methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 5-(chloromethyl)-2-(methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, using K₂CO₃ in place of Cs₂CO₃ and a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₂₉H₂₅NO₃S₂: 499.13, found: 517.0 [M+NH₄]⁺.

(E) (2*S*)-5-(2-(4-((2-(Methylsulfonyl)-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **39**) was prepared from (3*S*)-3-(4-((2-(methylsulfonyl)-3-(2-methylphenyl)[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 8.02 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.31 - 7.44 (m, 3H), 7.24 - 7.29 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.09 (s, 2H), 4.02 (br. s, 1H), 3.21 (d, *J* = 7.5 Hz, 2H), 2.96 (s, 3H), 1.94 (s, 3H), 1.74 (s, 3H). LC/MS: mass calcd. for C₂₉H₂₆N₄O₃S₂: 542.14, found: 543.0 [M+H]⁺.

Example 40

(2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridine, Cpd **40**



(A) A solution of 6-methoxypyridine-3-carbaldehyde (10 g, 73.00 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (11 g, 76.70 mmol) in water (150 mL) was stirred for 2 h at 75 °C, and then cooled in a water/ice bath. The resulting solids were collected by filtration and dried in an oven under reduced pressure to provide 5-((6-methoxypyridin-3-

yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione as a yellow powder (18 g, 99 %).

LC/MS: mass calcd. for $C_{13}H_{13}NO_5$: 263.25, found: 264.0 $[M+H]^+$.

(B) To a solution of bromo(prop-1-yn-1-yl)magnesium (114 mL, 57.03 mmol, 0.5 N in THF) in THF (300 mL) was added a solution of 5-((6-methoxypyridin-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (10 g, 38.02 mmol) in THF (100 mL) in drop-wise fashion and the resulting solution was stirred at rt overnight. The reaction was then quenched by the addition of of satd. aq. NH_4Cl (100 mL). The resulting mixture was extracted with 300 mL of hexane (which was discarded) and the aqueous layer was collected. The pH of the aqueous layer was adjusted to 2 with 1N HCl and the resulting solution was extracted with EtOAc (3 x 200 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 5-(1-(6-methoxypyridin-3-yl)but-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (10 g, 87%) as a yellow solid. LC/MS: mass calcd. for $C_{16}H_{17}NO_5$: 303.31, found: 304.0 $[M+H]^+$.

(C) A solution of 5-(1-(6-methoxypyridin-3-yl)but-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (5 g, 16.48 mmol), DMF (100 mL) and water (10 mL) was stirred overnight at 100 °C. The reaction was then quenched by the addition of satd. aq. NH_4Cl (200 mL) and the resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 3-(6-methoxypyridin-3-yl)hex-4-ynoic acid (3.5 g, 97 %) as a red oil, which was used directly without further purification. LC/MS: mass calcd. for $C_{12}H_{13}NO_3$: 219.24, found: 220.1 $[M+H]^+$.

(D) A solution of 3-(6-methoxypyridin-3-yl)hex-4-ynoic acid (8.8 g, 40.18 mmol), dioxane (20 mL), water (20 mL) and conc. HCl (5 mL) was stirred overnight at 100 °C. After cooling to rt, the solution was neutralized to pH 5 by the addition of satd. aq. $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 3-(6-hydroxypyridin-3-yl)hex-4-ynoic acid (7.6g, 92 %) as a brown oil, which was used directly without further purification. LC/MS: mass calcd. for $C_{11}H_{11}NO_3$: 205.21, found: 206.0 $[M+H]^+$.

(E) A solution of 3-(6-hydroxypyridin-3-yl)hex-4-ynoic acid (8 g, 39.00 mmol) in EtOH (45 mL) was treated with conc. H₂SO₄ (2 mL) and the resultant solution was stirred for 2 h at 80 °C. After cooling to rt, the solution was neutralized to pH 5 by the addition of satd. aq. NaHCO₃ and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-20% MeOH/DCM) to afford ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate (2.2 g, 24.2%). ¹H NMR (CDCl₃) δ 7.46 - 7.53 (m, 2H), 6.57 (d, *J* = 9.3 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.88 - 3.94 (m, 1H), 2.55 - 2.71 (m, 2H), 1.82 (d, *J* = 2.4 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H).

(F) Enantiomeric resolution of ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate was carried out by chiral super critical fluid chromatography on a ChiralPak AS-H 5 μ column (2 x 25 cm) using an isocratic mobile phase [EtOH (0.2% DEA) / CO₂ (50:50); 170 g/min] to afford (3*R*)-ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate (RT = 4.15 min) ¹H NMR (CDCl₃) δ 7.47 - 7.55 (m, 2H), 6.59 (d *J* = 9.3 Hz, 1H), 4.09 - 4.19 (m, 2H), 3.89 - 3.95 (m, 1H), 2.70 (dd, *J* = 7.5, 15.3 Hz, 1H), 2.59 (dd, *J* = 7.5, 15.6 Hz, 1H), 1.82 (s, 3H), 1.25 - 1.27 (m, 3H) and (3*S*)-ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate (RT = 5.97 min).

(G) To an ice-cooled solution of 5-hydroxymethyl-3-(2-methylphenyl)benzo[b]-thiophene (from Example 1B) (200 mg, 0.79 mmol) in DCM (20 mL) and DMF (2 mL) was added PBr₃ (148 μL, 1.57 mmol) in dropwise fashion. After stirring for 1 h, the mixture was neutralized to pH 6-7 with the addition of 1M aq. NaHCO₃, and the resulting mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to afford crude 5-bromomethyl-3-(2-methylphenyl)benzo[b]-thiophene, which was used directly without purification.

(H) To a solution of 5-bromomethyl-3-(2-methylphenyl)benzo[b]-thiophene from the above step in toluene (10 mL) was added (3*R*)-ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate (170 mg, 0.73 mmol) and Ag₂CO₃ (434 mg, 1.57 mmol) and the resulting mixture was stirred at 60 °C overnight. Water (20 mL) was then added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were concentrated

under reduced pressure and the resultant residue was purified by silica gel chromatography (0-20% EtOAc/petroleum ether) to afford (3*R*)-ethyl 3-(6-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoate (80 mg, 19% yield) as colorless oil. LC/MS: mass calcd. for C₂₉H₂₇NO₃S: 469.60, found: 470.3 [M+H]⁺.

(I) (3*R*)-3-(6-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid was prepared from (3*R*)-ethyl 3-(6-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH, a rt reaction temperature overnight and 1N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 8.01 - 8.09 (m, 2H), 7.62 - 7.69 (m, 2H), 7.46 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.20 - 7.42 (m, 5H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 2H), 3.95 - 4.05 (m, 1H), 2.40 - 2.50 (m, 2H), 2.06 (s, 3H), 1.75 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₂₇H₂₃NO₃S: 441.54, found: 442.0 [M+H]⁺.

(J) (3*R*)-3-(6-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynamide was prepared from (3*R*)-3-(6-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid following the procedure described in Example 6E. LC/MS: mass calcd. for C₂₇H₂₄N₂O₂S: 440.16, found: 441.2 [M+H]⁺.

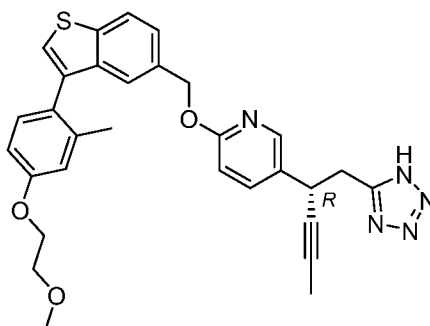
(K) (3*R*)-3-(6-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile was prepared from (3*R*)-3-(6-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₇H₂₂N₂OS: 422.15, found: 423.2 [M+H]⁺.

(L) (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridine (Cpd **40**) was prepared from (3*R*)-3-(6-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 8.05 (d, *J* = 2.7 Hz, 1H), 7.96 - 7.88 (m, 1H), 7.70 (m, 1H), 7.49 - 7.18 (m, 7H), 6.81 (m, 1H), 5.40 - 5.34 (m,

2H), 4.21 – 4.11 (m, 1H), 3.31 (s, 2H), 2.08 (d, $J = 3.4$ Hz, 3H), 1.83 – 1.77 (m, 3H).
 LC/MS: mass calcd. for $C_{27}H_{23}N_5OS$: 465.16, found: 466.2 $[M+H]^+$.

Example 41

(2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridine, Cpd 41



(A) 5-(Bromomethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophene was prepared from (3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol (from Example 8D) and PBr_3 , following the procedure described in Example 40G, and used directly in the next step.

(B) Ethyl 3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoate was prepared from 5-(bromomethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophene and ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate (from Example 40E) following the procedure described in Example 40H at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for $C_{32}H_{33}NO_5S$: 543.67, found: 544.4 $[M+H]^+$.

(C) 3-(6-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid was prepared from ethyl 3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH and 1N HCl for reaction acidification. 1H NMR ($DMSO-d_6$) δ 12.31 (br. s, 1H), 8.10 (d, $J =$

2.4 Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.71 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.64 (s, 1H), 7.42 - 7.48 (m, 2H), 7.16 (d, $J = 8.4$ Hz, 1H), 6.96 (d, $J = 2.4$ Hz, 1H), 6.88 (dd, $J = 2.7, 8.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 5.40 (s, 2H), 4.14 - 4.17 (m, 2H), 3.96 - 4.02 (m, 1H), 3.68 - 3.71 (m, 2H), 3.33 (s, 3H), 2.63 - 2.66 (m, 2H), 2.01 (s, 3H), 1.78 (s, 3H). LC/MS: mass calcd. for $C_{30}H_{29}NO_5S$: 515.62, found: 516.3 $[M+H]^+$.

(D) Enantiomeric resolution of 3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]-thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid was carried out by chiral chromatography on a ChiralPak AS-H 5 μ column (2 x 25 cm) using an isocratic mobile phase [hexane (0.1% HOAc) / EtOH (85:15); 20 mL/min] to afford (3*S*)-3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid (RT = 8 min) and (3*R*)-3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid (RT = 13.5 min).

(E) (3*R*-enantiomer): 1H NMR (DMSO- d_6) δ 8.10 (d, $J = 2.4$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.71 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.64 (s, 1H), 7.42 - 7.48 (m, 2H), 7.16 (d, $J = 8.4$ Hz, 1H), 6.96 (d, $J = 2.4$ Hz, 1H), 6.85 (dd, $J = 2.7, 8.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 5.40 (s, 2H), 4.14 - 4.17 (m, 2H), 3.96 - 4.02 (m, 2H), 3.68 - 3.71 (m, 2H), 3.33 (d, $J = 6.0$ Hz, 3H), 2.64 (dd, $J = 2.1, 7.8$ Hz, 2H), 2.01 (s, 3H), 1.77 (d, $J = 2.4$ Hz, 3H). LC/MS: mass calcd. for $C_{30}H_{29}NO_5S$: 515.62, found: 514.1 $[M-H]^-$.

(F) (3*R*)-3-(6-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynamide was prepared from (3*R*)-3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid following the procedure described in Example 6E. LC/MS: mass calcd. for $C_{30}H_{30}N_2O_4S$: 514.19, found: 515.3 $[M+H]^+$.

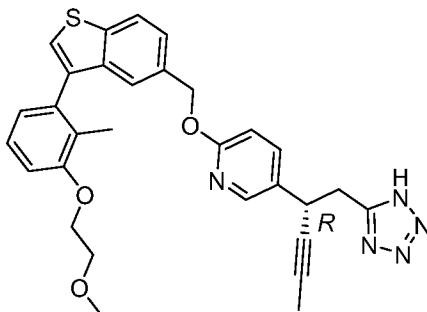
(G) (3*R*)-3-(6-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile was prepared from (3*R*)-3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-

ynamide following General Procedure I. LC/MS: mass calcd. for $C_{30}H_{28}N_2O_3S$: 496.18, found: 497.2 $[M+H]^+$.

(H) (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridine (Cpd **41**) was prepared from (3*R*)-3-(6-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile following General Procedure J, using Workup 2. 1H NMR (CD_3OD) δ 8.03 (d, $J = 2.5$ Hz, 1H), 7.95 – 7.85 (m, 1H), 7.64 (m, 1H), 7.47 – 7.38 (m, 2H), 7.35 (s, 1H), 7.13 (d, $J = 8.3$ Hz, 1H), 6.91 (d, $J = 2.6$ Hz, 1H), 6.83 (m, 1H), 6.76 (d, $J = 8.6$ Hz, 1H), 5.36 (s, 2H), 4.20 – 4.06 (m, 3H), 3.81 – 3.71 (m, 2H), 3.41 (s, 1H), 3.35 – 3.24 (m, 4H), 2.05 (s, 3H), 1.79 (d, $J = 2.4$ Hz, 3H). LC/MS: mass calcd. for $C_{30}H_{29}N_5O_3S$: 539.20, found: 540.25 $[M+H]^+$.

Example 42

(2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridine, Cpd **42**,



(A) (3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol was prepared from 1-Bromo-3-(2-methoxyethoxy)-2-methylbenzene (from Example 10A) and (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-5-yl)methanol (from Example 5A) following General Procedure A using $PdCl_2(dppf)CH_2Cl_2$ as the palladium catalyst and Cs_2CO_3 in place of K_2CO_3 . LC/MS: mass calcd. for $C_{19}H_{20}O_3S$: 428.43, found: 311.1 $[M-OH]^+$.

(B) 5-(Bromomethyl)-3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophene was prepared from (3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol following the procedure described in Example 40G and used directly in the following reaction.

(C) (3*R*)-Ethyl 3-(6-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoate was prepared from 5-(bromomethyl)-3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophene and (3*R*)-ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate (from Example 40F), following the procedure described in Example 40H. LC/MS: mass calcd. for C₃₂H₃₃NO₅S: 543.67, found: 544.1 [M+H]⁺.

(D) (3*R*)-3-(6-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid was prepared from (3*R*)-ethyl 3-(6-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH, a rt reaction temperature overnight and 2N HCl for reaction acidification. ¹H NMR (DMSO-*d*₆) δ 8.09 (d, *J* = 2.1 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.66 - 7.71 (m, 2H), 7.47 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.41 (s, 1H), 7.26 (t, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.39 (s, 2H), 4.15 - 4.19 (m, 2H), 3.96 - 4.01 (m, 1H), 3.71 - 3.74 (m, 2H), 3.35 (s, 3H), 2.54 - 2.61 (m, 2H), 1.92 (s, 3H), 1.76 (d, *J* = 2.1 Hz, 3H). LC/MS: mass calcd. for C₃₀H₂₉NO₅S: 515.62, found: 514.1 [M-H]⁻.

(E) (3*R*)-3-(6-((3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynamide was prepared from (3*R*)-3-(6-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid following the procedure described in Example 6E. LC/MS: mass calcd. for C₃₀H₃₀N₂O₄S: 514.19, found: 515.3 [M+H]⁺.

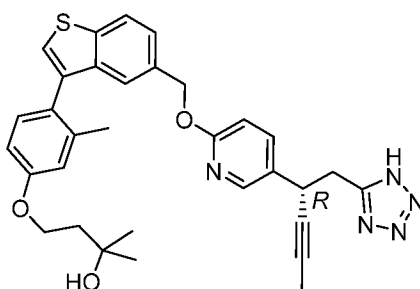
(F) (3*R*)-3-(6-((3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile was prepared from (3*R*)-3-(6-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-

ynamide following General Procedure I. LC/MS: mass calcd. for $C_{30}H_{28}N_2O_3S$: 496.18, found: 497.2 $[M+H]^+$.

(G) (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridine (Cpd 42) was prepared from (3*R*)-3-(6-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile following General Procedure J, using Workup 2. 1H NMR (CD_3OD) δ 8.03 (d, $J = 2.5$ Hz, 1H), 7.95 – 7.85 (m, 1H), 7.63-7.64 (m, 1H), 7.38 – 7.47 (m, 2H), 7.35 (s, 1H), 7.13 (d, $J = 8.3$ Hz, 1H), 6.91 (d, $J = 2.6$ Hz, 1H), 6.81-6.83 (m, 1H), 6.76 (d, $J = 8.6$ Hz, 1H), 5.36 (s, 2H), 4.06 – 4.20 (m, 3H), 3.41 (s, 1H), 3.24 – 3.35 (m, 1H), 2.05 (s, 3H), 1.98-1.99 (m, 2H), 1.79 (d, $J = 2.4$ Hz, 3H), 1.55-1.56 (m, 3H). LC/MS: mass calcd. for $C_{30}H_{29}N_5O_3S$: 539.20, found: 540.3 $[M+H]^+$.

Example 43

(2*R*)-4-(4-(5-(((5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)pyridin-2-yl)oxy)methyl)-benzo[*b*]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol, Cpd 43



(A) To a solution of 3-bromo-5-hydroxymethylbenzothiophene (1.0 g, 4.11 mmol) (from Example 1A) in DCM (20 mL) and DMF (1 mL) was added PBr_3 (1 mL, 10.6 mmol) in drop-wise fashion, and the resultant solution was stirred at rt for 1 h. Water (40 mL) was then added and the mixture was extracted with DCM (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford 3-bromo-5-(bromomethyl)-1-benzothiophene (1.1 g, 87 %) as colorless oil, which was used directly without further purification.

(B) A mixture of 3-bromo-5-(bromomethyl)-1-benzothiophene (1.1 g, 3.59 mmol), ethyl 3-(6-hydroxypyridin-3-yl)hex-4-ynoate (880 mg, 3.77 mmol) (from Example 40E) and Ag_2CO_3 (0.79g, 2.86 mmol) in toluene (30 mL) was stirred at 60 °C overnight. The mixture was then concentrated under reduced pressure and the resultant residue was purified directly by silica gel chromatography [EtOAc/ petroleum ether (0 – 11%) to provide ethyl 3-[6-[(3-bromo-1-benzothiophen-5-yl)methoxy]pyridin-3-yl]hex-4-ynoate (950 mg, 58 %) as light yellow oil. LC/MS: mass calcd for $\text{C}_{22}\text{H}_{20}\text{BrNO}_3\text{S}$: 458.37, found 458.2 $[\text{M}]^+$, 460.2 $[\text{M}+2]^+$.

(C) Ethyl 3-(6-[[3-(4-hydroxy-2-methylphenyl)-1-benzothiophen-5-yl]methoxy]pyridin-3-yl)hex-4-ynoate was prepared from ethyl 3-[6-[(3-bromo-1-benzothiophen-5-yl)methoxy]pyridin-3-yl]hex-4-ynoate and (4-hydroxy-2-methylphenyl)boronic acid following General Procedure A, using $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ as the palladium catalyst and Cs_2CO_3 in place of K_2CO_3 . LC/MS: mass calcd for $\text{C}_{29}\text{H}_{27}\text{NO}_4\text{S}$: 485.59, found 486.2 $[\text{M}+\text{H}]^+$.

(D) Ethyl 3-[6-([3-[4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)pyridin-3-yl]hex-4-ynoate was prepared from ethyl 3-(6-[[3-(4-hydroxy-2-methylphenyl)-1-benzothiophen-5-yl]methoxy]pyridin-3-yl)hex-4-ynoate and 3-methylbutane-1,3-diol following General Procedure B using PBU_3 and ADDP with toluene as solvent and a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for $\text{C}_{34}\text{H}_{37}\text{NO}_5\text{S}$: 571.73, found: 572.2 $[\text{M}+\text{H}]^+$.

(E) 3-[6-([3-[4-(3-Hydroxy-3-methylbutoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)pyridin-3-yl]hex-4-ynoic acid was prepared from ethyl 3-[6-([3-[4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl]-1-benzothiophen-5-yl]methoxy)pyridin-3-yl]hex-4-ynoate following General Procedure C, using LiOH as base, EtOH in place of MeOH, a rt reaction temperature overnight and 1N HCl for reaction acidification. Product purification was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% NH_4HCO_3) gradient (35 – 75%). ^1H NMR ($\text{DMSO}-d_6$) δ 8.10 (d, $J = 2.4$ Hz, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 7.70 (dd, $J = 8.4$ Hz, 2.4

Hz, 1H), 7.63 (s, 1H), 7.43 – 7.48 (m, 2H), 7.15 (d, $J = 8.4$ Hz, 1H), 6.93 (d, $J = 2.7$ Hz, 1H), 6.84 – 6.88 (m, 1H), 6.79 (d, $J = 8.7$ Hz, 1H), 5.40 (s, 2H), 4.14 (t, $J = 6.9$ Hz, 2H), 3.95 - 4.00 (m, 1H), 2.61 - 2.63 (m, 2H), 2.05 (s, 3H), 1.88 (t, $J = 7.2$ Hz, 2H), 1.77 (d, $J = 2.4$ Hz, 3H), 1.19 (s, 6H). LC/MS: mass calcd for $C_{32}H_{33}NO_5S$: 543.67, found 544.3 $[M+H]^+$.

(F) Enantiomeric resolution of 3-(6-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid was carried out by chiral chromatography on a ChiralPak AS-H 5 μ column (2 x 25 cm) using an isocratic mobile phase [hexane (0.1% HOAc) / EtOH (85:15); 20 mL/min] to afford (3*S*)-3-(6-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid (RT = 9.0 min) and (3*R*)-3-(6-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid (RT = 12.5 min).

(*S*-enantiomer): 1H NMR (DMSO- d_6) δ 8.10 (d, $J = 2.4$ Hz, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 7.70 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.63 (s, 1H), 7.43 - 7.48 (m, 2H), 7.15 (d, $J = 8.4$ Hz, 1H), 6.94 (d, $J = 2.7$ Hz, 1H), 6.85 - 6.88 (m, 1H), 6.79 (d, $J = 8.7$ Hz, 1H), 5.40 (s, 2H), 4.14 (t, $J = 6.9$ Hz, 2H), 3.95 - 4.05 (m, 1H), 2.61 - 2.73 (m, 2H), 2.05 (s, 3H), 1.88 (t, $J = 7.2$ Hz, 2H), 1.77 (d, $J = 2.4$ Hz, 3H), 1.19 (s, 6H). LC/MS: mass calcd. for $C_{32}H_{33}NO_5S$: 543.67, found: 541.9 $[M-H]^-$.

(*R*-enantiomer): 1H NMR (DMSO- d_6) δ 8.10 (d, $J = 2.4$ Hz, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 7.70 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.63 (s, 1H), 7.43 - 7.48 (m, 2H), 7.15 (d, $J = 8.4$ Hz, 1H), 6.94 (d, $J = 2.7$ Hz, 1H), 6.85 - 6.88 (m, 1H), 6.79 (d, $J = 8.7$ Hz, 1H), 5.40 (s, 2H), 4.14 (t, $J = 6.9$ Hz, 2H), 3.95 - 4.05 (m, 1H), 2.61 - 2.73 (m, 2H), 2.05 (s, 3H), 1.88 (t, $J = 7.2$ Hz, 2H), 1.77 (d, $J = 2.4$ Hz, 3H), 1.19 (s, 6H). LC/MS: mass calcd. for $C_{32}H_{33}NO_5S$: 543.67, found: 542.1 $[M-H]^-$.

(G) (3*R*)-3-(6-((3-(4-(3-Hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynamide was prepared from (3*R*)-3-(6-((3-(4-(3-hydroxy-

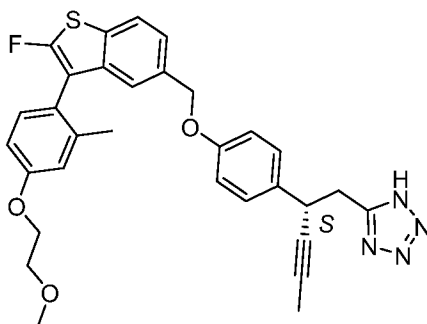
3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynoic acid following the procedure described in Example 6E. LC/MS: mass calcd. for C₃₂H₃₄N₂O₄S: 542.22, found: 543.3 [M+H]⁺.

(H) (3*R*)-3-(6-((3-(4-(3-Hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile was prepared from (3*R*)-3-(6-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₃₂H₃₂N₂O₃S: 524.21, found: 525.3 [M+H]⁺.

(I) (2*R*)-4-(4-(5-(((5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)pyridin-2-yl)oxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol (Cpd **43**) was prepared from (3*R*)-3-(6-((3-(4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)pyridin-3-yl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.96 (d, *J*=2.3 Hz, 1H), 7.91 (d, *J*=8.3 Hz, 1H), 7.61 (dd, *J*=8.6, 2.5 Hz, 1H), 7.44 (dd, *J*=8.4, 1.4 Hz, 1H), 7.37-7.41 (m, 2H), 7.18-7.26 (m, 1H), 7.00 (d, *J*=8.1 Hz, 1H), 6.86 (d, *J*=7.7 Hz, 1H), 6.73 (d, *J*=8.6 Hz, 1H), 5.34 (s, 2H), 4.19 (dd, *J*=5.4, 3.9 Hz, 2H), 4.06-4.13 (m, 1H), 3.78-3.84 (m, 2H), 3.45 (s, 3H), 3.12-3.28 (m, 2H), 1.95 (s, 3H), 1.77 (d, *J*=2.3 Hz, 3H), 0.88 (t, *J*=7.3 Hz, 3H). LC/MS: mass calcd. for C₃₂H₃₃N₅O₃S: 567.23, found: 568.3 [M+H]⁺.

Example 44

(2*S*)-5-(2-(4-((2-Fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **44**



(A) A solution of (3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol (from Example 8D) (1 g, 3.0 mmol), *tert*-butyldimethylsilyl chloride (690 mg, 4.6 mmol) and imidazole (625 mg, 9.2 mmol) in DCM (30 mL) was stirred at rt for 3 h. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated. The resultant residue was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford of *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane (1.0 g, 75%) as a colorless oil. LC/MS: mass calcd. for C₂₅H₃₄O₃SSi: 442.20, found: 311.1 [M-OTBS]⁺.

(B) *tert*-Butyl ((2-fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane was prepared from of *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane and N-fluoro-N-(phenylsulfonyl)benzenesulfonamide following the procedure described in Example 3A. LC/MS: mass calcd. for C₂₅H₃₃FO₃SSi: 460.19, found: 329.1 [M-OTBS]⁺.

(C) (2-Fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol was prepared from *tert*-butyl ((2-fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane following the procedure described in Example 2C, and was used directly without characterization.

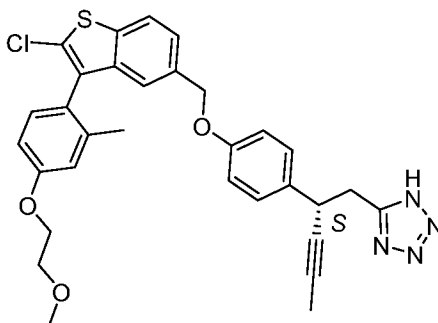
(D) 5-(Chloromethyl)-2-fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophene was prepared from (2-fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

(E) (3*S*)-3-(4-((2-Fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 5-(chloromethyl)-2-fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, at a reaction temperature of 60 °C overnight, and was used directly without characterization.

(F) (2*S*)-5-(2-(4-((2-Fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd 44) was prepared from (3*S*)-3-(4-((2-fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.92 (s, 1H), 6.83 - 6.86 (m, 3H), 5.06 (s, 2H), 4.12 - 4.15 (m, 2H), 4.02 (br. s, 1H), 3.73 - 3.76 (m, 2H), 3.42 (s, 3H), 3.23 (d, *J* = 7.2 Hz, 2H), 2.06 (s, 3H), 1.74 (s, 3H). LC/MS: mass calcd. for C₃₁H₂₉FN₄O₃S: 556.19, found: 557.1 [M+H]⁺.

Example 45

(2*S*)-5-(2-(4-((2-Chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 45



(A) *tert*-Butyl((2-chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane was prepared from *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane (from Example 44A) and NCS following the procedure described in Example 2B. LC/MS: mass calcd. for C₂₅H₃₃ClO₃SSi: 476.16, found: 344.9 [M-OTBS]⁺.

(B) (2-Chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol was prepared from *tert*-butyl((2-chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane following the procedure described in Example 2C. LC/MS: mass calcd. for C₁₉H₁₉ClO₃S: 362.07, found: 344.9[M-OH]⁺.

(C) 2-Chloro-5-(chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophene was prepared from (2-chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

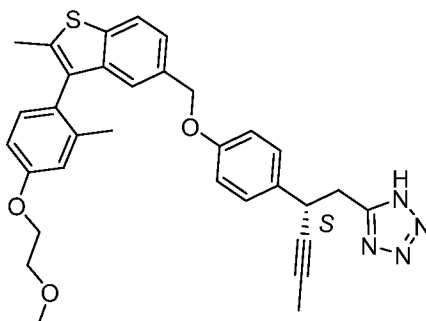
(D) (3*S*)-3-(4-((2-Chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 2-chloro-5-(chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₃₁H₂₈ClNO₃S: 529.15, found: 547.0 [M+NH₄]⁺.

(E) (2*S*)-5-(2-(4-((2-Chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **45**) was prepared from (3*S*)-3-(4-((2-chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* =

8.4 Hz, 1H), 7.16 - 7.19 (m, 3H), 7.05 (d, $J = 8.4$ Hz, 1H), 6.83 - 6.93 (m, 4H), 5.06 (s, 2H), 4.14 - 4.17 (m, 2H), 4.02 (br. s, 1H), 3.74 - 3.77 (m, 2H), 3.42 (s, 3H), 3.22 (d, $J = 7.5$ Hz, 2H), 1.98 (s, 3H), 1.74 (s, 3H). LC/MS: mass calcd. for $C_{31}H_{29}ClN_4O_3S$: 572.16, found: 573.0 $[M+H]^+$.

Example 46

(2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 46



(A) To a cooled (-78 °C) solution of *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)dimethylsilane (from Example 44A) (300 mg, 0.68 mmol) in THF (10 mL), maintained under an inert atmosphere of nitrogen, was added LDA (2.0 M in THF; 0.68 mL, 1.36 mmol). Iodomethane (290 mg, 2.04 mmol) was then added and the resultant mixture was stirred at -78 °C for 2 h. The reaction was then quenched by the addition of satd. aq NaCl, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resultant residue was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-methylbenzo[*b*]thiophen-5-yl)methoxy)dimethylsilane (220 mg, 71%) as a colorless oil. LC/MS: mass calcd. for $C_{26}H_{36}O_3SSi$: 456.22, found: 324.9 $[M-OTBS]^+$.

(B) (3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-methylbenzo[*b*]thiophen-5-yl)methanol was prepared from *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-

methylbenzo[b]thiophen-5-yl)methoxy)dimethylsilane following the procedure described in Example 2C. LC/MS: mass calcd. for C₂₀H₂₂O₃S: 342.13, found: 325.0 [M-OH]⁺.

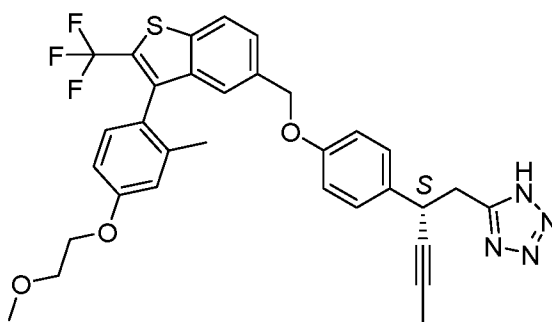
(C) 5-(Chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophene was prepared from (3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophen-5-yl)methanol following General Procedure D.

(D) (3*S*)-3-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 5-(chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, using K₂CO₃ in place of Cs₂CO₃ at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₃₂H₃₁NO₃S: 509.20, found: 527.1 [M+NH₄]⁺.

(E) (2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **46**) was prepared from (3*S*)-3-(4-((3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CD₃OD) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.10 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H), 6.82 - 6.85 (m, 3H), 5.02 (s, 2H), 4.12 - 4.15 (m, 2H), 4.03 (br. s, 1H), 3.73 - 3.76 (m, 2H), 3.42 (s, 3H), 3.22 (d, *J* = 7.5 Hz, 2H), 2.28 (s, 3H), 1.98 (s, 3H), 1.74 (s, 3H). LC/MS: mass calcd. for C₃₂H₃₂N₄O₃S: 552.22, found: 553.1 [M+H]⁺.

Example 47

5-((2*S*)-2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **47**



(A) To a solution of *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)dimethylsilane (Example 44A) (300 mg, 0.68 mmol) in THF (6 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 0.54 mL, 1.36 mmol) in dropwise fashion, and the resultant mixture was stirred at -78 °C for 10 min. At this time, a solution of triisopropoxyborane (510 mg, 2.71 mmol) in THF (2 mL) was added in dropwise fashion. The resultant mixture was stirred at -78 °C for 30 min and at rt for 1 h. The reaction was then quenched by the addition of water (10 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and the filtrate concentrated under reduced pressure to afford 5-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-2-ylboronic acid (250 mg) as a colorless oil, which was used in the next step without further purification. LC/MS: mass calcd. for C₂₅H₃₅BO₅SSi: 486.21, found: 354.9 [M-OTBS]⁺.

(B) To an ice-cooled mixture of 5-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-2-ylboronic acid (250 mg, 0.51 mmol), sodium trifluoromethanesulfinate (241 mg, 1.544 mmol), copper(I) chloride (51 mg, 0.515 mmol), DCM (5 mL), MeOH (5 mL) and water (4 mL) was added 2-hydroperoxy-2-methylpropane (232 mg, 2.574 mmol) in a dropwise fashion, and the resultant mixture was stirred at rt overnight. The reaction was then quenched by the addition of water (15 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and the filtrate concentrated under reduced pressure. The

resultant residue was purified by column chromatography on silica gel (0-10% EtOAc/petroleum ether) to afford *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane (200 mg, 76%) as a colorless oil. LC/MS: mass calcd. for C₂₆H₃₃F₃O₃SSi: 510.19, found: 378.9 [M-OTBS]⁺.

(C) (3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methanol was prepared from *tert*-butyl((3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)dimethylsilane following the procedure described in Example 2C. LC/MS: mass calcd. for C₂₀H₁₉F₃O₃S: 396.10, found: 378.8 [M-OH]⁺.

(D) 5-(Chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophene was prepared from (3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methanol following General Procedure D.

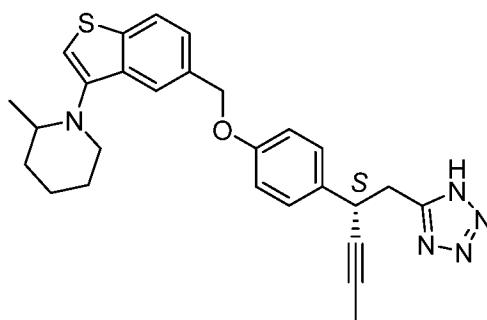
(E) (3*S*)-3-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from 5-(chloromethyl)-3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophene and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure E, at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₃₂H₂₈F₃NO₃S: 563.17, found: 581.0[M+NH₄]⁺.

(F) 5-((2*S*)-2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd 47) was prepared from (3*S*)-3-(4-((3-(4-(2-methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm)

using an acetonitrile / water (0.05% NH_4HCO_3) gradient (45 – 85%). ^1H NMR (CD_3OD) δ 8.00 (d, $J = 8.4$ Hz, 1H), 7.58 (d, $J = 8.7$ Hz, 1H), 7.16 - 7.24 (m, 3H), 7.06 (d, $J = 8.4$ Hz, 1H), 6.82 - 6.92 (m, 4H), 5.10 (s, 2H), 4.15 - 4.18 (m, 2H), 4.00 - 4.05 (m, 1H), 3.75 - 3.78 (m, 2H), 3.43 (s, 3H), 3.19 - 3.24 (m, 2H), 1.88 (d, $J = 3.6$ Hz, 3H), 1.74 - 1.76 (m, 3H). LC/MS: mass calcd. for $\text{C}_{32}\text{H}_{29}\text{F}_3\text{N}_4\text{O}_3\text{S}$: 606.19, found: 606.95 $[\text{M}+\text{H}]^+$.

Example 48

1-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-methylpiperidine, Cpd **48**



(A) To a solution of methyl 3-bromobenzo[*b*]thiophene-5-carboxylate (8.0 g, 29.5 mmol) in DCM (50 mL) and TFA (50 mL) was added H_2O_2 (30% in water; 3.35 mL, 29.5 mmol). After the mixture was stirred at rt overnight, water (100 mL) was added and the mixture was extracted with DCM (3 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-35% EtOAc/petroleum ether) to afford methyl 3-bromobenzo[*b*]thiophene-5-carboxylate 1,1-dioxide (7.5 g, 84%) as a light yellow solid. LC/MS: mass calcd. for $\text{C}_{10}\text{H}_7\text{BrO}_4\text{S}$: 301.92, found: 302.0, 304.0 $[\text{M}, \text{M}+2]^+$.

(B) To a solution of methyl 3-bromobenzo[*b*]thiophene-5-carboxylate 1,1-dioxide (700 mg, 2.31 mmol) in toluene (10 mL) was added 2-methylpiperidine (914 mg, 9.22 mmol) and the resulting mixture was stirred at 120 °C overnight. After cooling to rt, water (70 mL) was added and the mixture was extracted with EtOAc (3 x 70 mL). The combined

organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the resultant residue was purified by silica gel chromatography (0-40% EtOAc/petroleum ether) to afford methyl 3-(2-methylpiperidin-1-yl)benzo[*b*]thiophene-5-carboxylate 1,1-dioxide (600 mg, 48%) as light yellow oil. LC/MS: mass calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_4\text{S}$: 321.10, found: 322.0 $[\text{M}+\text{H}]^+$.

(C) To an ice-cooled solution of methyl 3-(2-methylpiperidin-1-yl)benzo[*b*]thiophene-5-carboxylate 1,1-dioxide (600 mg, 1.87 mmol) in THF (10 mL) under argon was added diisobutylaluminum hydride (1 M in DCM; 11.2 mL, 11.2 mmol) in drop-wise fashion. After stirring at rt for 4 h, satd. aq potassium sodium tartrate solution (60 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-25% EtOAc/heptane) to give (3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methanol (280 mg, 55%) as light yellow oil. LC/MS: mass calcd. for $\text{C}_{15}\text{H}_{19}\text{NOS}$: 261.12, found: 262.1 $[\text{M}+\text{H}]^+$.

(D) Ethyl (3*S*)-3-(4-((3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from (3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methanol and (3*S*)-ethyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Synnovator, Inc., Research Triangle Park, N.C.; Cat. # PB05708) following General Procedure B, using ADDP and Bu_3P at a reaction temperature of 60 °C for 1 h. LC/MS: mass calcd. for $\text{C}_{29}\text{H}_{33}\text{NO}_3\text{S}$: 475.22, found: 476.2 $[\text{M}+\text{H}]^+$.

(E) (3*S*)-3-(4-((3-(2-Methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from ethyl (3*S*)-3-(4-((3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using EtOH in place of MeOH, and LiOH (10 eq.) as base. LC/MS: mass calcd. for $\text{C}_{27}\text{H}_{29}\text{NO}_3\text{S}$: 447.19, found: 448.1 $[\text{M}+\text{H}]^+$.

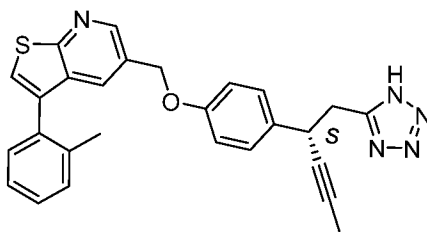
(F) (3*S*)-*N*-(2-Cyanoethyl)-3-(4-((3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*S*)-3-(4-((3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following the method described in Example 37B. LC/MS: mass calcd. for C₃₀H₃₃N₃O₂S: 499.23, found: 500.3 [M+H]⁺.

(G) 3-(5-((2*S*)-2-(4-((3-(2-Methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile was prepared from (3*S*)-*N*-(2-Cyanoethyl)-3-(4-((3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following the method described in Example 37C. LC/MS: mass calcd. for C₃₀H₃₂N₆OS: 524.24, found: 525.3 [M+H]⁺.

(H) 1-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-methylpiperidine (Cpd **48**) was prepared from 3-(5-((2*S*)-2-(4-((3-(2-methylpiperidin-1-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile following the method described in Example 37K. Product purification was carried out by preparative HPLC (Phenomenex C18 column, 5μm, 100 x 30 mm, 20-70% MeCN/H₂O (0.1%TFA v/v) over 16 min). Product-containing fractions were pooled, and partially concentrated to remove the organic solvent. The remaining aqueous solution was neutralized with satd. aq NaHCO₃ and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated to provide the title compound as a white solid. ¹H NMR (CDCl₃) δ 11.84 (br. s, 1H), 7.79 (s, 1H), 7.75 (dd, *J*=8.1, 2.0 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.18 (br. d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.1 Hz, 2H), 6.78 (d, *J*=3.0 Hz, 1H), 5.10 (s, 2H), 4.02-4.09 (m, 1H), 3.45 (br. s, 1H), 3.22-3.38 (m, 3H), 2.68-2.80 (m, 1H), 1.90-1.98 (m, 1H), 1.64-1.80 (m, 3H), 1.48-1.58 (m, 2H), 0.06 (dd, *J*=6.6, 1.0 Hz, 3H). LC/MS: mass calcd. for C₂₇H₂₉N₅OS: 471.21, found: 472.2 [M+H]⁺.

Example 49

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*b*]pyridine, Cpd **49**



(A) To a solution of 5-bromo-2-fluoronicotinaldehyde (6.0 g, 29.4 mmol) and ethyl 2-mercaptoacetate (4.2 g, 34.9 mmol) in THF (10 mL) was added NaH (60% in mineral oil, 2.4 g, 60.0 mmol,) in portions at 0 °C. The reaction mixture was refluxed for 3 h, then cooled to rt, and quenched with water (100 mL). The resulting solution was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford ethyl 5-bromothieno[2,3-*b*]pyridine-2-carboxylate (2.4 g, 28% yield), as light yellow oil. LC/MS: mass calcd. for C₁₀H₈BrNO₂S: 284.95, found: 285.9, 287.9 [M+H, M+H+2]⁺.

(B) 5-Bromothieno[2,3-*b*]pyridine-2-carboxylic acid was prepared from ethyl 5-bromothieno[2,3-*b*]pyridine-2-carboxylate following General Procedure C, using EtOH in place of MeOH, and LiOH as base. After the acidification step with 1N HCl, the precipitates were collected by filtration and dried under vacuum. LC/MS: mass calcd. for C₈H₄BrNO₂S: 256.91, found: 257.8, 259.8 [M+H, M+H+2]⁺.

(C) To a solution of 5-bromothieno[2,3-*b*]pyridine-2-carboxylic acid (6.6 g, 25.6 mmol) in DMA (50 mL) was added DBU (12.8 g, 84.1 mmol) and the resulting mixture was stirred at 150 °C overnight. After cooling to rt, the reaction was quenched with H₂O (100 mL) and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford 5-bromothieno[2,3-*b*]pyridine (3.3 g, 60%), as a white solid. LC/MS: mass calcd. for C₇H₄BrNS: 212.92, found: 213.8, 215.8 [M+H, M+H+2]⁺.

(D) To an ice-cooled solution of 5-bromothieno[2,3-*b*]pyridine (2.9 g, 13.5 mmol) in THF (30 mL) was added isopropylmagnesium chloride - lithium chloride complex (1.3M in THF; 31 mL, 40.3 mmol) in a drop-wise fashion with stirring at 0 °C. After stirring overnight at rt, the reaction was quenched by addition of DMF (3 mL) and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford thieno[2,3-*b*]pyridine-5-carbaldehyde (1.5 g, 67%), as light yellow oil. LC/MS: mass calcd. for C₈H₅NOS: 163.01, found: 163.8 [M+H]⁺.

(E) To a solution of thieno[2,3-*b*]pyridine-5-carbaldehyde (1.4 g, 8.58 mmol) in CHCl₃ (30 mL) under nitrogen was added bromine (5.5 g, 34.4 mmol) and the resulting solution was stirred at 70 °C overnight. After cooling to rt, the reaction was quenched with H₂O (50 mL) and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to afford 3-bromothieno[2,3-*b*]pyridine-5-carbaldehyde (500 mg, 19%), as light yellow oil. LC/MS: mass calcd. for C₈H₄BrNOS: 240.92, found: 241.8, 243.8 [M+H, M+H+2]⁺.

(F) (3-Bromothieno[2,3-*b*]pyridin-5-yl)methanol was prepared from 3-bromothieno[2,3-*b*]pyridine-5-carbaldehyde following General Procedure F. LC/MS: mass calcd. for C₈H₆BrNOS: 242.94, found: 243.9, 245.9 [M+H, M+H+2]⁺.

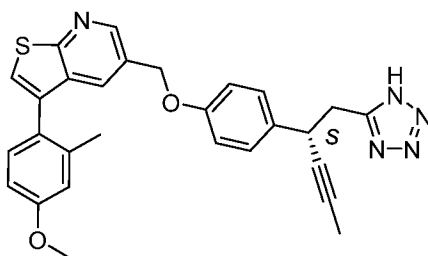
(G) (3*S*)-3-(4-((3-Bromothieno[2,3-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3-bromothieno[2,3-*b*]pyridin-5-yl)methanol and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure B, using ADDP and Bu₃P at a reaction temperature of 60 °C for 2 h. LC/MS: mass calcd. for C₂₀H₁₅BrN₂OS: 410.01, found: 411.2, 413.2 [M+H, M+H+2]⁺.

(H) (3*S*)-3-(4-((3-(2-Methylphenyl)thieno[2,3-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-bromothieno[2,3-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile and 2-methylphenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ as the base. LC/MS: mass calcd. for C₂₇H₂₂N₂OS: 422.15, found: 423.3 [M+H]⁺.

(I) (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*b*]pyridine (Cpd 49) was prepared from (3*S*)-3-(4-((3-(2-methylphenyl)thieno[2,3-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 1. ¹H NMR (DMSO-*d*₆) δ 8.71 (d, *J* = 1.6 Hz, 1H), 7.89 (s, 1H), 7.84 (d, *J* = 1.6 Hz, 1H), 7.25 - 7.42 (m, 4H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.24 (s, 2H), 4.08 - 4.10 (m, 1H), 3.22 (d, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 1.74 (d, *J* = 2.0 Hz, 3H). LC/MS: mass calcd. for C₂₇H₂₃N₅OS: 465.16, found: 466.05 [M+H]⁺.

Example 50

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*b*]pyridine, Cpd 50



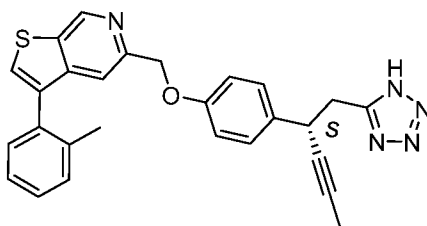
(A) (3*S*)-3-(4-((3-(4-Methoxy-2-methylphenyl)thieno[2,3-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-bromothieno[2,3-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile (from Example 49G) and 4-methoxy-2-methylphenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as

the palladium catalyst and Cs_2CO_3 as the base. LC/MS: mass calcd. for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$: 452.16, found: 453.2 $[\text{M}+\text{H}]^+$.

(B) (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*b*]pyridine was prepared from (3*S*)-3-(4-((3-(4-methoxy-2-methylphenyl)thieno[2,3-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 1. ^1H NMR ($\text{DMSO}-d_6$) δ 8.69 (d, $J = 2.0$ Hz, 1H), 7.80 - 7.83 (m, 2H), 7.19 - 7.24 (m, 3H), 6.88 - 6.97 (m, 4H), 5.23 (s, 2H), 4.05 - 4.12 (m, 1H), 3.81 (s, 3H), 3.05 - 3.15 (m, 2H), 2.10 (s, 3H), 1.73 (d, $J = 2.0$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2\text{S}$: 495.17, found: 496.1 $[\text{M}+\text{H}]^+$.

Example 51

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*c*]pyridine, Cpd **51**



(A) A solution of methyl 2-acetamido-2-(dimethoxyphosphoryl)acetate (8.45 g, 35.3 mmol) and DBU (5.38 g, 35.3 mmol) in DCM (50 mL) was added in drop-wise fashion to an ice-cooled solution of 2,3-thiophene dicarboxaldehyde (4.5 g, 32.1 mmol) in DCM (150 mL). After stirring at 0 °C for 1 h, the mixture was allowed to stir at rt overnight. The reaction was then concentrated under reduced pressure and the resultant residue was purified by silica gel chromatography (0-50% EtOAc/petroleum ether) to afford of methyl thieno[2,3-*c*]pyridine-5-carboxylate (3.3 g, 54%), as a white solid. LC/MS: mass calcd. for $\text{C}_9\text{H}_7\text{NO}_2\text{S}$: 193.02, found: 193.9 $[\text{M}+\text{H}]^+$.

(B) To a solution of methyl thieno[2,3-*c*]pyridine-5-carboxylate (3.1 g, 16.0 mmol) in CHCl_3 (100 mL) was added bromine (7.7 g, 48.1 mmol) and the resulting solution was stirred at 70 °C overnight. After cooling to rt, the reaction was quenched with 10% aq.

Na₂S₂O₃ (50 mL) and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (0-50% EtOAc/petroleum ether) to afford methyl 3-bromothieno[2,3-*c*]pyridine-5-carboxylate (3.8 g, 87%), as an off-white solid. LC/MS: mass calcd. for C₉H₆BrNO₂S: 270.93, found: 271.9, 274.0 [M+H, M+H+2]⁺.

(C) To a cooled (-30 °C) solution of methyl 3-bromothieno[2,3-*c*]pyridine-5-carboxylate (3.6 g, 13.2 mmol) in THF (100 mL) under an inert nitrogen atmosphere was added diisobutylaluminum hydride (1 M in hexane; 66 mL, 66 mmol) in drop-wise fashion. After stirring at rt for 1 h, the reaction was quenched by the addition of 1M aq. potassium sodium tartrate solution (50 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-50% EtOAc/heptane) to give (3-bromothieno[2,3-*c*]pyridin-5-yl)methanol (1.5 g, 45%), as yellow oil. LC/MS: mass calcd. for C₈H₆BrNOS: 242.94, found: 243.8, 245.8 [M+H, M+H+2]⁺.

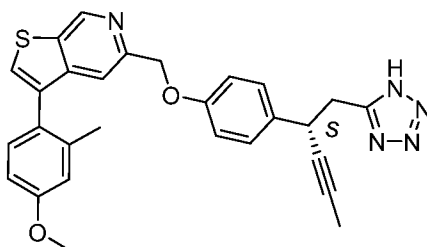
(D) (3*S*)-3-(4-((3-Bromothieno[2,3-*c*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3-bromothieno[2,3-*c*]pyridin-5-yl)methanol and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure B, using ADDP and Bu₃P at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for C₂₀H₁₅BrN₂OS: 410.01, found: 411.2, 413.1 [M+H, M+H+2]⁺.

(E) (3*S*)-3-(4-((3-(2-Methylphenyl)thieno[2,3-*c*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-bromothieno[2,3-*c*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile and 2-methylphenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ as the base. LC/MS: mass calcd. for C₂₇H₂₂N₂OS: 422.15, found: 423.2 [M+H]⁺.

(F) (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*c*]pyridine (Cpd **51**) was prepared from (3*S*)-3-(4-((3-(2-methylphenyl)thieno[2,3-*c*]pyridin-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 1. ¹H NMR (DMSO-*d*₆) δ 9.32 (s, 1H), 8.06 (s, 1H), 7.34 - 7.43 (m, 3H), 7.27 - 7.34 (m, 1H), 7.22 (m, 3H), 6.87 - 6.94 (m, 2H), 5.24 (s, 2H), 4.07 - 4.11 (m, 1H), 3.21 (d, *J* = 7.8 Hz, 2H), 2.01 (s, 3H), 1.71 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₂₇H₂₃N₅OS: 465.16, found: 466.2 [M+H]⁺.

Example 52

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*c*]pyridine, Cpd **52**



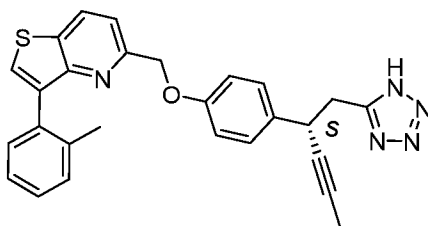
(A) (3*S*)-3-(4-((3-(4-Methoxy-2-methylphenyl)thieno[2,3-*c*]pyridin-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-bromothieno[2,3-*c*]pyridin-5-yl)methoxy)phenyl)hex-4-yne nitrile (from Example 51D) and 4-methoxy-2-methylphenylboronic acid following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ as the base. LC/MS: mass calcd. for C₂₈H₂₄N₂O₂S: 452.16, found: 453.4 [M+H]⁺.

(B) (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*c*]pyridine (Cpd **52**) was prepared from (3*S*)-3-(4-((3-(4-methoxy-2-methylphenyl)thieno[2,3-*c*]pyridin-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 1. ¹H NMR (DMSO-*d*₆) δ 9.30 (d, *J* = 1.0 Hz, 1H), 8.00 (s, 1H), 7.42 (d, *J* = 1.0 Hz, 1H), 7.20 - 7.26 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.90 - 6.97 (m, 3H), 6.87 - 6.97 (m, 1H), 5.24 (s, 2H), 4.08 - 4.09 (m, 1H), 3.80 (s,

3H), 3.21 (d, $J = 7.7$ Hz, 2H), 2.01 (s, 3H), 1.72 (d, $J = 2.4$ Hz, 3H). LC/MS: mass calcd. for $C_{28}H_{25}N_5O_2S$: 495.17, found: 496.2 $[M+H]^+$.

Example 53

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[3,2-*b*]pyridine, Cpd **53**



(A) A mixture of 5-chlorothieno[3,2-*b*]pyridine (1.8 g, 10.6 mmol), $PdCl_2(dppf) \cdot CH_2Cl_2$ (866 mg, 1.06 mmol) and Et_3N (3 mL) in MeOH (15 mL) was stirred overnight at 110 °C under an atmosphere of CO (g) (60 atm). After cooling to rt, the reaction was quenched by the addition of satd. aq NH_4Cl (50 mL) and the resulting solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (0-25% EtOAc/petroleum ether) to afford methyl thieno[3,2-*b*]pyridine-5-carboxylate (1.7 g, 82%), as a yellow solid. LC/MS: mass calcd. for $C_9H_7NO_2S$: 193.02, found: 193.8 $[M+H]^+$.

(B) Methyl 3-bromothieno[3,2-*b*]pyridine-5-carboxylate was prepared from methyl thieno[3,2-*b*]pyridine-5-carboxylate following the methods described in Example 51B. LC/MS: mass calcd. for $C_9H_6BrNO_2S$: 270.93, found: 271.8, 273.8 $[M+H, M+H+2]^+$.

(C) (3-Bromothieno[3,2-*b*]pyridin-5-yl)methanol was prepared from methyl 3-bromothieno[3,2-*b*]pyridine-5-carboxylate following the methods described in Example 51C. LC/MS: mass calcd. for C_8H_6BrNOS : 242.94, found: 243.8, 245.8 $[M+H, M+H+2]^+$.

(D) (3*S*)-3-(4-((3-Bromothieno[3,2-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3-bromothieno[3,2-*b*]pyridin-5-yl)methanol and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure B, using

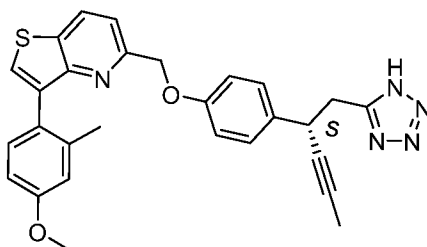
ADDP and Bu_3P at a reaction temperature of 60 °C overnight. LC/MS: mass calcd. for $\text{C}_{20}\text{H}_{15}\text{BrN}_2\text{OS}$: 410.01, found: 412.8 $[\text{M}+\text{H}+2]^+$.

(E) (3*S*)-3-(4-((3-(2-Methylphenyl)thieno[3,2-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-bromothieno[3,2-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile and 2-methylphenylboronic acid following General Procedure A, using $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ as the palladium catalyst and Cs_2CO_3 as the base. LC/MS: mass calcd. for $\text{C}_{27}\text{H}_{22}\text{N}_2\text{OS}$: 422.15, found: 423.2 $[\text{M}+\text{H}]^+$.

(F) (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[3,2-*b*]pyridine (Cpd **53**) was prepared from (3*S*)-3-(4-((3-(2-methylphenyl)thieno[3,2-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 1. ^1H NMR ($\text{DMSO}-d_6$) δ 8.57 (d, $J = 8.3$ Hz, 1H), 8.10 (s, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.21 - 7.37 (m, 6H), 6.94 - 7.01 (m, 2H), 5.20 (s, 2H), 4.05 - 4.14 (m, 1H), 3.22 (d, $J = 7.7$ Hz, 2H), 2.16 (s, 3H), 1.74 (d, $J = 2.4$ Hz, 3H). LC/MS: mass calcd. for $\text{C}_{27}\text{H}_{23}\text{N}_5\text{OS}$: 465.16, found: 466.2 $[\text{M}+\text{H}]^+$.

Example 54

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[3,2-*b*]pyridine, Cpd **54**

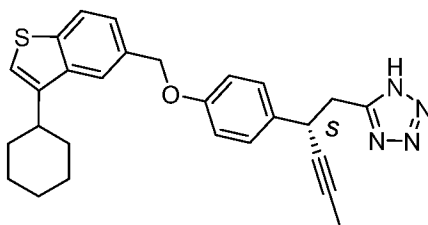


(A) (3*S*)-3-(4-((3-(4-Methoxy-2-methylphenyl)thieno[3,2-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-bromothieno[3,2-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-ynenitrile (from Example 53D) and 4-methoxy-2-methylphenylboronic acid following General Procedure A, using $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ as the palladium catalyst and Cs_2CO_3 as the base. LC/MS: mass calcd. for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$: 452.16, found: 453.2 $[\text{M}+\text{H}]^+$.

(B) (2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[3,2-*b*]pyridine (Cpd **54**) was prepared from (3*S*)-3-(4-((3-(4-methoxy-2-methylphenyl)thieno[3,2-*b*]pyridin-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 1. ¹H NMR (DMSO-*d*₆) δ 8.54 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.22 - 7.24 (m, 3H), 6.95 - 6.98 (m, 2H), 6.92 (d, *J* = 2.7 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.20 (s, 2H), 4.01 - 4.18 (m, 1H), 3.80 (s, 3H), 3.20 (d, *J* = 7.7 Hz, 2H), 2.14 (s, 3H), 1.73 (d, *J* = 2.4 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₅N₅O₂S: 495.17, found: 496.3 [M+H]⁺.

Example 55

(2*S*)-5-(2-(4-((3-Cyclohexylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **55**



(A) (3*S*)-3-(4-((3-Bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3-bromobenzo[*b*]thiophen-5-yl)methanol (from Example 1A) and (3*S*)-3-(4-hydroxyphenyl)hex-4-yne nitrile (from Example 2G) following General Procedure B, using ADDP and Bu₃P, at a reaction temperature of 60 °C overnight. ¹H NMR (DMSO-*d*₆) δ 8.02 - 8.15 (m, 2H), 7.81 - 7.88 (m, 1H), 7.56 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.28 - 7.41 (m, 2H), 7.00 - 7.09 (m, 2H), 5.29 (s, 2H), 3.94 - 4.16 (m, 1H), 2.84 - 3.03 (m, 2H), 1.85 (d, *J* = 2.4 Hz, 3H).

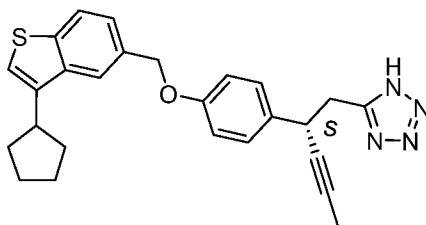
(B) To an ice-cooled solution of (3*S*)-3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile (500 mg, 1.22 mmol) in THF (2 ml) was added PdCl₂(dppf)·CH₂Cl₂ (100 mg, 0.123 mmol), followed by the addition of cyclohexylzinc (II) bromide (0.5M in THF; 7.3 mL, 3.65 mmol). After stirring at 60 °C for 2 h, the reaction was quenched with water (20 mL) and the resulting mixture was extracted with

EtOAc (3 x 20 mL). The combined organic extracts were concentrated under reduced pressure and the resultant residue was purified by silica gel chromatography (0-40% EtOAc/petroleum ether) to afford (3*S*)-3-(4-((3-cyclohexylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile (130 mg, 15%), as a yellow oil. LC/MS: mass calcd. for C₂₇H₂₇NOS: 413.18, found: 414.4 [M+H]⁺.

(C) (2*S*)-5-(2-(4-((3-Cyclohexylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **55**) was prepared from (3*S*)-3-(4-((3-cyclohexylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (55 – 75%). ¹H NMR (DMSO-*d*₆) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.42 (d, *J* = 9.7 Hz, 2H), 7.24 - 7.26 (m, 2H), 6.97 - 6.99 (m, 2H), 5.21 (s, 2H), 3.96 - 4.10 (m, 1H), 3.23 (d, *J* = 7.8 Hz, 2H), 2.85 - 2.93 (m, 1H), 1.96 - 1.98 (m, 2H), 1.62 - 1.89 (m, 6H), 1.43 - 1.49 (m, 4H), 1.25 - 1.28 (m, 1H). LC/MS: mass calcd. for C₂₇H₂₈N₄OS: 456.20, found: 457.5 [M+H]⁺.

Example 56

(2*S*)-5-(2-(4-((3-Cyclopentylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **56**

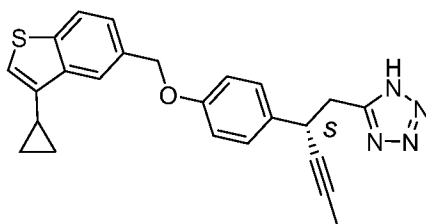


(A) (3*S*)-3-(4-((3-Cyclopentylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*S*)-3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile (from Example 55A) and cyclopentylzinc (II) bromide using the methods described in Example 55B. LC/MS: mass calcd. for C₂₆H₂₅NOS: 399.17, found: 422.3 [M+Na]⁺.

(B) (2*S*)-5-(2-(4-((3-Cyclopentylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **56**) was prepared from (3*S*)-3-(4-((3-cyclopentylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2. Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (55 – 75%). ¹H NMR (DMSO-*d*₆) δ 7.92 - 7.97 (m, 2H), 7.43 (d, *J* = 9.5 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.21 (s, 2H), 4.05 - 4.16 (m, 1H), 3.23 - 3.25 (m, 1H), 1.54 - 1.77 (m, 9H). LC/MS: mass calcd. for C₂₆H₂₆N₄OS: 442.18, found: 443.4 [M+H]⁺.

Example 57

(2*S*)-5-(2-(4-((3-Cyclopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **57**



(A) (3*S*)-3-(4-((3-Cyclopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from (3*S*)-3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile (from Example 55A) and 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General Procedure A, using PdCl₂(dppf)·CH₂Cl₂ as the palladium catalyst and Cs₂CO₃ as the base. ¹H NMR (CDCl₃) δ 7.89 - 8.03 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.39 - 7.49 (m, 1H), 7.30 - 7.37 (m, 2H), 6.94 - 7.05 (m, 3H), 5.20 (s, 2H), 3.90 - 3.96 (m, 1H), 2.72 (dd, *J* = 6.7, 2.2 Hz, 2H), 2.03 - 2.06 (m, 1H), 1.89 (d, *J* = 2.4 Hz, 3H), 0.95 - 1.00 (m, 2H), 0.68 - 0.74 (m, 2H).

(B) (2*S*)-5-(2-(4-((3-Cyclopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **57**) was prepared from (3*S*)-3-(4-((3-cyclopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 2.

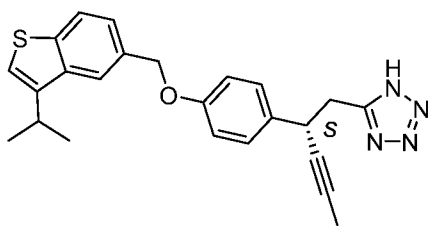
Additional purification of the product was carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (55 – 75%). ¹H NMR (DMSO-*d*₆) δ 8.03 (d, J = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.45 (dd, J₁ = 8.2 Hz, J₂ = 1.6 Hz, 1H), 7.29 (s, 1H), 7.20 - 7.22 (m, 2H), 6.93 - 6.95 (m, 2H), 5.20 (s, 2H), 4.06 - 4.08 (m, 1H), 3.07 - 3.12 (m, 1H), 2.96 - 3.07 (m, 1H), 2.09 - 2.15 (m, 1H), 1.73 (d, J = 2.4 Hz, 3H), 0.98 - 1.17 (m, 2H), 0.95 - 0.97 (m, 2H). LC/MS: mass calcd. for C₂₄H₂₂N₄OS: 414.15, found: 415.3 [M+H]⁺.

Examples 58 and 59

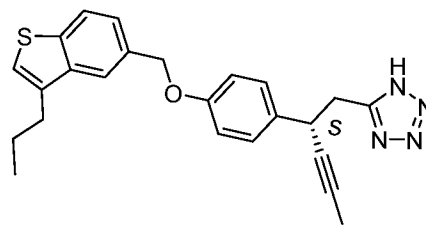
(2*S*)-5-(2-(4-((3-Isopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **58**

and

(2*S*)-5-(2-(4-((3-Propylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **59**



Cpd **58**



Cpd **59**

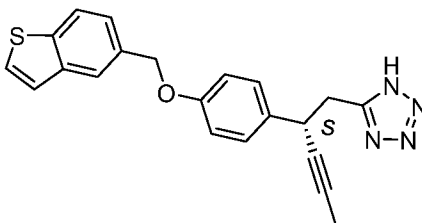
(A) (3*S*)-3-(4-((3-Isopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile and (3*S*)-3-(4-((3-propylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile were obtained as a mixture from (3*S*)-3-(4-((3-bromobenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile (from Example 55A) and isopropylzinc (II) bromide using the methods described in Example 55B. They were carried forward to next step as an unseparated mixture.

(B) (2*S*)-5-(2-(4-((3-Isopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **58**) and (2*S*)-5-(2-(4-((3-propylbenzo[*b*]thiophen-5-

yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **59**) were prepared from a mixture of (3*S*)-3-(4-((3-isopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile and (3*S*)-3-(4-((3-propylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile, following General Procedure J, using Workup 2. Additional purification of the products were carried out by preparative HPLC on a Waters SunFire™ Prep C18, 5 μ column (19 x 100 mm) using an acetonitrile / water (0.05% TFA) gradient (55 – 75%). Cpd **58**: ¹H NMR (DMSO-*d*₆) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.40 - 7.46 (m, 2H), 7.22 - 7.28 (m, 2H), 6.96 - 7.02 (m, 2H), 5.21 (s, 2H), 4.08 - 4.12 (m, 1H), 3.16 - 3.37 (m, 3H), 1.74 (d, *J* = 2.4 Hz, 3H), 1.31 (d, *J* = 6.8 Hz, 6H). LC/MS: mass calcd. for C₂₄H₂₄N₄OS: 416.17, found: 417.3 [M+H]⁺. Cpd **59**: ¹H NMR (DMSO-*d*₆) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.83 - 7.92 (m, 1H), 7.36 - 7.51 (m, 2H), 7.20 - 7.30 (m, 2H), 6.93 - 7.04 (m, 2H), 5.20 (s, 2H), 4.08 - 4.12 (m, 1H), 3.24 (d, *J* = 7.7 Hz, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.63 - 1.78 (m, 5H), 0.96 (t, *J* = 7.3 Hz, 3H). LC/MS: mass calcd. for C₂₄H₂₄N₄OS: 416.17, found: 417.3 [M+H]⁺.

Example 60

(2*S*)-5-(2-(4-(Benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **60**



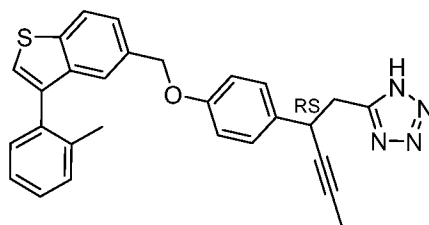
(A) (3*S*)-3-(4-(Benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile was prepared from benzo[*b*]thiophen-5-ylmethanol and (3*S*)-3-(4-hydroxyphenyl)hex-4-yne nitrile (from Example 2G) following General Procedure B, using ADDP and Bu₃P at a reaction temperature of 60 °C overnight, and was used in the next step without characterization.

(B) (2*S*)-5-(2-(4-(Benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **60**) was prepared from (3*S*)-3-(4-(benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-yne nitrile following General Procedure J, using Workup 1. ¹H NMR (DMSO-*d*₆) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.92 - 7.97 (m, 1H), 7.78 (d, *J* = 5.4 Hz, 1H), 7.46 (dd, *J* = 5.4, 0.8 Hz,

1H), 7.42 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.21 - 7.28 (m, 2H), 6.94 - 7.01 (m, 2H), 5.19 (s, 2H), 4.07 - 4.11 (m, 1H), 3.22 (d, $J = 7.7$ Hz, 2H), 1.73 (d, $J = 2.4$ Hz, 3H). LC/MS: mass calcd. for $C_{21}H_{18}N_4OS$: 374.12, found: 375.0 $[M+H]^+$.

Example 61

(2*RS*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **61**



(A) 5-(Chloromethyl)-3-(2-methylphenyl)benzo[*b*]thiophene was prepared from (3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol (from Example 1B) following General Procedure D. LC/MS: mass calcd. for $C_{16}H_{13}ClS$: 272.04, found: 273.0 $[M+H]^+$.

(B) (3*RS*)-Methyl 3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate was prepared from 5-(chloromethyl)-3-(2-methylphenyl)benzo[*b*]thiophene and methyl 3-(4-hydroxyphenyl)hex-4-ynoate (available from Oxchem Corporation, Irwindale, CA, catalog #AX8267763) following General Procedure E, at a reaction temperature of 40 °C. LC/MS: mass calcd. for $C_{29}H_{26}O_3S$: 454.16, found: 477.1 $[M+Na]^+$.

(C) (3*RS*)-3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*RS*)-methyl 3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoate following General Procedure C, using 1N aq NaOH as the base and at a reaction temperature of 35 °C. LC/MS: mass calcd. for $C_{28}H_{24}O_3S$: 440.14, found: 463.2 $[M+Na]^+$.

(D) (3*RS*)-3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride was prepared from (3*RS*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedure G.

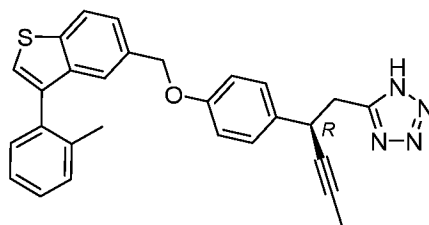
(E) (3*RS*)-3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*RS*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoyl chloride following General Procedure Hb. LC/MS: mass calcd. for C₂₈H₂₅NO₂S: 439.16, found: 440.2 [M+H]⁺.

(F) (3*RS*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*RS*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedure I. LC/MS: mass calcd. for C₂₈H₂₃NOS: 421.15, found: 444.1 [M+Na]⁺.

(G) (2*RS*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **61**) was prepared from (3*RS*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, and was purified by preparative HPLC (Phenomenex C18 column, 5μm, 100 x 30 mm, 20-70% MeCN/H₂O (0.1%TFA v/v) over 18 min). ¹H NMR (CDCl₃) δ 7.93 (d, *J*=8.6 Hz, 1H), 7.43-7.48 (m, 2H), 7.31-7.36 (m, 3H), 7.27-7.31 (m, 2H), 7.21-7.25 (m, 2H), 6.86-6.93 (m, 2H), 5.07 (s, 2H), 4.05 (ddd, *J*=8.2, 5.4, 2.5 Hz, 1H), 3.40-3.47 (m, 1H), 3.31-3.39 (m, 1H), 2.15 (s, 3H), 1.88 (d, *J*=2.5 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₄N₄OS: 464.17, found: 465.1 [M+H]⁺.

Example 62

(2*R*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **62**



(A) (3*R*)-3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid was prepared from (3*RS*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid (from Example 61C) through a chiral HPLC

separation (Chiralcel OJ-H 250×4.6 mm I.D., 5µm column; Mobile phase: 40 % of methanol (0.05% DEA) in CO₂, Flow rate: 2.5 mL/min; Column temp: 35 °C). LC/MS: mass calcd. for C₂₈H₂₄O₃S: 440.14, found: 463.2 [M+Na]⁺.

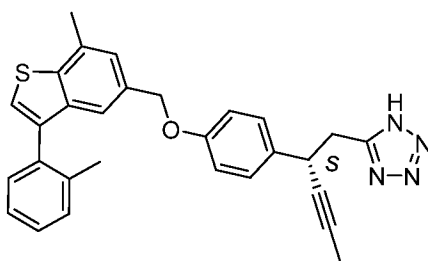
(B) (3*R*)-3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide was prepared from (3*R*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynoic acid following General Procedures G and H_b. LC/MS: mass calcd. for C₂₈H₂₅NO₂S: 439.16, found: 440.2 [M+H]⁺.

(C) (3*R*)-3-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (3*R*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynamide following General Procedures I. LC/MS: mass calcd. for C₂₈H₂₃NOS: 421.15, found: 444.1 [M+Na]⁺.

(D) (2*R*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **62**) was prepared from (3*R*)-3-(4-((3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, and was purified by preparative HPLC (Phenomenex C18 column, 5µm, 100 x 30 mm, 20-70% MeCN/H₂O (0.1%TFA v/v) over 18 min). ¹H NMR (CDCl₃) δ: 7.93 (d, *J*=8.6 Hz, 1H), 7.43-7.48 (m, 2H), 7.31-7.36 (m, 3H), 7.27-7.31 (m, 2H), 7.21-7.25 (m, 2H), 6.86-6.93 (m, 2H), 5.07 (s, 2H), 4.05 (ddd, *J*=8.2, 5.4, 2.5 Hz, 1H), 3.40-3.47 (m, 1H), 3.31-3.39 (m, 1H), 2.15 (s, 3H), 1.88 (d, *J*=2.5 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₄N₄OS: 464.17, found: 465.1 [M+H]⁺.

Example 63

(2*S*)-5-(2-(4-((7-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **63**



(A) To an ice-cooled solution of 3-thiopheneacetic acid (2.0 g, 14.1 mmol) and acetic anhydride (5.19 mL, 54.9 mmol) in ethyl ether (8 mL) was added boron trifluoride diethyl etherate (2.65 mL, 21.1 mmol) in drop-wise fashion over 15 min. The reaction mixture was then warmed to rt over 1 h, and was stirred at rt for 2.5 d. The reaction was quenched with water, and the mixture was extracted with EtOAc. The combined organic extracts were washed successively with satd. aq NaHCO₃, water and brine, and then dried (MgSO₄) filtered and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (20-80% EtOAc/heptanes) to afford 7-methyl-5*H*-thieno[2,3-*c*]pyran-5-one (2.34 g, 51%). LC/MS: mass calcd. for C₈H₆O₂S: 166.01, found: 167.1 [M+H]⁺.

(B) A suspension of 7-methyl-5*H*-thieno[2,3-*c*]pyran-5-one (1.19 g, 7.16 mmol) in ethyl propiolate (2.77 mL, 27.2 mmol) and toluene (10 mL) was distributed in 4 separate vials under N₂, each one of which was heated under microwave irradiation at 180 °C for 1 h. The mixtures were combined and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (10-60% EtOAc/heptanes) to afford ethyl 7-methylbenzo[*b*]thiophene-5-carboxylate (0.38 g, 24% yield). LC/MS: mass calcd. for C₁₂H₁₂O₂S: 220.06, found: 221.1 [M+H]⁺.

(C) To a solution of ethyl 7-methylbenzo[*b*]thiophene-5-carboxylate (0.38 g, 1.73 mmol) in AcOH (10 mL) was added Br₂ (0.1 mL, 1.90 mmol) in drop-wise fashion over 5 min. After stirring at rt for 2.5 h, the reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic extracts were washed successively with 10% aq Na₂S₂O₃, and satd. aq NaHCO₃, and then dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography

(5-20% EtOAc/heptanes) to afford ethyl 3-bromo-7-methylbenzo[*b*]thiophene-5-carboxylate (0.15 g, 29% yield). LC/MS: mass calcd. for C₁₂H₁₁BrO₂S: 297.97, found: 300.1 [M+2]⁺.

(D) Ethyl 7-methyl-3-(2-methylphenyl)benzo[*b*]thiophene-5-carboxylate was prepared from ethyl 3-bromo-7-methylbenzo[*b*]thiophene-5-carboxylate and 2-methylphenylboronic acid following General Procedure A, using PdCl₂(PPh₃)₂ as the palladium catalyst and Na₂CO₃ as the base. LC/MS: mass calcd. for C₁₉H₁₈O₂S: 310.10, found: 311.1 [M+H]⁺.

(E) To a cold (-78 °C) solution of ethyl 7-methyl-3-(2-methylphenyl)benzo[*b*]thiophene-5-carboxylate (0.46 g, 1.49 mmol) in DCM (40 mL) was added diisobutylaluminum hydride (1 M in toluene, 10 mL) in drop-wise fashion under a nitrogen atmosphere. After stirring at -78 °C for 1 h, the reaction was quenched with 2N aq HCl. The mixture was warmed to rt and extracted with DCM. The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (10-25% EtOAc/heptanes) to afford (7-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol (0.32 g, 80% yield). LC/MS: mass calcd. for C₁₇H₁₆OS: 268.09, found: 251.1 [M-OH]⁺.

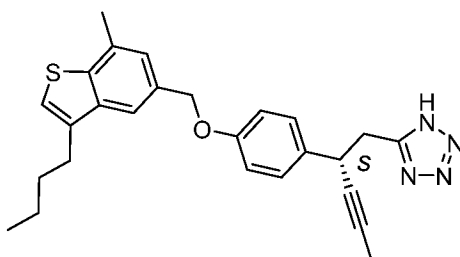
(F) (3*S*)-3-(4-((7-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile was prepared from (7-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol and (3*S*)-3-(4-hydroxyphenyl)hex-4-ynenitrile (from Example 2G) following General Procedure B, using ADDP and Bu₃P, at a reaction temperature of 60 °C for 4 h. LC/MS: mass calcd. for C₂₉H₂₅NOS: 435.17, found: 458.3 [M+Na]⁺.

(G) (2*S*)-5-(2-(4-((7-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **63**) was prepared from (3*S*)-3-(4-((7-methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)hex-4-ynenitrile following General Procedure J, using Workup 2. ¹H NMR (CDCl₃) δ 7.27-7.36 (m, 7H), 7.23 (d, *J*=8.6 Hz, 2H), 6.91 (d, *J*=8.6 Hz, 2H), 5.06 (s, 2H), 3.99-4.08 (m, 1H), 3.38-3.47

(m, 1H), 3.29-3.38 (m, 1H), 2.64 (s, 3H), 2.16 (s, 3H), 1.90 (d, $J=2.0$ Hz, 3H) LC/MS: mass calcd. for $C_{29}H_{26}N_4OS$: 478.18, found: 479.2 $[M+H]^+$.

Example 64

(2*S*)-5-(2-(4-((3-Butyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **64**



(A) (3-Bromo-7-methylbenzo[*b*]thiophen-5-yl)methanol was prepared from ethyl 3-bromo-7-methylbenzo[*b*]thiophene-5-carboxylate (from Example 63C) following the procedure described in Example 37I. LC/MS: mass calcd. for $C_{10}H_9BrOS$: 255.96, found: 238.9, 240.9 $[M-OH, M-OH+2]^+$.

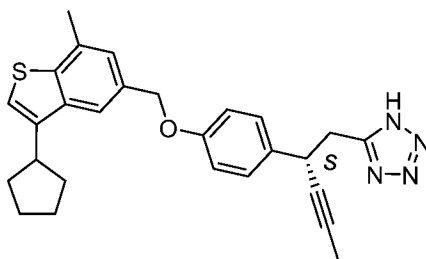
(B) (2*S*)-3-(5-(2-(4-((3-Bromo-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile was prepared from (3-bromo-7-methylbenzo[*b*]thiophen-5-yl)methanol and (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 37D) following the General Procedure B, using ADDP and Bu_3P , at a reaction temperature of 60 °C for 2 h. LC/MS: mass calcd. for $C_{25}H_{22}BrN_5OS$: 519.07, found: 520.2 $[M+H]^+$.

(C) To a solution of (2*S*)-3-(5-(2-(4-((3-bromo-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (30 mg, 0.058 mmol), butylzinc bromide (0.35 mL, 0.173 mmol) and $PdCl_2(dppf) \cdot CH_2Cl_2$ (4.7 mg, 0.006 mmol) in 1,4-dioxane (1.2 mL) was bubbled N_2 for 5 min and the mixture was then stirred overnight at 60 °C. After cooling to rt, 1N aq NaOH (0.6 mL) and MeOH (0.15 mL) were added, and the mixture was stirred at rt for 30 min. The mixture was then acidified with 2N aq HCl and extracted with DCM. The combined organic extracts were dried ($MgSO_4$),

filtered and concentrated under reduced pressure and the resultant residue was purified by preparative HPLC [Phenomenex C18 column, 5 μ m, 30 x 100 mm, 20%-100% MeCN/H₂O (0.1% TFA v/v)] to afford (2*S*)-5-(2-(4-((3-butyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **64**) (5.9 mg, 23% yield). ¹H NMR (CDCl₃) δ 7.64 (s, 1H), 7.24-7.30 (m, 2H), 7.23 (s, 1H), 7.11 (s, 1H), 6.98 (br. d, *J*=8.6 Hz, 2H), 5.15 (s, 2H), 4.06 (br. s, 1H), 3.40-3.49 (m, 1H), 3.31-3.40 (m, 1H), 2.84 (br. t, *J*=7.6 Hz, 2H), 2.57 (s, 3H), 1.90 (s, 3H), 1.73 (dt, *J*=15.2, 7.6 Hz, 3H), 1.43 (dq, *J*=15.0, 7.3 Hz, 3H), 0.96 (t, *J*=7.3 Hz, 3H). LC/MS: mass calcd. for C₂₆H₂₈N₄OS: 444.20, found: 445.2 [M+H]⁺.

Example 65

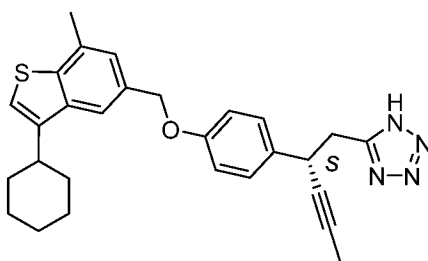
(2*S*)-5-(2-(4-((3-Cyclopentyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **65**



(2*S*)-5-(2-(4-((3-Cyclopentyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **65**) was prepared from (2*S*)-3-(5-(2-(4-((3-bromo-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 64B) and cyclopentylzinc bromide following the procedure described in Example 64C. ¹H NMR (CDCl₃) δ 7.69 (s, 1H), 7.19-7.30 (m, 3H), 7.12 (s, 1H), 6.97 (br. d, *J*=8.1 Hz, 2H), 5.14 (s, 2H), 4.07 (br. s, 1H), 3.29-3.49 (m, 3H), 2.57 (s, 3H), 2.10-2.22 (m, 2H), 1.89 (s, 3H), 1.64-1.86 (m, 6H). LC/MS: mass calcd. for C₂₇H₂₈N₄OS: 456.20, found: 457.2 [M+H]⁺.

Example 66

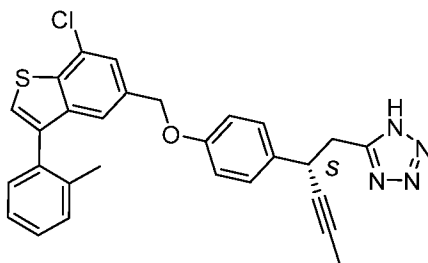
(2*S*)-5-(2-(4-((3-Cyclohexyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **66**



(2*S*)-5-(2-(4-((3-Cyclohexyl-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **66**) was prepared from (2*S*)-3-(5-(2-(4-((3-bromo-7-methylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 64B) and cyclohexylzinc bromide following the procedure described in Example 64C. ¹H NMR (CDCl₃) δ 7.66 (s, 1H), 7.24-7.30 (m, 2H), 7.22 (s, 1H), 7.10 (s, 1H), 6.98 (d, *J*=8.6 Hz, 2H), 5.15 (s, 2H), 4.07 (br. s, 1H), 3.51-3.51 (m, 1H), 3.31-3.48 (m, 2H), 2.90 (br. d, *J*=7.6 Hz, 1H), 2.57 (s, 3H), 2.07 (br. d, *J*=8.1 Hz, 2H), 1.75-1.93 (m, 7H), 1.20-1.55 (m, 4H). LC/MS: mass calcd. for C₂₈H₃₀N₄OS: 470.21, found: 471.2 [M+H]⁺.

Example 67

(2*S*)-5-(2-(4-((7-Chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **67**



(A) A mixture of 4-bromo-2-chlorobenzenethiol (4.1 g, 18.3 mmol), bromoacetaldehyde diethyl acetal (3.03 mL, 20.2 mmol) and K₂CO₃ (5.07 g, 36.7 mmol) in acetone (27 mL) was stirred at 60 °C for 3 h. The mixture was filtered, and the precipitates were washed with acetone. The combined filtrate was concentrated, and the resulting residue was purified by silica gel chromatography (2-8% EtOAc/heptanes) to afford (4-bromo-2-chlorophenyl)(2,2-diethoxyethyl)sulfane (5.67 g, 91% yield). ¹H NMR (CDCl₃) δ

7.52 (d, $J=1.5$ Hz, 1H), 7.31-7.36 (m, 1H), 7.23-7.28 (m, 1H), 4.67 (t, $J=5.6$ Hz, 1H), 3.64-3.75 (m, 2H), 3.49-3.62 (m, 2H), 3.13 (d, $J=5.6$ Hz, 2H), 1.20 (t, $J=7.1$ Hz, 6H).

(B) To a solution of (4-bromo-2-chlorophenyl)(2,2-diethoxyethyl)sulfane (1.56 g, 4.59 mmol) in *p*-xylene (78 mL) was added phosphoric acid (85% in water, 0.31 mL, 4.59 mmol) and the resulting mixture was stirred overnight at 180 °C with azeotropic removal of EtOH (Dean-Stark trap). After cooling to rt, water was added to quench the reaction, and the mixture was extracted with EtOAc/ether. The combined organic extracts were washed successively with satd. aq NaHCO₃ and brine, dried (MgSO₄) and concentrated. The residue thus obtained was purified by silica gel chromatography (100% heptanes) to afford 5-bromo-7-chlorobenzo[*b*]thiophene (0.41 g, 36% yield). ¹H NMR (CDCl₃) δ 7.87 (s, 1H), 7.53 (d, $J=5.6$ Hz, 1H), 7.48 (s, 1H), 7.31 (d, $J=5.6$ Hz, 1H).

(C) A mixture of 5-bromo-7-chlorobenzo[*b*]thiophene (0.41 g, 1.66 mmol), zinc cyanide (214 mg, 1.82 mmol) and Pd(PPh₃)₄ (191 mg, 0.166 mmol) in DMF (3 mL) was stirred at 120 °C under N₂ overnight. After cooling to rt, the mixture was filtered and the inorganics were washed with EtOAc. The combined organic filtrate was washed successively with water and brine, dried (MgSO₄) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (3-15% EtOAc/heptanes) to afford 7-chlorobenzo[*b*]thiophene-5-carbonitrile (0.20 g, 62.7% yield). ¹H NMR (CDCl₃) δ 8.07 (s, 1H), 7.68 (d, $J=5.6$ Hz, 1H), 7.58 (s, 1H), 7.47 (d, $J=5.6$ Hz, 1H).

(D) 3-Bromo-7-chlorobenzo[*b*]thiophene-5-carboxamide was prepared from 7-chlorobenzo[*b*]thiophene-5-carbonitrile following the procedure described in Example 63C (but at a reaction temperature of 95 °C), and was used in the next step without further purification.

(E) 7-Chloro-3-(2-methylphenyl)benzo[*b*]thiophene-5-carboxamide was prepared from 3-bromo-7-chlorobenzo[*b*]thiophene-5-carboxamide and 2-methylphenylboronic acid

following General Procedure A, using PdCl₂(PPh₃)₂ as the palladium catalyst and Na₂CO₃ as the base. LC/MS: mass calcd. for C₁₆H₁₂ClNOS: 301.03, found: 302.0 [M+H]⁺.

(F) A mixture of 7-chloro-3-(2-methylphenyl)benzo[*b*]thiophene-5-carboxamide (100 mg, 0.331 mmol), di-*tert*-butyl dicarbonate (152 mg, 0.696 mmol) and DMAP (4 mg, 0.033 mmol) in acetonitrile (8 mL) was stirred at rt for 3 h. The solution was concentrated, and the resulting residue was purified by silica gel chromatography (5-15% EtOAc/heptanes) to afford di-*tert*-butyl (7-chloro-3-(2-methylphenyl)benzo[*b*]thiophene-5-carbonyl) dicarbamate (130 mg, 78% yield). ¹H NMR (CDCl₃) δ 7.80 (d, *J*=4.0 Hz, 2H), 7.45 (s, 1H), 7.32-7.41 (m, 2H), 7.21-7.32 (m, 2H), 2.14 (s, 3H), 1.37 (s, 18H).

(G) To a solution of di-*tert*-butyl (7-chloro-3-(2-methylphenyl)benzo[*b*]thiophene-5-carbonyl) dicarbamate (130 mg, 0.26 mmol) in EtOH (5 mL) was added NaBH₄ (20 mg, 0.52 mmol) and the mixture was stirred at rt for 3 d. The reaction was quenched by the addition of water and 1N HCl, and the mixture was extracted with DCM. The combined organic extracts were dried (MgSO₄), concentrated under reduced pressure and the resultant residue was purified by silica gel chromatography (5-20% EtOAc/heptanes) to afford (7-chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol (42 mg, 56% yield). LC/MS: mass calcd. for C₁₆H₁₃ClOS: 288.04, found: 271.0 [M-OH]⁺.

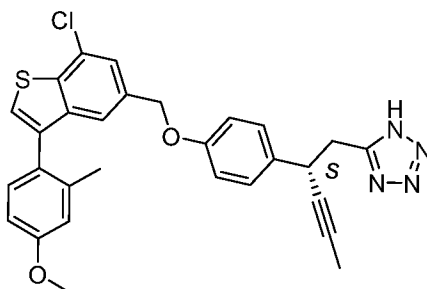
(H) (2*S*)-3-(5-(2-(4-((7-Chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile was prepared from (7-chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol and (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 37D) following the General Procedure B, using ADDP and Bu₃P, at a reaction temperature of 60 °C for 3 h. LC/MS: mass calcd. for C₃₁H₂₆ClN₅OS: 551.15, found: 552.2 [M+H]⁺.

(I) To a solution of (2*S*)-3-(5-(2-(4-((7-chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (68 mg, 0.123 mmol), in THF (2 mL) and MeOH (0.5 mL) was added 1N aq NaOH (1 mL) and the mixture was stirred at rt for 2 h. The mixture was then acidified with 1N aq HCl and extracted with

DCM. The combined organic extracts were dried (MgSO₄), concentrated under reduced pressure and the resultant residue was purified by preparative HPLC [Phenomenex C18 column, 5 μm, 30 x 100 mm, 40%-100% ME CN/H₂O (0.1% TFA v/v)] to afford (2*S*)-5-(2-(4-((7-chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **67**) (38 mg, 62% yield). ¹H NMR (CDCl₃) δ 7.49 (s, 1H), 7.32-7.40 (m, 4H), 7.20-7.30 (m, 4H), 6.89 (d, *J*=8.6 Hz, 2H), 5.06 (s, 2H), 4.05 (br. d, *J*=5.6 Hz, 1H), 3.40-3.49 (m, 1H), 3.30-3.39 (m, 1H), 2.14 (s, 3H), 1.89 (d, *J*=2.0 Hz, 3H). LC/MS: mass calcd. for C₂₈H₂₃ClN₄OS: 498.13, found: 499.1 [M+H]⁺.

Example 68

(2*S*)-5-(2-(4-((7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **68**



(A) 7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carboxamide was prepared from 3-bromo-7-chlorobenzo[*b*]thiophene-5-carboxamide (from Example 67E) and 4-methoxy-2-methylphenylboronic acid following General Procedure A, using PdCl₂(PPh₃)₂ as the palladium catalyst and Na₂CO₃ as the base. LC/MS: mass calcd. for C₁₇H₁₄ClNO₂S: 331.04, found: 332.1 [M+H]⁺.

(B) Di-*tert*-butyl (7-chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carbonyl) dicarbamate was prepared from 7-chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carboxamide following the procedure described in Example 67F. ¹H NMR (CDCl₃) δ 7.80 (s, 2H), 7.41 (s, 1H), 7.15 (d, *J*=8.1 Hz, 1H), 6.88 (d, *J*=2.0 Hz, 1H), 6.83 (dd, *J*=8.1, 2.5 Hz, 1H), 3.88 (s, 3H), 2.12 (s, 3H), 1.37 (s, 18H).

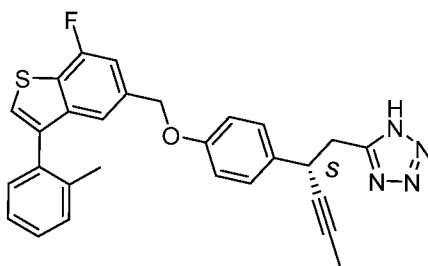
(C) (7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol was prepared from di-*tert*-butyl (7-chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carbonyl) dicarbamate following the procedure described in Example 67G. LC/MS: mass calcd. for C₁₇H₁₅ClO₂S: 318.05, found: 301.0 [M-OH]⁺.

(D) (2*S*)-3-(5-(2-(4-((7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile was prepared from (7-chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol and (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 37D) following the General Procedure B, using ADDP and Bu₃P, at a reaction temperature of 60 °C for 3 h. LC/MS: mass calcd. for C₃₂H₂₈ClN₅O₂S: 581.17, found: 582.2 [M+H]⁺.

(E) (2*S*)-5-(2-(4-((7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **68**) was prepared from (2*S*)-3-(5-(2-(4-((7-chloro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile following the procedure described in Example 67I. ¹H NMR (CDCl₃) δ 7.48 (d, *J*=1.0 Hz, 1H), 7.35 (d, *J*=1.0 Hz, 1H), 7.33 (s, 1H), 7.21-7.25 (m, 2H), 7.19 (d, *J*=8.1 Hz, 1H), 6.85-6.92 (m, 3H), 6.83 (dd, *J*=8.3, 2.8 Hz, 1H), 5.05 (s, 2H), 4.06 (ddd, *J*=8.1, 5.6, 2.5 Hz, 1H), 3.86 (s, 3H), 3.39-3.47 (m, 1H), 3.30-3.39 (m, 1H), 2.12 (s, 3H), 1.88 (d, *J*=2.0 Hz, 3H). LC/MS: mass calcd. for C₂₉H₂₅ClN₄O₂S: 528.14, found: 529.2 [M+H]⁺.

Example 69

(2*S*)-5-(2-(4-((7-Fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd **69**



(A) (4-Bromo-2-fluorophenyl)(2,2-diethoxyethyl)sulfane was prepared from 4-bromo-2-fluorobenzenethiol following the procedure described in Example 67A. $^1\text{H NMR}$ (CDCl_3) δ 7.29-7.34 (m, 1H), 7.20-7.28 (m, 2H), 4.62 (t, $J=5.6$ Hz, 1H), 3.61-3.70 (m, 2H), 3.48-3.57 (m, 2H), 3.07 (d, $J=5.6$ Hz, 2H), 1.18 (t, $J=7.1$ Hz, 6H).

(B) To a solution of (4-bromo-2-fluorophenyl)(2,2-diethoxyethyl)sulfane (7.84 g, 24.3 mmol) in toluene (60 mL) was added polyphosphoric acid (26.4 g, 243 mmol) and the mixture was refluxed for 4 h. The mixture was poured into ice-water, stirred for 30 min and extracted with toluene. The combined organic extracts were washed successively with aq. NaHCO_3 and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (2-8% EtOAc/heptanes) to afford 5-bromo-7-fluorobenzo[*b*]thiophene (1.05 g, 18.7% yield). $^1\text{H NMR}$ (CDCl_3) δ 7.77 (s, 1H), 7.52 (d, $J=5.6$ Hz, 1H), 7.28-7.32 (m, 1H), 7.20 (d, $J=9.1$ Hz, 1H).

(C) 7-Fluorobenzo[*b*]thiophene-5-carbonitrile was prepared from 5-bromo-7-fluorobenzo[*b*]thiophene following the procedure described in Example 67C. $^1\text{H NMR}$ (CDCl_3) δ 7.97 (s, 1H), 7.66 (d, $J=5.1$ Hz, 1H), 7.43-7.48 (m, 1H), 7.27 (d, $J=9.1$ Hz, 1H).

(D) To a solution of 7-fluorobenzo[*b*]thiophene-5-carbonitrile (200 mg, 1.13 mmol) in AcOH (4 mL) was added Br_2 (198 mg, 1.24 mmol) in drop-wise fashion. The mixture was stirred at 90 °C overnight, and was then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (3-15% EtOAc/heptanes) to afford compound A: 3-bromo-7-fluorobenzo[*b*]thiophene-5-carbonitrile (89 mg, 30.8% yield) and compound B: 3-bromo-7-fluorobenzo[*b*]thiophene-5-carboxamide (100 mg, 32% yield). Compound A: $^1\text{H NMR}$ (CDCl_3) δ 7.97 (s, 1H), 7.65 (s, 1H), 7.36 (d, $J=9.1$ Hz, 1H). Compound B: LC/MS: mass calcd. for $\text{C}_9\text{H}_5\text{BrFNOS}$: 272.93, found: 273.9 [$\text{M}+\text{H}$] $^+$.

(E) 7-Fluoro-3-(2-methylphenyl)benzo[*b*]thiophene-5-carbonitrile was prepared from 3-bromo-7-fluorobenzo[*b*]thiophene-5-carbonitrile and 2-methylphenylboronic acid following General Procedure A, using $\text{PdCl}_2(\text{PPh}_3)_2$ as the palladium catalyst and Na_2CO_3 as the base. LC/MS: mass calcd. for $\text{C}_{16}\text{H}_{10}\text{FNS}$: 267.05, found: 268.0 [$\text{M}+\text{H}$] $^+$.

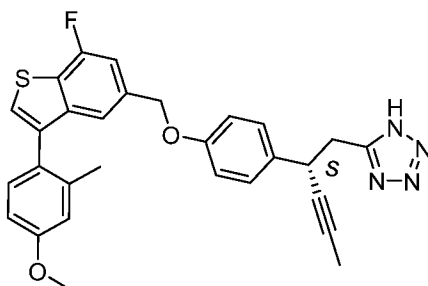
(F) To a cooled (-78 °C) solution of 7-fluoro-3-(2-methylphenyl)benzo[*b*]thiophene-5-carbonitrile (90 mg, 0.71 mmol) in DCM (5 mL) under an inert nitrogen atmosphere was added diisobutylaluminum hydride (1 M in toluene; 0.71 mL, 0.71 mmol) in a drop-wise fashion. After stirring at -78 °C for 1 h and then at rt for an additional hour, the reaction was quenched with 2N aq HCl and extracted with DCM. The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The resultant residue was re-dissolved in EtOH (3 mL) and treated with NaBH₄ (25 mg, 0.67 mmol). After stirring at rt for 3 d, the reaction was quenched by the addition of water and 1N aq HCl. The mixture was extracted with DCM and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (15-30% EtOAc/heptanes) to afford (7-fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol (31 g, 33.8%). LC/MS: mass calcd. for C₁₆H₁₃FOS: 272.07, found: 255.1 [M-OH]⁺.

(G) (2*S*)-3-(5-(2-(4-((7-Fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile was prepared from (7-fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol and (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 37D) following the General Procedure B, using ADDP and Bu₃P, at a reaction temperature of 60 °C for 3 h. LC/MS: mass calcd. for C₃₁H₂₆FN₅OS: 535.18, found: 536.2 [M+H]⁺.

(H) (2*S*)-5-(2-(4-((7-Fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **69**) was prepared from (2*S*)-3-(5-(2-(4-((7-fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile following the procedure described in Example 67I. ¹H NMR (CDCl₃) δ 7.21-7.38 (m, 8H), 7.18 (d, *J*=10.1 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 5.05 (s, 2H), 4.07 (br. s, 1H), 3.40-3.48 (m, 1H), 3.32-3.40 (m, 1H), 2.14 (s, 3H), 1.86 (s, 3H). LC/MS: mass calcd. for C₂₈H₂₃FN₄OS: 482.16, found: 483.3 [M+H]⁺.

Example 70

(2*S*)-5-(2-(4-((7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole, Cpd 70



(A) 7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carboxamide was prepared from 3-bromo-7-fluorobenzo[*b*]thiophene-5-carboxamide (from Example 69D, Compound B) and 4-methoxy-2-methylphenylboronic acid following General Procedure A, using PdCl₂(PPh₃)₂ as the palladium catalyst and Na₂CO₃ as the base. LC/MS: mass calcd. for C₁₇H₁₄FNO₂S: 315.07, found: 316.0 [M+H]⁺.

(B) Di-*tert*-butyl (7-fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carbonyl) dicarbamate was prepared from 7-fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carboxamide following the procedure described in Example 67F. ¹H NMR (CDCl₃) δ: 7.70 (s, 1H), 7.51 (d, *J*=10.1 Hz, 1H), 7.38 (s, 1H), 7.15 (d, *J*=8.1 Hz, 1H), 6.89 (d, *J*=2.0 Hz, 1H), 6.83 (dd, *J*=8.6, 2.5 Hz, 1H), 3.88 (s, 3H), 2.12 (s, 3H), 1.37 (s, 18H).

(C) (7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol was prepared from di-*tert*-butyl (7-fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophene-5-carbonyl) dicarbamate following the procedure described in Example 67G. LC/MS: mass calcd. for C₁₇H₁₅FO₂S: 302.08, found: 285.1 [M-OH]⁺.

(D) (2*S*)-3-(5-(2-(4-((7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile was prepared from (7-fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methanol and (2*S*)-3-(5-(2-(4-hydroxyphenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile (from Example 37D)

following the General Procedure B, using ADDP and Bu₃P, at a reaction temperature of 60 °C for 3 h. LC/MS: mass calcd. for C₃₂H₂₈FN₅O₂S: 565.19, found: 566.2 [M+H]⁺.

(E) (2*S*)-5-(2-(4-((7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole (Cpd **70**) was prepared from (2*S*)-3-(5-(2-(4-((7-fluoro-3-(4-methoxy-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazol-1-yl)propanenitrile following the procedure described in Example 67I. ¹H NMR (CDCl₃) δ 7.29 (s, 1H), 7.21-7.25 (m, 3H), 7.13-7.21 (m, 2H), 6.84-6.90 (m, 3H), 6.82 (dd, *J*=8.1, 2.5 Hz, 1H), 5.04 (s, 2H), 4.08 (ddd, *J*=8.3, 5.8, 2.5 Hz, 1H), 3.86 (s, 3H), 3.32-3.46 (m, 2H), 2.12 (s, 3H), 1.82 (d, *J*=2.5 Hz, 3H). LC/MS: mass calcd. for C₂₉H₂₅FN₄O₂S: 512.17, found: 513.2 [M+H]⁺.

Biological Examples

In Vitro Assay

GPR40 Calcium Flux Assay

Compounds were tested in a calcium flux assay using transfected HEK293 cells stably expressing either human GPR40 or rat GPR40. Human GPR40 expressing cells were cultured in DMEM-High Glucose media supplemented with 10% fetal bovine serum, 1 x L-Glutamine, 1 x Penicillin/Streptomycin and 500 µg/mL G418. Rat GPR40 expressing cells were cultured in DMEM-High Glucose media supplemented with 10% fetal bovine serum and 1 µg/mL puromycin. Cells were plated into poly-D-lysine coated 384-well plates and cultured overnight in a 37 °C humidified tissue culture incubator under 5 % CO₂/90 % O₂ atmosphere. On the day of the experiment, the culture media was replaced with assay buffer (HBSS, 20 mM HEPES, 0.1 % BSA) and the cells incubated at 37 °C for 1 h. Calcium-sensitive fluorescent dye (Fluo 8 No-Wash Calcium Dye, ABD Bioquest) was then added and the cells incubated for another 30 min at 37 °C followed by 15 min at room temperature while protected from the light. The cell plate and a plate of diluted compounds of Formula (I) were loaded into a fluorescent plate reader that added

compounds onto the cells while measuring the fluorescence intensity of each well. The plate reader recorded fluorescence intensity at 1 second intervals for 8 min and provided the data for analysis in an Excel format. EC₅₀ values were calculated using Prism (GraphPad) software. Resultant mean data are shown in Table 2.

Table 2. Ca²⁺ Mobilization Data

Cpd No	hGPR40 Ca²⁺ Assay EC₅₀ (μM)
1	0.002
2	0.02; 0.013
3	0.022; 0.008
4	0.02
5	0.065
6	0.19
7	0.17
8	0.009
9	0.27
10	0.054
11	0.088
12	0.028; 0.03
13	0.013
14	0.13
15	0.085
16	0.023

Cpd No	hGPR40 Ca²⁺ Assay EC₅₀ (μM)
17	0.097
18	0.08
19	0.028
20	0.024
21	0.051
22	0.067
23	1.74
24	0.55
25	0.037
26	0.034
27	0.061
28	0.027
29	0.42
30	0.43
31	0.029
32	0.011
33	0.008
34	0.019
35	0.028

Cpd No	hGPR40 Ca²⁺ Assay EC₅₀ (μM)
36	0.015
37	0.59
38	0.016
39	0.67
40	0.058
41	0.019
42	0.12
43	0.13
44	0.018
45	0.039
46	0.047
47	0.013
48	0.083
49	0.010
50	0.052
51	0.003
52	0.001
53	0.17
54	0.18

Cpd No	hGPR40 Ca²⁺ Assay EC₅₀ (μM)
55	0.11
56	0.054
57	0.86
58	0.1
59	0.13
60	0.11
61	0.034
62	0.91
63	0.13
64	0.33
65	0.44
66	1.12
67	0.063
68	0.025
69	0.023
70	0.01

In-vivo Assay

Oral Glucose Tolerance Test

Male SD rats (200-250 g) were housed 2 per cage in a temperature-controlled room with a 12-hour light/dark cycle. They were allowed *ad libitum* access to water and fed

with normal rodent chow. The night before the oral glucose tolerance test (oGTT), the rats were transferred to clean cages and fasted overnight. On the morning of the oGTT, the rats were weighed and randomized into groups based on fasted blood glucose and body weight. Rats were dosed with vehicle (0.5% methocel) or compounds (10 mg/kg, po) thirty to forty min prior to the oGTT (glucose, 2g/kg, po). Blood was collected from the tail vein at 0, 10, 30, 60 and 120 minutes after glucose challenge to measure blood glucose; plasma was used to determine insulin levels. The area under the curve for blood glucose excursion was calculated from t= 0 to t = 120 minutes. Percent lowering of glucose was calculated from the AUC data with respect to the vehicle-treated group. Resultant data are shown in Table 3.

Table 3.

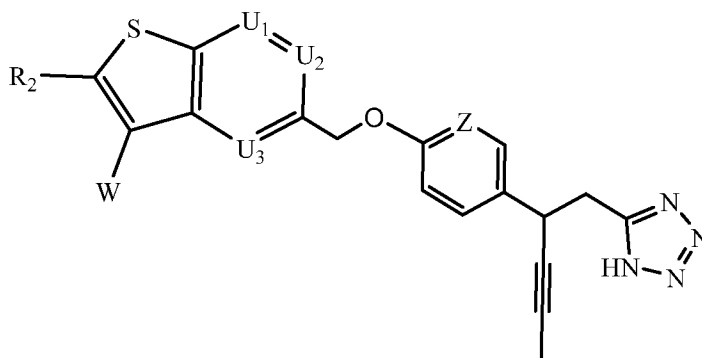
Cpd No.	Percent Lowering of Glucose (AUC compound vs. AUC Vehicle)
1	81 %
12	101 %
16	105 %
44	91 %
47	91 %

Note: AUC = Integrated area under the glucose excursion curve from t = 0 to t = 120 minutes.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

What is claimed is:

1. A compound of Formula (I)



Formula (I)

wherein

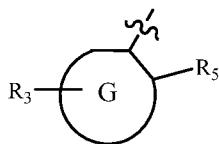
U_1 is N or C(R_1), wherein R_1 is selected from the group consisting of hydrogen, fluoro, chloro, or methyl;

U_2 and U_3 are independently selected from CH or N, such that only up to one of U_1 , U_2 , and U_3 is N in any instance;

R_2 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, cyano, and C_{1-4} alkylsulfonyl;

W is selected from the group consisting of

- i) hydrogen;



ii) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, pyrazinyl, and pyrimidinyl; and, when ring G is phenyl, substituents R₃ and R₅ are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, 2,2,-dimethylchroman-5-yl, or (1-ethylcarboxy-indolin-4-yl);

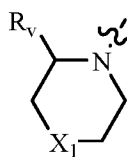
wherein R₃ is selected from the group consisting of hydrogen, chloro, C₁₋₄alkyl, 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, C₁₋₃alkylsulfonyl, C₁₋₃alkylsulfonylamino, and -OR₄;

wherein R₄ is

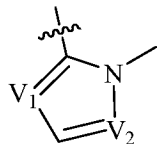
- i) C₁₋₈alkyl optionally independently substituted with one or two C₁₋₃alkoxy or hydroxy substituents;
 - ii) 4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-ylmethyl;
 - iii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
 - iv) tetrahydro-2*H*-pyran-4-yl;
 - v) C₁₋₃alkylsulfonylpropyl;
- or
- vi) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

iii) C₃₋₈cycloalkyl;



iv) ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;



v) ; wherein V_1 and V_2 are independently selected from CH or N;

and

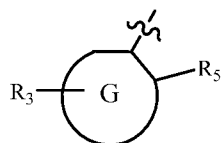
vi) C_{1-6} alkyl;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

2. The compound of claim 1 wherein U_1 is N or $C(R_1)$, wherein R_1 is hydrogen, fluoro, or chloro.
3. The compound of claim 1 wherein U_2 and U_3 are independently selected from CH or N, such that only up to one of U_1 , U_2 , and U_3 is N in any instance.
4. The compound of claim 3 wherein U_2 is independently selected from CH or N; and U_3 is CH, such that only one of U_1 and U_2 is N in any instance.
5. The compound of claim 1 wherein R_2 is selected from the group consisting of hydrogen, chloro, fluoro, bromo, iodo, methyl, methanesulfonyl, trifluoromethyl, and cyano.
6. The compound of claim 5 wherein R_2 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, and cyano.

7. The compound of claim 6 wherein R₂ is selected from the group consisting of hydrogen, chloro, fluoro, bromo, trifluoromethyl, and cyano.
8. The compound of claim 1 wherein W is selected from the group consisting of



- i) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R₃ and R₅ are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

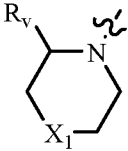
wherein R₃ is selected from the group consisting of hydrogen, chloro, C₁₋₄alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and -OR₄;

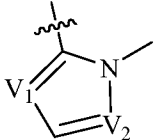
wherein R₄ is

- i) C₁₋₈alkyl independently substituted with one or two C₁₋₃alkoxy or hydroxy substituents;
- ii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
- iii) C₁₋₃alkylsulfonylpropyl;
- or
- iv) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

- ii) C₅₋₈cycloalkyl;

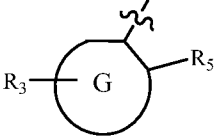
- iii)  ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;

- iv)  ; wherein V₁ and V₂ are independently selected from CH or N;

and

- v) C₁₋₆alkyl.

9. The compound of claim 8 wherein W is selected from the group consisting of

- i)  ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R₃ and R₅ are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

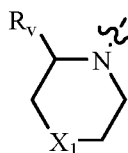
wherein R₃ is selected from the group consisting of hydrogen, chloro, C₁₋₄alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and -OR₄;
wherein R₄ is

- i) C₁₋₆alkyl independently substituted with one or two C₁₋₃alkoxy substituents;
ii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
iii) C₁₋₃alkylsulfonylpropyl;

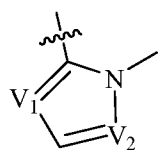
or

iv) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

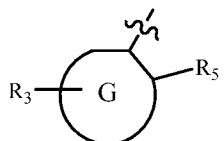
wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

ii)  ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;

and

iii)  ; wherein V₁ is independently selected from CH or N, and V₂ is CH.

10. The compound of claim 9 wherein W is selected from the group consisting of

i)  ; wherein ring G is selected from the group consisting of phenyl and pyridyl; and, when ring G is phenyl, substituents R₃ and R₅ are optionally taken together with the atoms to which they are attached to form (1-ethylcarboxy-indolin-4-yl);

wherein R₃ is selected from the group consisting of hydrogen, and -OR₄;

wherein R₄ is

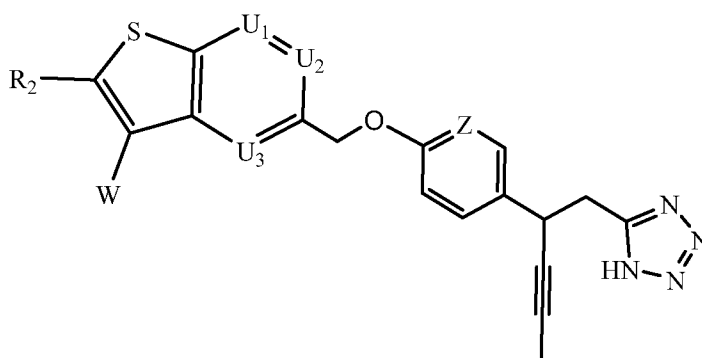
- i) C₁₋₆alkyl independently substituted with one or two C₁₋₃alkoxy substituents;
- ii) C₁₋₃alkylsulfonylpropyl;

or

iii) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl.

11. The compound of claim 1 wherein W is selected from the group consisting of 2-methylphenyl, 2-bromophenyl, 2-chloro-5-methylpyridin-4-yl, 2-methyl-4-(4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxyphenyl, 2-methyl-4-(3-methyl-3-hydroxybutoxy)phenyl, 2-methyl-4-(2-methoxyethoxy)phenyl, 2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl, 2-methyl-3-(2-methoxyethoxy)phenyl, 2-methylpyridin-3-yl, 2-methyl-4-(3-methyl-1,1-dioxidothietan-3-yl)methoxy)phenyl, 2-trifluoromethylphenyl, 2-methyl-4-(methanesulfonyl)phenyl, 2-methyl-5-(2-methoxyethoxy)phenyl, 2-methyl-4-(3-methanesulfonylpropyloxy)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yloxy)phenyl, 2,6-dimethylphenyl, 2-(2-methoxyethoxy)-4-methylpyridin-5-yl, 1-methyl-1*H*-pyrazol-5-yl, 1-methyl-1*H*-1,2,4-triazol-5-yl, 4-methylpyrimidin-5-yl, 5-(2-methoxyethoxy)-3-methylpyridin-2-yl, dihydrobenzo[*b*][1,4]dioxin-5-yl, 1-(ethylcarboxy)-indolin-4-yl, 2-methyl-5-(methanesulfonylamino)phenyl, 2,2,-dimethylchroman-5-yl, 2-methyl-4-(2,3-dihydroxy-propyloxy)phenyl, 2-chlorophenyl, 5-(2-methoxyethoxy)-2-methylpyridin-3-yl, cyclopropyl, cyclohexyl, cyclopentyl, isopropyl, 2-methylpiperidin-1-yl, 2-methyl-4-methoxyphenyl, *n*-propyl, hydrogen, and *n*-butyl.
12. A compound of Formula (I)



Formula (I)

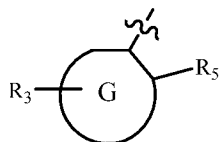
wherein

U_1 is N or C(R_1), wherein R_1 is hydrogen, fluoro, or chloro;

U_2 and U_3 are independently selected from CH or N, such that only up to one of U_1 , U_2 , and U_3 is N in any instance;

R_2 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, and cyano;

W is selected from the group consisting of



i) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R_3 and R_5 are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

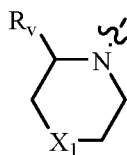
wherein R_3 is selected from the group consisting of hydrogen, chloro, C_{1-4} alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and -OR₄;

wherein R_4 is

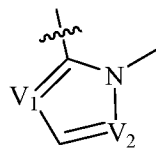
- i) C₁₋₈alkyl independently substituted with one or two C₁₋₃alkoxy or hydroxy substituents;
- ii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
- iii) C₁₋₃alkylsulfonylpropyl;
- or
- iv) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

- ii) C₅₋₈cycloalkyl;



- iii) ; wherein X₁ is selected from the group consisting of CH₂, O, S, NH, and N(C₁₋₄alkyl); and wherein R_v is hydrogen or methyl;



- iv) ; wherein V₁ and V₂ are independently selected from CH or N;

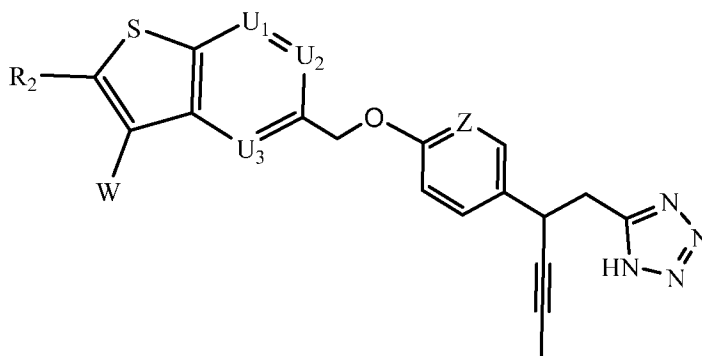
and

- v) C₁₋₆alkyl;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

13. A compound of Formula (I)



Formula (I)

wherein

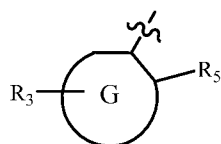
U_1 is N or C(R_1), wherein R_1 is hydrogen, fluoro, or chloro;

U_2 is independently selected from CH or N;

U_3 is CH, such that only one of U_1 and U_2 is N in any instance;

R_2 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, bromo, iodo, trifluoromethyl, and cyano;

W is selected from the group consisting of



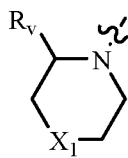
- i) ; wherein ring G is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl; and, when ring G is phenyl, substituents R_3 and R_5 are optionally taken together with the atoms to which they are attached to form an unsubstituted or substituted bicyclic ring system selected from dihydrobenzo[b][1,4]dioxin-5-yl, or (1-ethylcarboxy-indolin-4-yl);

wherein R_3 is selected from the group consisting of hydrogen, chloro, C_{1-4} alkyl, 1,1-dioxido-3,6-dihydro-2*H*-thiopyran-4-yl, and $-OR_4$;

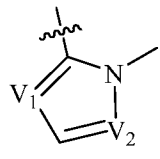
wherein R_4 is

- ii) C_{1-6} alkyl independently substituted with one or two C_{1-3} alkoxy substituents;
 - iii) 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl;
 - iv) C_{1-3} alkylsulfonylpropyl;
- or
- v) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R_5 is methyl, bromo, chloro, or trifluoromethyl;

- ii)  ; wherein X_1 is selected from the group consisting of CH_2 , O, S, NH, and $N(C_{1-4}alkyl)$; and wherein R_v is hydrogen or methyl;

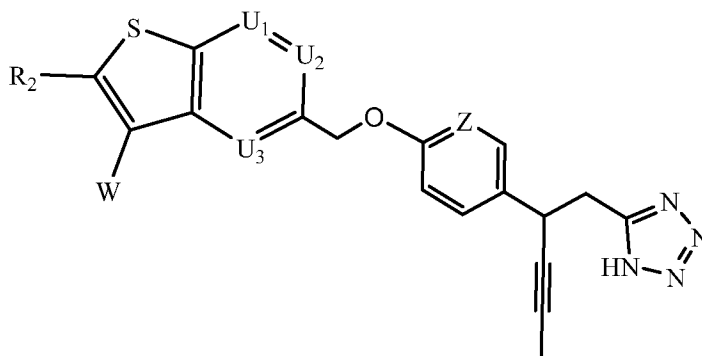
and

- iii)  ; wherein V_1 is independently selected from CH or N, and V_2 is CH;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

14. A compound of Formula (I)



Formula (I)

wherein

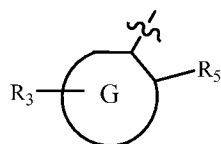
U_1 is N or C(R_1), wherein R_1 is hydrogen, fluoro, or chloro;

U_2 is independently selected from CH or N;

U_3 is CH, such that only one of U_1 and U_2 is N in any instance;

R_2 is selected from the group consisting of hydrogen, chloro, fluoro, bromo, trifluoromethyl, and cyano;

W is selected from the group consisting of



i) ; wherein ring G is selected from the group consisting of phenyl and pyridyl; and, when ring G is phenyl, substituents R_3 and R_5 are optionally taken together with the atoms to which they are attached to form (1-ethylcarboxy-indolin-4-yl);

wherein R_3 is selected from the group consisting of hydrogen, and -OR₄;

wherein R_4 is

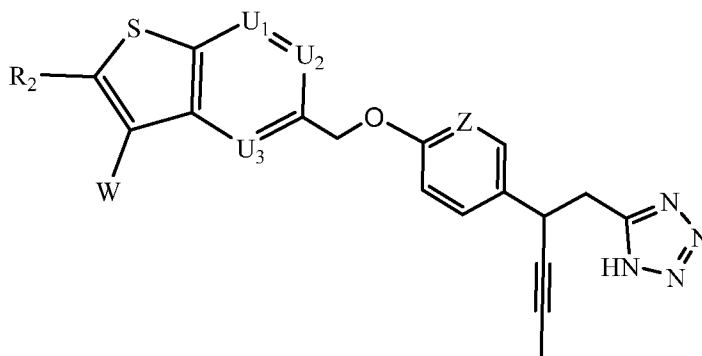
- i) C₁₋₆alkyl independently substituted with one or two C₁₋₃alkoxy substituents;
- ii) C₁₋₃alkylsulfonylpropyl;
- or
- iii) (3-methyl-1,1-dioxidothietan-3-yl)methyl;

wherein R₅ is methyl, bromo, chloro, or trifluoromethyl;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

15. A compound of Formula (I)



Formula (I)

wherein

U₁ is N or C(R₁), wherein R₁ is hydrogen, methyl, fluoro, or chloro;

U₂ is independently selected from CH or N;

U₃ is CH or N, such that only one of U₁ and U₂ is N in any instance;

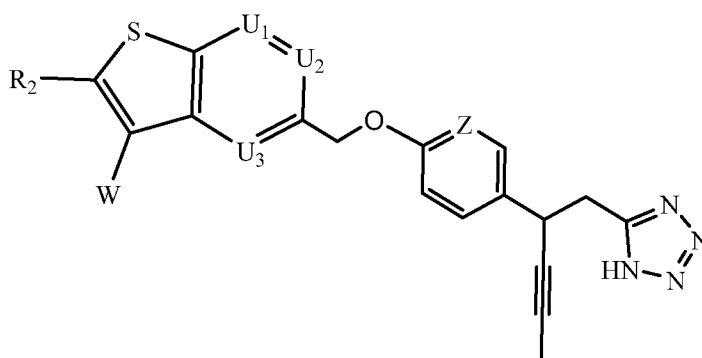
R₂ is selected from the group consisting of hydrogen, chloro, fluoro, bromo, iodo, methyl, methanesulfonyl, trifluoromethyl, and cyano;

W is selected from the group consisting of 2-methylphenyl, 2-bromophenyl, 2-chloro-5-methylpyridin-4-yl, 2-methyl-4-(4-hydroxy-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxyphenyl, 2-methyl-4-(3-methyl-3-hydroxybutoxy)phenyl, 2-methyl-4-(2-methoxyethoxy)phenyl, 2-methyl-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl, 2-methyl-3-(2-methoxyethoxy)phenyl, 2-methylpyridin-3-yl, 2-methyl-4-(3-methyl-1,1-dioxidothietan-3-yl)methoxyphenyl, 2-trifluoromethylphenyl, 2-methyl-4-(methylsulfonyl)phenyl, 2-methyl-5-(2-methoxyethoxy)phenyl, 2-methyl-4-(3-methanesulfonylpropyloxy)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)phenyl, 2-methyl-4-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yloxy)phenyl, 2,6-dimethylphenyl, 2-(2-methoxyethoxy)-4-methylpyridin-5-yl, 1-methyl-1*H*-pyrazol-5-yl, 1-methyl-1*H*-1,2,4-triazol-5-yl, 4-methylpyrimidin-5-yl, 5-(2-methoxyethoxy)-3-methylpyridin-2-yl, dihydrobenzo[*b*][1,4]dioxin-5-yl, 1-(ethylcarboxy)-indolin-4-yl, 2-methyl-5-(methanesulfonylamino)phenyl, 2,2,-dimethylchroman-5-yl, 2-methyl-4-(2,3-dihydroxy-propyloxy)phenyl, 2-chlorophenyl, 5-(2-methoxyethoxy)-2-methylpyridin-3-yl, cyclopropyl, cyclohexyl, cyclopentyl, isopropyl, 2-methylpiperidin-1-yl, 2-methyl-4-methoxyphenyl, *n*-propyl, hydrogen, and *n*-butyl;

Z is CH or N;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

16. A compound of Formula (I)



Formula (I)

selected from the group consisting of

- (2*S*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- 5-((2*S*)-2-(4-((2-Chloro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- 5-((2*S*)-2-(4-((2-Fluoro-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(2-Bromophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-4-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-chloro-5-methylpyridine;
- (2*S*)-4-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)methyl)-4-hydroxytetrahydro-2*H*-thiopyran 1,1-dioxide;
- (2*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol;
- (2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

- (2*S*)-5-(2-(4-((3-(2-Methyl-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(3-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-methylpyridine;
- (2*S*)-3-((4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)methyl)-3-methylthietane 1,1-dioxide;
- (2*S*)-5-(2-(4-((3-(2-(Trifluoromethyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(2-Methyl-4-(methylsulfonyl)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(5-(2-Methoxyethoxy)-2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(2-Methyl-4-(3-(methylsulfonyl)propoxy)phenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-4-(4-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenyl)tetrahydro-2*H*-thiopyran 1,1-dioxide;
- 4-(4-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-2-methylbenzo[*b*]thiophen-3-yl)-3-methylphenoxy)tetrahydro-2*H*-thiopyran 1,1-dioxide;
- 5-((2*S*)-2-(4-((2-Methyl-3-(2-methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(2,6-Dimethylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

- (2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-(2-methoxyethoxy)-4-methylpyridine;
- (2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-pyrazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(1-Methyl-1*H*-1,2,4-triazol-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylpyrazine;
- (2*S*)-5-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-4-methylpyrimidine;
- (2*S*)-2-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-5-(2-methoxyethoxy)-3-methylpyridine;
- (2*S*)-5-(2-(4-((3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-1-(4-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)indolin-1-yl)propan-1-one;
- (2*S*)-*N*-(3-(5-((4-(1-(1*H*-tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-4-methylphenyl)methanesulfonamide;
- (2*S*)-5-(2-(4-((3-(2,2-dimethylchroman-5-yl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- 3-(4-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-3-methylphenoxy)propane-1,2-diol;
- (2*S*)-5-(2-(4-((3-(2-Chlorophenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-3-(5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-5-(2-methoxyethoxy)-2-methylpyridine;

- 5-((2*S*)-2-(4-((2-Bromo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- 5-((2*S*)-2-(4-((2-Iodo-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- 5-((2*S*)-2-(4-((2-Trifluoromethyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-ynyl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-Cyclopropyl-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- 5-((2*S*)-2-(4-((2-Cyano-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((2-(Methylsulfonyl)-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridine;
- (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridine;
- (2*R*)-5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)-2-((3-(3-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)pyridine;
- (2*R*)-4-(4-(5-(((5-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)pyridin-2-yl)oxy)methyl)-benzo[b]thiophen-3-yl)-3-methylphenoxy)-2-methylbutan-2-ol;
- (2*S*)-5-(2-(4-((2-Fluoro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((2-Chloro-3-(4-(2-methoxyethoxy)-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- (2*S*)-5-(2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;
- 5-((2*S*)-2-(4-((3-(4-(2-Methoxyethoxy)-2-methylphenyl)-2-(trifluoromethyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

1-(5-((4-((2*S*)-1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)benzo[*b*]thiophen-3-yl)-2-methylpiperidine;

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*b*]pyridine;

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*b*]pyridine;

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[2,3-*c*]pyridine;

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[2,3-*c*]pyridine;

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(2-methylphenyl)thieno[3,2-*b*]pyridine;

(2*S*)-5-((4-(1-(1*H*-Tetrazol-5-yl)pent-3-yn-2-yl)phenoxy)methyl)-3-(4-methoxy-2-methylphenyl)thieno[3,2-*b*]pyridine;

(2*S*)-5-(2-(4-((3-Cyclohexylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((3-Cyclopentylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((3-Cyclopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((3-Isopropylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((3-Propylbenzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-(Benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*RS*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*R*)-5-(2-(4-((3-(2-Methylphenyl)benzo[*b*]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((7-Methyl-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((3-Butyl-7-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((3-Cyclopentyl-7-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((3-Cyclohexyl-7-methylbenzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((7-Chloro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((7-Chloro-3-(4-methoxy-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((7-Fluoro-3-(2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole;

(2*S*)-5-(2-(4-((7-Fluoro-3-(4-methoxy-2-methylphenyl)benzo[b]thiophen-5-yl)methoxy)phenyl)pent-3-yn-1-yl)-1*H*-tetrazole

or a pharmaceutically acceptable salt form thereof.

17. A pharmaceutical composition comprising a compound of claim 1 or 16 and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.
18. The pharmaceutical composition of claim 17, wherein the composition is a solid oral dosage form.
19. The pharmaceutical composition of claim 17, wherein the composition is a syrup, an elixir or a suspension.

20. A method of treating a disorder modulated by the GPR40 receptor, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of claim 1.
21. A method of treating a disorder, wherein said disorder is affected by the agonism of the GPR40 receptor, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of claim 1.
22. The method of claim 21 wherein said disorder is selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema.
23. The method of claim 22 wherein said disorder is Type II diabetes mellitus.
24. A method of treating a disorder selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, comprising administering to a subject in need thereof a therapeutically effective amount of the composition of claim 1.
25. A method of treating a condition selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to

unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of claim 1.

26. The use of a compound as in claim 1 for the preparation of a medicament for treating a disorder or condition selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, in a subject in need thereof.
27. The use of a compound as in claim 1, for use in a method for treating a disorder selected from the group consisting of Type II diabetes mellitus, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, metabolic syndrome, diabetic nephropathy, other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged cholesterol and/ or lipid levels, osteoporosis, inflammation, and eczema, in a subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/026924

A. CLASSIFICATION OF SUBJECT MATTER					
INV.	C07D409/12	C07D409/14	C07D495/04	A61K31/4439	A61K31/41
	A61P3/10	A61P3/04	A61P9/12	A61P19/10	A61P29/00
ADD.					
According to International Patent Classification (IPC) or to both national classification and IPC					

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols) C07D
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :	
<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>

Date of the actual completion of the international search 20 June 2017	Date of mailing of the international search report 29/06/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Kiernan, Andrea

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/026924

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	WO 2014/073904 A1 (LG LIFE SCIENCES LTD.) 15 May 2014 (2014-05-15) abstract; claims; examples -----	1-27
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