

METHODS FOR THE PREPARATION OF SSTR4 AGONISTS AND SALTS THEREOF

FIELD OF THE INVENTION

[0001] The present invention is directed to methods for the preparation of SSTR4 agonists, such as 3-azabicyclo[3.1.0]hexane-6-carboxamide derivatives. The present invention is also directed to the preparation of salts of SSTR4 agonists. The present invention is also directed to novel hydrates and novel salts of certain SSTR4 agonists.

BACKGROUND OF THE INVENTION

[0002] Somatostatin, or somatotropin-release inhibitory factor (SRIF), is a cyclic peptide found in humans. It is produced widely in the human body and acts both systemically and locally to inhibit the secretion of various hormones, growth factors and neurotransmitters. The effects of somatostatin are mediated by a family of G protein-coupled receptors, of which five subtypes are known. These subtypes are divided into two subfamilies, the first comprising SSTR2, SSTR3 and SSTR5 and the second SSTR1 and SSTR4.

[0003] Somatostatin is involved in the regulation of methods such as for example cellular proliferation, glucose homeostasis, inflammation, and pain. In this aspect, somatostatin or other members of the somatostatin peptide family are believed to inhibit nociceptive and inflammatory methods via the SSTR4 pathway.

[0004] WO 2014/184275 discloses certain 3-azabicyclo[3.1.0]hexane-6-carboxamide derivatives which are SSTR4 agonists, and which are useful for preventing or treating medical disorders related to SSTR4. However, it can be challenging to synthesize 3-azabicyclo[3.1.0]hexane-6-carboxamide derivatives with sufficient enantiomeric and diastereomeric purity. Lab scale synthetic pathways are known, but many steps used in previous synthetic pathways can be impractical and/or too expensive to utilize at commercial scale.

[0005] Thus, there is a need for alternative ways to prepare certain SSTR4 agonists at commercial scale with sufficient purity. Accordingly, the present invention is directed to methods for the preparation of certain SSTR4 compounds, such as

(1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide and pharmaceutically acceptable salts, solvates, and/or hydrates thereof.

[0006] Diabetic neuropathy is a common complication of diabetic microvascular disease. Approximately 40% of patients with diabetes mellitus experience diabetic microvascular disease, and approximately 80% of patients with diabetic neuropathy present with peripheral polyneuropathy.

[0007] Symptoms of diabetic peripheral neuropathy include hyperalgesia, paresthesia, and a deep aching sensation. Diabetic peripheral neuropathy (DPNP) symptoms are associated with poor sleep, mobility, depression, and poor quality of life.

[0008] Unfortunately, treatment options for DPNP are limited. There are only 3 medications approved by the US FDA for this indication: pregabalin, duloxetine, and tapentadol. While pregabalin and duloxetine each demonstrated efficacy in multiple placebo-controlled clinical trials, both medications require titration to minimize adverse reactions. Tapentadol is an opioid mu-receptor agonist, with the same pharmacological limitations and adverse reaction profile as other opioid analgesics. Other classes of medications are used clinically in an off-label fashion, including gabapentin, selective serotonin norepinephrine uptake inhibitors, tricyclic antidepressants, and anticonvulsants. Dose-limiting toxicity of all these agents prevents patients from tolerating the therapeutic dose, leading to the use of a subtherapeutic dose in the clinic, and further decreasing the efficacy of these agents. In addition, only 50% of patients continue therapy after 3 months.

[0009] Due to the suboptimal dosing and the poor tolerability profile of the nonopioid analgesics used for the management of DPNP, opioids are used as a last resort. Although opioids are efficacious against acute pain, there is evidence suggesting they provide little clinical benefit in chronic pain, not to mention the possibility of reduced efficacy due to tolerance.

[0010] Additionally, while opioid compounds are known for providing relief from pain symptoms, opioid compounds are also associated with numerous undesirable side effects, including hallucinations, nausea, dizziness, sedation, constipation, urinary retention, dependency, and addiction. As many as 25% of patients undergoing opioid pain therapy for even a short duration can develop a dependence on opioid compounds. In fact, opioid addiction was declared as a National Public Health Emergency on October

26, 2017 by U.S. President Donald Trump. As such, there is a long-felt, but unmet need for the development of non-opioid compounds and dosing regimens for non-opioid compounds to provide relief from pain symptoms without the possibility for the development of addiction and/or dependency.

[0011] Accordingly, the present invention is directed to new methods to synthesize SSSTR4 agonists and novel hydrates and/or salts of SSSTR4 agonists, which have potential uses in the treatment of pain, such as neuropathic pain and/or diabetic neuropathy and/or mixed neuropathy.

BRIEF DESCRIPTION OF THE FIGURES

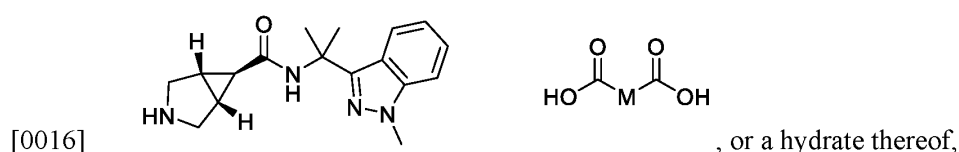
[0012] FIG. 1 shows an XRPD pattern of (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide monohydrate

[0013] FIG. 2 shows an XRPD pattern of (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide succinate

[0014] FIG. 3 shows an XRPD pattern of (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide adipate

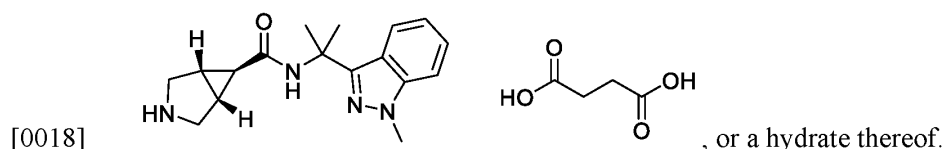
SUMMARY OF THE INVENTION

[0015] Disclosed herein is a compound of the formula:



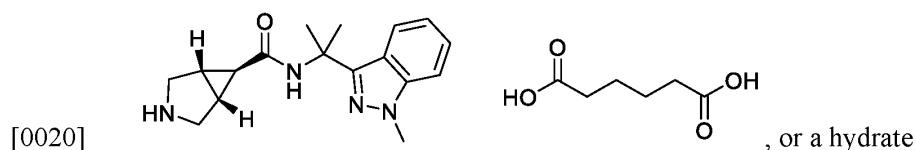
wherein M is null or C₁ to C₆ alkyl.

[0017] Also disclosed herein is a compound of the formula:



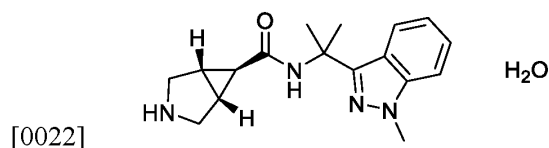
[0019] Also disclosed herein is a compound of the formula:

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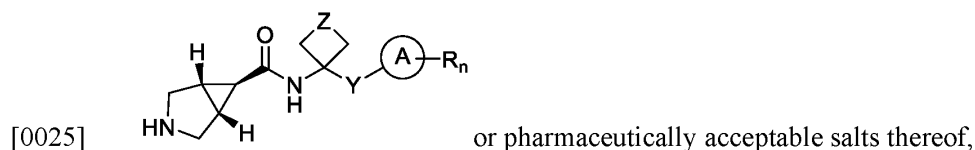
thereof.

[0021] Also disclosed herein is a compound of the formula:



[0023] Also disclosed herein is a method for the preparation of certain SSTR4 agonist compounds, and pharmaceutically acceptable salts and/or hydrates thereof, such as (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1H-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide.

[0024] Also disclosed herein is a method for preparing a compound of the formula:

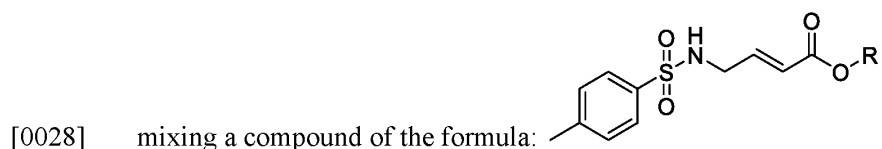


[0026] wherein Y is covalent bond, O, S, C₁ to C₆ ether, or C₁ to C₆ thioether, Z is

null, a covalent bond, CH₂, or CH₂CH₂, (A) is an 8-member to 10-member heteroaryl

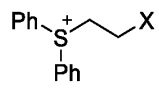
with from 1 to 4 heteroatoms in the heteroaryl or C₆ to C₁₀ aryl, (A) is substituted with one or more R_n, and Each R_n is independently OH, F, Cl, Br, I, NH₂, CF₃, C₁ to C₆ alkyl, C₃ to C₇ cycloalkyl, C₁ to C₇ ether, or C₁ to C₇ thioether,

[0027] and the method comprising:



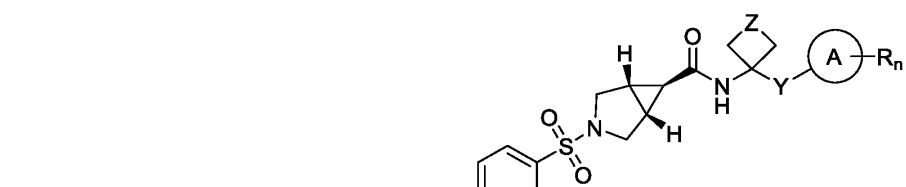
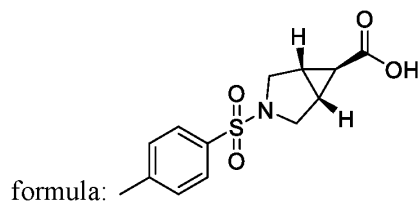
wherein R is a C₁ to C₆ alkyl,

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 A^{-} 

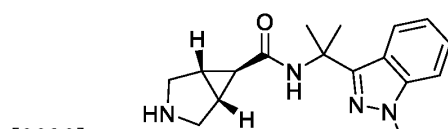
with a sulfonium salt of the formula:

wherein X is a halogen and A is an anion to yield an intermediate compound of the

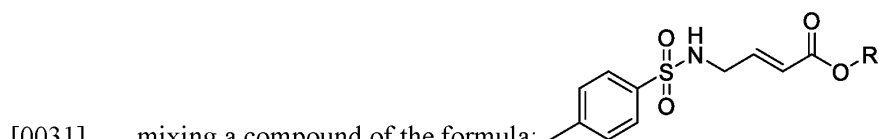


removing tosyl functional group from to yield the compound.

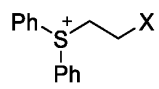
[0029] Also disclosed herein is a method for preparing a compound of the formula:



, or pharmaceutically acceptable salts thereof; and the method comprising:

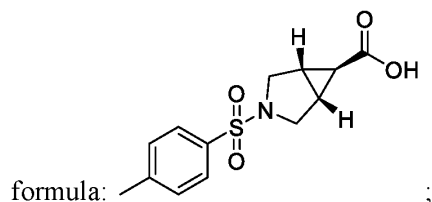


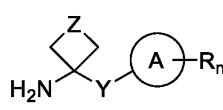
wherein R is a C₁ to C₆ alkyl,

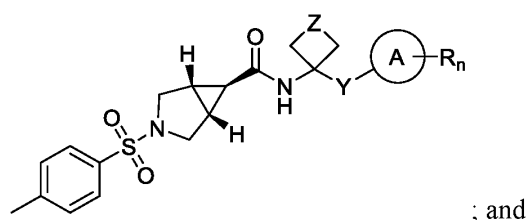
 A^{-} 

with a sulfonium salt of the formula:

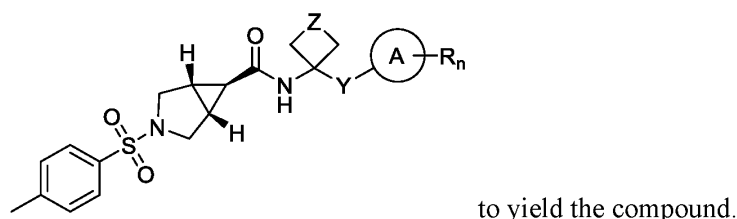
wherein X is a halogen and A is an anion to yield an intermediate compound of the



mixing the intermediate compound with  to yield



[0032] removing tosyl functional group from



[0033] Also disclosed herein is a product comprising a compound, such as (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide, or pharmaceutically acceptable salts and/or hydrates thereof, prepared by the method described herein.

DETAILED DESCRIPTION OF THE INVENTION

[0034] While methods for the preparation of certain SSTR4 compounds are disclosed in WO 2014/184275, WO 2021/233427, and WO 2022/012534, these compounds were produced at laboratory scale, which can include synthetic steps that are impractical at commercial scale. In these previous preparations, the synthetic pathways used: (1) expensive catalysts, including palladium and/or rhodium, and/or used lithium aluminum hydride to perform reduction steps, and (2) led to a mixture of diastereomers

that needed epimerization after the cyclization of the heterocycle. Both (1) and (2) can increase the overall cost of the preparation and add additional purification steps to remove trace amounts of Pd, Rh, Li, Al, and/or undesirable diastereomers with lower activity.

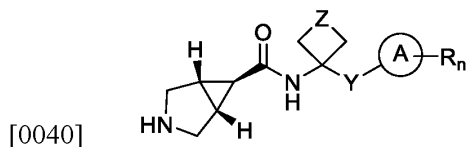
[0035] Disclosed herein, is a new route to certain SSTR4 compounds, such as (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide and pharmaceutically acceptable salts, hydrates, or solvates thereof, which can be performed at commercial scale without the use of transition metal catalysts, such as Pd, Pt, Mo, Rh, Fe, Ni, Cr, W, or combinations thereof, and/or aluminum hydride salts, such as lithium aluminum hydride. Additionally, the disclosed method includes a cyclization step including a reaction with a (2-haloethyl)diphenylsulfonium salt which leads to a single diastereomer intermediate without requiring a subsequent epimerization step. Finally, the disclosed method has fewer total steps than the previously disclosed routes, such as less than 8 or from 4 to 7 total steps.

[0036] The present invention is also directed to novel hydrates of certain SSTR4 agonists, such as (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide monohydrate. The present invention is also directed to novel salts of certain SSTR4 agonists, such as (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide succinate and as (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide adipate.

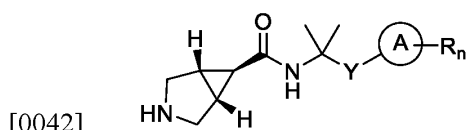
[0037] SSTR4 Agonists

[0038] The disclosed method can be used to prepare the compounds of Formula I or Formula I-A, wherein Z can be null, a covalent bond, CH₂, or CH₂CH₂, Y can be covalent bond, O, S, C₁ to C₆ ether, or C₁ to C₆ thioether, ^(A) is an 8-member to 10-member heteroaryl with from 1 to 4 heteroatoms in the heteroaryl or C₆ to C₁₀ aryl, ^(A) can be substituted with one or more R_n, and each R_n can be independently OH, F, Cl, Br, I, NH₂, CF₃, C₁ to C₆ alkyl, C₃ to C₇ cycloalkyl, C₁ to C₇ ether, C₁ to C₇ thioether, or combinations thereof.

[0039] The disclosed method can also be used to prepare salts, solvates, hydrates, and/or combinations thereof of Formula I or Formula I-A.



[0041] Formula I. SSTR4 Agonist



[0043] Formula I-A. SSTR4 Agonist

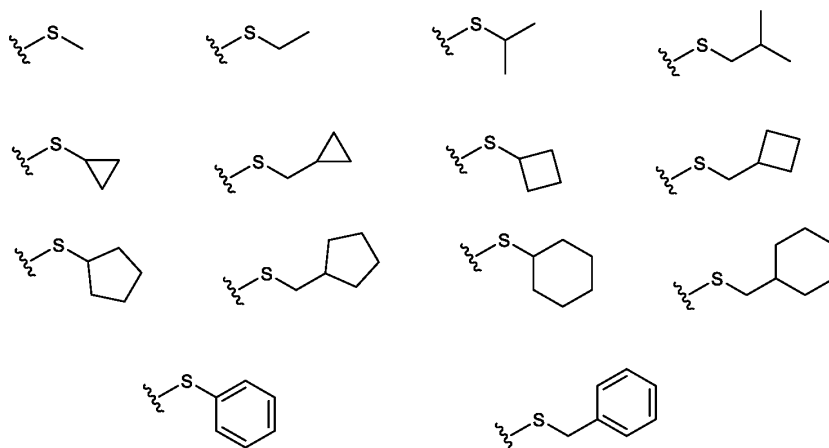
[0044] $\textcircled{\text{A}}$, as described herein, can be a C_6 to C_{10} aryl or a 5-member to 10-member heteroaryl with from 1 to 4 heteroatoms selected from O, N, or S. In some embodiments, $\textcircled{\text{A}}$ can be an 8-member to 10-member heteroaryl with from 1 to 4 heteroatoms selected from O, N, or S. In some embodiments, $\textcircled{\text{A}}$ can be a monocyclic, bicyclic, or polycyclic system. If $\textcircled{\text{A}}$ is a monocyclic system, $\textcircled{\text{A}}$ can be a C_5 to C_6 aryl or five-member to six-member heteroaryl with 1 or 2 heteroatoms selected from O, N, or S. If $\textcircled{\text{A}}$ is a bicyclic system, each of the ring systems can include a C_5 to C_6 aryl or five-member to six-member heteroaryl with 1 or 2 heteroatoms selected from O, N, or S.

[0045] In some embodiments, $\textcircled{\text{A}}$ can be substituted with one or more R_n . R_n can be independently selected from OH, F, Cl, Br, I, NH_2 , C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, C_1 to C_7 ether, C_1 to C_7 thioether, or combinations thereof. In some embodiments, n can represent the number of substitutions on $\textcircled{\text{A}}$. For example, R_1 can be a first substitution on $\textcircled{\text{A}}$ and R_2 can be a second substitution on $\textcircled{\text{A}}$, *etc.*

[0046] In some embodiments, Y can be covalent bond, O, S, C₁ to C₆ ether, or C₁ to C₆ thioether. When Y is null,  is connected via a covalent bond to the dimethyl substituted carbon atom immediately adjacent to the amide functional group.

[0047] In some embodiments Z can be null, a covalent bond, CH₂, or CH₂CH₂. When Z is null, there no connection between the two methyl substituents at the alpha carbon atom. When Z is a covalent bond, the alpha carbon atom forms a cyclopropyl functional group. When Z is CH₂, the alpha carbon atom forms a cyclobutyl functional group. When Z is CH₂CH₂, the alpha carbon atom forms a cyclopentyl functional group.

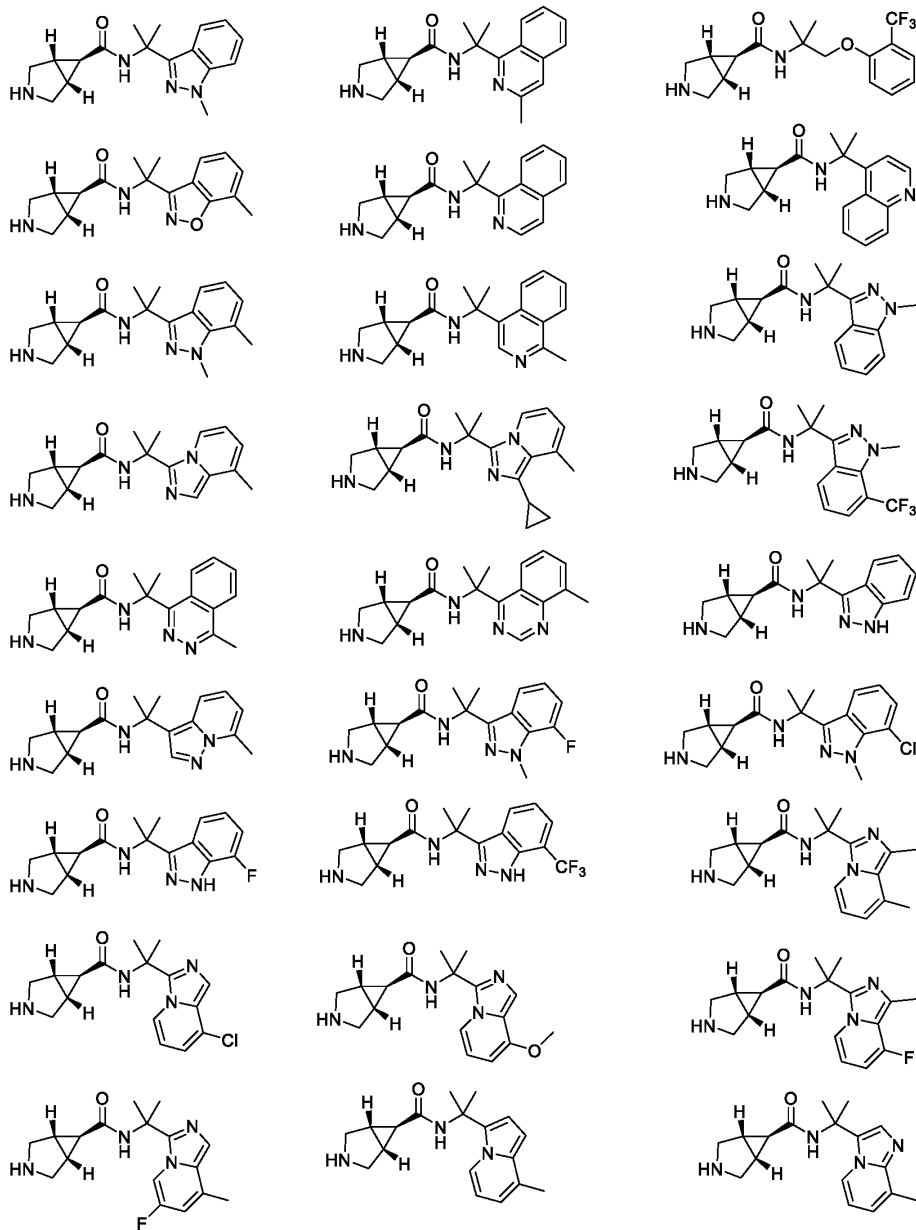
[0048] In some embodiments, the C₁ to C₇ thioether can be a thioether selected from Formula II.



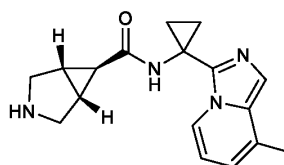
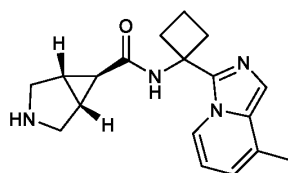
[0049]

[0050] Formula II. Thioethers

[0051] The disclosed method can be used to prepare the compounds of Formula III. The disclosed method can also be used to prepare solvates, hydrates, and/or combinations thereof of Formula III and/or Formula III-A.



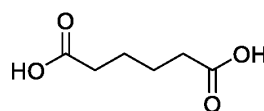
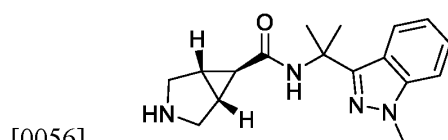
[0052] Formula III. SSTR4 Agonists that can be made by the disclosed method.



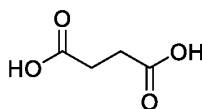
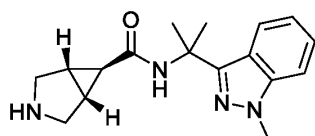
[0053]

[0054] Formula III-A. Additional SSTR4 Agonists that can be made by the disclosed method

[0055] The disclosed method can be used to prepare the compounds of Formula IV. The disclosed method can also be used to prepare solvates, hydrates, and/or combinations thereof of Formula IV.



[0056]

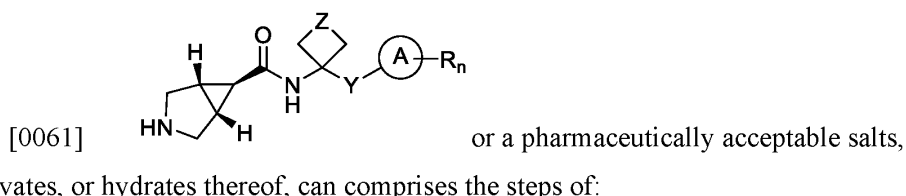


[0057] Formula IV. (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1H-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide succinate (top) (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1H-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide adipate (bottom).

[0058] Method

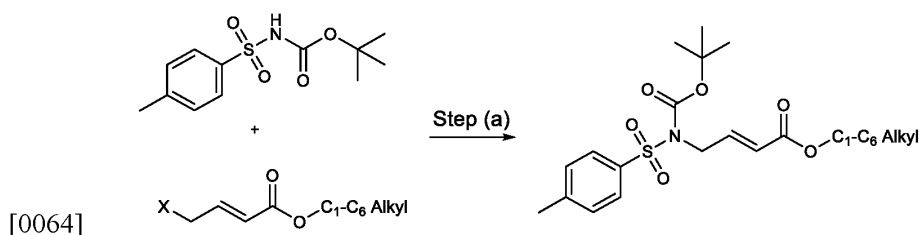
[0059] Disclosed herein is a method for preparing a SSTR4 agonist compound. The method for preparing a SSTR4 agonist compound can be used in the commercial scale production of an SSTR4 agonist compound, a pharmaceutically acceptable salt, and/or a solvate/hydrate thereof, as further discussed herein. In the disclosed method, preferably the reactions are performed using batch methoding methodology. In an embodiment, the batches are produced at method scale. In an embodiment the batches are produced in at least 1 kilogram. In an embodiment, the batches by are produced in at least 10 kilograms. In an embodiment, the batches are produced in at least 100 kilograms.

[0060] The method for preparing a SSTR4 agonist compound of the formula:



[0062] (a) Mixing *tert*-Butyl tosyl carbamate with a suitable C₁-C₆ Alkyl 4-halobut-2-enoate

[0063] Step (a) of the method to prepare a SSTR4 agonist compound can include the mixing *tert*-Butyl tosyl carbamate with a suitable C₁-C₆ Alkyl 4-halobut-2-enoate compound in a polar aprotic solvent as shown in Formula V, wherein X is a halogen leaving group, such as Cl, Br, or I.



[0065] Formula V. Step (a) of Method for Preparing SSTR4 Agonist Compound

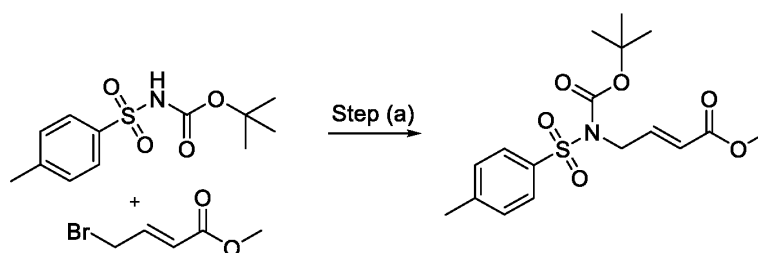
[0066] The components of step (a) can be combined in a polar aprotic solvent at a temperature of from about 10 °C to about 25 °C, from about 15 °C to 25 °C, or from 20 °C to 25 °C. The temperature of the mixture of components in step (a) can be increased to from about 25 °C to about 50 °C, from about 25 °C to about 40 °C, or about 30 °C. The

product mixture of step (a) can be filtered, and the collected residue washed with a polar aprotic solvent to yield the product in solution.

[0067] Suitable polar aprotic solvents are well known to a person of ordinary skill in the art of organic synthesis design. Suitable polar aprotic solvents can include acetonitrile, acetone, dimethyl sulfoxide, N,N-dimethylformamide, tetrahydrofuran, among others.

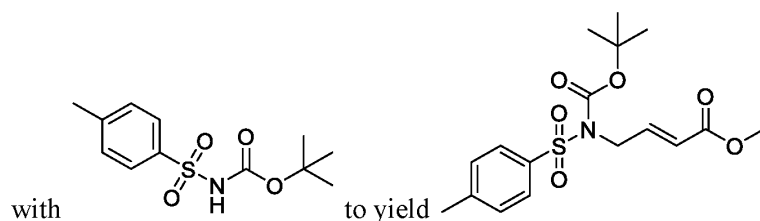
[0068] In another embodiment, the method can include the mixing *tert*-Butyl tosyl carbamate with (E) Methyl 4-bromobut-2-enoate compound in MeCN to yield Methyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate, as shown in Formula VI.

[0069]



[0070] Formula VI. Step (a) of Method for Preparing SSTR4 Agonist Compound

[0071] In another embodiment, step (a) can comprise mixing

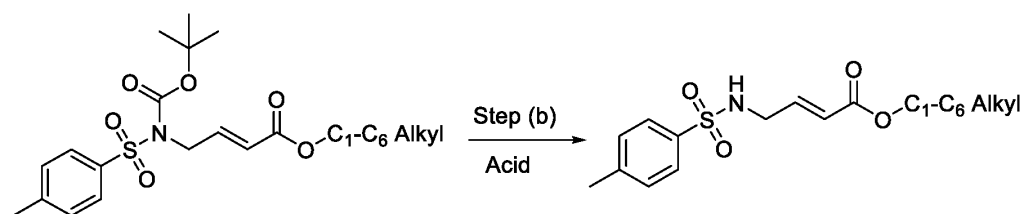


[0072] Additional components to step (a) may include a base, such as potassium carbonate, and/or a salt, such as potassium iodide.

[0073] (b) Mixing C₁-C₆ Alkyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate with an acid

[0074] Step (b) of the method to prepare a SSTR4 agonist compound can include the mixing the product generated in step (a), C₁-C₆ Alkyl (E)-4-((N-(*tert*-

butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate, with a suitable acid in a polar aprotic solvent as shown in Formula VII.



[0075] Formula VII. Step (b) of Method for Preparing SSSTR4 Agonist Compound

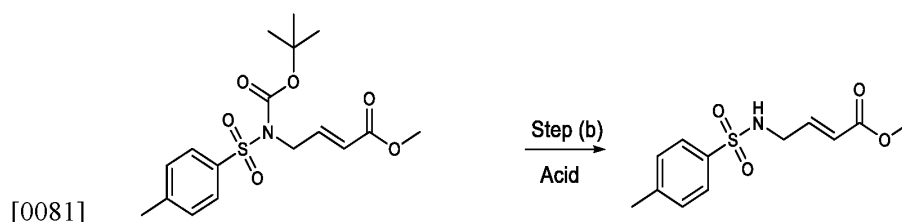
[0076] The components of step (b) can be combined in a polar aprotic solvent at a temperature of from about 10 °C to about 25 °C, from about 15 °C to 25 °C, or from 20 °C to 25 °C. The temperature of the mixture of components in step (b) can be increased to from about 40 °C to about 75 °C, from about 40 °C to about 60 °C, or from about 55 °C to about 60 °C. The reaction solution can remain at the elevated temperature for at least 4 hrs., at least 10 hrs., or at least 12 hrs.

[0077] After mixture of the step (b) components are heated to the elevated temperatures, the solution can be concentrated, and the remaining polar aprotic solvent exchanged with toluene and/or ethyl acetate.

[0078] The polar aprotic solvent can be the same solvent as in step (a) so that the product can remain in solution without any additional purification steps other than filtration of byproducts or the solvent can be a different polar aprotic solvent.

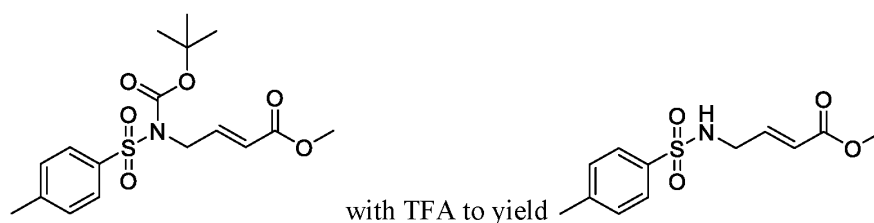
[0079] The suitable acid in step (b) can be any acid that can be used to remove the *tert*-butyl ester from the tertiary amine to form a secondary amine. Suitable acids include TFA, hydrochloric acid, sulfuric acid, hydrofluoric acid, among other acids.

[0080] In another embodiment, step (b) can comprise mixing methyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate with TFA in MeCN to yield methyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate as shown in Formula VIII.



[0082] Formula VIII. Step (b) of Method for Preparing SSTR4 Agonist

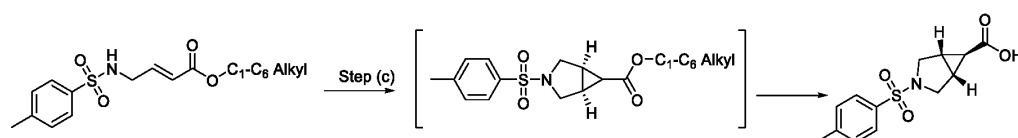
[0083] In another embodiment, step (b) can comprise mixing



[0084] Step (c) Mixing C₁-C₆ Alkyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate with Sulfonium Salt

[0085] Step (c) of the method to prepare a SSTR4 agonist compound can include the mixing the product generated in step (b), C₁-C₆ Alkyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate, with a sulfonium salt in a suitable heterocycle solvent as shown in Formula IX to yield an intermediate compound, (1R,5S)-3-(p-Tolylsulfonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

[0086]



[0087] Formula IX. Step (c) of Method for Preparing SSTR4 Agonist

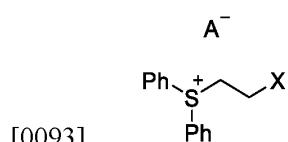
[0088] The components of step (c) can be combined at from -10 °C to 10 °C or about 0 °C. In addition to the sulfonium salt and the C₁-C₆ Alkyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate, potassium fluoride and/or potassium hydroxide may be added. The temperature of the solution can be gradually or step-wise increased to 30 °C over a period of from about 10 hrs. to about 30 hrs.

[0089] Suitable heterocycle solvents include tetrahydrofuran, furan, 2-methyl-tetrahydrofuran, among others.

[0090] After the temperature of the solution has been increased, a base, such as lithium hydroxide, can be added at the increased temperature and the reaction can be allowed to proceed for an additional period of time. The additional period of time can be from about 8 hrs. to about 24 hrs., from about 12 hrs. to about 18 hrs., or about 16 hrs.

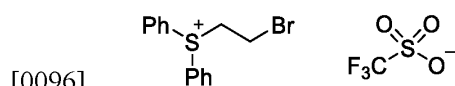
[0091] The intermediate compound, (1R,5S)-3-(p-Tolylsulfonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid can be separated from solution using traditional synthetic organic chemistry separation techniques well known to a person of ordinary skill in the art.

[0092] The sulfonium salt used in step (c) can be represented by Formula X, wherein X is a halogen leaving group, such as Cl, Br, or I and A is any suitable anion, which will be well known to a person of ordinary skill in the art.



[0094] Formula X. Sulfonium Salt for Step (c)

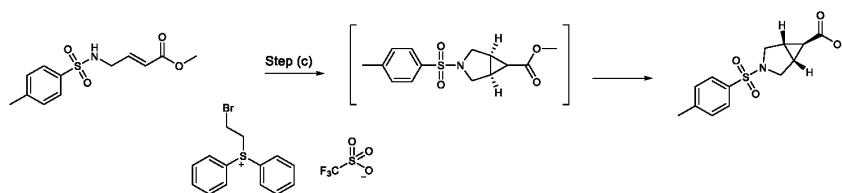
[0095] The sulfonium salt used in step (c) can also be represented by Formula XI.



[0097] Formula XI. Sulfonium Salt for Step (c)

[0098] In another embodiment, step (c) can comprise mixing Methyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate with 2-(bromoethyl)diphenylsulfonium triflate to yield (1R,5S)-3-(p-Tolylsulfonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid, the intermediate compound as shown in Formula XII.

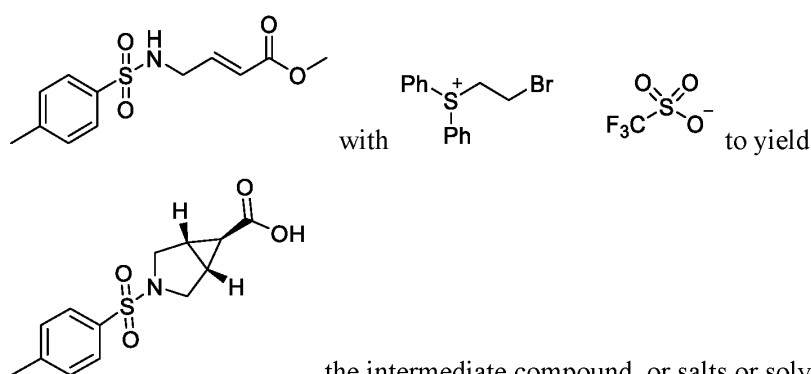
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[0099]

[0100] Formula XII. Step (c) of Method for Preparing SSTR4 Agonist

[0101] In another embodiment, step (c) can comprise mixing

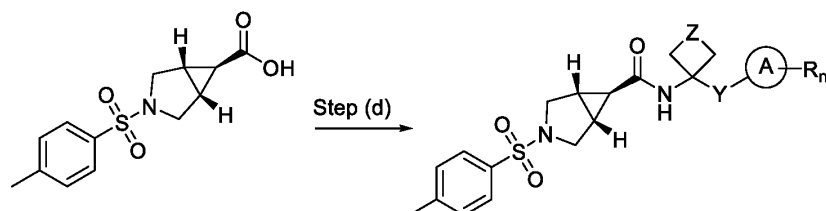


, the intermediate compound, or salts or solvates thereof.

[0102] Step (d) Mixing (1R,5S)-3-(p-Tolylsulfonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid with a suitable amine, such as 2-(1-methyl-1H-indazol-3-yl)propan-2-amine

[0103] Step (d) of the method to prepare a SSTR4 agonist compound can include the mixing the intermediate compound generated in step (c), (1R,5S)-3-(p-Tolylsulfonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid, with a suitable as shown in Formula XIII-A.

[0104]



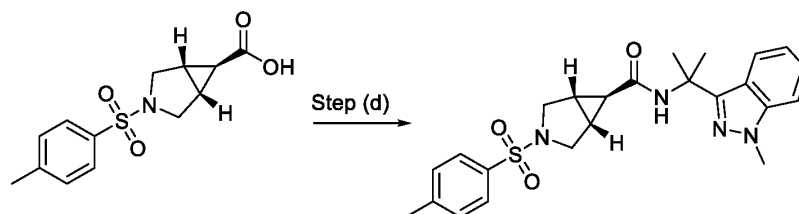
[0105]

[0106] Formula XIII-A. Step (d) of Method for Preparing SSTR4 Agonist

[0107] Step (d) of the method to prepare a SSTR4 agonist compound can also include the mixing the intermediate compound generated in step (c), (1R,5S)-3-(p-

tolylsulfonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid, with 2-(1-methyl-1H-indazol-3-yl)propan-2-amine, as shown in Formula XIII-B.

[0108]



[0109]

[0110] Formula XIII-B - Step (d) of Method for Preparing SSTR4 Agonist

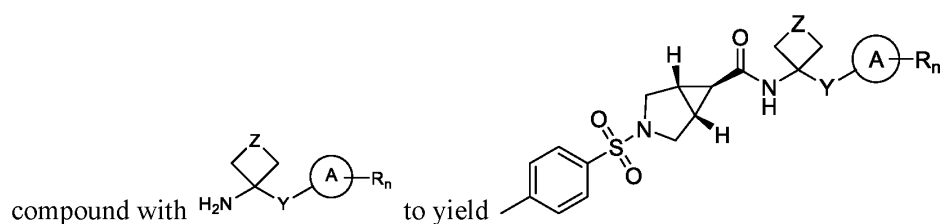
[0111] Prior to the addition of the suitable amine, the intermediate compound can be reacted with a suitable reagent, such as oxalyl chloride or thionyl chloride, to generate an acid chloride *in situ*, replacing the -OH functional group with a -Cl under synthetic conditions well known to a person of ordinary skill in the art.

[0112] The generated acid chloride can be combined with a suitable amine at a temperature of from about -10 °C to about 10 °C or from about 0 °C to about 10 °C.

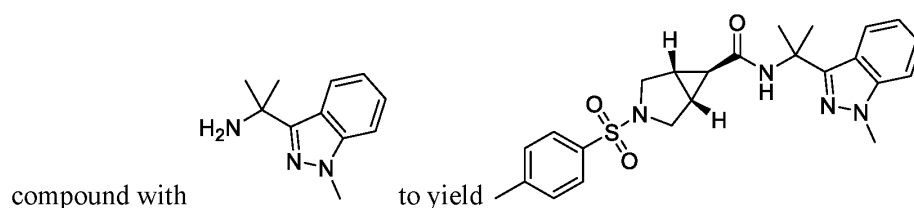
[0113] The solution temperature can be increased to from about 15 °C to about 25 °C after from about 2 to about 4 hrs.

[0114] Some examples of suitable amines include 2-methyl-1-((3-methylpyridin-2-yl)oxy)propan-2-amine, 2-(1-methyl-1H-indazol-3-yl)propan-2-amine, among others. Suitable amines can be selected to yield the desired SSTR4 agonist compound.

[0115] In another embodiment, step (d) can comprise mixing intermediate

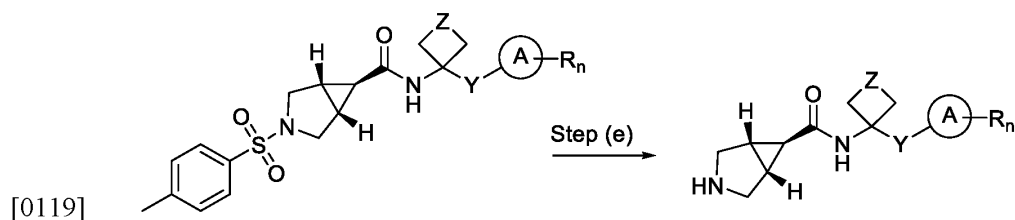


[0116] In another embodiment, step (d) can comprise mixing intermediate



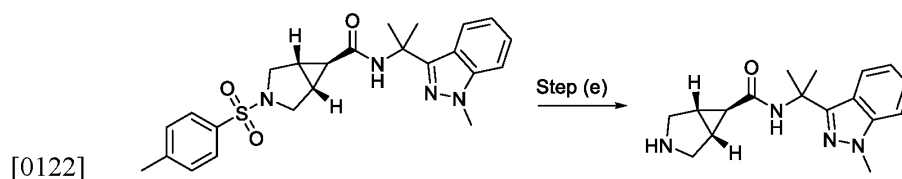
[0117] Step (e) Removal of Tosyl Functional Group with potassium diphenylphosphine

[0118] Step (e) of the method to prepare a SSTR4 agonist compound can include the mixing the product generated in step (d) with potassium diphenylphosphine as shown in Formula XIV-B.



[0120] Formula XIV-A. Step (e) of Method for Preparing SSTR4 Agonist

[0121] Step (e) of the method to prepare a SSTR4 agonist compound can include the mixing the product generated in step (d), such (1R,5S,6r)-N-(2-(1-methyl-1H-indazol-3-yl)propan-2-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane-6-carboxamide, with potassium diphenylphosphine as shown in Formula XIV-B.



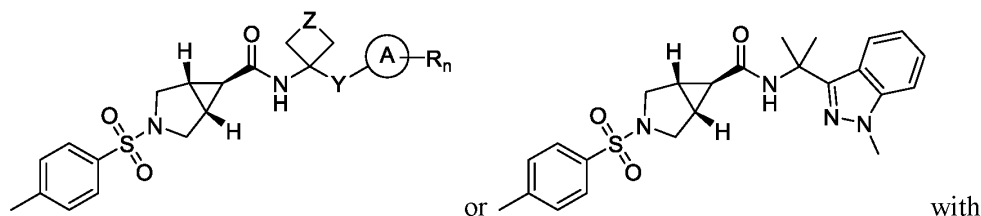
[0123] Formula XIV-B. Step (e) of Method for Preparing SSTR4 Agonist

[0124] (1R,5S,6r)-N-(2-(1-methyl-1H-indazol-3-yl)propan-2-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane-6-carboxamide, or another suitable SSTR4 agonist precursor generated in step (d) can be dissolved in a suitable solvent, such as methyl *tert*-butyl ether. The temperature can be decreased to from about -100 °C to about -50 °C, from about -80 °C to about -55 °C, or from about -70 °C to about -60 °C. Potassium diphenylphosphine can be added dropwise with the decreased temperature maintained.

[0125] After the entire amount of potassium diphenylphosphine has been added, the solution decreased temperature can be maintained for at least 4 hrs., at least 6 hrs., or at least 8 hrs. The solution can then be allowed to rise to a temperature of from about 15 °C to about 25 °C and the SSTR agonist compound, (1R,5S,6r)-N-(2-(1-Methyl-1H-

indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide can be isolated from solution using typical methods well known to a person of ordinary skill in the art.

[0126] In another embodiment, step (e) can comprise mixing



potassium diphenylphosphine to yield the SSTR4 agonist compound.

[0127] Salts of SSTR4 Agonist Compound

[0128] Also disclosed herein is a method for preparing a pharmaceutically acceptable salt of a SSTR4 agonist compound. The method for preparing a pharmaceutically acceptable salt of a SSTR4 agonist compound can comprise (1) the disclosed method for preparing a SSTR4 agonist compound and (2) generating a pharmaceutically acceptable salt of the SSTR4 agonist through: (i) reaction with an acid, (ii) a salt metathesis reaction, and/or (iii) other reactions that can result in the formation of a pharmaceutically acceptable salt of the SSTR4 agonist compound.

[0129] Suitable pharmaceutically acceptable salts of SSTR4 agonist compounds can comprise adipate, bromide, chloride, besylate, esylate, mesylate, tosylate, phosphate, succinate, sulfate, citrate, tartrate, L-tartrate, malate, and/or L-malate anions. Other suitable salts can include (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide succinate, which can be described by the XRPD pattern of FIG. 2, and as (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide adipate, which can be described by the XRPD pattern of FIG. 3. Other suitable salts are shown in Formula IV.

[0130] Hydrates of SSTR4 Agonist Compound

[0131] Also disclosed herein are hydrates of SSTR4 agonist compound and hydrates of salts of SSTR4 agonist compound. A suitable hydrate includes (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide hydrate, which can be described by the XRPD pattern shown in FIG. 1.

[0132] Compositions

[0133] Also disclosed herein is a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof with one or more pharmaceutically acceptable carriers, diluents, or excipients. In some embodiments, the composition further comprises one or more therapeutic agents.

[0134] In some embodiments, the pharmaceutical composition is a tablet composition, a capsule composition, or an aqueous composition. Suitable inactive ingredients in the tablet composition include microcrystalline cellulose, croscamellose sodium, sodium stearyl fumarate, among others.

[0135] In some embodiments, the pharmaceutical composition is a capsule composition. In some embodiments, the capsule composition can include the SSTR4 agonist compound, or a hydrate or pharmaceutically acceptable salt thereof, without any inactive ingredients. In some embodiments, the capsule composition can include one or more pharmaceutically acceptable carriers, diluents, or excipients. In some embodiments, the capsule composition can include microcrystalline cellulose, silica dioxide, colloidal silica dioxide, among other suitable inactive ingredients.

[0136] Methods of Treatment

[0137] Also disclosed herein is a method of treating pain in a patient comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof with one or more pharmaceutically acceptable carriers, diluents, or excipients.

[0138] Also disclosed herein is a method of treating chronic back pain, including chronic lower back pain, in a patient comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or

Formula IV or a hydrate thereof with one or more pharmaceutically acceptable carriers, diluents, or excipients.

[0139] Also disclosed herein is a method of treating neuropathic pain in a patient comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof with one or more pharmaceutically acceptable carriers, diluents, or excipients. In some embodiments, the neuropathic pain is diabetic peripheral neuropathic pain, central neuropathic pain, and/or mixed neuropathy.

[0140] Also disclosed herein is a method of treating pain associated with osteoarthritis in a patient comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof with one or more pharmaceutically acceptable carriers, diluents, or excipients.

[0141] Also disclosed herein is a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof, for use in therapy. Additionally, disclosed herein is a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof for use in the treatment of pain. Also disclosed herein is a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof for use in the treatment of chronic back pain, including chronic lower back pain. Also disclosed herein is a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof for use in the treatment of neuropathic pain. In some embodiments the neuropathic pain is diabetic peripheral neuropathic pain, central neuropathic pain, and/or

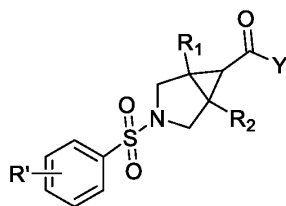
mixed neuropathy. Also disclosed herein is a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof for use in the treatment of pain associated with osteoarthritis.

[0142] In addition, also disclosed herein is the use of a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, Formula I-A, or a pharmaceutically acceptable salt or hydrate thereof, Formula III or a pharmaceutically acceptable salt or hydrate thereof, or Formula IV or a hydrate thereof for the manufacture of a medicament for the treatment of a disease or condition selected from pain, chronic back pain, including chronic lower back pain, neuropathic pain and pain associated with osteoarthritis. In some embodiments the neuropathic pain is diabetic peripheral neuropathic pain, central neuropathic pain, and/or mixed neuropathy.

[0143] Intermediate Compound

[0144] Also disclosed herein are new intermediate compounds generated during the disclosed method for the preparation of the SSSTR4 agonist compounds or pharmaceutically acceptable salts thereof, hydrates thereof, and/or solvates thereof. Suitable intermediates can be generated at any time during the disclosed method. Suitable intermediates can be isolated as a neat compound or generated only in solution.

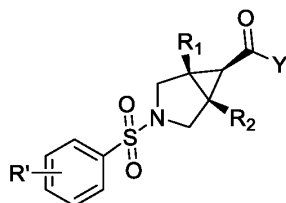
[0145] Suitable intermediates for the preparation of SSSTR4 agonist compounds or pharmaceutically acceptable salts thereof, hydrates thereof, and/or solvates thereof, can include the intermediates of Formula XV or pharmaceutically acceptable salts thereof, hydrates thereof, and/or solvates thereof, wherein Y is H, OH, NH₂, Cl, Br, I, C₁ to C₆ alkyl, C₁ to C₆ ether, or combinations thereof, R₁ and R₂ are independently H, OH, NH₂, Cl, Br, I, C₁ to C₆ alkyl, C₁ to C₆ ether, or combinations thereof, and the phenyl functional group is substituted with one or more R' and wherein each R' group are independently H, OH, NH₂, Cl, Br, I, C₁ to C₆ alkyl, C₁ to C₆ ether, or combinations thereof. In an embodiment, Y can be OH, Cl, Br, I, or NH₂, R₁ and R₂ can be H, and R' can be CH₃ in the *para* position.



[0146]

[0147] Formula XV. Intermediate Compound

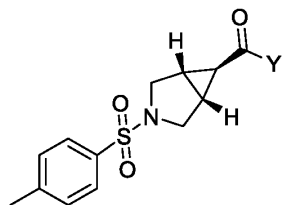
[0148] In an embodiment, the intermediate compound can also be represented by Formula XVI or pharmaceutically acceptable salts thereof, hydrates thereof, and/or solvates thereof, wherein Y can be H, OH, NH₂ Cl, Br, I, C₁ to C₆ alkyl, C₁ to C₆ ether, or combinations thereof, R₁ and R₂ independently can be H, OH, NH₂ Cl, Br, I, C₁ to C₆ alkyl, C₁ to C₆ ether, or combinations thereof, and the phenyl functional group is substituted with one or more R' and wherein each R' group are independently H, OH, NH₂ Cl, Br, I, C₁ to C₆ alkyl, C₁ to C₆ ether, or combinations thereof. In an embodiment, Y can be OH, Cl, Br, I, or NH₂ R₁ and R₂ can be H, and R' can be CH₃ in the *para* position.



[0149]

[0150] Formula XVI. Intermediate Compound

[0151] In an embodiment, the intermediate compound can also be represented by Formula XVII or pharmaceutically acceptable salts thereof, hydrates thereof, and/or solvates thereof, Y can be H, OH, NH₂ Cl, Br, I, C₁ to C₆ alkyl, C₁ to C₆ ether, or combinations thereof. In an embodiment, Y can be OH, NH₂ Cl, Br, or I.

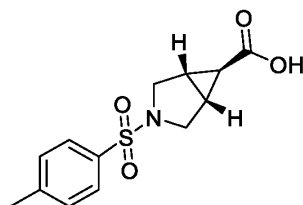


[0152]

[0153]

[0154] Formula XVI. Intermediate Compound

[0155] In an embodiment, the intermediate compound can also be represented by Formula XVIII or pharmaceutically acceptable salts thereof, hydrates thereof, and/or solvates thereof.



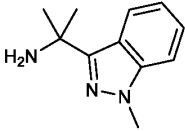
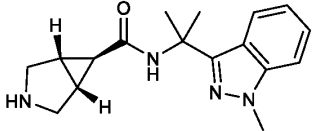
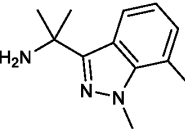
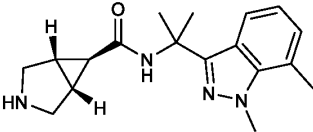
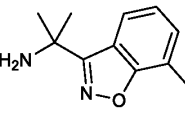
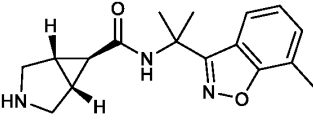
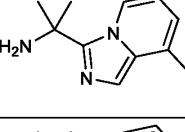
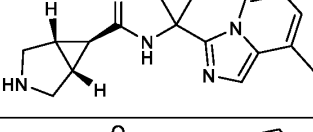
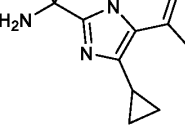
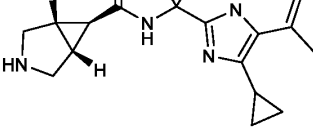
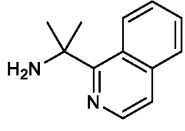
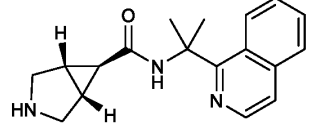
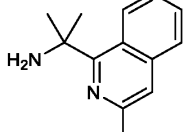
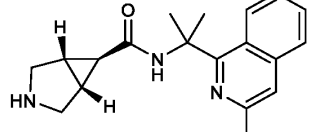
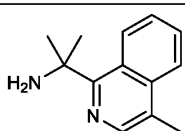
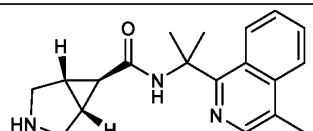
[0156]

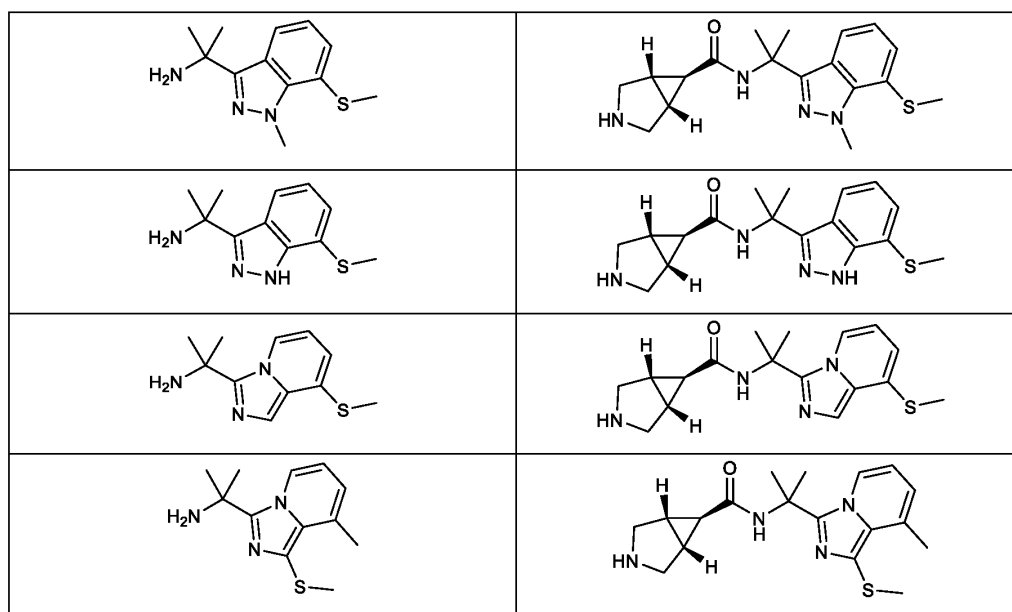
[0157] Formula XVIII. Intermediate Compound

[0158] The intermediate compound, as described herein, can be used for the preparation of the SSTR4 agonist compound or pharmaceutically acceptable salts thereof, hydrates thereof, and/or solvates thereof. The intermediate compound offers a stable scaffold to produce a variety of SSTR4 agonist compounds through an amide-carboxylic acid coupling reaction, such as in step (d) of the method for preparing the SSTR4 agonist compound, as described herein and illustrated in Formula VIII.

[0159] TABLE A displays some possible SSTR4 agonist compounds that can be synthesized using the disclosed method through the intermediate compound.

TABLE 1. SSTR4 Agonist Compounds that Can be Synthesized Using Amide Coupling Reaction with Intermediate Compound

Amine	SSTR4 Agonist Compound
	
	
	
	
	
	
	
	



[0160] As used herein, the terms “a,” “an,” “the,” and similar terms used in the context of the present disclosure (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[0161] As used herein, the terms “treating” or “to treat” includes restraining, slowing, stopping, or reversing the progression or severity of an existing symptom or disorder.

[0162] As used herein, the term “patient” refers to a mammal, such as a mouse, guinea pig, rat, dog, or human. It is understood that the preferred patient is a human.

[0163] As used herein, the term “effective amount” refers to the amount or dose of compound of the invention which, upon single or multiple dose administration to the patient, provides the desired effect in the patient under diagnosis or treatment.

[0164] An effective amount can be readily determined by one skilled in the art by the use of known techniques. In determining the effective amount for a patient, a number of factors are considered, including, but not limited to: the species of patient; its size, age, and general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the

bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

[0165] As used herein, the term “alkyl” means saturated linear or branched-chain monovalent hydrocarbon radical, containing the indicated number of carbon atoms. For example, “C₁-C₂₀ alkyl” means a radical having 1-20 carbon atoms in a linear or branched arrangement.

[0166] As used herein, the term “C₁-C_n thioether” refers to a straight, or branched chain saturated hydrocarbon containing 1 to n carbon atoms containing a terminal “S” in the chain, *i.e.*, -S(alkyl), wherein the thioether group can be attached to the desired location at the sulfur atom. The term “C₁-C_n thioether” also refers to a cycloalkyl or aryl radical containing a terminal “S” in the molecule, *i.e.*, -S(aryl), wherein the thioether group can be attached to the desired location at the sulfur atom. The term “C₁-C_n thioether” can include a saturated hydrocarbon chain and either a cycloalkyl or aryl, *i.e.*, -S-CH₂-(aryl), with n referring to the number of total carbon atoms in the substituent.

[0167] As used herein, the term “C₁-C_n ether” refers to a straight, or branched chain saturated hydrocarbon containing 1 to n carbon atoms containing a terminal “O” in the chain, *i.e.*, -O(alkyl), wherein the ether group can be attached to the desired location at the oxygen atom. The term C₁-C_n ether also refers to a cycloalkyl or aryl radical containing a terminal “O” in the molecule, *i.e.*, -O(aryl), wherein the ether group can be attached to the desired location at the oxygen atom. The term “C₁-C_n ether” can also include a saturated hydrocarbon chain and either a cycloalkyl or aryl, *i.e.*, -O-CH₂-(aryl), with n referring to the number of total carbon atoms in the substituent.

[0168] As used herein, the term “cycloalkyl” means a radical derived from a non-aromatic monocyclic or polycyclic ring comprising carbon and hydrogen atoms. The cycloalkyl can have one or more carbon-carbon double bonds in the ring as long as the ring is not rendered aromatic by their presence. The cycloalkyl group can be unsubstituted or substituted with from one to three suitable substituents, which are well known to a person of ordinary skill in the art. The cycloalkyl group can be referred to by the number of total carbon atoms in the monocyclic or polycyclic ring. For example, a C₃ to C₇ cycloalkyl includes cycloalkyl radical group with 3, 4, 5, 6, or 7 carbon atoms.

[0169] As used herein, the term “heterocycloalkyl” means a radical derived from a non-aromatic monocyclic or polycyclic ring comprising one or more carbon atoms and

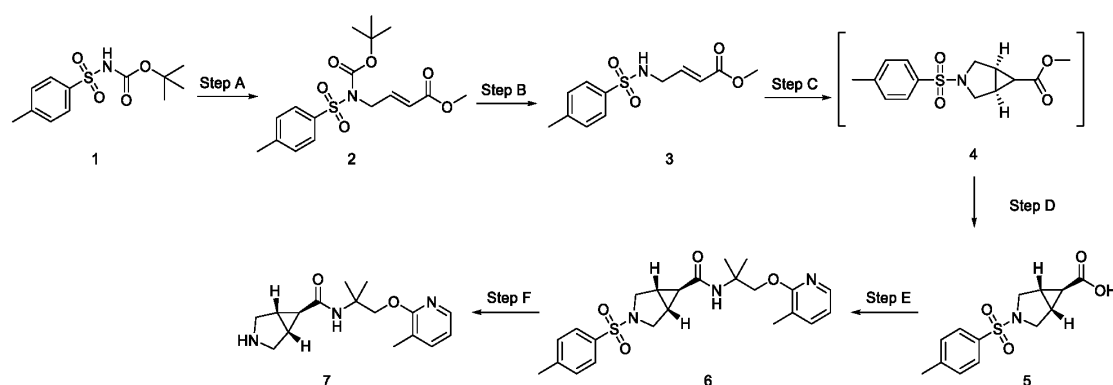
one or more heteroatoms, such as nitrogen, oxygen, and sulfur. A heterocycloalkyl group can have one or more carbon-carbon double bonds or carbon-heteroatoms double bonds in the ring as long as the ring is not rendered aromatic by their presence. Examples of heterocycloalkyl groups include aziridinyl, pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. The heterocycloalkyl group can be referred to by the number of total atoms in the monocyclic or polycyclic ring. For example, a four member to seven-member heterocycloalkyl includes four, five, six, or seven members (including carbon atoms and heteroatoms).

[0170] As used, herein, the term “aryl” means a radical derived from an aromatic monocyclic or polycyclic ring including only carbon atoms in the monocyclic or polycyclic ring. The aryl group can be unsubstituted or the aryl group can be substituted with from 1 to 5 suitable substituents, which are well known to a person of ordinary skill in the art. The aryl group can be referred to by the number of total carbon atoms in the monocyclic or polycyclic ring. For example, a C₅ to C₇ aryl includes an aryl radical group with 5, 6, or 7 carbon atoms.

[0171] As used herein, the term “heteroaryl” means a radical derived from an aromatic monocyclic or polycyclic ring including one or more carbon atoms and one or more heteroatoms in the monocyclic or polycyclic ring. The heteroaryl group can be unsubstituted or the heteroaryl group can be substituted with from 1 to 5 suitable substituents, which are well known to person of ordinary skill in the art. The heteroaryl group can be referred to by the number of total atoms in the monocyclic or polycyclic ring. For example, a four member to seven-member heteroaryl includes four, five, six, or seven members (including carbon atoms and heteroatoms).

EXAMPLES

[0172] Certain abbreviations are defined as follows: “DCM” refers to dichloromethane; “DMAP” refers to 4-dimethylaminopyridine; “DMF” refers to dimethylformamide; “EtOAc” refers to ethyl acetate; “EtOH” refers to ethanol; “hr/hrs” refers to hr/hrs; “MeCN” refers to acetonitrile; “MeOH” refers to methanol; “MTBE” refers to methyl tert-butyl ether; “MeTHF” refers to methyltetrahydrofuran; “Ph₂PK” refers to potassium diphenylphosphide; “TEA” refers to triethylamine; “TFA” refers to trifluoroacetic acid; and “THF” refers to tetrahydrofuran.



[0173] Scheme 1. Commercial Synthesis of an SSSTR4 Agonist

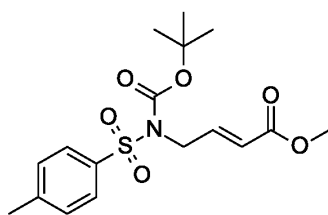
[0174] Ring A, Rⁿ, and Y are as defined earlier.

[0175] Scheme 1, step A depicts a coupling mixing compound (1) with methyl 4-bromobut-2-enoate using an appropriate base such as potassium carbonate and potassium iodide in a suitable solvent such as MeCN at a suitable temperature (e.g., 30 to 60 °C) to give compound (2). Step B shows the deprotection of compound (2) using an acid such as TFA in solvents such as MeCN to give compound (3). Step C shows a cyclization mixing compound (3) using (2-haloethyl)diphenylsulfonium such as (2-bromoethyl)diphenylsulfonium triflate in presence of base KOH, KF, and a suitable solvent such as 2-MeTHF to give compound (4). In step D, water, and a base such as LiOH are used to convert compound (4) to compound (5). Step E shows a coupling mixing compound (5) with a heteroaryl or aryl compound such as 2-(1-methyl-1H-indazol-3-yl)propan-2-amine or 2-methyl-1-((3-methylpyridin-2-yl)oxy)propan-2-amine

in the presence of a catalyst such as COCl_2 and solvents such as DMF, toluene, and DCM to give compound (6). Step F shows conversion of compound (6) to compound (7) by reacting compound (6) with Ph_2PK in a solvent such as MTBE or THF under a suitable temperature (e.g., heating from 60 to 70 °C) to give compound (7). Step G shows the method of generating a salt with a method such as reaction with an acid, salt metathesis reaction, and/or other reactions that can result in the formation of a pharmaceutically acceptable salt (8). The salt can include for example citrate, succinate, adipate, tartrate, L-tartrate, malate, and/or L-malate anions.

[0176] Preparation 1

[0177] Methyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate

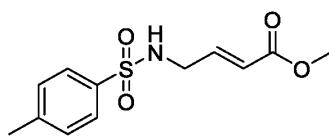


[0178]

Methyl 4-bromobut-2-enoate (36.29 g, 202.7 mmol) was dissolved in MeCN (500 mL) at 15~25 °C. *tert*-Butyl tosylcarbamate (50.00 g, 184.3 mmol), K_2CO_3 (30.57 g, 221.2 mmol) and KI (3.06 g, 202.7 mmol) were added to the solution at 15~25 °C, and warmed under nitrogen at 30 °C for 20 hrs. The solution was cooled to 20 °C and the mixture filtered. The filtered residue was washed with MeCN (100 mL) to give the title product as a solution to be used directly in the next step without isolation.

[0179] Preparation 2

[0180] Methyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate



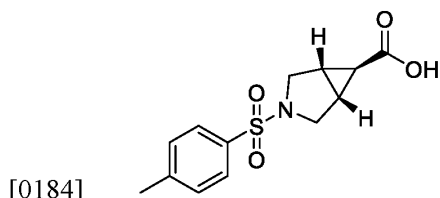
[0181]

[0182] Methyl 4-bromobut-2-enoate (36.29 g, 202.7 mmol) was dissolved in MeCN (500 mL) at 15-25 °C. *tert*-Butyl tosylcarbamate (50.00 g, 184.3 mmol) was

added at 15-25 °C. K_2CO_3 (30.57 g, 221.2 mmol) and KI (3.06 g, 202.7 mmol) were added to the solution at 15-25 °C, and warmed under nitrogen at 30 °C for 20 hrs. The solution was cooled to 20 °C and the mixture filtered. The filtered residue was washed with MeCN (100 mL) to give methyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate. TFA (101.03 g, 886.06 mmol) was added to the methyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate in MeCN solution (483.72 g, 143 mmol) and heated to 55-60 °C for 16 hrs. The reaction solution was concentrated *in vacuo* to ~50 mL and solvent exchanged with toluene (2 x 250 mL). Toluene (500 mL) was added followed by EtOAc (50 mL) at 15-25 °C, and heated to 60 °C for 1 hr., then cooled to 0 °C for 12 hrs. The solution was filtered, and the wet cake rinsed with n-heptane (50 mL). The cake was dried in vacuum at 50 °C to give the title compound (37.85 g, 74.4%) as a white solid. 1H NMR ($CDCl_3$) δ 7.68 (d, J = 8.0Hz, 2H) 7.25 (d, J = 8.0Hz, 2H) 6.71 (dt, J = 15.6, 5.2Hz, 1H) 5.88 (dt, J = 15.6, 1.6Hz, 1H) 4.55 (t, J = 6.4Hz, 1H) 3.71 – 3.67 (m, 2H) 3.65 (s, 3H) 2.37 (s, 3H); HRMS (ESI^+) Calculated for $[C_{12}H_{15}NO_4S+H]^+$: 270.0795, Found: 270.0788 (M+H).

[0183] Preparation 3

(1R,5S,6r)-3-Tosyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



[0185] Methyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate (36.50 g 111.4

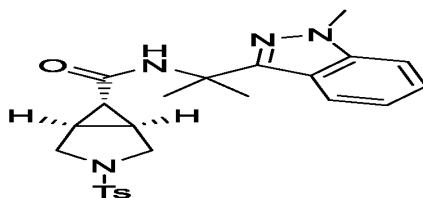
mmol) was dissolved in 2-MeTHF (600 mL) at 0 °C. Added (2-bromoethyl)diphenylsulfonium triflate (51.90 g, 117.1 mmol), KF (6.47 g, 111.6 mmol), KOH (18.75 g, 334 mmol) to the solution at 0 °C. Warmed the solution to 15 °C for 22 hrs. then 30 °C for 3 hrs. Added water (100 mL) and MeOH (100 mL) into the solution. Added LiOH·H₂O (4.77 g, 113mmol) and stirred at 30 °C for 16 hrs. Cooled to 15-25 °C and added n-heptane (100 mL). Stirred at 15-25 °C for 10 min. Separated and collected the aqueous phase and washed the aqueous phase with n-heptane/2-MeTHF (50 mL/200 mL x 2). Concentrated the aqueous phase *in vacuo* to ~50 mL and added 3M aqueous

HCl dropwise to adjust pH to 1~2. Stirred the mixture at 20-30 °C for 2 hrs. Filtered the solution and rinsed through with EtOH/H₂O (15 mL 1:4). Dried the wet cake at 45 °C for 8-10 hrs. to give the title compound as gray solid (20.37 g, 65%) ¹H NMR (CDCl₃) δ 7.67 (d, *J* = 8.2 Hz, 2 H) 7.34 (d, *J* = 8.2 Hz, 2 H) 3.63 (d, *J* = 9.4 Hz, 2 H) 3.12 (d, *J* = 9.4 Hz, 2 H) 2.46 – 2.40 (m, 4 H) 2.07 – 2.01 (m, 2 H); HRMS (ESI⁺) Calcd. for [C₁₃H₁₅NO₄S+H]⁺: 282.0795, Found: 282.0795 (M+H).

[0186] Preparation 4

[0187] (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane-6-carboxamide

[0188]



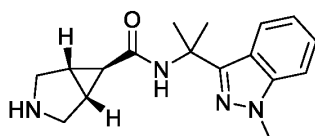
[0189]

[0190] Oxalyl chloride (91.6 g, 721.5 mmol) was added to a mixture of (1*R*,5*S*,6*r*)-3-tosyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (135.2 g, 481 mmol) in toluene (1350 mL), followed by addition of DMF (3.51 g, 48 mmol). The mixture was heated at 50 °C for 30 minutes. After cooling to ambient temperature, the solvent was removed under reduced pressure. The residual was co-evaporated with THF (2 x 600 mL). THF (1350 mL) was added to the residual, followed by addition of TEA (145.7 g, 1443 mmol), DMAP (2.93 g, 24 mmol) and 2-(1-methyl-1*H*-indazol-3-yl)propan-2-amine (CAS No. 1539323-37-9, 100 g, 529.1 mmol) at 0 °C. The reaction was stirred at 0 °C for 15 minutes, then at ambient temperature for 2 hrs. The solvent was removed under reduced pressure and the residue was diluted with DCM (800 mL) and water (800 mL). Two layers were separated, and the aqueous layer was extracted with DCM (3 x 400 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was triturated with a 10 to 1 mixture of MTBE and DCM (1000 mL) for 16 hrs. The mixture was filtered to give the title product (136.5 g, 63%) as light brown solid. ¹H-NMR (CDCl₃) δ = 7.78 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.69 (dt, *J* = 8.4, 2 Hz, 2H),

7.42 – 7.31 (m, 5 H), 7.15 – 7.11 (m, 1 H), 4.05 (s, 3H), 3.66 (d, $J = 9.6$ Hz, 2H), 3.05 (dd, $J = 8.0, 1.2$ Hz, 2H), 2.43 (s, 3 H), 1.96 – 1.95 (m, 2H), 1.90 (s, 6H), 1.69 (t, $J = 3.2$ Hz, 1H) ES/MS m/z : 453 [M+1]. $R_t = 3.4$ min

[0191] Example 1

[0192] (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide

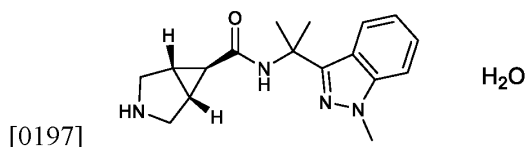


[0193]

[0194] Potassium *tert*-butoxide (27.2 g, 243 mmol) was added at ambient temperature to a solution of diphenylphosphine (45.2 g, 243 mmol) in anhydrous THF (240 mL). The suspension was stirred at ambient temperature for 10 minutes. The resulting potassium diphenylphosphine solution was then transferred to a solution of compound (1*R*,5*S*,6*r*)-*N*-(2-(1-methyl-1*H*-indazol-3-yl)propan-2-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane-6-carboxamide (110 g, 243 mmol) in anhydrous THF (1500 mL) at 66 °C. The fresh prepared potassium diphenylphosphine solution was added every 1.5 hrs. The reaction was stirred at 66 °C for additional 16 hrs. After cooling to ambient temperature, the reaction mixture was adjusted to pH 1 with 3.0 M HCl (650 mL). The volatiles were removed under reduced pressure. The aqueous solution was washed with EtOAc (600 mL and 5 x 300 mL). The aqueous layer was adjusted to pH 8 with saturated potassium carbonate, and extracted with DCM (600 mL), then adjusted to pH 12 with saturated potassium carbonate and extracted with DCM (6 x 300 mL). The combined organic layers were dried over sodium sulfate (100 g), filtered, and concentrated under reduced pressure. The residue was purified using column chromatography eluting with 10% DCM in MeOH with 10% ammonium hydroxide to give the title product (62.77 g, 87% yield) as off-white solid. ¹H-NMR (CDCl₃) δ = 7.80 (d, $J = 8.4$ Hz, 1H), 7.41 – 7.35 (m, 2H), 7.20 (brs, 1 H), 7.15 – 7.11 (m, 1 H), 4.02 (s, 3 H), 3.09 (d, $J = 11.2$ Hz, 1H), 3.0 (d, $J = 11.2$ Hz, 1H), 1.96 (s, 2 H), 1.93 (s, 6H), 1.37 (t, $J = 3.2$ Hz, 1H). ES/MS m/z : 299.2 (M+1). $R_t = 3.1$ min.

[0195] Example 2

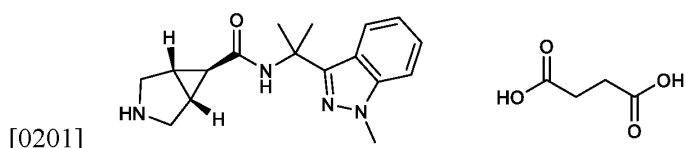
[0196] (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide monohydrate



[0198] Preparation of monohydrate (30 g) was placed in a reactor vessel with a 100 mL of ACN/H₂O (20:80). The suspension was mixed at room temperature and isolated after 24 hours of mixing. The solids were isolated by vacuum filtration and dried in vacuum oven to recover 8.2 g of the (1*R*,5*S*,6*r*)-*N*-(2-(1-methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide monohydrate.

[0199] Example 3

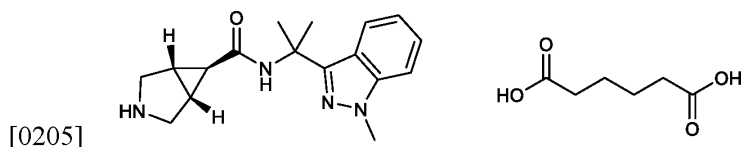
[0200] (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide succinate



[0202] 200 mg of (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide was dissolved in 3 mL of IPA at 40 °C. 67 mg of succinic acid (1.1 mol) was added in 3 mL IPA. A suspension was produced and cooled to room temperature for isolation. Scale up procedure used 10 g of (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide dissolved in 100 mL of IPA:H₂O (88:12). 4.5 g of succinic acid was added and heated to 55 °C for 1 hr. Cooled to 45 °C and seeded with material from procedure above for crystal growth. The suspension was cooled to room temperature after 2 hrs. at 45 °C. The solids were isolated by vacuum filtration after an additional 50 mL of IPA was added to increase the yield. 5.8 g of succinate salt was recovered after drying in vacuum oven at 45 °C.

[0203] Example 4

[0204] (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide adipate



[0206] 300 mg of (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide was dissolved in 5 mL of IPA at 30 °C. 148 mg of adipic acid (1 mol) was added to the solution. After acid addition a suspension was produced and cooled to room temperature for isolation. Scale up procedure used 15.4 grams of (1*R*,5*S*,6*r*)-*N*-(2-(1-Methyl-1*H*-indazol-3-yl)propan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide dissolved in 225ml of IPA at 50 °C. 9.1 g of adipic acid was added and seeded with the small-scale lot. The seeds were held for crystal growth. The suspension was cooled to room temperature. The solids were isolated by vacuum filtration and dried to give the adipate salt.

[0207] X-Ray Powder diffraction (XRPD) method

[0208] The XRPD patterns of crystalline solids are obtained on a Bruker D8 Endeavor X-ray powder diffractometer, equipped with a CuK α (1.5418Å) source and a Lynxeye™ detector, operating at 40 kV and 40 mA. The sample is scanned between 4 and 42 2 θ° , with a step size of 0.009 2 θ° and a scan rate of 0.5 seconds/step, and using 0.3° primary slit opening, and 3.9° PSD opening. The dry powder is packed on a quartz sample holder and a smooth surface is obtained using a glass slide. The crystal form diffraction patterns are collected at ambient temperature and relative humidity. Crystal peak positions are determined in MDI-Jade after whole pattern shifting based on an internal NIST 675 standard with peaks at 8.853 and 26.774 2 θ° . It is well known in the crystallographic art that, for any given crystal form, the relative intensities of the diffraction peaks may vary due to preferred orientation resulting from factors such as crystal morphology and habit. Where the effects of preferred orientation are present, peak intensities are altered, but the characteristic peak positions of the polymorph are unchanged. See, *e.g.* The United States Pharmacopeia #23, National Formulary #18, pages 1843-1844, 1995. Furthermore, it is also well known in the crystallography art that for any given crystal form the angular peak positions may vary slightly. For example,

peak positions can shift due to a variation in the temperature at which a sample is analyzed, sample displacement, or the presence or absence of an internal standard. In the present case, a peak position variability of $\pm 0.2^\circ$ is presumed to take into account these potential variations without hindering the unequivocal identification of the indicated crystal form. Confirmation of a crystal form may be made based on any unique combination of distinguishing peaks.

[0209] XRPD of Example 2

[0210] A prepared sample of Example 2 is characterized by an XRPD pattern using CuK α radiation as comprising diffraction peaks (2-theta values) as described/shown in Table 1, Table 2, and FIG. 1, and, in particular, comprising a peak at diffraction angle 2-theta of 10.1° and one or more of peaks 12.8° , 17.3° , or 21.9° ; with a tolerance for the diffraction angles of 0.2 degrees.

[0211] XRPD of Example 3

[0212] A prepared sample of Example 3 is characterized by an XRPD pattern using CuK α radiation as comprising diffraction peaks (2-theta values) as described/shown in TABLE 3, TABLE 4, and FIG. 2, and in particular comprising a peak at diffraction angle 2-theta of 22.6° and one or more of peaks 12.9° , 14.8° , or 18.2° ; with a tolerance for the diffraction angles of 0.2 degrees.

[0213] XRPD of Example 4

[0214] A prepared sample of Example 4 is characterized by an XRPD pattern using CuK α radiation as comprising diffraction peaks (2-theta values) as described/shown in TABLE 5, TABLE 6, and FIG. 3, and in particular comprising a peak at diffraction angle 2-theta of 11.5° and one or more of peaks 12.2° , 18.0° , or 22.4° ; with a tolerance for the diffraction angles of 0.2 degrees.

TABLE 1. X-ray powder diffraction peaks of Example 2 arranged by angle

	Example 2	
Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	10.1	100.0%
2	11.4	20.4%
3	12.8	53.1%
4	13.7	15.7%
5	15.0	12.1%
6	17.3	59.2%
7	19.9	7.7%
8	20.6	14.8%
9	21.0	8.0%
10	21.9	49.3%
11	23.7	18.8%
12	25.6	14.7%
13	26.5	22.2%

TABLE 2. X-ray powder diffraction peaks of Example 2 arranged by relative intensity

Peak	Example 2	
	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	10.1	100.0%
2	17.3	59.2%
3	12.8	53.1%
4	21.9	49.3%
5	26.5	22.2%
6	11.4	20.4%
7	23.7	18.8%
8	13.7	15.7%
9	20.6	14.8%
10	25.6	14.7%
11	15.0	12.1%
12	21.0	8.0%
13	19.9	7.7%

TABLE 3. X-ray powder diffraction peaks of Example 3 arranged by angle

	Example 3	
Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	12.9	35.1%
2	14.1	19.7%
3	14.8	67.0%
4	16.1	4.6%
5	16.4	5.9%
6	18.2	28.0%
7	19.7	7.5%
8	20.3	5.3%
9	21.3	11.7%
10	21.7	10.8%
11	22.6	100.0%
12	23.1	18.4%
13	26.0	6.8%

TABLE 4. X-ray powder diffraction peaks of Example 3 arranged by relative intensity

	Example 3	
Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	22.6	100.0%
2	14.8	67.0%
3	12.9	35.1%
4	18.2	28.0%
5	14.1	19.7%
6	23.1	18.4%
7	21.3	11.7%
8	21.7	10.8%
9	19.7	7.5%
10	26.0	6.8%
11	16.4	5.9%
12	20.3	5.3%
13	16.1	4.6%

TABLE 5. X-ray powder diffraction peaks of Example 4 arranged by angle

Example 4 (Adipate Salt)		
Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	5.9	6.7%
2	10.9	18.6%
3	11.5	100.0%
4	12.2	89.3%
5	13.7	23.3%
6	15.4	14.8%
7	15.8	25.8%
8	18.0	71.9%
9	18.7	19.2%
10	20.1	28.9%
11	22.4	45.4%
12	23.2	27.3%
13	25.3	15.4%

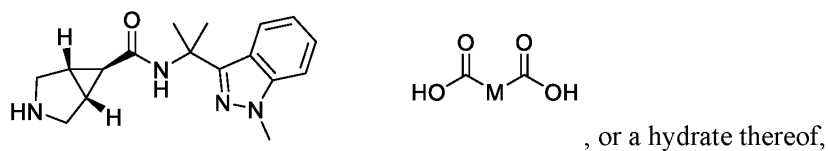
TABLE 6. X-ray powder diffraction peaks of Example 4 arranged by relative intensity

Example 4 (Adipate Salt)		
Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	11.5	100.0%
2	12.2	89.3%
3	18.0	71.9%
4	22.4	45.4%
5	20.1	28.9%
6	23.2	27.3%
7	15.8	25.8%
8	13.7	23.3%
9	18.7	19.2%
10	10.9	18.6%
11	25.3	15.4%
12	15.4	14.8%
13	5.9	6.7%

CLAIMS

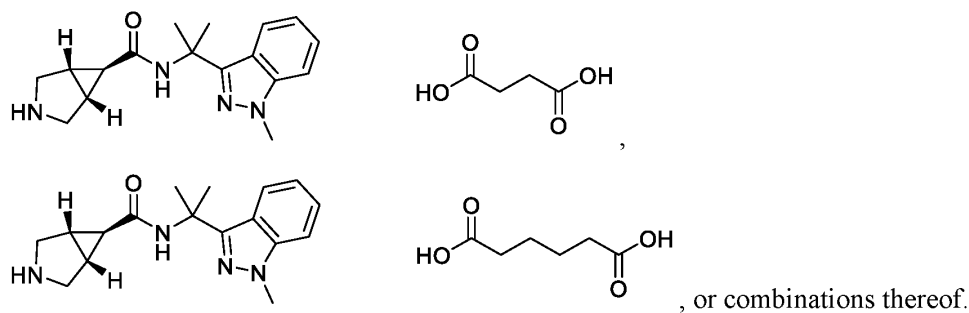
What is claimed is:

1. A compound of the formula:

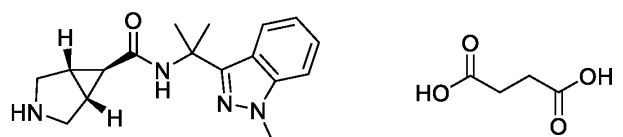


Wherein M is null or C₁ to C₆ alkyl.

2. The compound of claim 1, wherein the compound is of the formula:



3. The compound of claim 1 or 2, wherein the compound is of the formula:

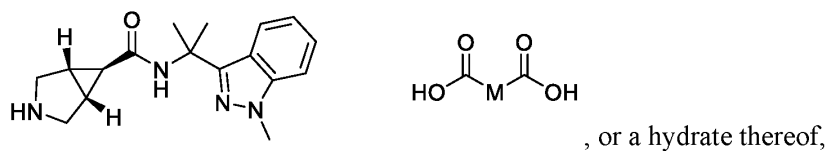


4. The compound of any one of claims 1 to 3, wherein the compound is crystalline.

CLAIMS

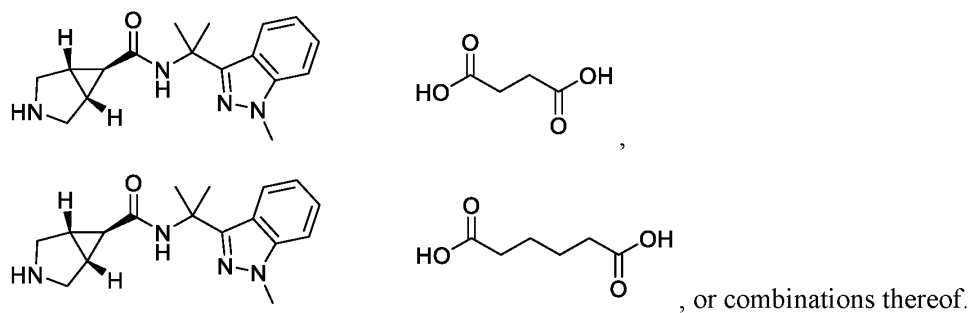
What is claimed is:

1. A compound of the formula:

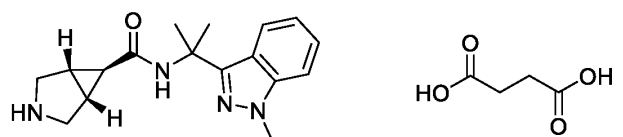


Wherein M is null or C₁ to C₆ alkyl.

2. The compound of claim 1, wherein the compound is of the formula:



3. The compound of claim 1 or 2, wherein the compound is of the formula:

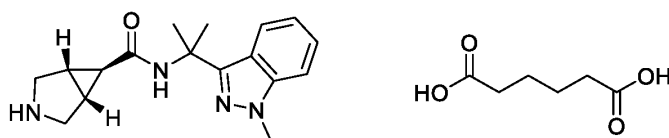


4. The compound of any one of claims 1 to 3, wherein the compound is crystalline.

5. The compound of claim 4, wherein the compound is characterized by an X-ray powder diffraction pattern using Cu K α radiation comprising a peak at diffraction angle 2θ of $22.6^\circ \pm 0.2^\circ$ and one or more of peaks 12.9° , 14.8° , or $18.2^\circ \pm 0.2^\circ$.

6. The compound of claim 4 or claim 5, wherein the compound is characterized by an X-ray powder diffraction pattern using Cu K α radiation comprising peaks at diffraction angle 2θ of 12.9° , 14.1° , 14.8° , 16.1° , 16.4° , 18.2° , 19.7° , 20.3° , 21.3° , 21.7° , 22.6° , 23.1° , and 26.0° .

7. The compound of claim 1 or 2, wherein the compound is of the formula:



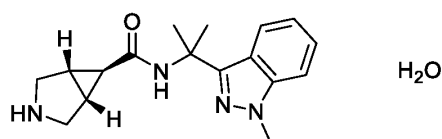
8. The compound of any one of claims 1, 2, or 7, wherein the compound is crystalline.

9. The compound of claim 8, wherein the compound is characterized by an X-ray powder diffraction pattern using Cu K α radiation comprising a peak at diffraction angle 2θ of $11.5^\circ \pm 0.2^\circ$ and one or more of peaks 12.2° , 18.0° , or $22.4^\circ \pm 0.2^\circ$.

10. The compound of claim 8 or 9, wherein the compound is characterized by an X-ray powder diffraction pattern using Cu K α radiation comprising peaks at diffraction angle 2θ of 5.9° , 10.9° , 11.5° , 12.2° , 13.7° , 15.4° , 15.8° , 18.0° , 18.7° , 20.1° , 22.4° , 23.2° , and $25.3^\circ \pm 0.2^\circ$.

11. A compound of the formula:

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12. The compound claim 11, which is crystalline and which is characterized by an X-ray powder diffraction pattern using Cu K α radiation comprising a peak at diffraction angle 2θ of $10.1^\circ \pm 0.2^\circ$ and one or more of peaks 12.8° , 17.3° , or $21.9^\circ \pm 0.2^\circ$.

13. The compound of claim 11 or 12, which is crystalline, and which is characterized by an X-ray powder diffraction pattern using Cu K α radiation comprising peaks at diffraction angle 2θ of 10.1° , 11.4° , 12.8° , 13.7° , 15.0° , 17.3° , 19.9° , 20.6° , 21.0° , 21.9° , 23.7° , 25.6° , and $26.5^\circ \pm 0.2^\circ$.

14. A pharmaceutical composition comprising:

- (a) the compound of any one of claims 1 to 13, and
- (b) one or more pharmaceutically acceptable carriers, diluents, or excipients.

15. A method of treating pain in a patient comprising administering to said patient in need of such treatment an effective amount of the compound of any one of claims 1 to 13.

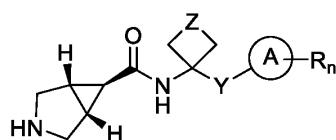
16. A method of treating chronic back pain in a patient comprising administering to said patient in need of such treatment an effective amount of any one of claims 1 to 13.

17. A method of treating neuropathic pain in a patient comprising administering to said patient in need of such treatment an effective amount of any one of claims 1 to 13.

18. The method of claim 17, wherein the neuropathic pain is diabetic peripheral neuropathic pain and/or central neuropathic pain.

19. A method of treating pain associated with osteoarthritis in a patient comprising administering to said patient in need of such treatment an effective amount of the compound of any one of claims 1 to 13.

20. A method for preparing a compound of the formula:



or pharmaceutically acceptable salts thereof,

wherein

Y is covalent bond, O, S, C₁ to C₆ ether, or C₁ to C₆ thioether,

Z is null, a covalent bond, CH₂, or CH₂CH₂,

$\textcircled{\text{A}}$ is an 8-member to 10-member heteroaryl with from 1 to 4 heteroatoms in the heteroaryl or C₆ to C₁₀ aryl,

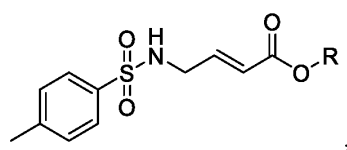
$\textcircled{\text{A}}$ is substituted with one or more R_n, and

Each R_n is independently OH, F, Cl, Br, I, NH₂, CF₃, C₁ to C₆ alkyl, C₃ to C₇ cycloalkyl, C₁ to C₇ ether, or C₁ to C₇ thioether,

the method comprising:

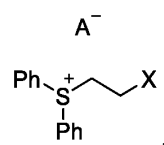
mixing a compound of the formula:

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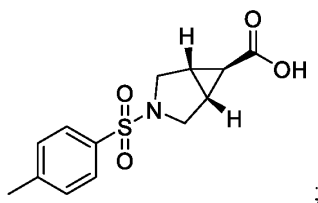


wherein R is a C₁ to C₆ alkyl,

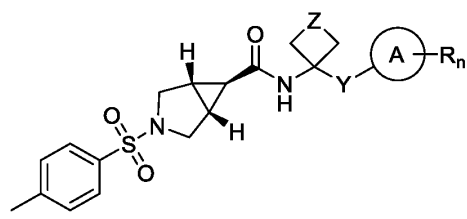
with a sulfonium salt of the formula:



wherein X is a halogen and A is an anion to yield an intermediate compound of the formula:

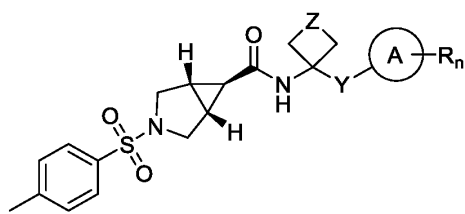


mixing the intermediate compound with $\text{H}_2\text{N}-\text{C}(\text{Z})(\text{Y})-\text{A}-\text{R}_n$ to yield



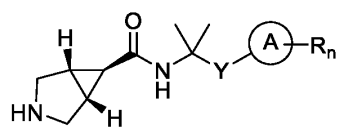
; and

removing tosyl functional group from the compound.



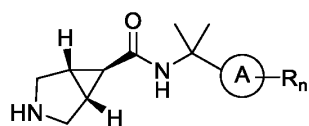
to yield

21. The method of claim 20, wherein Z is null, and the compound is of the formula:



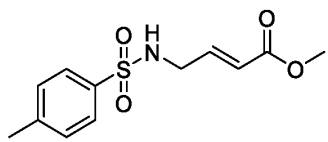
or pharmaceutically acceptable salts thereof.

22. The method of claim 21, wherein Y is a covalent bond, and the compound is of the formula:

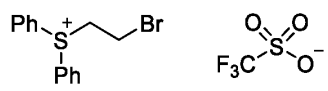


, or pharmaceutically acceptable salts thereof.

23. The method of any one of claims 20 to 22, wherein the method comprises:
mixing a compound of the formula:



with a sulfonium salt of the formula:



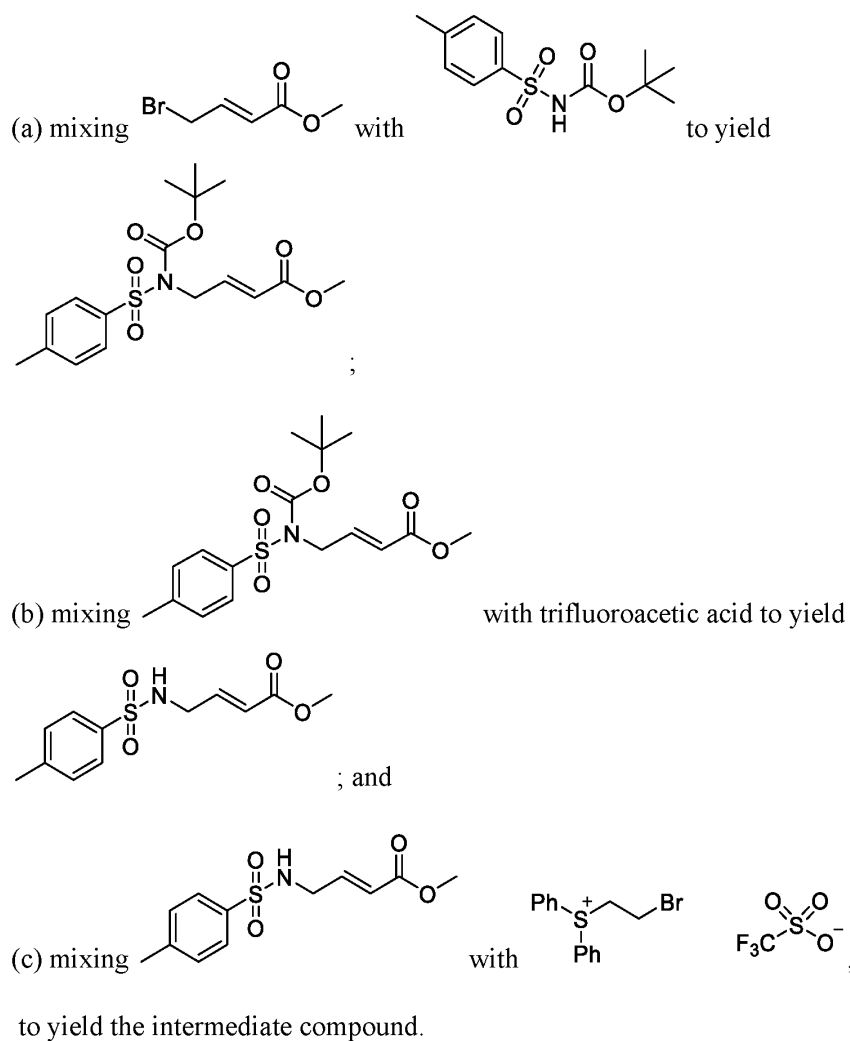
to yield the intermediate compound.

24. The method of any one of claims 20 to 23, wherein the method comprises less than 8 synthetic steps.

25. The method of any one of claims 20 to 24, wherein the method does not include a metal catalyst.

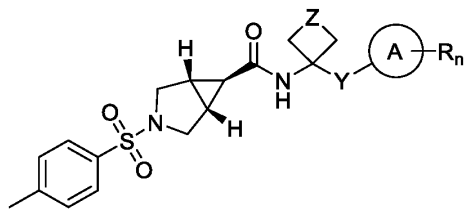
26. The method of any one of claims 20 to 25, wherein the method does not utilize a hydride salt.

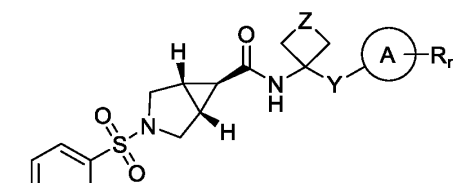
27. The method of any one of claims 20 to 26, wherein the method comprises the steps of:

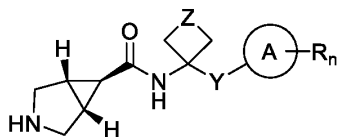


28. The method of claim 27, wherein the method further comprises the steps of:

(d) mixing the intermediate compound with $\text{H}_2\text{N}-\text{C}(\text{Z})_2-\text{Y}-\text{A}-\text{R}_n$ to yield

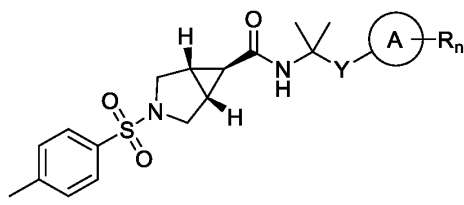


(e) mixing  with potassium diphenylphosphine to yield compound of the formula:

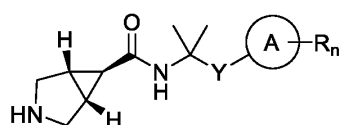
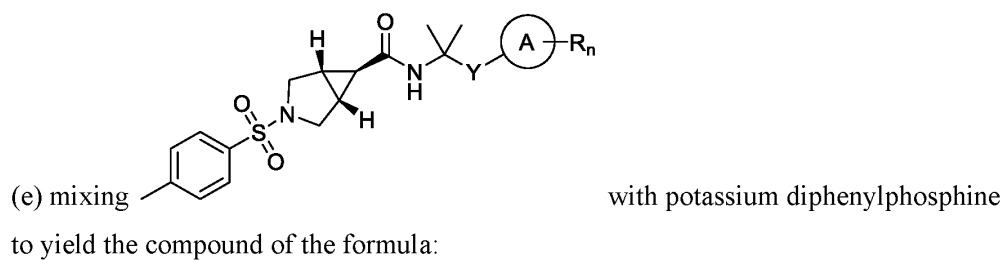


29. The method of claim 27, wherein the method further comprises the steps of:

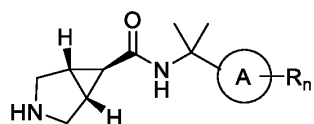
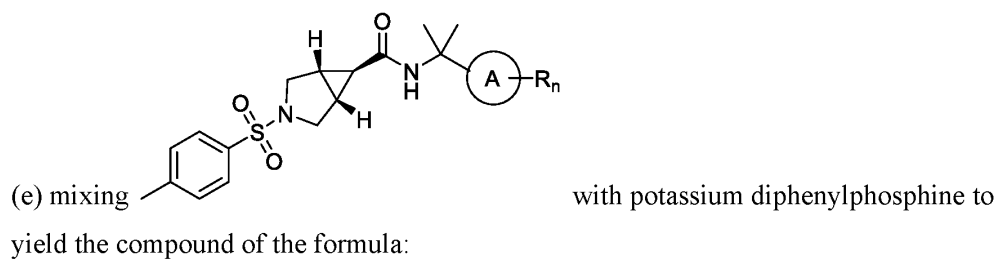
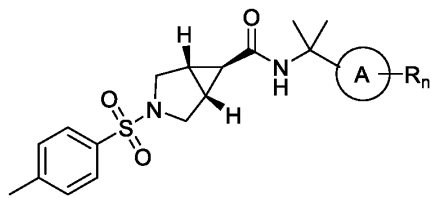
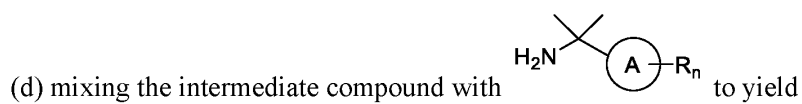
(d) mixing the intermediate compound with $\text{H}_2\text{N}-\text{C}(\text{Z})_2-\text{Y}-\text{A}-\text{R}_n$ to yield



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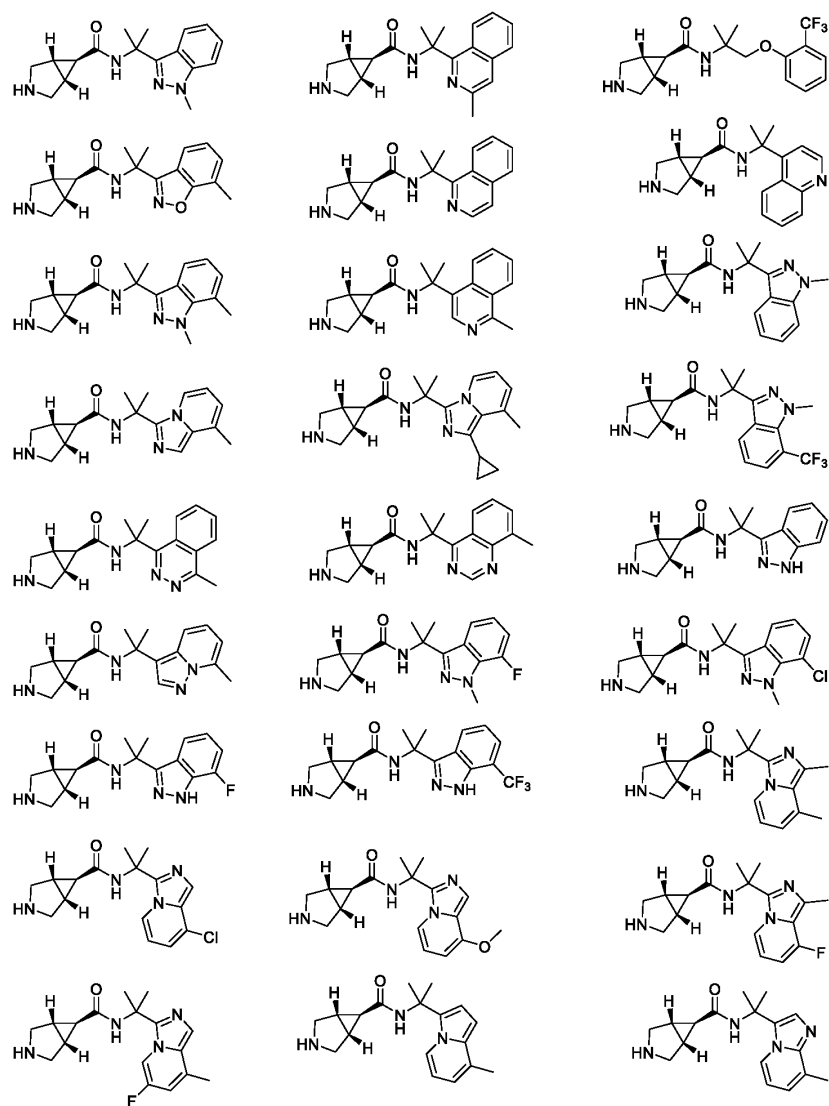


30. The method of claim 27, wherein the method further comprises the steps of:



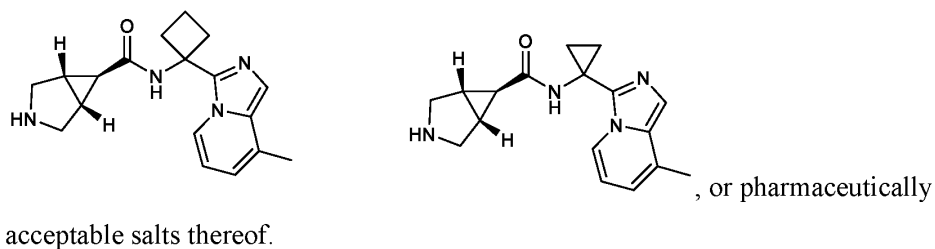
31. The method of any one of claims 20 to 30, wherein  is a 9-member heteroaryl with 1 or 2 heteroatoms.

32. The method of any one of claims 20 to 31, wherein the compound is of the formula:



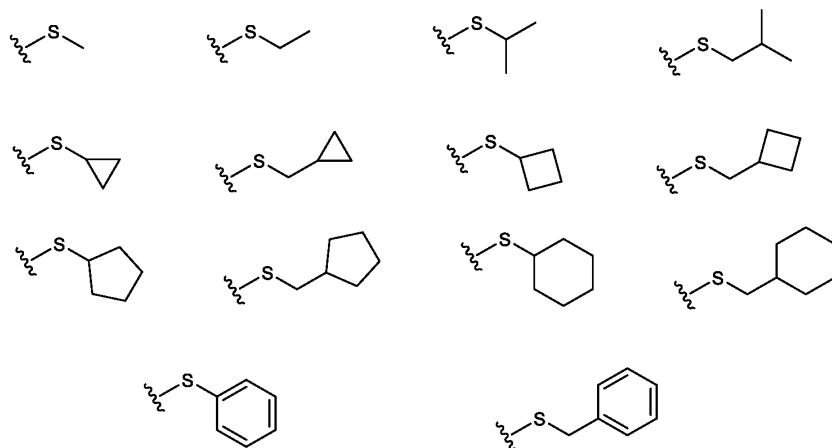
or pharmaceutically acceptable salts thereof.

33. The method of any one of claims 20 to 32, wherein the compound is of the formula:

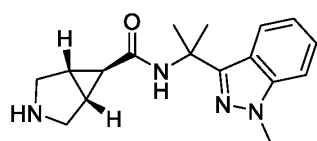


34. The method of any one of claims 20 to 33, wherein Y is null, $\textcircled{\text{A}}$ is substituted with a single R_n , referred to as R_1 , and R_1 is a C_1 to C_7 thioether.

35. The method of claim 34, wherein the C_1 to C_7 thioether is selected from the group consisting of:



36. The method of any one of claims 20 to 32, wherein the compound is of the formula:



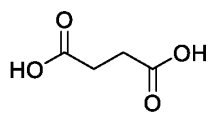
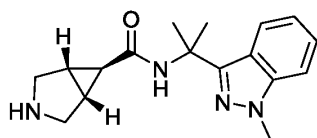
, or pharmaceutically acceptable salts thereof.

37. The method of any one of claims 27 to 36, wherein the method further comprises:

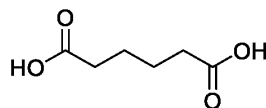
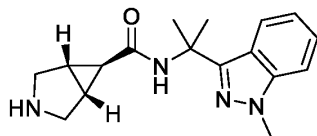
(f) mixing the compound with an acid or a salt comprising a conjugate base of the acid.

38. The method of claim 37, wherein the acid comprises succinic acid, adipic acid, or combinations thereof.

39. The method of claim 36 or 38, wherein the compound is of the formula”

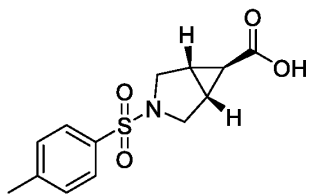


,



, or combinations thereof.

40. A method for preparing an intermediate compound of the formula:

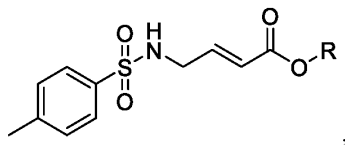


or pharmaceutically acceptable salts thereof; and

the method comprising:

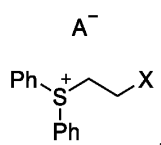
mixing a compound of the formula:

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wherein R is a C₁ to C₆ alkyl,

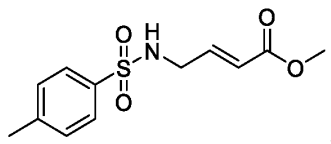
with a sulfonium salt of the formula:



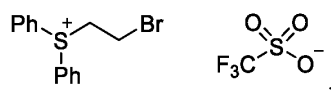
wherein X is a halogen and A is an anion to yield the intermediate compound.

41. The method of claim 40, wherein the method comprises:

mixing a compound of the formula:



with a sulfonium salt of the formula:



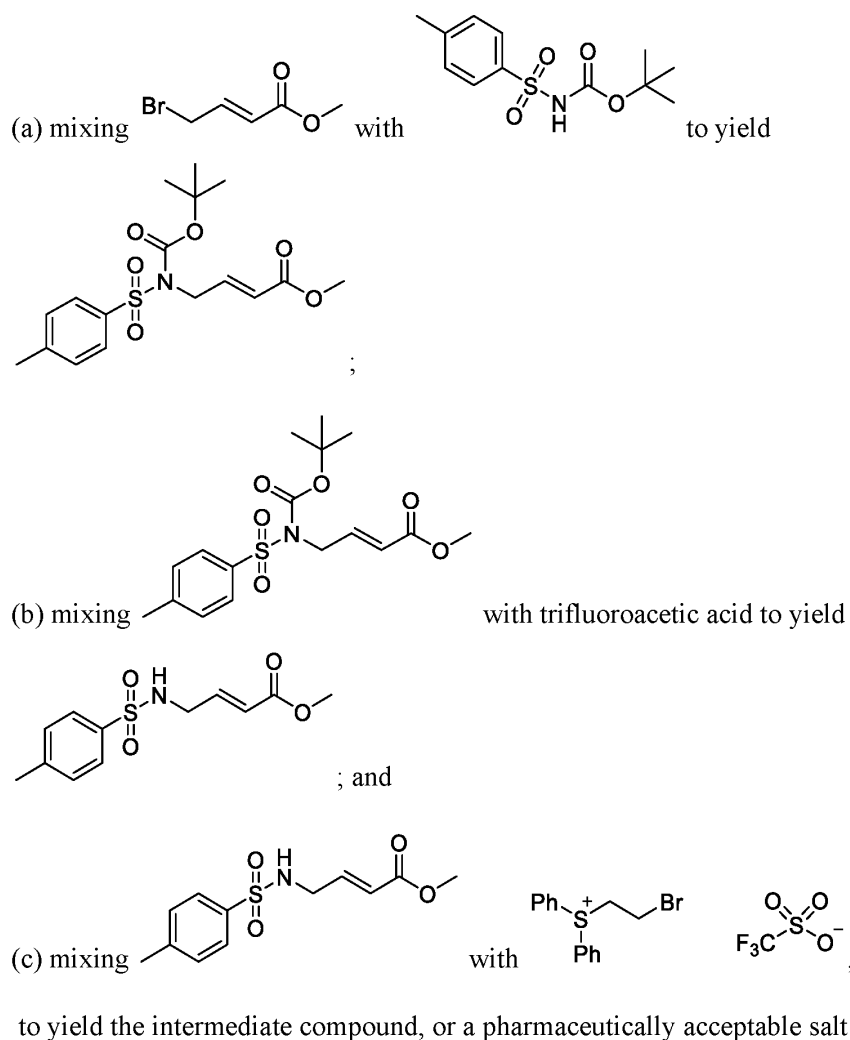
to yield the intermediate compound, or a pharmaceutically acceptable salt thereof.

42. The method of claim 40 or 41, wherein the method comprises less than 8 synthetic steps.

43. The method of any one of claims 40 to 42, wherein the method does not include a metal catalyst.

44. The method of any one of claims 40 to 43, wherein the method does not utilize a hydride salt.

45. The method of any one of claims 40 to 44, wherein the method comprises the steps of:



46. The method of any one of claims 40 to 45, wherein the method comprises the steps of:

- (a) Mixing methyl (E) 4-bromobut-2-enoate with *tert*-Butyl tosylcarbamate to yield methyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate;
- (b) Mixing methyl (E)-4-((N-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)but-2-enoate with trifluoroacetic acid to yield methyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate; and
- (c) Mixing methyl (E)-4-((4-methylphenyl)sulfonamido)but-2-enoate with 2-bromoethyl)diphenylsulfonium triflate to yield the intermediate compound, or a pharmaceutically acceptable salt thereof.