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(71) Applicant: **HUA MEDICINE (SHANGHAI) LTD.** [CN/CN]; 275 Ai Di Sheng Road, Pudong, Shanghai 201203 (CN).

(72) Inventors: **CHEN, Li**; 275 Ai Di Sheng Road, Pudong, Shanghai 201203 (CN). **DUAN, Yuejiao**; 275 Ai Di Sheng Road, Pudong, Shanghai 201203 (CN). **SHE, Jin**; 275 Ai Di Sheng Road, Pudong, Shanghai 201203 (CN). **WU, Chengde**; 275 Ai Di Sheng Road, Pudong, Shanghai 201203 (CN).

(74) Agent: **LIU, SHEN & ASSOCIATES**; 10th Floor, Building 1, 10 Caihefang Road, Haidian District, Beijing 100080 (CN).

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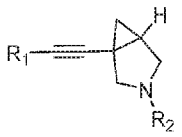
(54) Title: PYRROLIDINE DERIVATIVES



(I)

(57) Abstract: Provided herein are compounds of the formula (I), as well as pharmaceutically acceptable salts thereof, wherein the substituents are as those disclosed in the specification. These compounds, and the pharmaceutical compositions containing them, are useful for the treatment or prevention of mGluR5 mediated disorders, such as acute and/or chronic neurological disorders, cognitive disorders and memory deficits, as well as acute and chronic pain.

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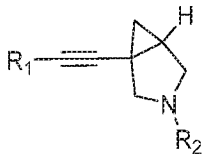
PYRROLIDINE DERIVATIVES

Field of the Invention

[0001] The invention is directed to compounds of the formula I



(I) ,

or a pharmaceutically acceptable salt thereof, and to pharmaceutical compositions comprising said compounds or a pharmaceutically acceptable salt thereof, wherein the definitions of R_1, R_2, are as defined below. The compounds and compositions disclosed herein are mGluR5 antagonists useful for the treatment or prevention of mGluR5 mediated disorders, such as acute and/or chronic neurological disorders, cognitive disorders and memory deficits, as well as acute and chronic pain.

[0002] All documents cited or relied upon below are expressly incorporated herein by reference.

Background of the Invention

[0003] Glutamate is the most prominent neurotransmitter in the body, being present in over 50% of nervous tissue. Glutamate mediates its effects through two major groups of receptors: ionotropic and metabotropic. Ionotropic glutamate receptors are ion channel receptors which are often responsible for fast excitatory transmission. They are generally divided into N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainite receptors. By contrast, metabotropic glutamate receptors (mGluRs) belong to the class C G-protein-coupled receptor (GPCR) protein family and are mainly involved in the modulation of fast excitatory transmission. As such, they are attractive therapeutic targets for treatment of disorders involving malfunction of glutamate signaling. The mGluRs are further divided into three groups (Group I, II and III) based on amino acid sequence homology, signal transduction

mechanism and pharmacological properties. Group I receptors include mGluR1 and mGluR5, Group II includes mGluR2 and mGluR3 and Group III includes mGluR4, mGluR6, mGluR7 and mGluR8. The Group I mGluR1 and mGluR5 couple to G-proteins of the Gq family, Gq and G11, and their activation leads to activation of phospholipase C, resulting in the hydrolysis of membrane phosphatidylinositol (4, 5)-bisphosphate to diacylglycerol, which subsequently activates protein kinase C, and inositol trisphosphate, which in turn activates the inositol trisphosphate receptor to promote the release of intracellular calcium.

[0004] Anatomical studies demonstrate a broad and selective distribution of mGluRs in the mammalian nervous system. For example, mGluR5 are abundantly expressed in the striatum, cortex, hippocampus, caudate-putamen and nucleus accumbens; see for example: Shigemoto, R., Nomura, S., Hidemitsu, S., et al. *Neuroscience Lett.* 1993, 163, 53-57. As these brain areas have been shown to be involved in emotion, motivational processes, learning and memory, as well as motor control, mGluR5 modulators have long been regarded as possessing therapeutic potential for a wide range of indications.

[0005] mGluR5 antagonists can be used for modulating the activity of the mGluR5 and for use in the treatment or prevention of mGluR5 mediated disorders, such as acute and/or chronic neurological disorders, cognitive disorders and memory deficits, acute and chronic pain, protection against drug or disease induced liver damage or failuare, urinary inconsistence. Other diseases contemplated include cerebral ischemia, chronic neurodegeneration including Huntington's chorea, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of pulmonary system and respiration, motor control and function, attention deficit disorders, concentration disorders, mental retardation (including mental retardation related to Fragile X syndrome), autism spectrum disorders (ASDs), pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, migraine, dyskinesia, eating disorders, vomiting, muscle spasms, urinary inconsistence, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia and astrocytomas,

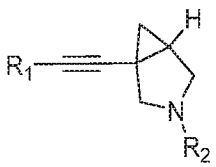
diseases of the cardiovascular system, diseases of the gastrointestinal system such as gastroesophageal reflux disease and irritable bowel syndrome, diseases of the endocrine system, diseases of the exocrine system, diseases of the skin, cancer and diseases of the ophthalmic system. The development and use of mGluR5 antagonists has been summarized in numerous review articles for example: Gasparini, F., Bilbe, G., Gomez-Mancilla, G., and Spooren, W., *Current Opinion in Drug Discovery & Developmen*, 655-665, 2008, 11(5); Rocher, J.-P., Bonnet, B., Boléa, C., et al., *Current Topics in Medicinal Chemistry*. 2011, 11, 680-695; Dekundy, A., Gravius, A., Hechenberger, M, et al., J. *Neural Transm*. 2011, 118, 1703-1716; Niswender, C. M.; Conn, P. J., *Annu Rev Pharmacol Toxicol*, 2010, 50, 295-322; Emmitte KA. mGluR5 negative allosteric modulators: a patent review (2010-2012). Guiying Li, Morten Jørgensen, *Expert Opin Ther Pat*. 2013, Apr. 23(4), 393-408; and Brian M Campbell. Metabotropic glutamate receptor 5-negative allosteric modulators for the treatment of psychiatric and neurological disorders (2009-July 2013), *Pharmaceutical Patent Analyst*. 2(6): 767-802.

Summary of the Invention

[0006] The present invention is directed to compounds of the formula I, or a pharmaceutically acceptable salt thereof, pharmaceutical compositions containing them and to methods of treating diseases and disorders. The compounds and compositions disclosed herein are mGluR5 antagonists useful for the treatment of mGluR5 mediated disorders, including acute and/or chronic neurological disorders, cognitive disorders and memory deficits, as well as acute and chronic pain.

Detailed Description of the Invention

[0007] In an embodiment of the present invention, provided are compounds of formula I:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is a 5- to 10-membered mono- or bicyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-O-CF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic aryl ring, wherein the 5- to 10-membered aryl ring is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form a 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring.

R_2 is alkanoyl, arylalkanoyl, herteroaryl acyl, aryl sulfonyl, heteroaryl sulfonyl, alkoxycarbonyl, -C(O)O-aryl, arylalkoxycarbonyl, acylamino, wherein the aryl or heteroaryl are optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl,

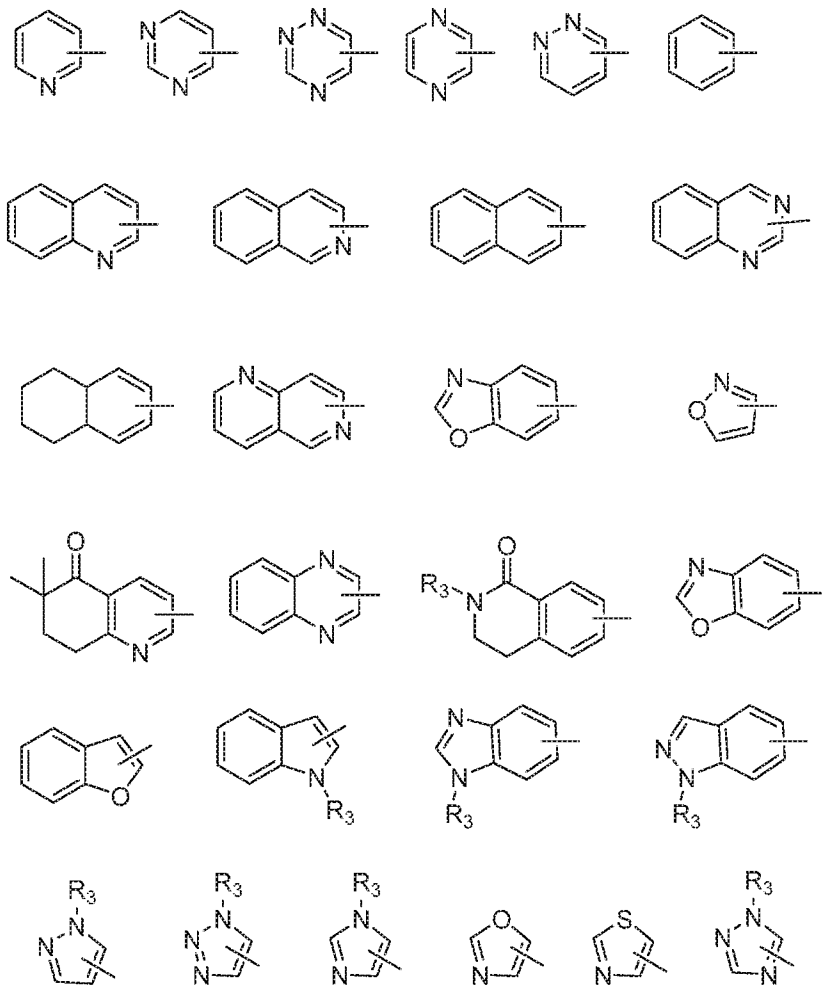
-C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-O-CF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic aryl ring, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring.

[0008] In a further embodiment of the present invention, provided is a compound according to formula I, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is a substituted or unsubstituted ring selected from the following list:



Wherein the ring is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring;

R_3 where presents is -H or lower alkyl;

R_2 is alkanoyl, arylalkanoyl, herteroaryl acyl, aryl sulfonyl, heteroaryl sulfonyl, alkoxycarbonyl, -C(O)O-aryl, arylalkoxycarbonyl, acylamino, wherein the aryl or

heteroaryl are optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-O-CF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic aryl ring, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring.

[0009] In a further embodiment of the present invention, provided is a compound according to formula I, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is an optionally mono- or disubstituted 5- to 6-membered monocyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S;

R_2 is optionally mono- or disubstituted 5- to 10-membered mono- or bicyclic aryl, or optionally mono- or disubstituted mono- or bicyclic heteroaryl that contains 1-3 heteroatoms selected from the group consisting of N, O and S, or optionally substituted -C(O)-C_1-C_5-alkyl, -C(O)-C_1-C_5-alkyl-aryl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-C_1-C_5-alkyl, -C(O)O-C_1-C_5-alkyl-aryl or -S(O_2)-phenyl.

[00010] In a further embodiment of the present invention, provided is a compound according to formula I, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is 2-pyridinyl or substituted 2-pyridinyl, 4-pyridinyl or substituted 4-pyridinyl, or

R_1 is pyrimidinyl, pyrazinyl, pyridazinyl or thiazoly.

[00011] In a further embodiment of the present invention, provided is a compound according to formula I, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is 2-pyridinyl optionally substituted with 1 or 2 substituents independently selected fromhalogen, -C_1-C_4-alkyl, -O-C_1-C_4-alkyl,wherein halogen includes -F, -Cl, -Br or -I; -C_1-C_4-alkyl includes, but are not limited to, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl; -O-C_1-C_4-alkyl includes, but are not limited to methoxyl, ethyoxyl, propoxyl, iso-propoxyl, butoxyl, iso-butoxyl or tert-butoxyl, or

R_1 is 4-pyridinyl optionally substituted with 1 or 2 substituents independently selected from halogen, -C_1-C_4-alkyl, -O-C_1-C_4-alkyl, wherein halogen includes -F, -Cl, -Br or -I; -C_1-C_4-alkyl includes, but are not limited to, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl;, -O-C_1-C_4-alkyl includes, but are not limited to methoxyl, ethyoxyl, propoxyl, iso-propoxyl, butoxyl, iso-butoxyl or tert-butoxyl; or

R_1 is pyrimidinyl, pyrazinyl, pyridazinyl or thiazoly optionally substituted with 1 or 2 substituents independently selected fromhalogen, -C_1-C_4-alkyl, -O-C_1-C_4-alkyl, wherein halogen includes -F, -Cl, -Br or -I; -C1-C4-alkyl includes, but are not limited to, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl; the -O-C_1-C_4-alkyl includes, but are

not limited to methoxyl, ethyoxyl, propoxyl, iso-propoxyl, butoxyl, iso-butoxyl or tert-butoxyl.

R_2 is a 5- to 10-membered mono- or bicyclic aryl or heteroaryl ring that contains 1, 2, or 3 heteroatoms independently selected from the group consisting of N, O and S, wherein the 5- to 10-membered ring system is optionally substituted with 1or 2 substituents independently selected from -C_1-C_4-alkyl, halogen, -CN, nitro, -CF_3, -OCF_3, -O-C_1-C_4-alkyl, -SCH_3, -S(O)-CH_3, -S(O_2)-CH_3, -CO_2CH_3, -C(O)NH_2, -C(O)NH(CH_3), -C(O)N(CH_3)$_2$, phenyl, wherein halogen includes -F, -Cl, -Br or -I; the -C_1-C_4-alkyl includes, but are not limited to methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl; the -O-C_1-C_4-alkyl includes, but are not limited to methoxyl, ethoxyl, propoxyl, *iso*-proxyl, butoxyl, *iso*-butoxyl, *tert*-butoxyl, wherein the 5- to 10-membered ring system is preferably phenyl, pyridinyl, benzimidazolyl, azaindolyl; or

R_2 is -C(O)-C_1-C_5-alkyl, -C(O)-C_1-C_5-alkyl-aryl, -C(O)-phenyl, -C(O)-benzyl, -CO-pyridinyl, -C(O)O-C_1-C_5-alkyl, -C(O)O-C_1-C_5-alkyl-phenyl, -C(O)O-phenyl, -C(O)O-benzyl -S(O_2)-phenyl, -C(O)N-aryl, -C(O)N-alkyl, -C(O)N-alkyl-CF_3, wherein -C_1-C_5-alkyl includes methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, *iso*-pentyl, *tert*-pentyl, *neo*-pentyl. The benzyl or phenyl in the substitutens is optionally further substituted with 1 or 2 substituents selected from halogen, -C_1-C_4-alkyl, -CN or -O-CF_3 which is optionally further substituted with a 1 or 2 substituents independent selected from halogen, -C_1-C_4-alkyl, -CN or -O-CF_3 wherein halogen includes -F, -Cl, -Br or -I; -C_1-C_4-alkyl includes, but are not limited to, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl.

[00011] In a still further embodiment of the present invention, provided is a pharmaceutical composition, comprising a therapeutically effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[00012] It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments, and is not intended to be limiting. Further, although any

methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

[00013] As used herein, the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

[00014] As used herein, the term "alkenyl", alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having an olefinic bond of two to twenty carbon atoms, preferably two to sixteen carbon atoms, more preferably two to ten carbon atoms.

[00015] The term "cycloalkyl" refers to a monovalent mono- or polycarbocyclic radical of three to ten, preferably three to six carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, indanyl and the like. In a preferred embodiment, the "cycloalkyl" moieties can optionally be substituted with one, two, three or four substituents, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise in the Examples or claims below. Each substituent can independently be, alkyl, alkoxy, halogen, amino, hydroxyl or oxygen (O=) unless otherwise specifically indicated. Examples of cycloalkyl moieties include, but are not limited to, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclopentenyl, optionally substituted cyclohexyl, optionally substituted cyclohexylene, optionally substituted cycloheptyl, and the like or those which are specifically exemplified herein.

[00016] The term "heterocycloalkyl" denotes a mono- or polycyclic alkyl ring, wherein one, two or three of the carbon ring atoms is replaced by a heteroatom such as N, O or S. Examples of heterocycloalkyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-

dioxanyl and the like. The heterocycloalkyl groups may be unsubstituted or substituted and attachment may be through their carbon frame or through their heteroatom(s) where appropriate, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise in the Examples or claims below.

[00017] The term "lower alkyl", alone or in combination with other groups, refers to a branched or straight-chain alkyl radical of one to nine carbon atoms, preferably one to six carbon atoms, more preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, *n*-pentyl, 3-methylbutyl, *n*-hexyl, 2-ethylbutyl and the like.

[00018] The term "aryl" refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1, 2, 3, 4-tetrahydronaphthalene, 1, 2-dihydronaphthalene, indanyl, 1H-indenyl and the like.

[00019] The alkyl, lower alkyl and aryl groups may be substituted or unsubstituted. When substituted, there will generally be, for example, 1 to 4 substituents present, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise in the Examples or claims below. These substituents may optionally form a ring with the alkyl, lower alkyl or aryl group with which they are connected. Substituents may include, for example: carbon-containing groups such as alkyl, aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g. trifluoromethyl); oxygen-containing groups such as alcohols (e.g. hydroxyl, hydroxyalkyl, aryl(hydroxyl)alkyl), ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl, more preferably, for example, methoxy and ethoxy), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arycarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as esters(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono-or di-alkylaminocarbonylalkyl, arylaminocarbonyl), carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino,

aminocarbonyloxy, mono-or di-alkylaminocarbonyloxy, arylminocarbonloxy) and ureas (e.g. mono- or di- alkylaminocarbonylamino or arylaminocarbonylamino); nitrogen-containing groups such as amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arysulfinyl, arysulfonyl, arythioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and heterocyclic groups containing one or more heteroatoms, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

[00020] The term "heteroaryl," refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the remaining ring atoms being C. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of such groups include, but are not limited to, pyrimidinyl, pyridyl, indoyl, quinolinyl, pyridon-2-yl, isoquinolinyl, 5,6,7,8-tetrahydroquinolinyl, thienyl, furanyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyrazolidinyl, pyrazinyl, pyridazinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and the like.

[00021] The heteroaryl group described above may be substituted independently with one, two, or three substituents, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise in the Examples or claims below. These substituents may optionally form a ring with the heteroaryl group to which they are connected.

Substituents may include, for example: carbon-containing groups such as alkyl, aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g. trifluoromethyl); oxygen-containing groups such as alcohols (e.g. hydroxyl, hydroxyalkyl, aryl(hydroxyl)alkyl), ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono-or di-alkylaminocarbonylalkyl, arylaminocarbonyl), carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono-or di-alkylaminocarbonyloxy, arylminocarbonloxy) and ureas (e.g. mono- or di- alkylaminocarbonylamino or arylaminocarbonylamino); nitrogen-containing groups such as amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arysulfinyl, arysulfonyl, arythioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and heterocyclic groups containing one or more heteroatoms, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzothiazoyl and carbolinyl).

[00022] As used herein, the term "alkoxy" means alkyl-O-; and "alkanoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by, for example, one or more alkyl groups, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise in the Examples or claims below.

[00023] As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical, and more preferably a fluorine or chlorine radical.

[00024] Compounds of formula I can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). The invention embraces all of these forms.

[00025] As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula I. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, *p*-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminum salts.

[00026] In the practice of the method of the present invention, an effective amount of any one of the compounds of this invention or a combination of any of the compounds of this invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. The compounds or compositions can thus be administered orally (e.g., buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form or solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be

conducted in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conJunction with a lipophilic salt such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous or intramuscular administration.

[00027] Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases. Thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic with the blood) for inJectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions or of the active ingredient(s) which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The compositions may be subJected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in **Remington's Pharmaceutical Sciences** by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

[00028] The dose of a compound of the present invention depends on a number of factors, such as, for example, the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the active compound as determined by the attending physician or veterinarian is referred to herein, and in the claims, as a "therapeutically

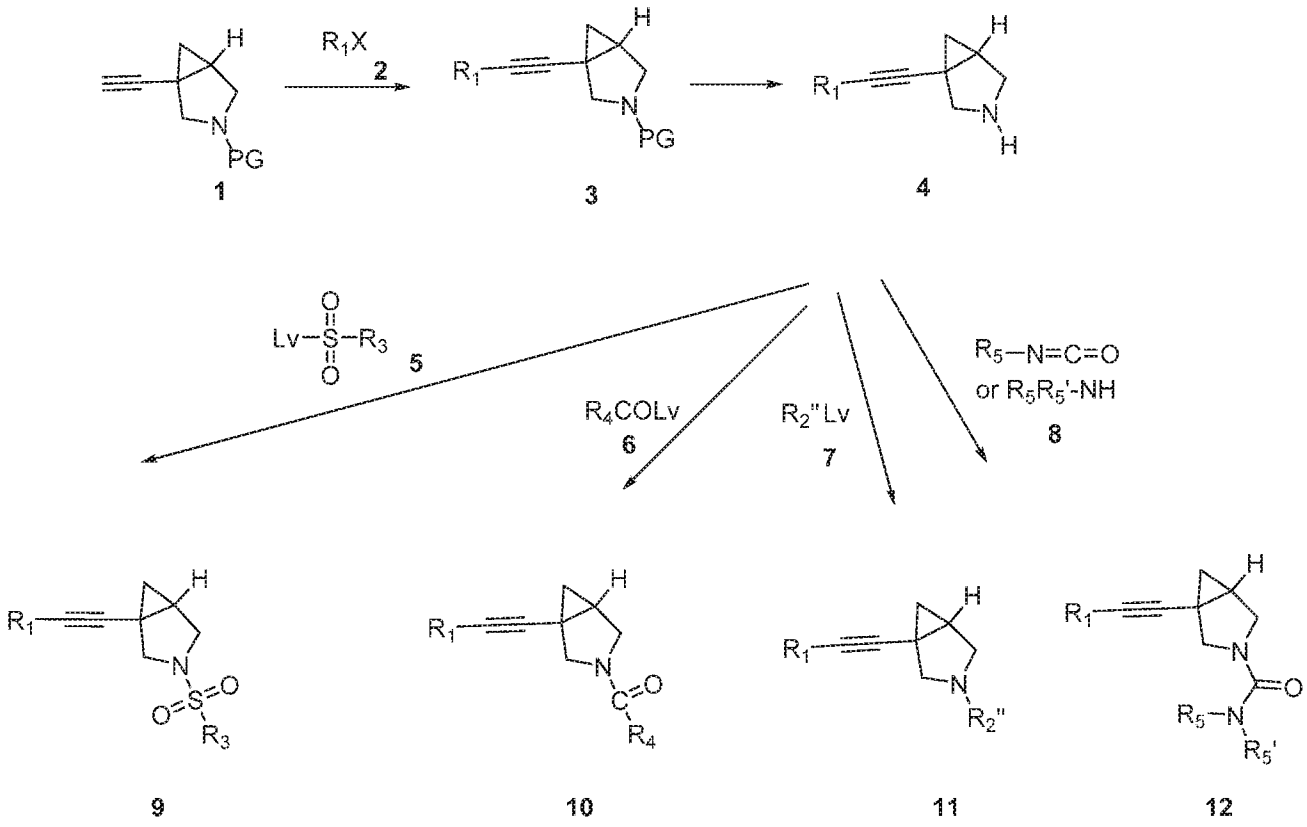
effective amount". For example, the dose of a compound of the present invention is typically in the range of about 1 mg to about 1000 mg per day. Preferably, the therapeutically effective amount is in an amount of from about 1 mg to about 500 mg per day.

[00029] It will be appreciated, that the compounds of general formula I in this invention may be derivatized at functional groups to provide derivatives which are capable of conversion back to the parent compound *in vivo*. Physiologically acceptable and metabolically labile derivatives, which are capable of producing the parent compounds of general formula I *in vivo* are also within the scope of this invention.

[00030] Compounds of the present invention can be prepared beginning with commercially available starting materials and utilizing general synthetic techniques and procedures known to those skilled in the art. Chemicals may be purchased from companies such as for example Aldrich, Argonaut Technologies, VWR and Lancaster.

[00031] The compounds of formula I can be prepared by the following General Reaction Scheme:

Scheme 1



In Scheme 1 compound of formula **1**, in which PG is a protecting group, for example a 1,1-dimethylethoxycarbonyl (Boc) group, is known as a common intermediate, and the preparation of compound **1** would be described in Scheme 3.

[00032] Reaction of compounds **1** and **2** to form the alkyne **3** can be achieved by Sonogashira coupling of the alkyne **1** and halohydrocarbon **2** in a suitable inert solvent, for example THF, by adding $Pd(PPH_3)_2Cl_2$, Et_3N and CuI, then the reaction mixture microwaved at a medium temperature, for example 90°C, after reaction is complete and the newly formed compound **3** can be isolated using conventional technics, for example by quenching the reaction with an aqueous solution followed by extraction of the products into an organic solvent, washing with brine, drying and chromatography over silica gel, if necessary (Sonogashira, K. (2002), "Development of Pd-Cu catalyzed cross-coupling of terminal acetylenes with sp^2-carbon halides",

J. Organomet. Chem. 653: 46-49; King, A. O.; Yasuda, N. (2004), "Palladium-Catalyzed Cross-Coupling Reactions in the Synthesis of Pharmaceuticals Organometallics in Process Chemistry", *Top. Organomet. Chem.* **6**: 205-245).

[00033] Conditions for the removal of the protecting group in **3** to give a compound of structure **4**, will depend on the particular choice of protecting group employed. Skilled organic chemists will be familiar with the various potential protecting and the procedures for their removal. In this regard, reference to a compendium of protecting groups such asWuts, P.G. and Greene, T. W., *Greene's Protective Groups in Organic Synthesis*, 4th ed., cited above may be useful. In one convenient implementation, a Boc ((1,1-dimethylethoxy)carbonyl) group may be used. In this case, its removal to give a compound of structure **4** may be readily achieved by treatment with an acid, for example trifluoroacetic acid (TFA) in a suitable solvent, for example dichloromethane followed by a conventional workup.

[00034] Further transformation of compounds of structure **4** to compounds of the invention will depend on the particular target compound desired. In the case that introduction of a sulfonyl group is desired to give a compound of structure **8**, a compound of structure **4** may be treated with an activated sulfonyl derivative **5** in which Lv is a leaving group, for example a chloride. Such transformations are generally carried out in the presence of an organic or inorganic base, for example trimethylamine (TEA) in a suitable solvent such as dichloromethane. Skilled organic chemists will be familiar with the general reaction scope and be able to choose appropriate conditions for the target compound of interest.

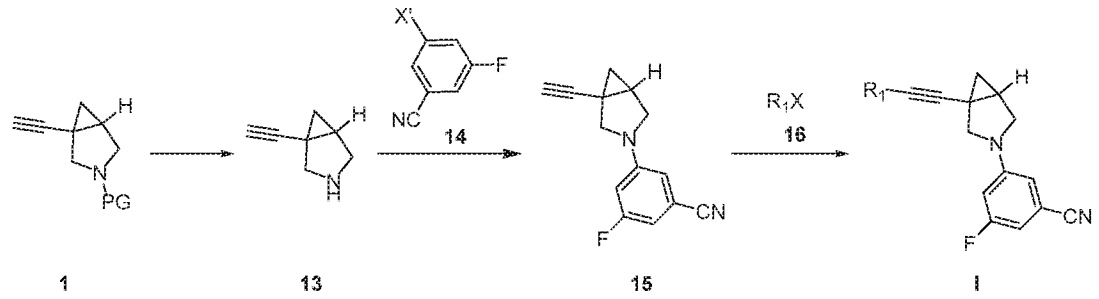
[00035] In the event that an amide or carbamate of structure **9** is desired (R_4 = aryl, heteroaryl, alkyl, alkoxy, or arylalkoxy), a compound of structure **4** may be treated with an activated ester derivative **6** in which Lv is a suitable leaving group for acylation reactions, for example a halogen atom such as a chloride. Such reactions may be carried out under a wide variety of conditions well known to skilled organic chemists. In one set of conditions, an acyl chloride **6**, in which Lv is chloride can be allowed to react with the amine **4** in an inert solvent such as dichloromethane at a suitable temperature, for example room temperature in the presence of base, for example TEA followed by a conventional workup involving quenching with an

aqueous solution, extraction of the product into an organic solvent, drying, evaporation and optionally, chromatographic purification of the residue.

[00036] In case the desired compound is an N-aryl or N-heteroaryl derivative of structure **11**, a compound of structure **4** may be reacted with a compound of structure **7** in which Lv represents a leaving group suitable for participation in a Buchwald reaction or Chan-Lam coupling reaction and R_2'' represents a R_2 of the invention or incorporates functionality that can transformed into a R_2 of the invention through manipulation of substituents and protecting groups after the coupling reaction. Typical groups include iodide, bromide and chloride. Reactions typically are run in the presence of a base, which can either be a strong base such as LiHMDS or a weaker base such as Cs_2CO_3 in the presence of a palladium catalyst and suitable ligand. The selection of the base, solvent and ligand for a particular desired transformation may be guided by literature precedent (Surry, D. S. and Buchwald, S. L, *Chem. Sci.* 2011, 2: 27-50; D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winteres, *Tetrahedron Lett.* 1998, 39: 2933-2936). For aryl and heteroaryl moieties with highly reactive leaving groups, for example 2-fluoropyridine, a direct reaction between that compound and compound **4** in the presence of a suitable base, for example potassium carbonate at an elevated temperature, for example 90-130°C can affect their transformation to a compound of structure **11.**

[00037] In case the desired compound is the urea derivative of structure of **12** (R_5 = aryl、heteroaryl、C_1-C_4-alkyl、trifluoromethylalkyl , R_5' = hydrogen , C_1-C_4-alkyl , wherein R_5, R_5' and the nitrogen atom to which they are attached may be combined to form an azacycloalkane), compound of structure **4** may be treated with isocyanate in the presence of presence of base, for example TEA, or treated with amine in the presence of CDI, to get the desired compound of structure of **12** (Johnson Douglas S., Ahn Kay, Kesten Suzanne, et al. Bioorganic & medicinal chemistry letters 2009, 19(10):2865-2869; Satoshi Sasaki , Nobuo Cho , Yoshi Nara, et al. J. Med. Chem. 2003, 46 (1): 113-124) .

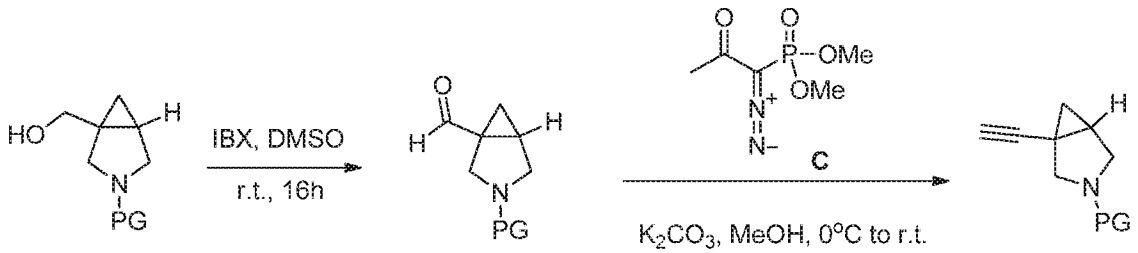
Scheme 2



1 13 15 I

[00038] The method for preparation of compounds of formula **I** (for R_2=3-cyano-5-fluorophenyl) is shown in Scheme 2. Compounds **1** as described in Scheme 1 by deprotecting to give alkyne **13**, may then undergo a Buchwald coupling reaction with compound **14** in which X' is halogen, like iodide, bromide and chloride to give compound **15**. Compound **15** and **16** undergo a Sonogashira coupling reaction (Sonogashira, K., "Development of Pd-Cu catalyzed cross-coupling of terminal acetylenes with sp^2-carbon halides", *J. Organomet. Chem.* 2002, 653: 46-49) to give the compounds of formula **I** (for R_2=3-cyano-5-fluorophenyl).

Scheme 3



A B 1

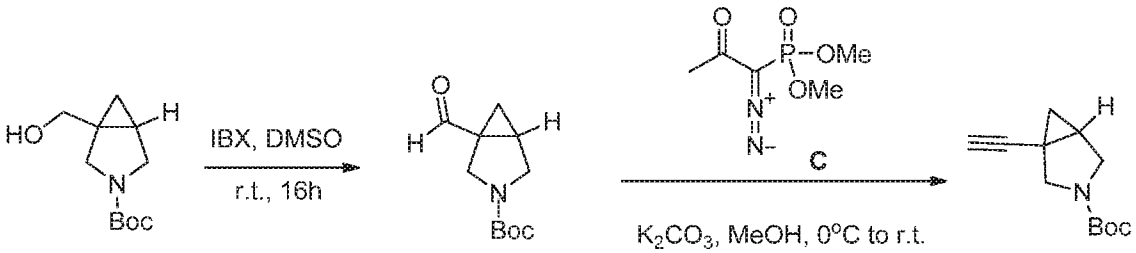
[00039] The procedure for preparation of compound **1** is shown in Scheme 3. Compound **A** is commercially available from Wuxi AppTech, treatmentment of **A** with an appropriate oxidant, like IBX in an inert solvent DMSO for example to give aldehyde **B** (Frigerio, M.; Santadostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* 1995, 60, 7272). Reacting **B** with Bestmann-Ohira Reagent Dimethyl (1-diazo-2-oxopropyl)-phosphonate through Seyferth-Gilbert homologation in the presence of base like potassium carbonate in a solvent such as methanol yields the desired compounds of formular **1** (S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, Synlett, 1996, 521-522; Ohira, S. Synthetic Commun. 1989, 19: 561-564).

[00040] The invention will now be further described in the Examples below, which are intended as an illustration only and do not limit the scope of the invention.

EXAMPLES

Example 1

Preparation of tert-butyl 1-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate:



A B 1

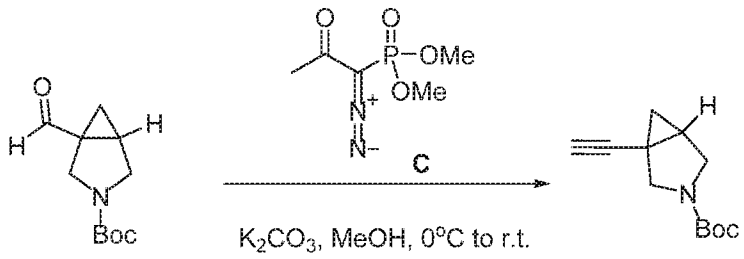
Experimental section:

Procedure for preparation of B:

A B

To a solution of compound **A** (3.50g, 16.4mmol) in DMSO (30mL) was added IBX (6.89g, 24.6mmol). The mixture was stirred at rt. for 16 hrs. TLC indicated compound **A** was consumed completely. The white suspension was diluted with EA (50mL), filtered by celite pad. The filter was washed with saturated $NaHCO_3$ (50mL), then saturated Na_2SO_3 (50mL) (KI paper test, negative), brine (50mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product **B** (2.95g, yield: 85%) was used for the next step without further purification.

Procedure for preparation of 1:

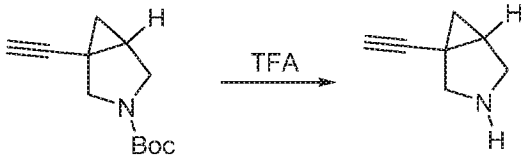


B 1

To a solution of compound **B** (2.95g, 13.9mmol) in MeOH (30mL) was added K_2CO_3 (5.79g, 41.8mmol), and then **C** (4.83g, 25.1mmol) was added at 0°C. The mixture was stirred at rt. for 16 hrs. TLC indicated compound **B** was consumed completely and one new spot formed. The reaction mixture was diluted with DCM (50mL) and H_2O (40mL). The combined organic layers were washed with brine (60mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give product **1** (2.70g, yield: 93%).

Example 2

Procedure for preparation of 1-ethynyl-3-azabicyclo[3.1.0]hexane:

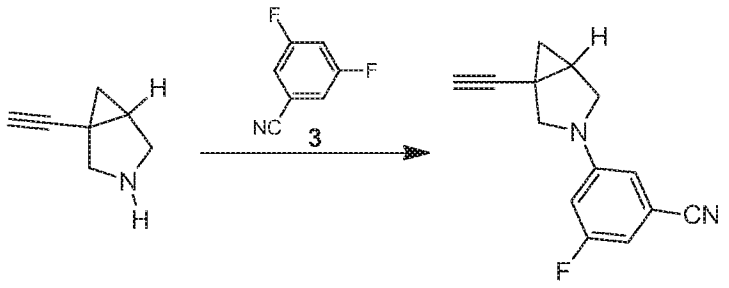


1 2

To a solution of **1** (2.0g, 9.65mmol) in DCM (20mL) was added TFA (10mL). The mixture was stirred at rt. for 1hr., LCMS showed that **1** was consumed completely. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH, then neutralized pH to 8-9 by basic resin, filtered and concentrated under reduced pressure to give the crude product **2** (1.0g, crude), which was used for the next step without purification.

Example 3

Preparation of 3-(1-ethynyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluorobenzonitrile:



2 4

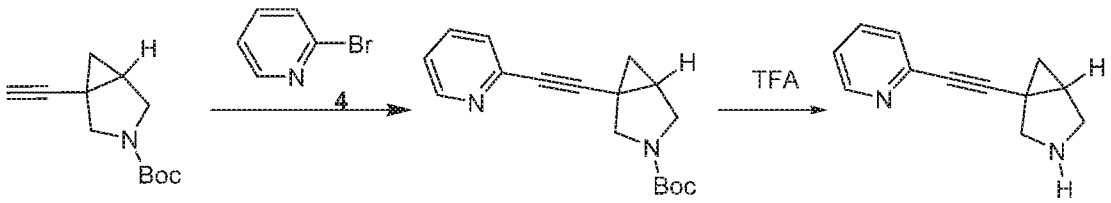
Experimental section:

Procedure for preparation of 4:

To a solution of **2** (1.0g, 9.33mmol) and **3** (1.5g, 11.2mmol) in DMF (10mL) was added K_2CO_3 (2.5g, 18.6mmol). The mixture was stirred at 110°C for 16hrs. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20mL) and extracted with EA (30mL x 3), filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give product **4** (450mg, yield: 21%).

Example 4

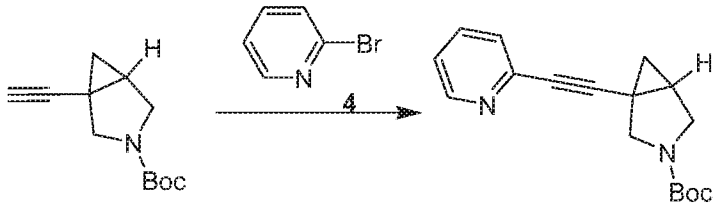
Preparation of 1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



1 5 6

Experimental section:

Procedure for preparation of 5:

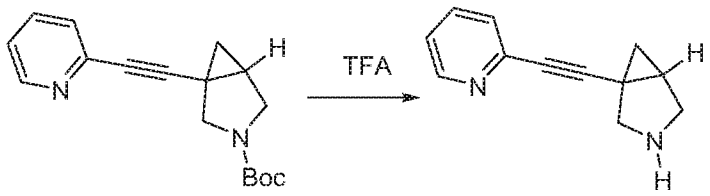


1 5

A mixture of **1** (640.00mg, 3.09mmol), **4** (732.33mg, 4.64mmol), $Pd(PPh_3)_2Cl_2$ (216.89mg, 309.00μmol), Et_3N (625.35mg, 6.18mmol) and CuI (58.85mg, 309.00μmol) were taken up into a microwave tube in THF (20mL). The sealed tube was degassed with N_2 twice and then heated at 90°C for 1hr under microwave. TLC showed the starting material was consumed. After cooling to rt., EA (20mL) and water (20mL) were added. The aqueous layer was extracted with EA (20mL x 2). The combined organic layers were washed with brine (30mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude product , which was purified by chromatograph column to give product **5** (800.00mg, yield: 91.05%).

LCMS: *m/z*, 285 $(M+H)^+$.

Procedure for preparation of 6:

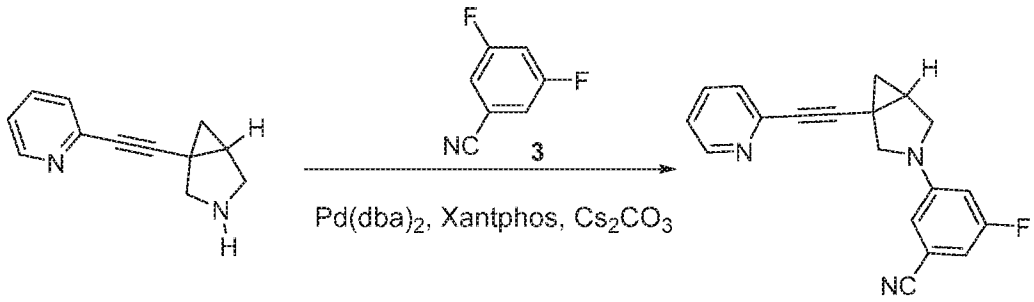


5 6

To a mixture of **5** (700.00mg, 2.46mmol) in DCM (20mL) was added TFA (4mL) in one portion at rt., the mixture was stirred at rt. for 1hr. LCMS showed the reaction was completed. The mixture was concentrated in reduced pressure at 50°C. The residue was poured into saturated $NaHCO_3$ solution (50mL) and stirred for 10 min. The aqueous phase was extracted with EA (30mL x 3). The combined organic phase was washed with saturated brine (30mL x 1), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford product **6** (400.00mg, yield: 88.26%).

Example Compound 1

Preparation of 3-fluoro-5-(1-(pyridin-2-ylethynyl)-3-azabicyclo [3.1.0] hexan-3-yl) benzonitrile:



6 **Compound 1**

Experimental section:

Procedure for preparation of Compound 1:

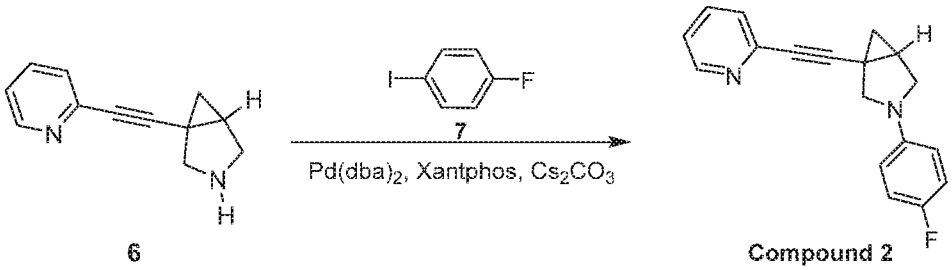
A mixture of **6** (400.00mg, 2.17mmol) and **3** (868.04mg, 4.34mmol) in toluene (20mL) was added $Pd(dba)_2$ (124.84mg,217.00μmol), Cs_2CO_3 (1.41g,4.34mmol) and Xantphos (125.62mg, 217.00μmol) in one portion at rt. under N_2 atmosphere. The mixture was then heated at 110°C and stirred for 18hrs. LCMS showed the reaction was completed. The mixture was cooled to rt. and filtered. The filtrate was concentrated in reduced pressure at 60°C. The residue was purified by prep-HPLC to afford **Compound 1** (292.00mg, yield: 44.06%).

LCMS: *m/z,* 304 $(M+H)^+$;

^{1}H NMR (400 MHz, CDCl3): δ 8.54 (d, *J* = 4.65Hz, 1H), 7.63 (td, *J* = 7.76, 1.59Hz, 1H), 7.38 (d, *J* = 7.83Hz, 1H), 7.21 (dd, *J* = 7.09, 5.38Hz, 1H), 6.66 (d, *J* = 7.58Hz, 1H), 6.54 (s, 1H), 6.38-6.45 (m, 1H), 3.72 (d, *J* = 9.05Hz, 1H), 3.41-3.54 (m, 3H), 2.19 (dt, *J* = 8.31, 4.40Hz, 1H), 1.43 (dd, *J* = 8.07, 4.89Hz, 1H), 0.98 (t, *J* = 5.01Hz, 1H).

Example Compound 2

Preparation of 3-(4-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo [3.1.0] hexane:



6 Compound 2

Experimental section:

Procedure for preparation of Compound 2:

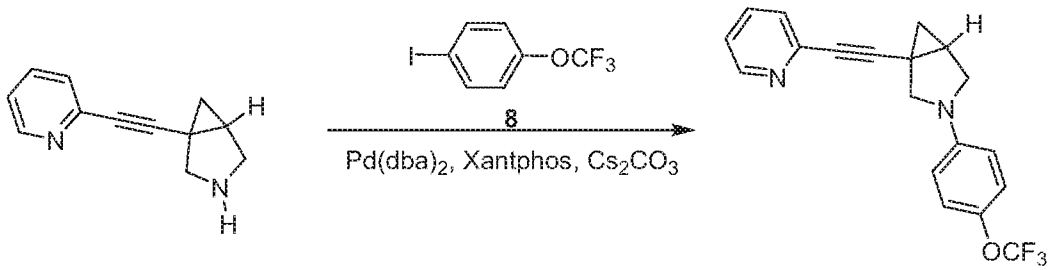
To a mixture of **6** (100.00mg, 542.77μmol) and **7** (361.49mg, 1.63mmol) in toluene (5.00mL) was added $Pd(dba)_2$ (31.21mg, 54.28μmol), Cs_2CO_3 (353.69mg,1.09mmol) and Xantphos (31.41mg, 54.28μmol) in one portion at rt. under N_2 atmosphere. The mixture was then heated to 110°C and stirred for 18hrs. LCMS showed the reaction was completed. The mixture was cooled to rt. and filtered. The filtrate was concentrated in reduced pressure at 60°C. The residue was purified by prep-HPLC to afford the desired product **Compound 2** (15.00mg, yield: 9.72%).

LCMS: *m/z*, 279 $(M+H)^+$;

^{1}HNMR (400 MHz, CDCl3) : δ 8.48 (d, *J* = 4.85Hz, 1H), 7.56 (td, *J* = 7.72, 1.76Hz, 1H), 7.32 (d, *J* = 7.94Hz, 1H), 7.09-7.17 (m, 1H), 6.86 (t, *J* = 8.71Hz, 2H), 6.37-6.47 (m, 2H), 3.69 (d, *J* = 8.60Hz, 1H), 3.48 (d, *J* = 8.82Hz, 1H), 3.19-3.35 (m, 2H), 2.07 (dt, *J* = 8.21, 4.38Hz, 1H), 1.27 (dd, *J* = 8.05, 4.52Hz, 1H), 1.05 (t, *J* = 4.63Hz, 1H).

Example Compound 3

Preparation of 1-(pyridin-2-ylethynyl)-3-(4-(trifluoromethoxy)phenyl)-3-azabicyclo [3.1.0] hexane:



6 Compound 3

Experimental section:

Procedure for preparation of Compound 3:

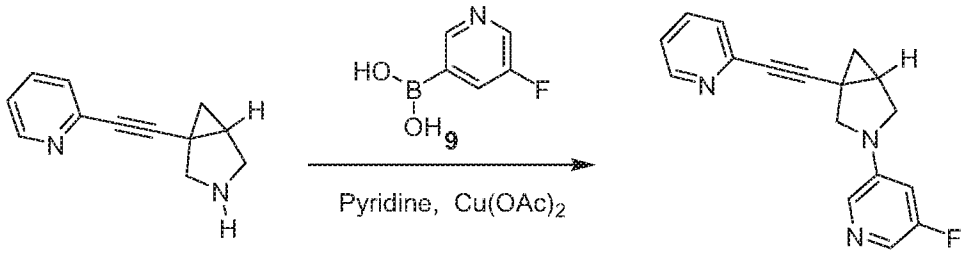
To a mixture of **6** (100.00mg, 542.77μmol) and **8** (299.73mg, 1.09mmol) in toluene (5.00mL) was added $Pd(dba)_2$(31.21mg, 54.28μmol), Cs_2CO_3 (353.69mg, 1.09mmol) and Xantphos (31.41mg, 54.28μmol) in one portion at rt. under N_2 atmosphere. The mixture was then heated to 110°C and stirred for 18 hours. LCMS showed the reaction was completed. The mixture was cooled to rt. and filtered. The filtrate was concentrated in reduced pressure at 60°C. The residue was purified by prep-HPLC to afford the desired product **Compound 3** (8.00 mg, yield: 4.36%).

LCMS: *m/z*, 345 $(M+H)^+$;

^{1}HNMR (400 MHz, CDCl3) : δ 8.54 (d, *J* = 4.85Hz, 1H), 7.63 (td, *J* = 7.72, 1.76Hz, 1H), 7.39 (d, *J* = 7.72Hz, 1H), 7.20 (dd, *J* = 7.06, 5.51Hz, 1H), 7.07 (d, *J* = 8.60Hz, 2H), 6.51 (d, *J*=9.26Hz, 2H), 3.76 (d, *J* = 8.82Hz, 1H), 3.55 (d, *J* = 9.04Hz, 1H), 3.32-3.46 (m, 2H), 2.10-2.19 (m, 1H), 1.36 (dd, *J* = 8.05, 4.52Hz, 1H), 1.05 (t, *J* = 4.63Hz, 1H).

Example Compound 4

Preparation of 3-(5-fluoropyridin-3-yl)-1-(pyridin-2-ylethynyl)-3-azabicyclo [3.1.0] hexane:



6 **Compound 4**

Experimental section:

Procedure for preparation of Compound 4:

To a mixture of **6** (100.00mg, 542.77μmol) and **9** (152.96mg, 1.09mmol) in DCM (20mL), was added $Cu(OAc)_2$ (197.17mg, 1.09mmol) and Pyridine (128.80mg, 1.63mmol) in one portion at rt. in the open air. The mixture was stirred at rt. for 15hrs. TLC showed the reaction was completed. The mixture was concentrated in reduced pressure. The residue was purified by prep-TLC

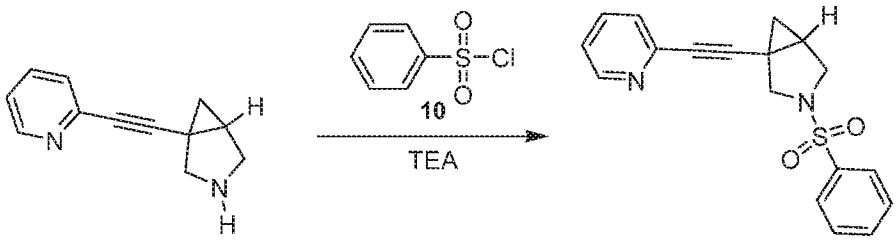
followed by prep-HPLC purification to afford the desired product **Compound 4** (30.00mg, yield: 19.64%).

LCMS: *m/z*, 280.0 $(M+H)^+$;

^{1}HNMR (400 MHz, CDCl3): δ 8.55-8.54 (m, 1H), 7.84 (s, 1H), 7.79 (s, 1H), 7.64-7.61 (m, 1H), 7.40-7.38 (m, 1H), 7.23-7.21 (m, 1H), 6.54-6.51 (m, 1H), 3.78-3.76 (m, 1H), 3.57-3.55 (m, 1H), 3.48-3.45 (m, 2H), 2.20-2.18 (m, 1H), 1.44-1.40 (m, 1H), 1.04-1.01 (m, 1H).

Example Compound 5

Preparation of 3-(phenylsulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo [3.1.0] hexane:



6 **Compound 5**

Experimental section:

Procedure for preparation of Compound 5:

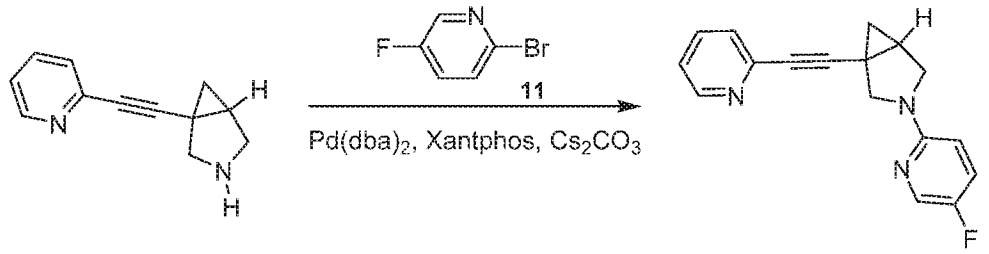
To a mixture of **6** (150.00mg, 814.16μmol) and TEA (247.15mg, 2.44 mol) in DCM (15mL), was added **10** (287.59mg, 1.63mmol) dropwise at rt.. The mixture was stirred at rt. for 3hr. LCMS showed the reaction was completed. The mixture was quenched with water (10mL), the aqueous phase was extracted with DCM (20mL x 2). The combined organic phase was washed with saturated brine (5mL), dried over anhydrous Na_2SO4, filtered and concentrated in vacuo. The residue was purified by prep-HPLC to afford product **Compound 5** (100.00mg, yield: 33.51%).

LCMS: m/z, 325.0 $(M+H)^+$;

1HNMR (400 MHz, CDCl3): δ 8.51-8.49 (m, 1H), 7.80-7.79 (m, 2H), 7.63-7.54 (m, 4H), 7.33-7.31 (m, 1H), 7.20-7.18 (m, 1H), 3.76-3.74 (m, 1H), 3.60-3.58 (m, 1H), 3.18-3.12 (m, 2H), 1.90-1.88 (m, 1H), 1.23-1.20 (m, 1H), 1.14-1.11 (m, 1H).

Example Compound 6

Preparation of 3-(5-fluoropyridin-2-yl)-1-(pyridin-2-ylethynyl)-3-azabicyclo [3.1.0] hexane:



6 **Compound 6**

Experimental section:

Procedure for preparation of Compound 6:

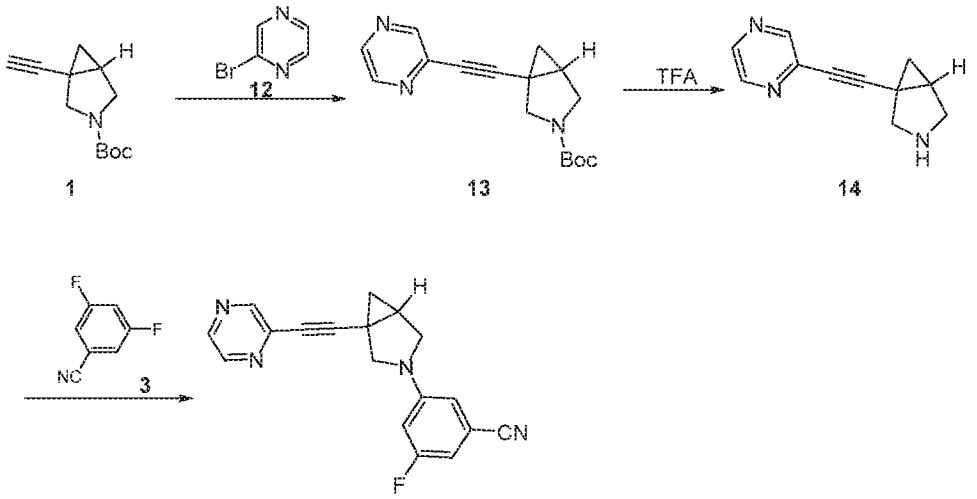
A mixture of **6** (100.00mg, 542.77μmol), **11** (191.04mg, 1.09mmol), Xantphos (31.41mg, 54.28μmol), Cs_2CO_3 (530.54mg, 1.63mmol) and $Pd(dba)_2$ (31.21mg, 54.28μmol) were taken up into a microwave tube in toluene (8mL). The sealed tube was heated at 130°C for 1hr under microwave. TLC showed the starting material was consumed completely, after cooling to rt., the reaction mixture was concentrated in reduced pressure. The residue was purified by prep-TLC followed by prep-HPLC purification to afford **Compound 6** (17.00mg, yield: 5.10%).

LCMS: *m/z*, 280.0 $(M+H)^+$;

^{1}**HNMR** (400 MHz, CDCl3): δ 8.54-8.53 (m, 1H), 8.01-7.99 (m, 1H), 7.64-7.62 (m, 1H), 7.39-7.37 (m, 1H), 7.23-7.20 (m, 2H), 6.31-6.28 (m, 1H), 3.92-3.89 (m, 1H), 3.75-3.72 (m, 1H), 3.57-3.50 (m, 2H), 2.16-2.12 (m, 1H), 1.39-1.36 (m, 1H), 1.02-1.00 (m, 1H).

Example Compound 7

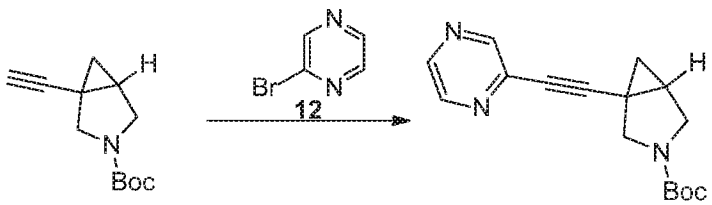
Preparation of 3-fluoro-5-(1-(pyrazin-2-ylethynyl)-3-azabicyclo [3.1.0] hexan-3-yl) benzonitrile:



Compound 7

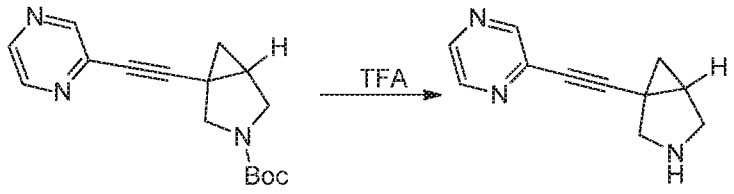
Experimental section:

Procedure for preparation of 13:



To a solution of **1** (300.00mg, 1.45mmol) and **12** (345.16mg, 2.17mmol) in THF (5mL), $Pd(PPh_3)_2Cl_2$ (50.80mg, 72.37μmol), TEA (439.38mg, 4.34mmol) and CuI (27.57mg, 144.74μmol) were added, the reaction mixture was taken up into a microwave tube. The sealed tube was heated at 90°C for 1hr under microwave. TLC showed the starting material was consumed completely, the reaction mixture was diluted with EA (10mL), washed with brine (5mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude product which was purified by prep-HPLC to afford product **13** (300.00mg, yield: 72.41%).

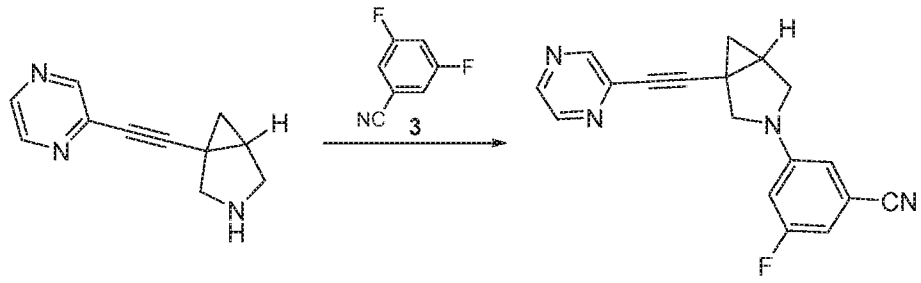
Procedure for preparation of 14:



13 14

Compound **13** (300.00mg, 1.05mmol) was dissolved in TFA (1mL) and DCM (5mL), the solution was stirred at rt. for 3hr, TLC showed the reaction was completed. The reaction mixture was concentrated to dryness and the residue was basified by adding 15% aq. NaOH (10mL), extracted with EA (10mL x 3). The combined organic phase was washed with water (10mL), brine (10mL), dried over anhydrous Na_2SO_4, and concentrated to dryness to afford product **14** (160.00mg, crude), which was used for the next step directly.

Procedure for preparation of Compound 7:



14 Compound 7

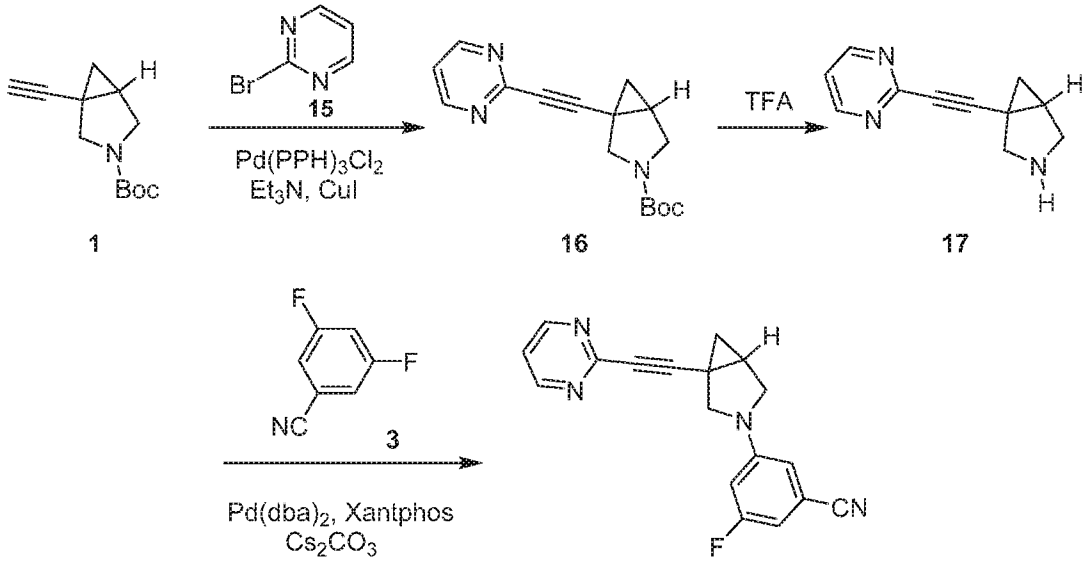
A mixture of **3** (160.00mg, 863.84μmol), **14** (320.06mg, 1.30mmol), $Pd(dba)_2$ (49.67mg, 86.38μmol), Cs_2CO_3 (844.37mg, 2.59mmol) and Xantphos (41.18mg, 86.38μmol) were taken up into a microwave tube in toluene (4mL). The sealed tube was heated at 120°C for 1hr under microwave. TLC showed the starting material was consumed completely. After cooling to rt., EA (10mL) and water (10mL) were added. The aqueous layer was extracted with EA (5mL x 3). The combined organic layers were washed with brine (5mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude product which was purified by prep-HPLC to afford product **Compound 7** (85.00mg, yield: 32.33%).

LCMS: *m/z*, 305.1 $(M+H)^+$;

^{1}**HNMR** (400 MHz, CDCl3): δ 1.06 (t, *J* = 5.2Hz, 1H), 1.48 (dd, *J* = 5.2, 8.0Hz, 1H), 2.25 (t, *J* = 4.0Hz, 1H), 3.48-3.53 (m, 3H), 3.76 (d, *J* = 9.2Hz, 1H), 6.44 (d, *J* = 11.8Hz, 1H), 6.57 (s, 1H), 6.69 (d, *J* = 7.6Hz, 1H), 8.47 (d, *J* = 2.8Hz, 1H), 8.52 (s, 1H), 8.64 (s, 1H).

Example Compound 8

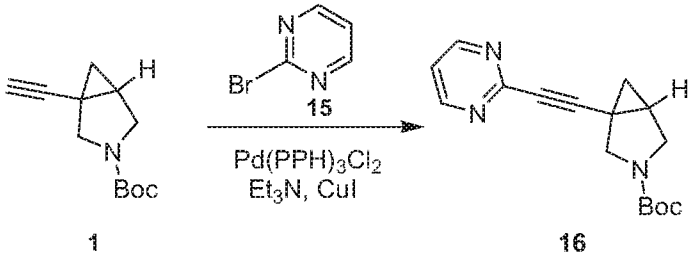
Preparation of 3-fluoro-5-(1-(pyrimidin-2-ylethynyl)-3-azabicyclo [3.1.0] hexan-3-yl) benzonitrile:



Compound 8

Experimental section:

Procedure for preparation of 16:

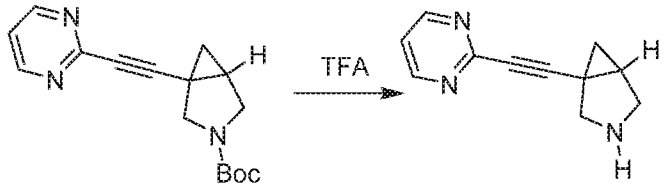


A mixture of **1** (300.00mg, 1.45mmol), **15** (460.21mg, 2.89mmol), CuI (27.57mg, 144.74μmol), TEA (439.38mg, 4.34mmol) and $Pd(PPh_3)_2Cl_2$ (50.80mg, 72.37μmol,) were taken up into a microwave tube in THF (10mL). The sealed tube was heated at 90°C for 1 hr under

microwave. LCMS showed the starting material was consumed completely. After cooling to rt., the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford product **16** (300.00mg, yield: 61.89%).

LCMS: *m/z*, 230.2 $(M+H)^+$.

Procedure for preparation of 17:

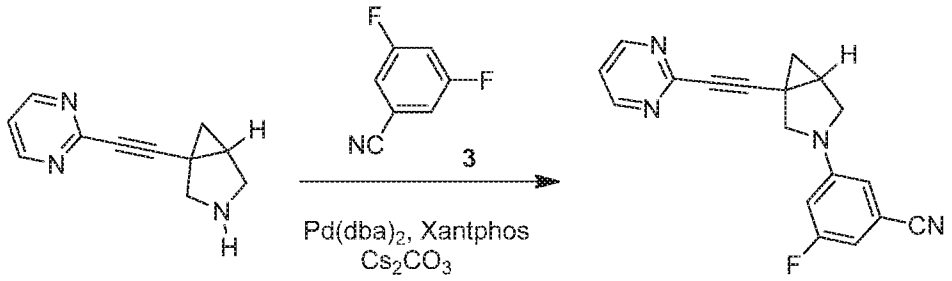


16 **17**

To a solution of **16** (250.00mg, 876.15μmol) in DCM (4.5 mL), was added TFA (1.5mL) in one portion at rt.. The mixture was stirred at rt. for 3hr. LCMS showed the reaction was completed. The reaction mixture was added saturated Na_2CO_3 (3mL).The aqueous phase was extracted with DCM (20mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford product **17** (150.00mg, crude).

LCMS: *m/z*, 186.1 $(M+H)^+$.

Procedure for preparation of Compound 8:



17 **Compound 8**

A mixture of **17** (150.00mg, 809.85μmol), **3** (400.08mg, 1.62mmol), Xantphos (46.86mg, 80.98μmol), Cs_2CO_3 (791.59mg, 2.43mmol) and $Pd(dba)_2$ (46.57mg, 80.98μmol) were taken up into a microwave tube in toluene (8mL). The sealed tube was heated at 110°C for 1hr under microwave. LCMS showed the starting material was consumed completely, after cooling to rt.,

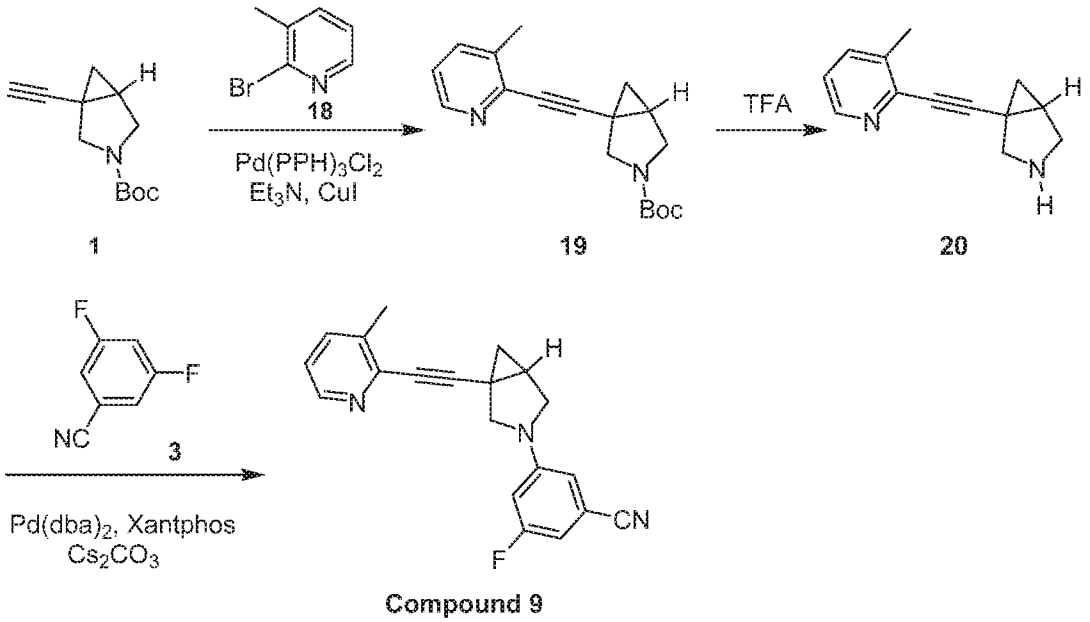
the reaction mixture was concentrated in reduced pressure. The residue was purified by prep-HPLC to afford product **Compound 8** (30.00mg, yield: 12.15%).

LCMS: *m/z*, 305.1 $(M+H)^+$;

^{1}HNMR (400 MHz, CDCl3): δ 8.71-8.69 (m, 1H), 7.25-7.22 (m, 1H), 6.68-6.66 (m, 1H), 6.54 (s, 1H), 6.43-6.40 (m, 1H), 3.75-3.73 (m, 1H), 3.54-3.52 (m, 2H), 3.46-3.44 (m, 1H), 2.29-2.25 (m, 1H), 1.53-1.49 (m, 1H), 1.05-1.02 (m, 1H).

Example Compound 9

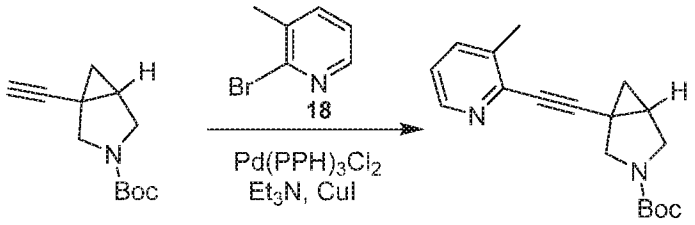
Preparation of 3-fluoro-5-(1-((3-methylpyridin-2-yl) ethynyl)-3-azabicyclo [3.1.0] hexan-3-yl) benzonitrile:



Compound 9

Experimental section:

Procedure for preparation of 19:

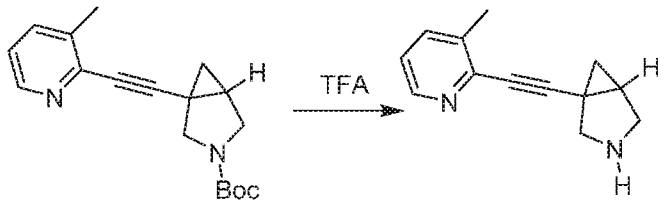


1 19

A mixture of **1** (500.00mg, 2.41mmol), **18** (539.46mg, 3.14mmol), CuI (22.97mg, 120.62μmol), Et_3N (732.31mg, 7.24mmol) and $Pd(PPh_3)_2Cl_2$ (84.66mg, 120.62μmol) were taken up into a microwave tube in THF (8mL). The sealed tube was heated at 95°C for 1hr under microwave. LCMS showed the starting material was consumed completely and the title compound was detected. After cooling to rt., EA (80mL) and saturated aqueous of Na_2CO_3 (20mL) were added. The aqueous layer was extracted with EA (40mL x 2). The combined organic layers were washed with brine (30mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude product, which was purified by column chromatography to afford product **19** (600.00 mg, yield: 83.44%).

LCMS: *m/z*, 299.1 $(M+H)^+$.

Procedure for preparation of 20:

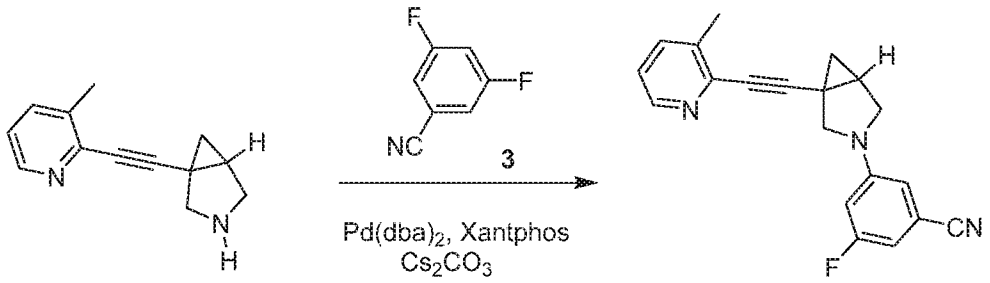


19 20

To a solution of **19** (350.00mg, 1.17mmol) in DCM (5mL) was added TFA (1mL) at rt., the mixture was stirred at rt. for 2hr. LCMS showed the starting material was consumed completely and the title compound was detected, then, the reaction mixture was concentrated to dryness and diluted with water (10mL).The aqueous phase was basified with saturated aqueous $NaHCO_3$ till pH= 7, the aqueous layer was extracted with EA (40mL x 2), the organic layer was washed with brine (20mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford product **20** (200.24mg, crude).

LCMS: *m/z*, 199.2 $(M+H)^+$.

Procedure for preparation of Compound 9:



20 **Compound 9**

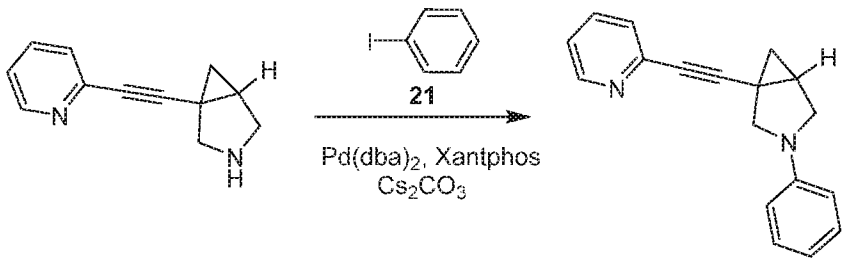
A mixture of **20** (150.00mg, 756.58μmol), **3** (224.26mg, 907.90μmol), Xantphos (3.61mg, 7.57μmol), Cs_2CO_3 (739.53mg, 2.27mmol) and $Pd(dba)_2$ (4.35mg, 7.57μmol) were taken up into a microwave tube in DMF (8mL). The sealed tube was heated at 120°C for 1hr under microwave. TLC showed the starting material was consumed completely. After cooling to rt., EA (80mL) and saturated aqueous of Na_2CO_3 (20mL) were added. The aqueous layer was extracted with EA (60mL x 2). The combined organic layers were washed with brine (30mL), dried over anhydrous Na_2SO_4, concentrated in reduced pressure to give the crude product, which was purified by prep-HPLC to afford product **Compound 9** (59.00mg, yield: 24.42%).

LCMS: *m/z*, 318.1 $(M+H)^+$;

^{1}HNMR (400 MHz, CDCl3): δ 8.38 (d, *J* = 4.19Hz, 1H), 7.51-7.47 (m, 1H), 7.15-7.12 (m, 1H), 6.68-6.62 (m, 1H), 6.55 (s, 1H), 6.45-6.41 (m, 1H), 3.77-3.74 (m, 1H), 3.42-3.58 (m, 3H), 2.42 (s, 3H), 2.14-2.25 (m, 1H), 1.38-1.51 (m, 1H), 1.00 (t, *J* = 4.96Hz, 1H).

Example Compound 10

Preparation of 3-phenyl-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 **Compound 10**

Experimental section:

Procedure for preparation of Compound 10:

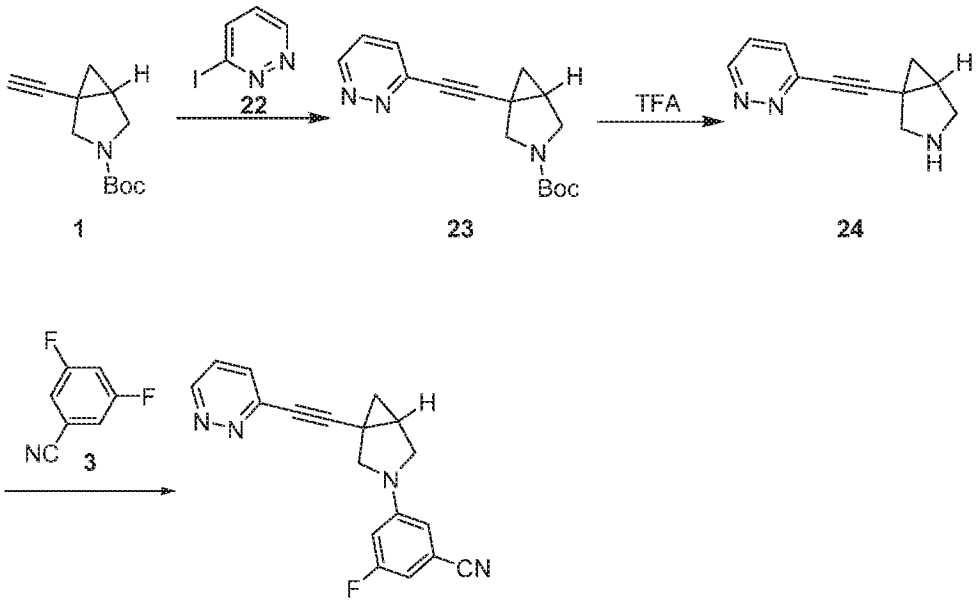
To a mixture of **6** (100.00mg, 542.77μmol) and **21** (110.73mg, 542.77μmol) in toluene (5mL) was added $Pd(dba)_2$ (31.21mg, 54.28μmol), Cs_2CO_3 (353.69mg, 1.09mmol) and Xantphos (31.41mg, 54.28μmol) in one portion at rt. under N_2 atmosphere. The mixture was then heated to 110°C and stirred for 18hrs. LCMS showed the reaction was completed. The mixture was cooled to rt. and filtered. The filtrate was concentrated in reduced pressure at 60°C. The residue was purified by prep-HPLC to afford product **Compound 10** (9.00mg, yield: 6.14%).

LCMS: *m/z*, 261.1 $(M+H)^+$;

^{1}**HNMR** (400 MHz, $CDCl_3$): δ ppm 8.54 (d, *J* = 4.41Hz, 1H), 7.55-7.69 (m, 1H), 7.40 (s, 1H), 7.21 (d, *J* = 7.72Hz, 3H), 6.72 (t, *J* = 7.28Hz, 1H), 6.57 (d, *J* = 8.16Hz, 2H), 3.80 (d, *J* = 8.82Hz, 1H), 3.59 (d, *J* = 9.26Hz, 1H), 3.31-3.46 (m, 2H), 2.10-2.18 (m, 1H), 1.34 (dd, *J* = 8.05, 4.52Hz, 1H), 1.08 (t, *J* = 4.63Hz, 1H).

Example Compound 11

Preparation of 3-fluoro-5-(1-(pyridazin-3-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile:

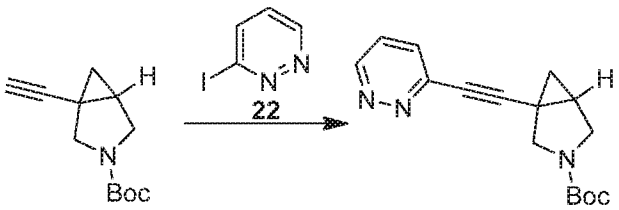


1 23 24

Compound 11

Experimental section:

Procedure for preparation of 23:

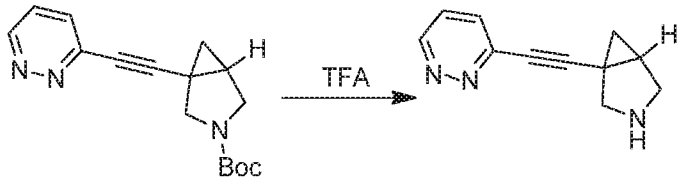


1 23

A mixture of **1** (300.54mg, 1.45mmol), **22** (448.01mg, 2.17mmol), $Pd(PPh_3)_2Cl_2$ (101.78mg, 145.00μmol), Et_3N (293.45mg, 2.90mmol) and CuI (27.62mg, 145.00μmol) were taken up into a microwave tube in THF (10mL). The sealed tube was degassed with N_2 twice and then heated at 90°C for 1 hr under microwave. TLC showed the starting material was consumed. After cooling to rt., EA (60mL) and water (60mL) were added. The aqueous layer was extracted with EA (60mL x 2). The combined organic layers were washed with brine (60mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude product , which was purified by chromatograph column to give product **23** (220.00mg, yield: 53.17%).

LCMS: *m/z*, 286.1 $(M+H)^+$.

Procedure for preparation of 24:

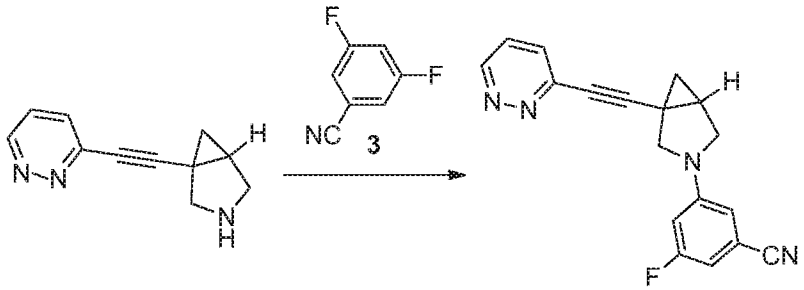


23 **24**

To a mixture of **23** (220.00mg, 771.01μmol) in DCM (8mL) was added TFA (2mL) in one portion at rt.. The mixture was stirred at rt. for 1hr. LCMS showed the reaction was completed. The mixture was concentrated in reduced pressure at 50°C. The residue was poured into saturated $NaHCO_3$ solution (30mL) and stirred for 2min. The aqueous phase was extracted with EA (20 mL x 3). The combined organic phase was washed with saturated brine (20mL x 1), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford product **24** (100.00mg, crude).

LCMS: *m/z*, 186.1 $(M+H)^+$.

Procedure for preparation of Compound 11:



24 **Compound 11**

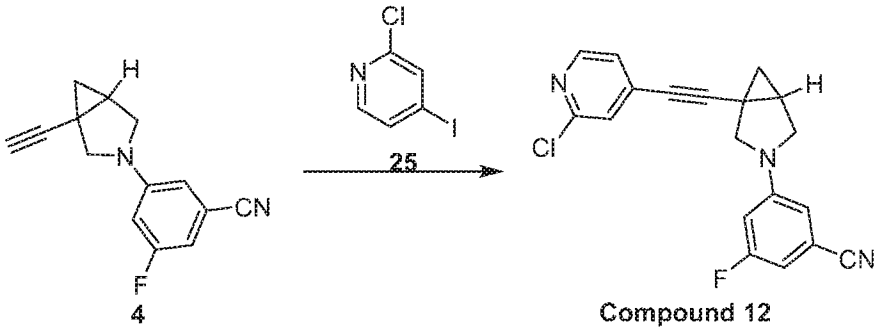
To a mixture of **24** (80.00mg, 431.92μmol) and **3** (160.03mg, 647.88μmol) in toluene (5mL) was added $Pd(dba)_2$ (24.84mg, 43.19μmol), Cs_2CO_3 (281.46mg, 863.84μmol) and Xantphos (24.99mg, 43.19μmol) in one portion at rt. under N_2 atmosphere. The mixture was then heated to 110°C and stirred for 1hr. TLC showed the reaction was completed. The mixture was cooled to rt. and filtered. The filtrate was concentrated in reduced pressure at 60°C to give the residue, which was purified by prep-HPLC to give the desired product **Compound 11** (3.40mg, yield: 2.53%).

LCMS: *m/z*, 305.1 $(M+H)^+$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (dd, *J*=5.01, 1.59Hz, 1H), 7.42-7.50 (m, 1H), 7.37 (dd, *J*=8.44, 5.01Hz, 1H), 6.62 (d, *J*=7.83Hz, 1H), 6.50 (s, 1H), 6.34-6.40 (m, 1H), 3.67-3.74 (m, 1H), 3.47 (s, 3H), 2.20 (dt, *J*=8.31, 4.40Hz, 1H), 1.44 (dd, *J*=8.19, 5.01Hz, 1H), 1.00 (t, *J*=5.01Hz, 1H).

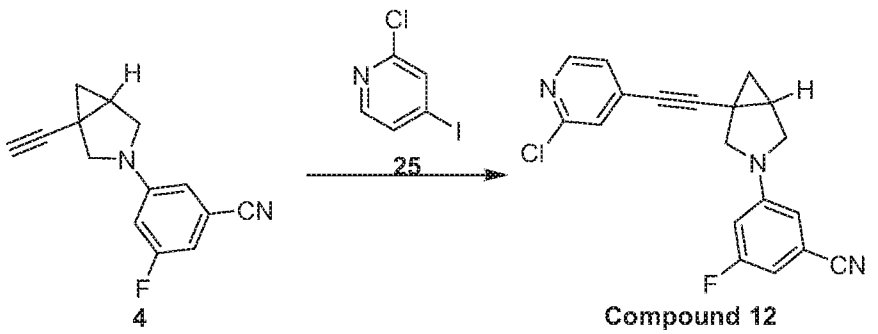
Example Compound 12

Preparation of compound 3-(1-((2-chloropyridin-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluorobenzonitrile:



Experimental section:

Procedure for preparation of Compound 12:



A mixture of compound **4** (30.0mg, 132.6μmol), **25** (31.7mg, 132.6μmol), CuI (2.5mg, 13.2μmol), PPh_3 (3.4mg, 13.2μmol) and $Pd(PPh_3)_2Cl_2$ (4.6mg, 6.63μmol) in TEA (12mL) and THF (12mL)was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 35~40°C for 16hrs under N_2 atmosphere. LCMS showed **4** was consumed completely. The

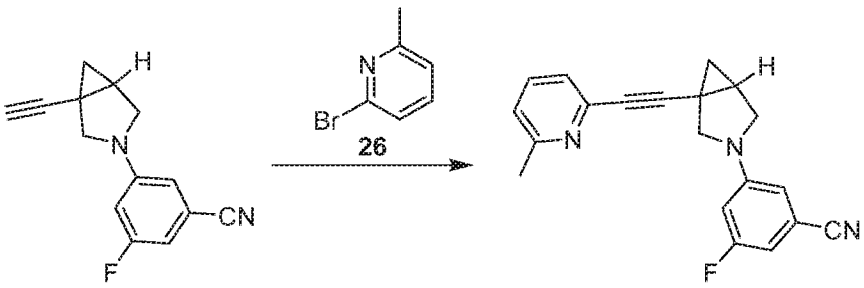
reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 12** (15mg, yield: 33%).

LCMS: *m/z*, 337.1 $(M+H)^+$;

^{1}HNMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 5.2Hz, 1H), 7.24 (s, 1H), 7.10 (dd, *J* = 4.8Hz, 1H), 6.62 (d, *J* = 7.2Hz, 1H), 6.5 (s, 1H), 6.37 (dt, *J* = 13.6Hz, 1H), 3.67 (d, *J* = 9.2Hz, 1H), 3.48(m, 3H), 2.14(m, 1H), 1.36 (dd, *J* = 8.4Hz, 1H), 0.99 (t, *J* = 10Hz, 1H).

Example Compound 13

Preparation of 3-fluoro-5-(1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl) benzonitrile:



Experimental section:

Procedure for preparation of Compound 13:

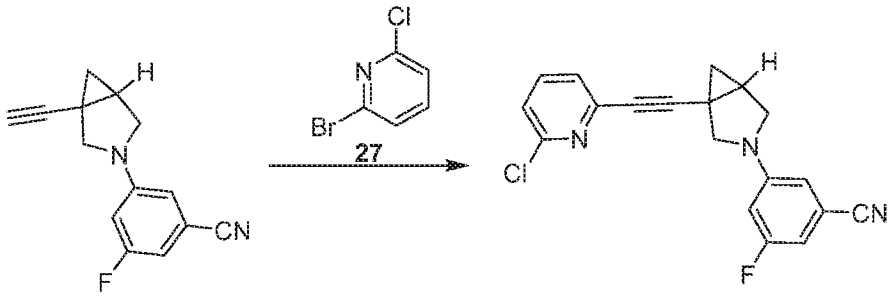
A mixture of compound **4** (70.0mg, 309μmol), **26** (53.0mg, 309μmol), CuI (5.8mg, 30.9μmol), PPh_3 (8.1mg, 30.9μmol) and $Pd(PPh_3)_2Cl_2$ (10.8mg, 15.4μmol) in TEA (1mL) and THF (1mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at rt. for 1hr under N_2 atmosphere. LCMS showed that **4** was consumed completely. The reaction mixture was quenched by addition water (10ml) at rt., and then diluted with EA (15mL) and extracted with EA (15mL x 3). The combined organic layers were washed with NaCl (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 13** (23mg, yield: 23%).

LCMS: *m/z*, 317.1 $(M+H)^+$;

^{1}HNMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.27 (d, *J* = 7.6Hz, 1H), 7.13 (d, *J* = 7.2Hz, 1H), 6.70 (d, *J* = 7.2Hz, 1H), 6.57 (s, 1H), 6.45 (d, *J* = 11.6Hz, 1H), 3.75 (d, *J* = 9.2Hz, 1H), 3.55 (m, 3H), 2.85 (s, 3H), 2.23 (s, 1H), 1.48 (s, 1H), 1.01 (t, *J* = 9.6Hz, 1H).

Example Compound 14

Preparation of 3-(1-(6-chloropyridin-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluorobenzonitrile:



4 **Compound 14**

Experimental section:

Procedure for preparation of Compound 14:

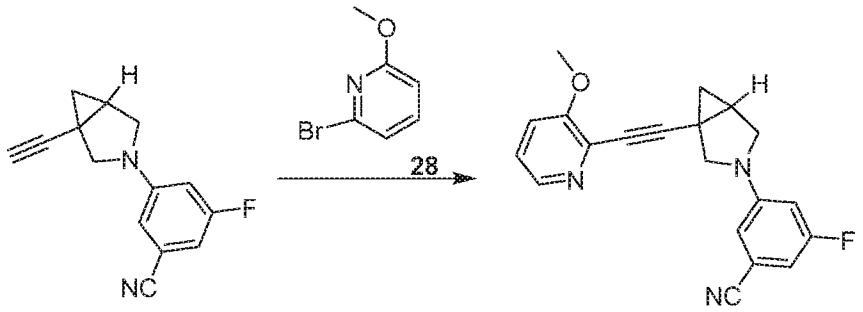
A mixture of compound **4** (80.0mg, 353μmol), **27** (68.0mg, 353μmol), CuI (6.7mg, 35.3μmol), PPh_3 (9.2mg, 35.3μmol) and $Pd(PPh_3)_2Cl_2$ (12.4mg, 17.6μmol) in TEA (1mL) and THF (1mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 35~40°C for 16hrs under N_2 atmosphere. LCMS showed **4** was consumed completely. The reaction mixture was quenched by addition water (10ml) at rt., and then diluted with EA (15mL) and extracted with EA (15mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 14** (26mg, yield: 21%).

LCMS: *m/z*, 337.1 $(M+H)^+$;

^{1}HNMR (400 MHz, $CDCl_3$): δ 7.57 (t, *J* = 16Hz, 1H), 7.35 (t, *J* = 18Hz, 2H), 6.71 (d, *J* = 7.6Hz, 1H), 6.57 (s, 1H), 6.46 (d, *J* = 11.6Hz, 1H), 3.76 (d, *J* = 8.8Hz, 1H), 3.56 (m, 3H), 2.25 (m, 1H), 1.48 (m, 1H), 1.04 (t, *J* = 10Hz, 1H).

Example Compound 15

Preparation of 3-fluoro-5-(1-((6-methoxypyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl) benzonitrile:



4 **Compound 15**

Experimental section:

Procedure for preparation of Compound 15:

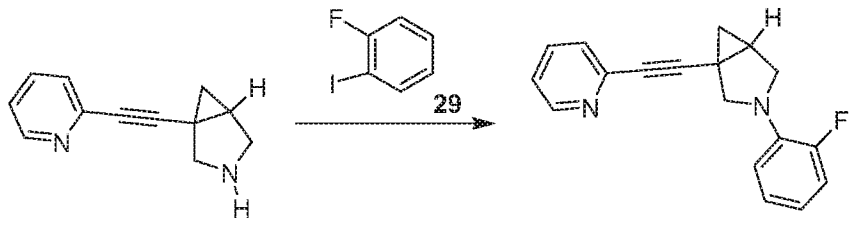
A mixture of compound **4** (80.0mg, 353μmol), **28** (66.4mg, 353μmol), CuI (6.7mg, 35.3μmol), PPh_3 (9.2mg, 35.3μmol) and $Pd(PPh_3)_2Cl_2$ (12.4mg, 17.6μmol) in TEA (1mL) and THF (1mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 35~40°C for 16hrs under N_2 atmosphere. LCMS showed that **4** was consumed completely. The reaction mixture was quenched by addition water (10ml) at rt., and then diluted with EA (15mL) and extracted with EA (15mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 15** (15.0, yield: 12%).

LCMS: *m/z*, 333.1 $(M+H)^+$;

^{1}**HNMR** (400 MHz, $CDCl_3$): δ 7.55 (t, *J* = 15.6Hz, 1H), 7.04 (d, *J* = 7.2Hz, 2H), 6.73 (t, *J* = 19.6Hz, 2H), 6.58 (s, 1H), 6.46 (d, *J* = 11.6Hz, 1H), 3.98 (s, 3H), 3.76 (d, *J* = 8.8Hz, 1H), 3.55 (m, 3H), 2.25 (m, 1H), 1.49 (t, *J* = 13.2Hz, 1H), 1.02 (t, *J* = 10Hz, 1H).

Example Compound 16

Preparation of 3-(2-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 Compound 16

Experimental section:

Procedure for preparation of Compound 16:

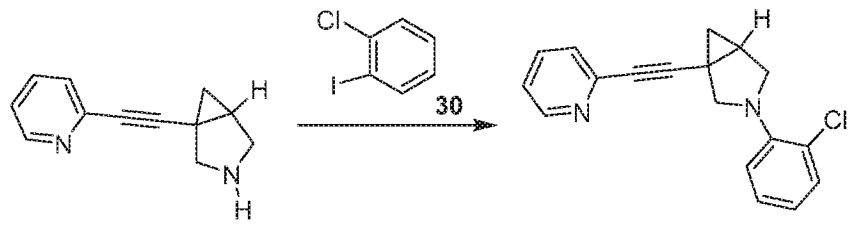
A mixture of **6** (60.0mg, 325μmol), **29** (72.3mg, 325μmol), Cs_2CO_3 (212.0mg, 651μmol), Xantphos (18.8mg, 32.5μmol) and $Pd_2(dba)_3$ (29.8mg, 32.5μmol) in dioxane (4mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 2hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at rt., and then diluted with EA (10mL) and extracted with EA (10mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 16** (30mg, yield: 33%).

LCMS: *m/z,* 304.1 $(M+H)^+$;

^{1}HNMR (400 MHz, $CDCl_3$): δ 8.48 (d, *J* = 4.8Hz, 1H), 7.55 (m, 1H), 7.33 (d, *J* = 8Hz, 1H), 7.17 (m, 1H), 6.94 (m, 2H), 6.69 (m, 2H), 3.86 (m, 1H), 3.68 (m, 1H), 3.38 (m, 2H), 2.01 (m, 1H), 1.20 (t, *J* = 7.6Hz, 2H).

Example Compound 17

Preparation of 3-(2-chlorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 Compound 17

Experimental section:

Procedure for preparation of Compound 17:

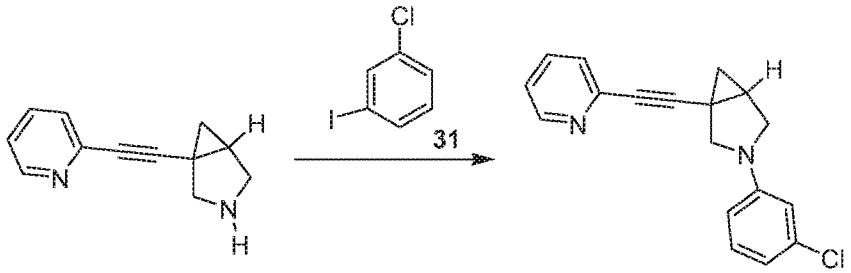
A mixture of compound **6** (100mg, 542μmol), **30** (129mg, 542μmol), Cs_2CO_3 (353mg, 1.09mmol), Xantphos (31.4mg, 54.2μmol) and $Pd_2(dba)_3$ (49.7mg, 54.2μmol) in dioxane (1mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (15 mL) at rt., and then diluted with EA (30mL) and extracted with EA (20mL x 3). The combined organic layers were washed with brine (30mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 17** (33mg, yield: 20%).

LCMS: *m/z,* 278.1 $(M+H)^+$;

^{1}HNMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 4Hz, 1H), 7.63 (m, 1H), 7.39 (d, *J* = 8Hz, 1H), 7.31 (m, 1H), 7.20 (m, 2H), 6.96 (m, 2H), 3.90 (d, *J* = 8.8Hz, 1H), 3.76 (d, *J* = 9.2Hz, 1H), 3.33 (m, 2H), 2.03 (m, 1H), 1.50 (t, *J* = 9.2Hz, 1H), 1.20 (m, 1H).

Example Compound 18

Preparation of 3-(3-chlorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 **Compound 18**

Experimental section:

Procedure for preparation of Compound 18:

A mixture of compound **6** (80mg, 434μmol), **31** (103mg, 434μmol), Cs_2CO_3 (282mg, 868 μ mol), Xantphos (24.1mg, 43.4μmol) and $Pd_2(dba)_3$ (39.7mg, 43.4μmol) in dioxane (4mL) was

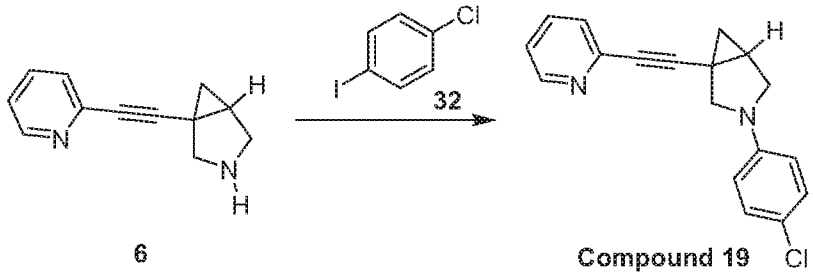
degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (10mL) at rt., and then diluted with EA (10mL) and extracted with EA (15mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 18** (34mg, yield: 26%).

LCMS: *m/z*, 294.1 $(M+H)^+$;

^{1}H NMR (400 MHz CDCl3): δ 8.48 (d, *J* = 4.4Hz, 1H), 7.58 (m, 1H), 7.33 (d, *J* = 7.6Hz, 1H), 7.15 (m, 1H), 7.06 (t, *J* = 16Hz, 1H), 6.62 (d, *J* = 8 Hz, 1H), 6.46 (s, 1H), 6.37 (m, 1H), 3.70 (d, *J* = 8.8Hz, 1H), 3.48 (d, *J* = 9.2Hz, 1H), 3.38 (m, 2H), 2.10 (m, 1H), 1.32 (m, 1H), 0.97 (t, *J* = 9.6Hz, 1H).

Example Compound 19

Preparation of 3-(4-chlorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 **Compound 19**

Experimental section:

Procedure for preparation of Compound 19:

A mixture of **6** (100mg, 542μmol), **32** (129mg, 542μmol), Cs_2CO_3 (353mg, 1.09mmol), Xantphos (31.4mg, 54.2μmol) and $Pd_2(dba)_3$ (49.7mg, 54.2μmol) in dioxane (4mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (15mL) at rt., and then diluted with EA (15mL) and extracted with EA (20mL x 3). The combined organic layers were washed with brine (30mL x 2), filtered

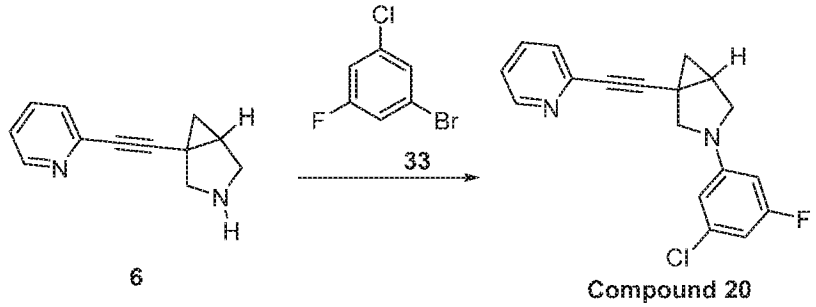
and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 19** (43mg, yield: 26%).

LCMS: *m/z*, 294.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$):δ 8.58 (d, *J* = 4.4Hz, 1H), 7.67 (m, 1H), 7.42 (d, *J* = 8Hz, 1H), 7.24 (m, 3H), 6.51 (d, *J* = 9.2Hz, 2H), 3.79 (d, *J* = 8.8Hz, 1H), 3.58 (d, *J* = 8.8Hz, 1H), 3.44 (m, 2H), 2.19 (m, 1H), 1.40 (m, 1H), 1.10 (t, *J* = 9.2Hz, 1H).

Example Compound 20

Preparation of 3-(3-chloro-5-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



Experimental section:

Procedure for preparation of Compound 20:

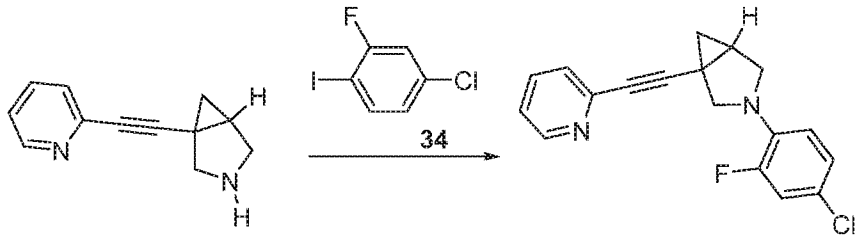
A mixture of **6** (100mg, 542μmol), **33** (113mg, 542μmol), Cs_2CO_3 (353mg, 1.09mmol), Xantphos (31.4mg, 54.2μmol) and $Pd_2(dba)_3$ (49.7mg, 54.2μmol) in dioxane (4mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at rt., and then diluted with EA (10mL) and extracted with EA (10mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 20** (35mg, yield: 20%).

LCMS: *m/z*, 294.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.58 (d, *J* = 4.4Hz, 1H), 7.68 (m, 1H), 7.42 (d, *J* = 8Hz, 1H), 7.25 (m, 1H), 6.46 (d, *J* = 9.2Hz, 1H), 6.33 (s, 1H), 6.17 (d, *J* = 11.6Hz, 1H), 3.75 (d, *J* = 9.2Hz, 1H), 3.53 (m, 3H), 2.20 (m, 1H), 1.44 (m, 1H), 1.03 (t, *J* = 9.6Hz, 1H).

Example Compound 21

Preparation of 3-(4-chloro-2-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 **Compound 21**

Experimental section:

Procedure for preparation of Compound 21:

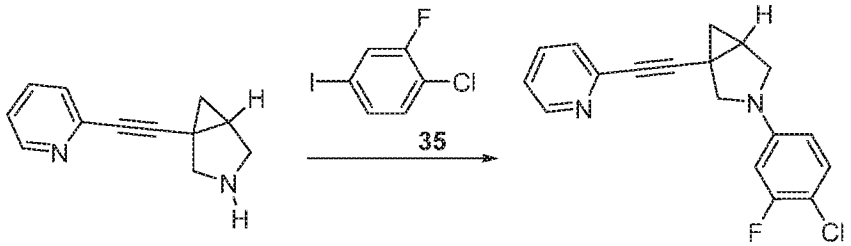
A mixture of **6** (100mg, 542μmol), **34** (139mg, 542μmol), Cs_2CO_3 (353mg, 1.09mmol), Xantphos (31.4mg, 54.2μmol) and $Pd_2(dba)_3$ (49.7mg, 54.2μmol) in dioxane (4mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (15mL) at rt., and then diluted with EA (15mL) and extracted with EA (20mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 21** (43mg, yield: 25%).

LCMS: *m/z,* 312.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.58 (d, *J* = 4Hz, 1H), 7.67 (t, *J* = 14Hz, 1H), 7.42 (d, *J* = 7.6Hz, 1H), 7.24 (t, *J* = 12Hz, 1H), 7.03 (m, 1H), 6.63 (d, *J* = 8.8Hz, 1H), 3.91 (m, 1H), 3.73 (d, *J* = 7.2Hz, 1H), 3.45 (m, 2H), 2.11 (m, 3H), 1.32 (m, 2H).

Example Compound 22

Preparation of 3-(4-chloro-3-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 Compound 22

Experimental section:

Procedure for preparation of Compound 22:

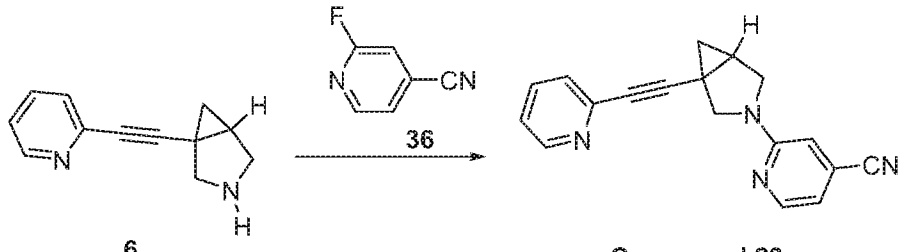
A mixture of **6** (100mg, 542μmol), **35** (139mg, 542μmol), Cs_2CO_3 (353mg, 1.09mmol), Xantphos (31.4 mg, 54.2 μmol) and $Pd_2(dba)_3$ (49.7 mg, 54.2 μmol) in dioxane (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (15mL) at rt., and then diluted with EA (15mL) and extracted with EA (20mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 22** (30mg, yield: 17%).

LCMS: *m/z,* 312.1 $(M+H)^+$;

^{1}H NMR (400 MHz CDCl3): δ 8.58 (d, *J* = 4.4Hz, 1H), 7.67 (t, *J* = 14Hz, 1H), 7.42 (d, *J* = 8Hz, 1H), 7.25 (m, 2H), 6.36 (m, 2H), 3.75 (d, *J* = 8.8Hz, 1H), 3.54 (d, *J* = 9.2Hz, 1H), 3.46 (m, 2H), 2.20 (m, 1H), 1.43 (m, 2H), 1.07 (t, *J* = 9.2Hz, 1H).

Example Compound 23

Preparation of 2-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)isonicotinonitrile:



6 Compound 23

Experimental section:

Procedure for preparation of Compound 23:

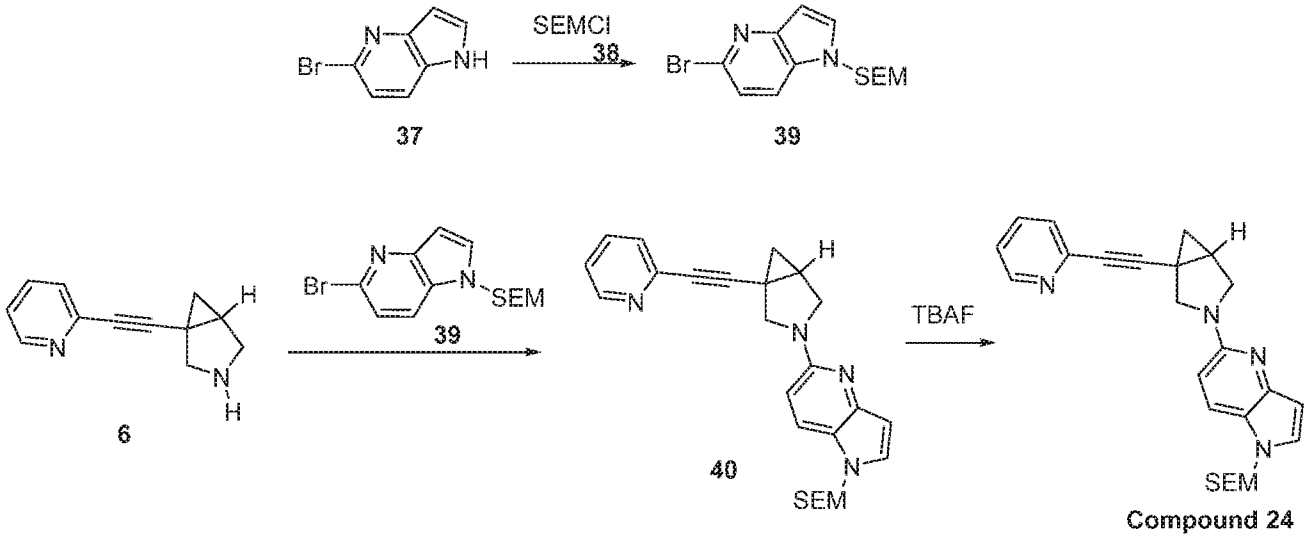
To a solution of compound **6** (99mg, 0.54mmol) and **36** (99mg, 81mmol) in DMF (2mL) was added K_2CO_3 (0.15 g, 1.09mmol) and the mixture was stirred at 110°C for 16hrs. After the DMF evaporated under vacuo, the residue was diluted with EA (5mL), then washed with water, the organic layer was purified by prep-HPLC to give the desired product **Compound 23** (100mg, yield: 64%).

LCMS: *m/z*, 286.1 $(M+H)^+$;

^{1}H NMR (400 MHz CDCl3): δ 8.58 (d, *J* = 4 Hz, 1H), 8.28 (d, *J* = 5.2 Hz, 1H), 7.67 (m, 1H), 7.43(d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 12.4 Hz, 1H), 6.77 (d, *J* = 4.8 Hz, 1H), 6.54 (s, 1H), 4.00 (d, *J* = 10.4 Hz, 1H), 3.80 (d, *J* = 10 Hz, 1H), 3.68 (m, 2H), 2.23 (m, 1H), 1.48 (m, 2H), 0.98 (t, *J* =10 Hz, 1H).

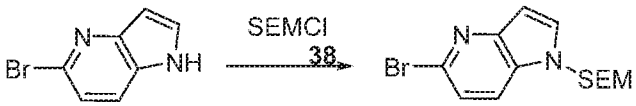
Example Compound 24

Preparation of 5-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-1H-pyrrolo[3,2-b]pyridine:



Experimental section:

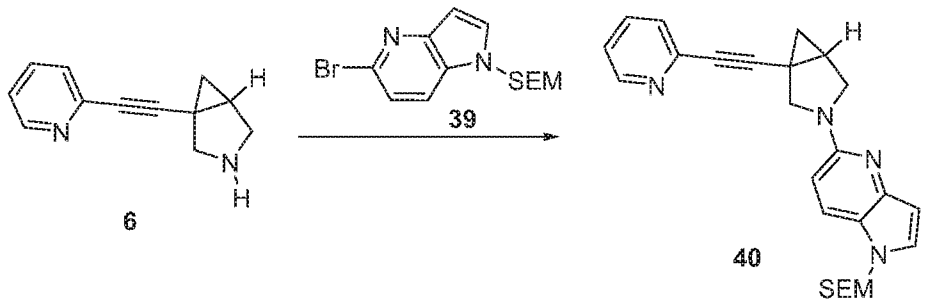
Procedure for preparation of Compound 39:



37 39

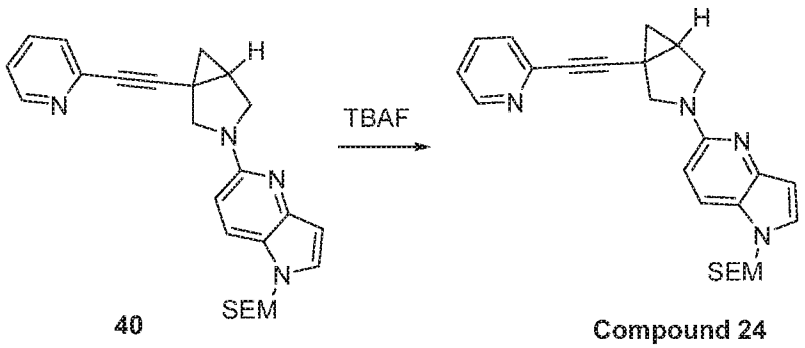
To a solution of **37** (300mg, 1.52mmol) in THF (10mL) was added NaH (109mg, 4.56mmol) at 0°C. The mixture was stirred at 0°C for 0.5h, then **38** (380mg, 2.28mmol) was added, the mixture was stirred at 0~25°C for 4hrs. LCMS showed **37** was consumed completely and one main peak with desired MS was detected. The reaction mixture was quenched by addition water (15mL), and then diluted with EA (30mL) and extracted with EA (20mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography to give product **37** (380mg, yield: 76%).

Procedure for preparation of 40:



A mixture of **6** (150mg, 814μmol), **39** (266mg, 814μmol), Cs_2CO_3 (530mg, 1.63 mmol), Xantphos (47mg, 81μmol,) and $Pd_2(dba)_3$ (74mg, 81μmol) in dioxane (3mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. The reaction mixture was quenched by addition water (20mL) at rt., and then diluted with EA (20mL) and extracted with EA (30mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography to give product **40** (200mg, yield: 57%).

Procedure for preparation of Compound 24:



40 **Compound 24**

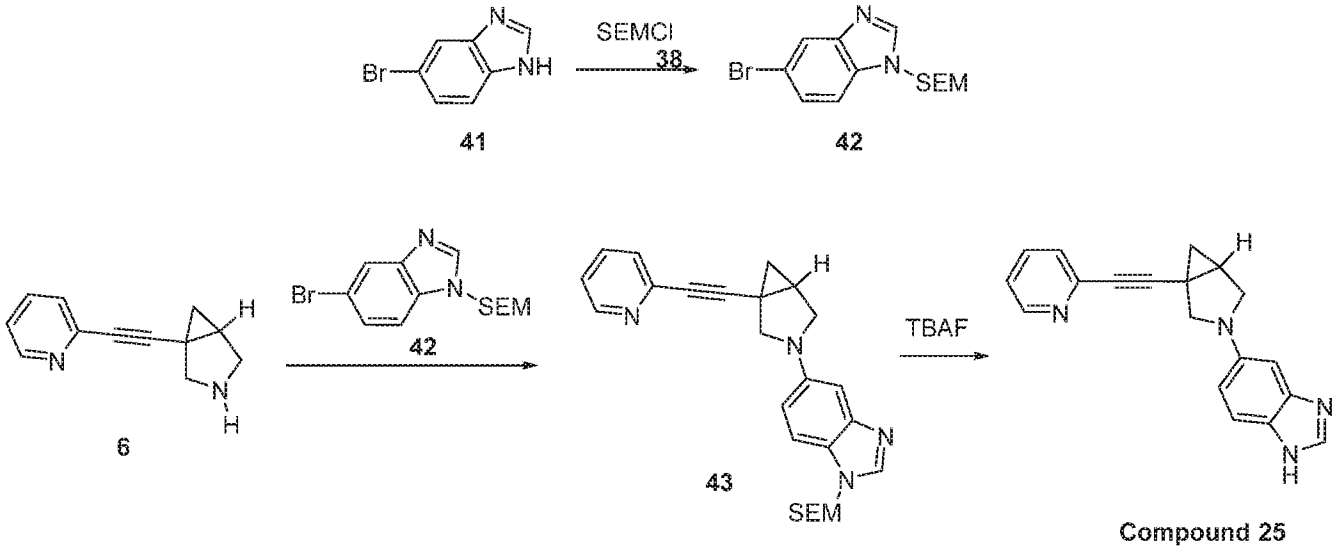
To a solution of **40** (200mg, 464μmol) in THF (2mL) was added TBAF (1M, 696uL). The mixture was stirred at 80°C for 16hrs. LCMS showed that **40** was consumed completely. The reaction mixture was quenched by addition water (15mL) at rt., and extracted with EA (20mL x 3), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give desired product **Compound 24** (6.02mg, yield: 4.3%).

LCMS: *m/z*, 300.1 $(M+H)^+$;

^{1}H NMR (400 MHz, MeOD): δ 11.79 (s, 1H), 8.80 (d, *J* = 5.6Hz, 1H), 8.57 (t, *J* = 8Hz, 1H), 8.17(m, 2H), 8.02 (t, *J* = 7.2Hz, 1H), 7.63 (s, 1H), 7.07 (d, *J* = 9.2Hz, 1H), 6.59 (s, 1H), 4.22 (d, *J* = 9.6Hz, 1H), 3.98 (m, 3H), 2.63 (m, 1H), 1.60 (m, 1H), 1.30 (m, 1H).

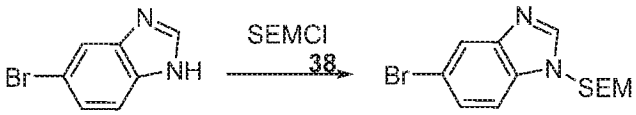
Example Compound 25

Preparation of 5-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazole:



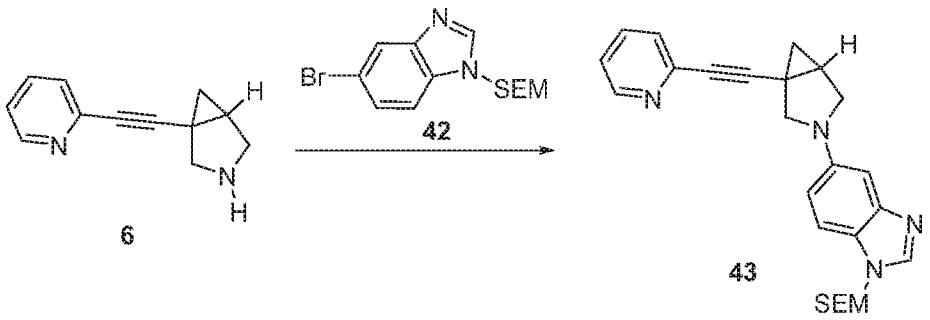
Experimental section:

Procedure for preparation of 42:



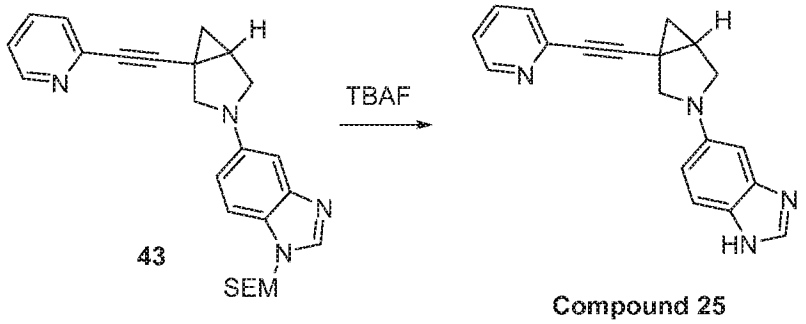
To a solution of **41** (400mg, 2.03mmol) in THF (10mL) was added NaH (146mg, 6.09mmol) at 0°C. The mixture was stirred at 0°C for 0.5hr, then **38** (507mg, 3.04mmol) was added, the mixture was stirred at 0~25°C for 4hrs. LCMS showed that **41** was consumed completely and one main peak with desired MS was detected. The reaction mixture was quenched by addition water (20mL), and then diluted with EA (30mL) and extracted with EA (30 mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography to give the desired product **42** (503mg, yield: 75%).

Procedure for preparation of 43:



A mixture of **6** (200mg, 1.09mmol), **42** (356mg, 1.09mmol), Xantphos (63mg, 109μmol,) and $Pd_2(dba)_3$ (99mg, 109μmol) and t-BuONa (209mg, 2.18mmol) in dioxane (4mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. LCMS showed that **6** was consumed completely. The reaction mixture was quenched by addition water (20mL) at rt., and then diluted with EA (20mL) and extracted with EA (40mL x 3). The combined organic layers were washed with brine (40mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography to give product **43** (259mg, yield: 55%).

Procedure for preparation of Compound 25:



To a solution of **43** (227.00mg, 527.15μmol) in THF (1mL) was added TBAF (0.15mL, 1N TBAF/THF). The mixture was stirred at 60°C for 3hrs, TLC was showed that most of **43** was consumed, the reaction was quenched with water (5mL), extracted with EA (10 mL x 2), the combined organic layers were washed brine (5mL), dried, concentrated. The residue was purified by prep-HPLC to give the desired product **Compound 25** (30.00mg, yield: 18.95%).

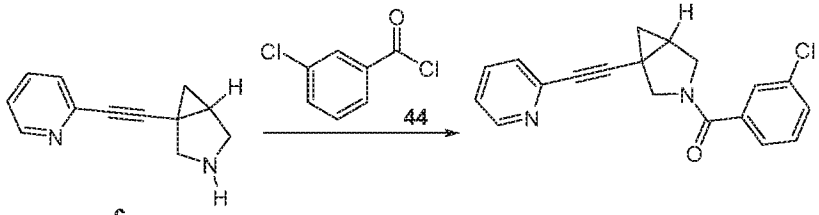
LCMS: *m/z*, 300.1 $(M+H)^+$;

^{1}H NMR (400 MHz MeOD): δ 9.12 (s, 1H), 8.78 (d, *J* = 5.2Hz, 1H), 8.58 (t, *J* = 8Hz, 1H), 8.12(d, *J* = 8Hz, 1H), 8.02 (t, *J* = 7.2Hz, 1H), 7.66 (d, *J* = 9.6Hz, 1H), 7.07 (d, *J* = 8.8Hz, 1H),

6.87 (s, 1H), 4.01 (d, J = 8.8Hz, 1H), 3.79 (d, J = 9.2Hz, 1H), 3.56 (d, J = 8.8Hz, 1H), 3.50 (m, 1H), 2.49 (m, 1H), 1.60 (m, 1H), 1.30 (m, 1H).

Example Compound 26

Preparation of (3-chlorophenyl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone:



Experimental section:

Procedure for preparation of Compound 26:

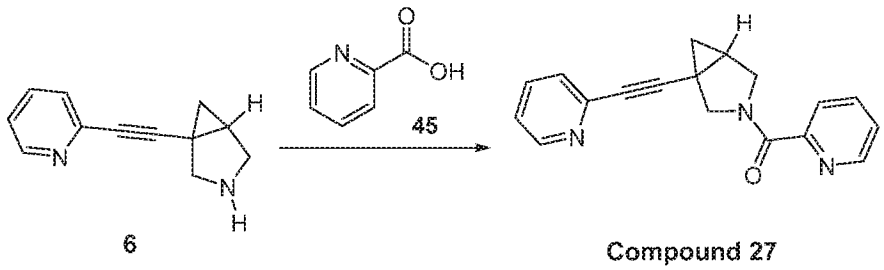
To a solution of **6** (50.0mg, 271μmol) in DCM (1mL) was added TEA (54.9mg, 542μmol) and **44** (49.8mg, 284μmol). The mixture was stirred at 0°C for 1hr. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 0°C, and then extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 26** (31.0mg, yield: 35%).

LCMS: *m/z*, 322.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.56 (s, 1H), 7.65 (t, J = 15.6Hz, 1H), 7.45 (m, 4H), 7.23 (d, J = 5.2Hz, 1H), 4.48 (m, 1H), 3.85 (m, 3H), 2.09 (dt, J = 3.6Hz, 1H), 1.39 (t, J = 13.2Hz, 1H), 0.85 (s, 1H).

Example Compound 27

Preparation of pyridin-2-yl(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone:



6 Compound 27

Experimental section:

Procedure for preparation of Compound 27:

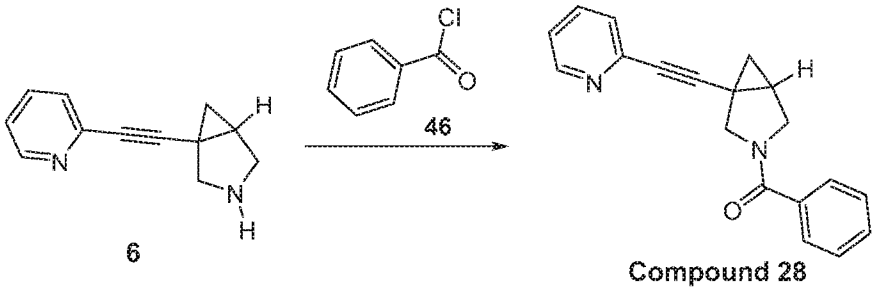
To a solution of **6** (100mg, 542μmol) in DCM (1mL) was added HATU (227mg, 597.05μmol), TEA (109mg, 1.09mmol), **45** (73.5mg, 597μmol) at 0°C. The mixture was stirred at 20°C for 5hrs. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and then extracted with DCM (10mL x 2). The combined organic layer concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 27** (59.0mg, yield: 37%).

LCMS: m/z, 289.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.61 (m, 2H), 7.85 (m, 2H), 7.67 (m, 1H), 7.44 (m, 2H), 7.24 (m, 1H), 4.44 (m, 2H), 4.10 (m, 1H), 3.77 (t, *J* = 12.8Hz, 1H), 2.10 (m, 1H), 1.38 (m, 1H), 0.92 (m, 1H).

Example Compound 28

Preparation of phenyl(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone:



6 Compound 28

Experimental section:

Procedure for preparation of Compound 28:

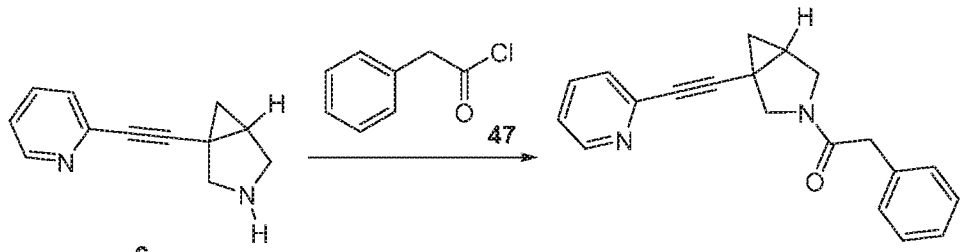
To a solution of **6** (100mg, 542μmol) in DCM (2mL) was added TEA (109mg, 1.09mmol), **46** (80.1mg, 569μmol). The mixture was stirred at 0~20 °C for 2hrs. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 28** (67mg, yield: 42%).

LCMS: *m/z*, 288.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.54 (s, 1H), 7.65 (m, 1H), 7.45 (d, *J* = 6Hz, 4 H), 7.36 (d, *J* = 7.6Hz, 1 H), 7.23 (d, *J* = 4.8Hz, 1 H), 7.50 (m, 1H), 3.85 (m, 3H), 2.09 (m, 1H), 1.37 (m, 1H), 0.85 (s, 1H).

Example Compound 29

Preparation of 2-phenyl-1-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)ethanone:



6 **Compound 29**

Experimental section:

Procedure for preparation of Compound 29:

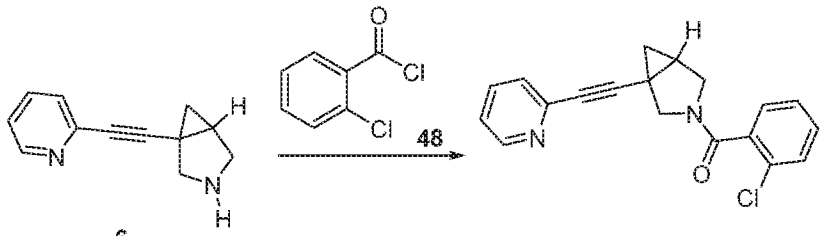
To a solution of **6**(100mg, 542μmol) in DCM (2mL), was added was added TEA (109mg, 1.09mmol) and **47** (92.3mg, 597μmol). The mixture was stirred at 0～20°C for 2hrs. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 29** (76.0mg, yield: 46%).

LCMS: *m/z*, 302.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.55 (d, *J* = 2.8Hz, 1 H), 7.64 (m, 1H), 7.34 (m, 7 H), 4.16 (d, *J* = 11.6Hz, 1 H), 3.96 (m, 1 H), 3.68(m, 4H), 2.03 (m, 1H), 1.35 (m, 1H), 0.76 (m, 1H).

Example Compound 30

Preparation of (2-chlorophenyl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone:



6 Compound 30

Experimental section:

Procedure for preparation of Compound 30:

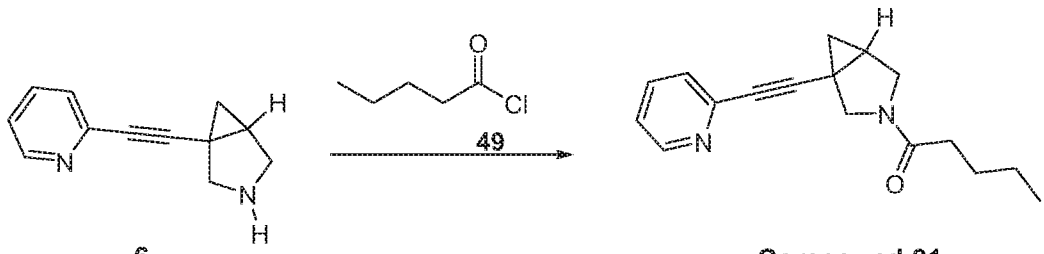
To a solution of **6** (50.0mg, 271μmol) in DCM (1mL) was added TEA (54.9mg, 542μmol), and **48** (47.5mg, 271μmol,). The mixture was stirred at 0°C for 1hr. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 0°C, and then extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 30** (35.0mg, yield: 39%).

LCMS: *m/z*, 322.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.56 (m , 1 H), 7.66 (m, 1H), 7.42 (m, 4 H), 7.34 (m, 2 H), 4.41 (m, 1 H), 3.72 (m, 2 H), 3.46(m, 1H), 2.13 (m, 1H), 1.41 (m, 1H), 1.00 (s, 1H).

Example Compound 31

Preparation of 1-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)pentan-1-one:



6 Compound 31

Experimental section:

Procedure for preparation of Compound 31:

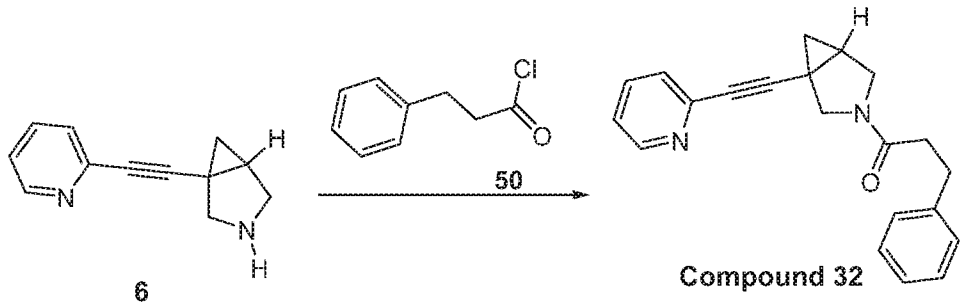
To a solution of **6** (100mg, 542μmol) in DCM (2mL) was added TEA (109mg, 1.09mmol), and **49** (68.7mg, 569μmol). The mixture was stirred at 0~20 °C for 2hrs. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 31** (98mg, yield: 67%).

LCMS: *m/z*, 268.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.53 (t, *J* = 8Hz, 1 H), 7.61 (m, 1H), 7.37 (t, *J* = 14Hz, 1 H), 7.19 (m, 1 H), 4.10 (d, *J* = 12Hz, 1 H), 3.89 (d, *J* = 12Hz, 1 H), 3.78 (d, *J* = 10Hz, 1 H), 3.72 (m, 1H), 3.56 (m, 2H), 2.24 (m, 2H), 2.05 (m, 1H), 1.60 (m, 1H), 1.36 (m, 3H), 0.92 (m, 3H),0.81 (t, *J* = 10Hz, 1H).

Example Compound 32

Preparation of 3-phenyl-1-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one:



6 Compound 32

Experimental section:

Procedure for preparation of Compound 32:

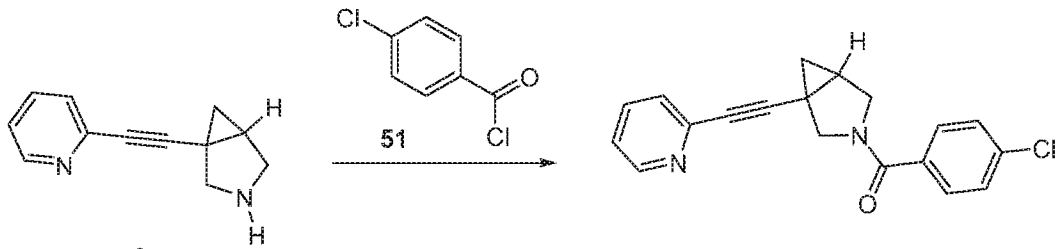
To a solution of **6** (100mg, 542μmol) in DCM (2mL), was added was added TEA (109mg, 1.09mmol) and **50** (91.5mg, 542μmol). The mixture was stirred at 0~20°C for 2hrs. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 32** (86.0mg, yield: 50%).

LCMS: *m/z*, 316.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.55 (d, *J* = 4.4Hz, 1 H), 7.64 (m, 1H), 7.38 (m, 7 H), 4.12 (m, 1 H), 3.70 (m, 3 H), 2.98 (t, *J* = 15.6Hz, 2 H), 2.56 (m, 2 H), 2.02(m, 1H), 1.34 (m, 1H), 0.72 (m, 1H).

Example Compound 33

Preparation of (4-chlorophenyl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone:



Compound 33

Experimental section:

Procedure for preparation of Compound 33:

To a solution of **6** (50.0mg, 271μmol) in DCM (1mL) was added TEA (54.9mg, 542μmol) and **51** (47.5mg, 271μmol). The mixture was stirred at 0°C for 1hr. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated

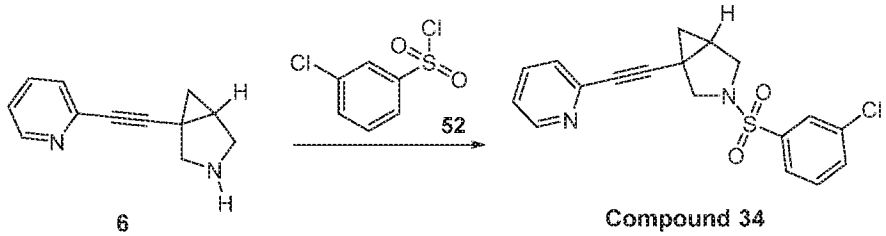
under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 33** (34.0mg, yield: 38%).

LCMS: *m/z*, 322.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.56 (s, 1H), 7.65 (d, *J* = 7.2Hz, 1H), 7.41 (m, 5H), 7.23 (m, 1H), 4.49 (m, 1H), 3.86 (m, 3H),2.09 (m, 1H), 1.38 (m, 1H), 0.85(s, 1H).

Example Compound 34

Preparation of 3-((3-chlorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



6 Compound 34

Experimental section:

Procedure for preparation of Compound 34:

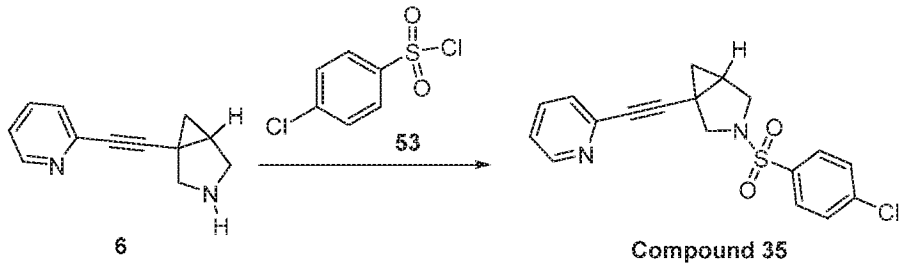
To a solution of **6** (100mg, 542μmol) in DCM (2mL) was added TEA (109mg, 1.09mmol), and **52** (120mg, 569μmol). The mixture was stirred at 0~20 °C for 1hr. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 34** (93.0mg, yield: 47%).

LCMS: *m/z*, 358.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.55 (d, *J* = 4.4Hz, 1H), 7.82 (s, 1H), 7.72 (d, *J* = 7.6Hz, 1H), 7.70 (m, 2H), 7.53 (t, *J* = 8Hz, 1 H), 7.35 (d, *J* = 8Hz, 1 H), 7.22 (m, 1 H), 3.81 (d, *J* = 9.2 Hz, 1 H), 3.64 (d, *J* = 9.6 Hz, 1 H), 3.23 (m, 2H), 1.98 (m, 1H), 1.30 (m, 1H), 1.17 (t, *J* = 10.4 Hz, 1 H).

Example Compound 35

Preparation of 3-((4-chlorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



Experimental section:

Procedure for preparation of Compound 35:

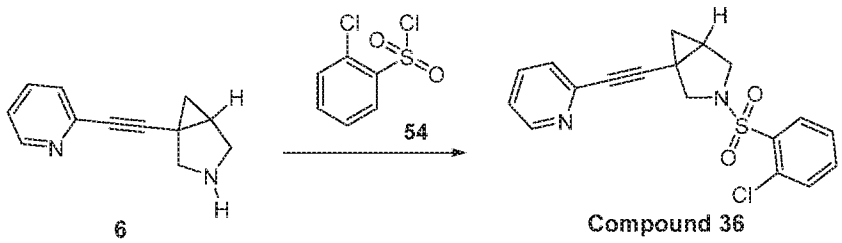
To a solution of **6** (100mg, 542μmol) in DCM (2mL) was added TEA (109mg, 1.09mmol) and **53** (120mg, 569μmol). The mixture was stirred at 0～20 °C for 2hrs. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 35** (84.0mg, yield: 43%).

LCMS: *m/z*, 358.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 8.50 (d, *J* = 4.4Hz, 1H), 7.73 (d, *J* = 8.8Hz, 2H), 7.59 (t, *J* = 7.6Hz, 1H), 7.52 (d, *J* = 8.4Hz, 2H), 7.32 (d, *J* = 7.6Hz, 1H), 7.19 (t, *J* = 6Hz, 1H), 3.75 (d, *J* = 9.2Hz, 1H), 3.58 (d, *J* = 9.6Hz, 1H), 3.16 (m, 2H), 1.92 (m, 1H), 1.25 (m, 1H), 1.13 (t, *J* = 10Hz, 1H).

Example Compound 36

Preparation of 3-((2-chlorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane:



Experimental section:

Procedure for preparation of Compound 36:

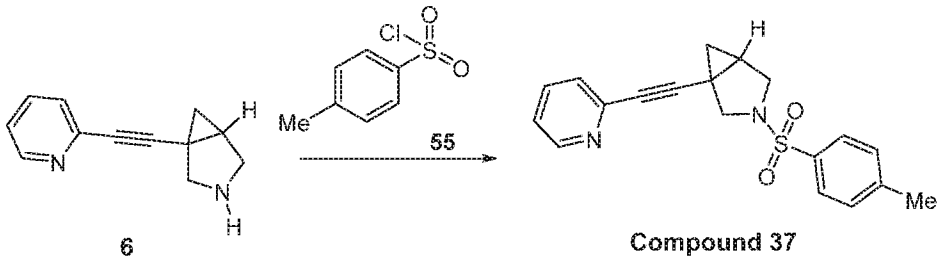
To a solution of **6** (100mg, 542μmol) in DCM (2mL) was added TEA (109mg, 1.09mmol) and **54** (120mg, 569μmol). The mixture was stirred at 0～20 °C for 1hr. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 36** (73.0 mg, 37% yield) was obtained as a white solid.

LCMS: *m/z*, 358.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 8.55 (d, *J* = 4.4Hz, 1H), 8.09 (d, *J* = 8Hz, 1H), 7.65 (m, 1H), 7.55 (m, 2H), 7.43 (m, 2H), 7.22 (m, 1H), 3.85 (d, *J* = 9.6Hz, 1H), 3.71 (d, *J* = 10Hz, 1H), 3.58 (m, 2H), 2.02 (m, 1H), 1.32 (m, 1H), 1.15 (t, *J* = 10Hz, 1H).

Example Compound 37

Preparation of 1-(pyridin-2-ylethynyl)-3-tosyl-3-azabicyclo[3.1.0]hexane:



Experimental section:

Procedure for preparation of Compound 37:

To a solution of **6** (100mg, 542μmol) in DCM (2mL) was added TEA (109mg, 1.09mmol) and **55** (108mg, 569μmol). The mixture was stirred at 0～20 °C for 1hr. LCMS showed **6** was consumed completely. The reaction mixture was quenched by addition water (5mL) at 20°C, and extracted with DCM (10mL x 2). The combined organic layers were filtered and concentrated

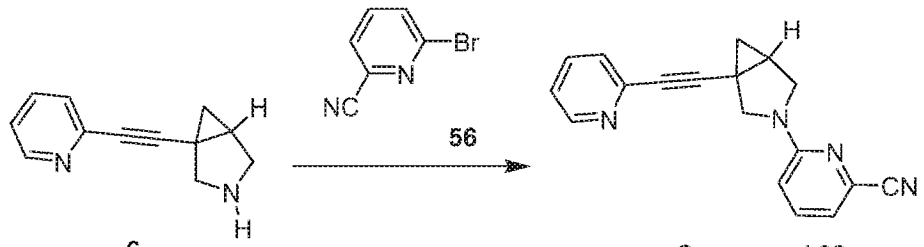
under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 37** (68.0mg, yield: 37%).

LCMS: *m/z*, 338.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 8.54 (d, *J* = 4.4Hz, 1H), 7.71 (m, 3H), 7.38 (t, *J* = 17.2Hz, 3H), 7.22 (t, *J* = 5.2Hz, 1H), 3.77 (d, *J* = 9.2Hz, 1H), 3.61 (d, *J* = 9.2Hz, 1H), 3.18 (m, 2H), 2.47 (s, 3H), 1.93 (m, 1H), 1.27 (m, 2H).

Example Compound 38

Preparation of 6-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)picolinonitrile:



Experimental section:

Procedure for preparation of Compound 38:

A mixture of compound **6**(100mg,542μmol), **54**(109mg,597μmol),Cs_2CO_3 (353mg,1.09mmol), Xantphos (31.4mg, 54.2μmol) and $Pd_2(dba)_3$ (49.7mg, 54.2μmol) in dioxane (5mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16hrs under N_2 atmosphere. LCMS showed 10% of reactant **6** was remained. The reaction mixture was quenched by addition H_2O (5mL) at rt., and then diluted with EA (10mL) and extracted with EA (15mL x 3). The combined organic layers were washed with brine (20mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 38** (9.00mg, yield: 5%).

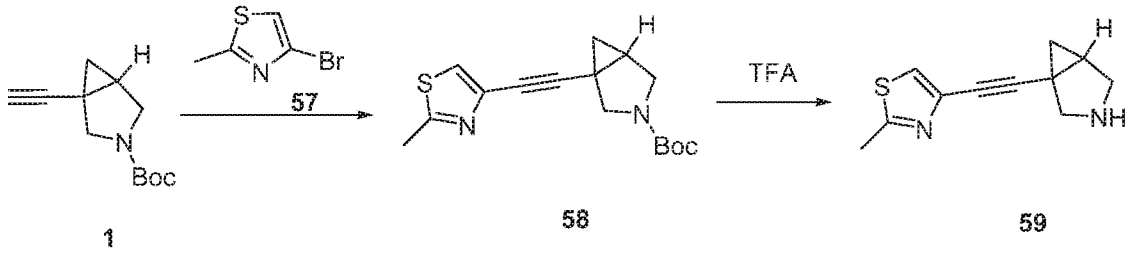
LCMS: m/z, 286.1 (M+H)+;

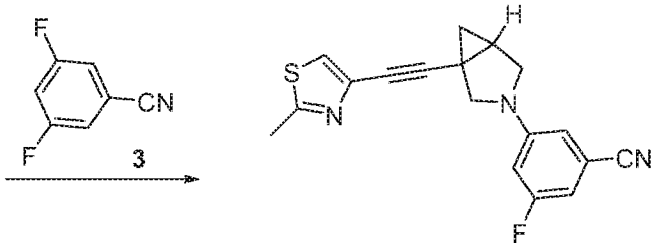
1H NMR(400MHz CDCl3): δ 8.56 (d, *J* = 4.8Hz, 1H), 7.64 (t, *J* = 7.6Hz, 1H), 7.51 (t, *J* = 7.6Hz, 1H), 7.41 (d, *J* = 8Hz, 1H), 7.23 (m, 1H), 6.98 (d, *J* = 7.2Hz, 1H), 6.54 (d, *J* = 8.8Hz, 1H), 3.98

(d, J = 10Hz, 1H), 3.82 (d, J = 10.4Hz, 1H), 3.65 (m, 2H), 2.20 (m, 1H), 1.45 (m, 1H), 0.96 (t, J = 6Hz, 1H).

Example Compound 39

Preparation of 3-fluoro-5-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile:

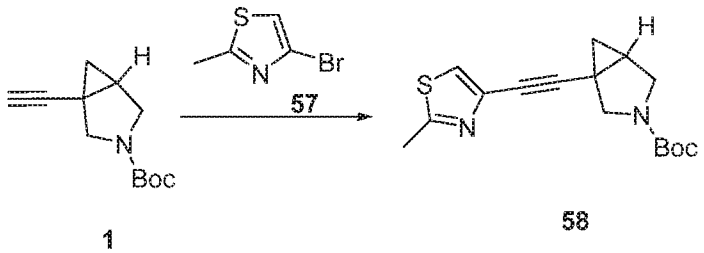




Compound 39

Experimental section:

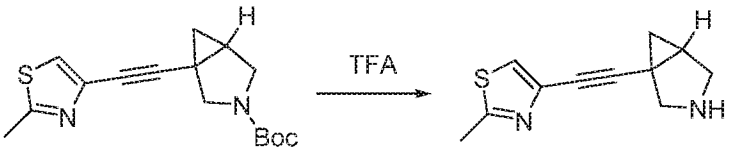
Procedure for preparation of 58:



A mixture of **1** (1.00g, 4.82mmol), **57** (944mg, 5.30mmol), CuI (91.8mg, 482μmol), PPh_3 (126mg, 482μmol) and $Pd(PPh_3)_2Cl_2$ (169mg, 241μmol) in THF (10mL) and TEA (10mL) was

degassed and purged with N_2 for 3 times, and then the mixture was stirred at 35~40°C for 16hrs under N_2 atmosphere. LCMS and TLC showed reactant **1** was consumed completely. The reaction mixture was concentrated under vacuo at 40°C. The residue was purified by silica column chromatography to give product **58** (921mg, yield: 62%).

Procedure for preparation of 59:

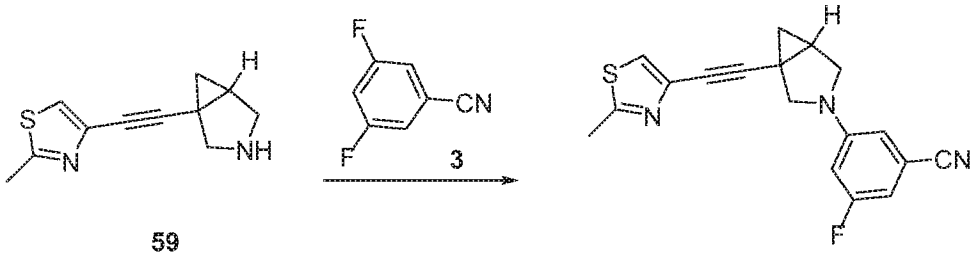


58 **59**

To a solution of **58** (500mg, 1.64mmol) in DCM (10mL) was added TFA (7.65mg, 67.0mmol). The mixture was stirred at 20°C for 1hr. LCMS showed reactant **58** was consumed completely. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved in MeOH (50mL) then the pH debugging to 8-9 by basic resin, filtered and concentrated under reduced pressure to give a residue to give product **59** (302mg, crude), which was used for the next step without purification.

LCMS: *m/z*, 205.2 $(M+H)^+$;

Procedure for preparation of Compound 39:



59 **Compound 39**

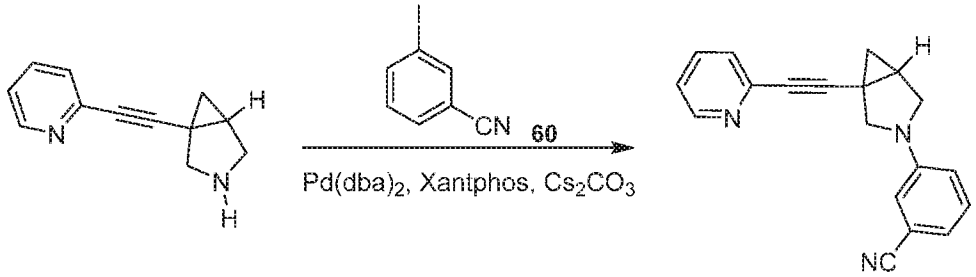
To a solution of **59** (150mg, 734μmol) in DMF (1mL) was added K_2CO_3 (202mg, 1.47mmol) and **3** (112mg, 807μmol). The mixture was stirred at 110°C for 16hrs. LCMS showed 28% of reactant **59** was remained. The reaction mixture was quenched by addition water (10mL) at 20°C, and extracted with EA (20mL x 2). The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 39** (73.0mg, yield: 30%).

LCMS: *m/z*, 323.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 7.28 (d, *J* = 6.4Hz, 1H), 6.69 (d, *J* = 7.6Hz, 1H), 6.56 (s, 1H), 6.45 (m, 1H), 3.73 (d, *J* = 9.2Hz, 1H), 3.54 (m, 3H), 2.72(s, 3H), 2.20 (m, 1H), 1.43 (m, 1H), 0.99 (t, *J* = 9.6 Hz, 1H).

Example Compound 40

Preparation of 3-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile :



6 **Compound 40**

Experimental section:

Procedure for preparation of Compound 40:

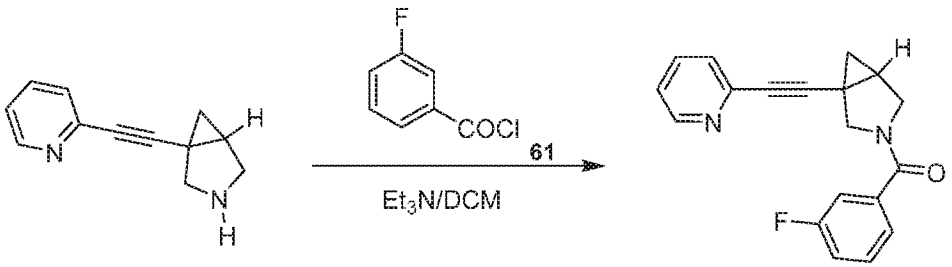
To a mixture of **6** (300 mg, 1.63 mmol) in anhydrous dioxane (10.00 mL) was added Cs_2CO_3 (1.59 g, 4.89 mmol), Xtanphos (94.32 mg, 163.00 μmol), **60** (373.30 mg, 1.63 mmol) and $Pd_2(dba)_3$ (149.26 mg, 163.00 μmol) at 5-10°C. The mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hr. LCMS showed the starting material was consumed completely and the desired product was detected. TLC showed the starting material was consumed completely. The mixture was cooled to 15°C and concentrated to remove dioxane. The mixture was dissolved in EtOAc (50mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give the crude product. The crude product was purified by prep-HPLC to give the desired product **Compound 40** (44.25 mg, yield: 9%) as a yellow solid.

LCMS: *m/z*, 286.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 8.55 (d, *J* = 4.4 Hz, 1H), 7.64 (t, *J* = 5.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.20-7.29 (m, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.73-6.67 (m, 2H), 3.77 (d, *J* = 8.8 Hz, 1H), 3.56 (d, *J* = 8.8 Hz, 1H), 3.47 (d, *J* = 8.8 Hz, 1H), 3.40-3.43 (m, 1H), 2.17-2.21 (m, 1H), 1.41 (dd, *J* = 8.0, 3.2 Hz, 1H), 1.03 (t, *J* = 4.8 Hz, 1H).

Example Compound 41

Preparation of (3-fluorophenyl)-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



6 **Compound 41**

Experimental section:

Procedure for preparation of Compound 41:

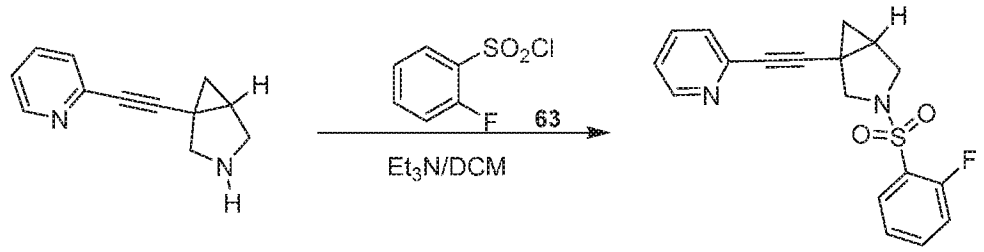
To a solution of compound **6** (250 mg, 1.36 mmol) in DCM (1.00 mL) was added Et_3N (549 mg, 5.43 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 mins. Then **61** (258 mg, 1.63 mmol) was added to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hr. TLC showed the starting material was consumed completely. The mixture was poured into H_2O (5 mL) at 5-10°C. The aqueous layer was extracted with DCM (5 mL x 2), the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 41** (25.15 mg, yield: 6%) as yellow oil.

LCMS: *m/z*, 307.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 8.55 (s, 1H), 7.61-7.67 (m, 1H), 7.36-7.41 (m, 2H), 7.15-7.23 (m, 4H), 4.25-4.48 (m, 1H), 3.50-3.85 (m, 3H), 2.00-2.09 (m, 1H), 1.36 (t, *J* = 6.4 Hz, 1H), 0.84 (br.s, 1H).

Example Compound 42

Preparation of 3-((2-fluorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane :



6 **Compound 42**

Experimental section:

Procedure for preparation of Compound 42

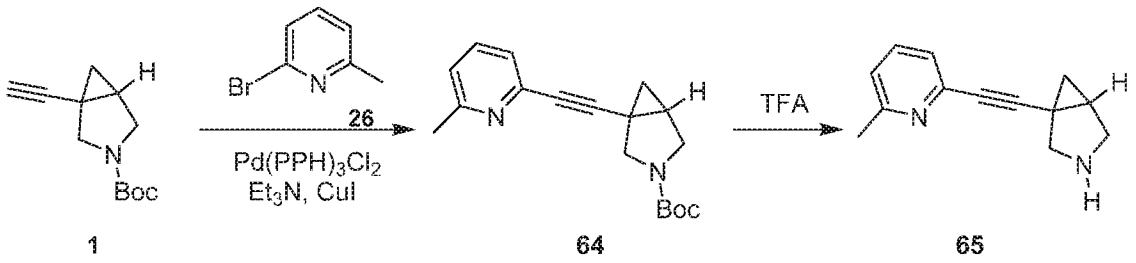
To a solution of compound **6** (250 mg, 1.36 mmol) in DCM (1.00 mL) was added Et_3N (549 mg, 5.43 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 mins. Then added **63** (317 mg, 1.63 mmol) to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hr. TLC showed the starting material was consumed completely. The mixture was poured into H_2O (5 mL) at 5-10°C. The aqueous layer was extracted with DCM (5 mL x 2), the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give the desired product **Compound 42** (28.18 mg, yield: 6%) as a yellow solid.

LCMS: *m/z*, 343.1 $(M+H)^+$;

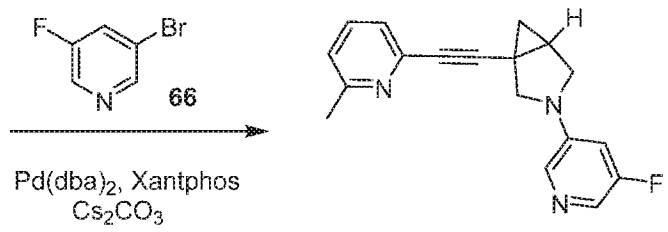
^{1}H NMR (400 MHz $CDCl_3$) : δ 8.51 (d, *J* = 4.0 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.59-7.61 (m, 2H), 7.20-7.35 (m, 4H), 3.81 (d, *J* = 9.2 Hz, 1H), 3.66 (d, *J* = 9.2 Hz, 1H), 3.39-3.42 (d, *J* = 9.2 Hz, 2H), 1.94-2.04 (m, 1H), 1.24-1.28 (m, 1 H), 1.08 (t, *J* = 5.2 Hz, 1H).

Example Compound 43

Preparation of 3-(5-fluoropyridin-3-yl)-1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexane :



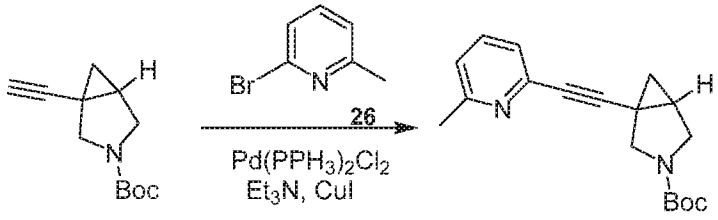
1 64 65



Compound 43

Experimental section:

Procedure for preparation of 65:



1 64

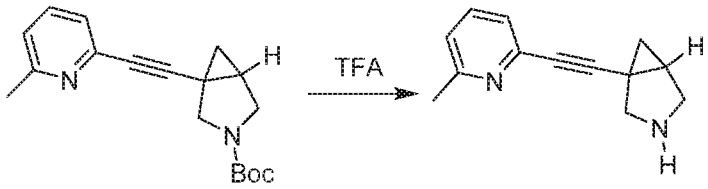
To a solution of compound **1** (1.00 g, 4.82 mmol) and Et_3N (6.83 g, 67.5 mmol) in THF (3 mL) was added **26** (994.96 mg, 5.78 mmol), $Pd(PPh_3)_2Cl_2$ (169.16 mg, 241.00 μmol),PPh_3 (126.42 mg, 482 μmol) and CuI (91.8 mg, 482 μmol) at 15°C. The mixture was bubbling with N_2 at 15°C. The mixture was stirred at 40°C for 16 hr. TLC showed the starting material was consumed completely and a main spot was detected. The mixture was poured into H_2O (30 mL) at 5-10°C. The aqueous layer was extracted with EtOAc (15 mL x 3). The combined organic layers were

washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give the desired product **64** (0.65 g, yield: 45%) as yellow oil.

5

^{1}H NMR (400 MHz CDCl3): δ 7.52 (t, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 6.4 Hz, 1H) 7.07 (d, *J* = 8.0 Hz, 1H), 3.74-3.87 (m, 1H), 3.45-3.66 (m, 3H), 2.45 (s, 3H), 1.94-1.95 (m, 1H), 1.45 (s, 9H), 1.31 (dd, *J* = 8.0, 4.8 Hz, 1H), 0.83 (t, *J* = 4.8 Hz, 1H).

Procedure for preparation of 66:

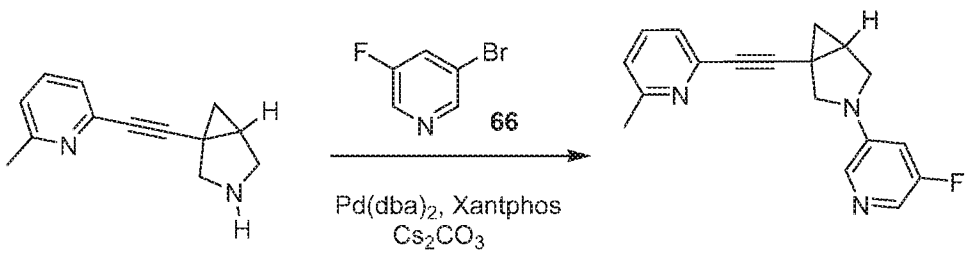


10 **64** **65**

To a solution of compound **64** (650 mg, 2.18 mmol) in DCM (10 mL) was added TFA (4.47 g, 39.2 mmol) at 5-10°C. The mixture was stirred at 15°C for 2 hr. TLC showed the starting material was consumed completely. The mixture was concentrated to give product **65** (1.20 g, crude) as yellow oil, which was used to the next step directly.

15 **^{1}H NMR**(400 MHz $CDCl_3$)**:** δ 8.21 (t, *J* = 8.0 Hz, 1H), 7.58-7.73 (m, 3H), 3.58-3.74 (m, 4H), 2.83 (s, 3H), 2.39 (s, 1H), 1.53-1.56 (m, 2H).

Procedure for preparation of Compound 43:



65 **Compound 43**

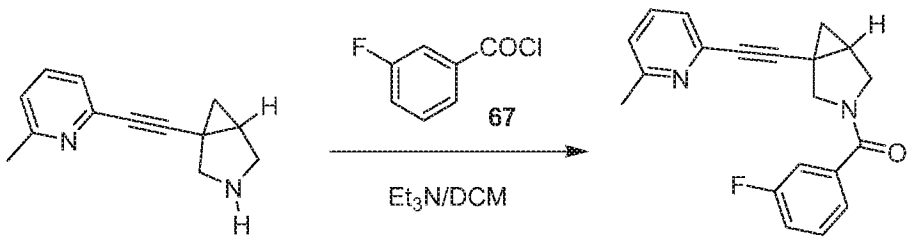
To a solution of compound **65** (300 mg, 1.51 mmol) in anhydrous dioxane (10.00 mL) was added Cs_2CO_3 (1.48 g, 4.53 mmol), Xtanphos (87.4 mg, 151.00 μmol), **66** (266 mg, 1.51 mmol) and $Pd_2(dba)_3$ (138.27 mg, 151.00 μmol) at 5-10°C. The mixture was degessed with N_2 with 3 times and the mixture was stirred at 80°C for 16 hr. TLC showed the starting material was consumed completely and the main spot was detected. The mixture was cooled to 15°C. The mixture was poured into H_2O (50 mL) at 0-5°C. The aqueous layer ware extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give the crude product. The crude product was purified by prep-HPLC to give the desired product **Compound 43** (23.15 mg, yield: 5%) as yellow oil.

LCMS: *m/z*, 294.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 7.86 (d, *J* = 2.0 Hz, 1 H), 7.80 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.51-6.55 (m, 1H), 3.77 (d, *J* = 8.8 Hz, 1H), 3.42-3.58 (m, 3H), 2.18-2.22 (m, 1H), 1.42-1.45 (m, 1H), 1.02 (t, *J* = 4.8 Hz, 1 H).

Example Compound 44

Preparation of (3-fluorophenyl)-(1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



65 **Compound 44**

Experimental section:

Procedure for preparation of Compound 44:

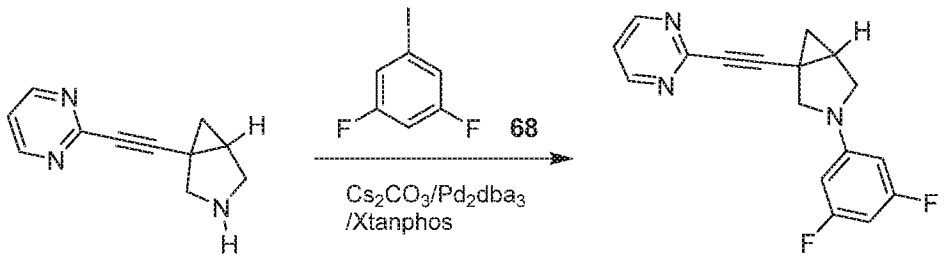
To a solution of compound **65** (250 mg, 1.26 mmol) in DCM (2.00 mL) was added Et_3N (1.28 g, 12.6 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 mins. **67** (240 mg, 1.51 mmol) was added to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hr. TLC showed the starting material was consumed completely. The mixture was poured into ice-water (5 mL), the aqueous layer was extracted with DCM (5 mL x 2), the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 44** (42.15 mg, yield: 10%) as yellow oil.

LCMS: *m/z*, 321.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 7.48-7.51 (m, 1 H), 7.35-7.46 (m, 1H), 7.06-7.23 (m, 5H), 4.21-4.44 (m, 1H), 3.46-3.82 (m, 3H), 2.51 (d, J = 7.2 Hz, 3H), 1.96-2.08 (m, 1H), 1.31-1.35 (m, 1H), 0.79 (t, J = 4.8 Hz, 1H 1H).

Example Compound 45

Preparation of 3-(3,5-difluorophenyl)-1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane :



17 **Compound 45**

Experimental section:

Procedure for preparation of Compound 45:

To a solution of **17** (300 mg, 1.62 mmol) in anhydrous dioxane (10 mL) was added Cs_2CO_3 (1.58 g, 4.86 mmol), compound **72** (389 mg, 1.62 mmol), Xtanphos (93.7 mg, 162 μmol) and $Pd_2(dba)_3$ (148 mg, 162 μmol) at 5-15°C. The mixture was degessed with N_2 for 3 times and stirred at 80°C for 16 hr. LCMS showed the starting material was consumed completely and the desired product was detected. TLC showed the starting material was consumed completely. The mixture was cooled to 15°C and concentrated to remove dioxane. The mixture was dissolved

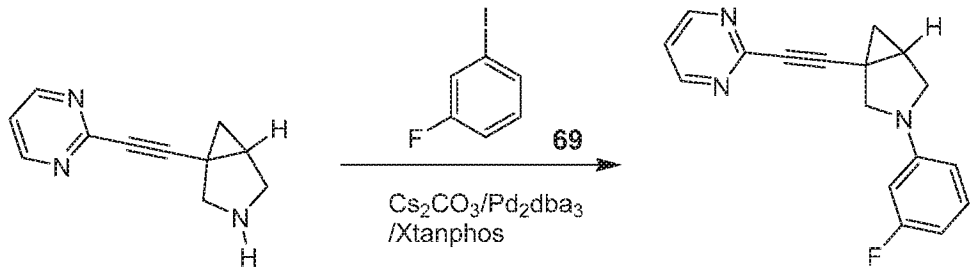
EtOAc (50mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give the crude product. The crude product was purified by prep-HPLC to give the desired product Compound **45** (20.13 mg, yield: 4%) as a yellow solid.

LCMS: *m/z*, 298.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.24 (t, *J* = 4.8 Hz, 1H), 6.17 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.03 (d, *J* = 8.4 Hz, 2H), 3.73 (d, *J* = 8.8 Hz, 1H), 3.50 (d, *J* = 8.0 Hz, 1H), 3.40-3.43 (m, 1H), 2.22-2.27 (m, 1H), 1.47-1.50 (m, 1H), 1.07 (t, *J* = 4.8 Hz, 1H).

Example Compound 46

Preparation of 3-(3-fluorophenyl)-1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane :



17 **Compound 46**

Experimental section:

Procedure for preparation of Compound 46:

To a mixture of **17** (300 mg, 1.62 mmol) in anhydrous dioxane (10 mL) was Cs_2CO_3 (1.58 g, 4.86 mmol), Xtanphos (93.7 mg, 162 μmol), compound **69** (359 mg, 1.62 mmol) and $Pd_2(dba)_3$ (148 mg, 162 μmol) at 5-10°C. The mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16 hrs under N_2 atmosphere. LCMS showed the starting material was consumed completely and the desired product was detected. TLC showed the starting material was consumed completely. The mixture was poured into H_2O (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 3) and the combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under

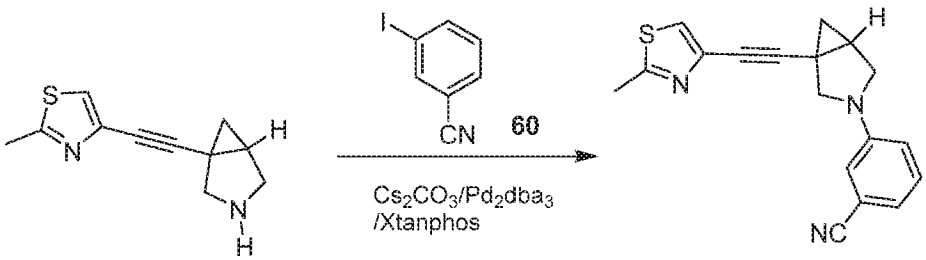
reduced pressure to give a residue. The residue was purified by column chromatography to give the crude product. The crude product was purified by prep-HPLC to give the desired **Compoud 46** (34.29 mg, yield: 8%) as a yellow solid.

LCMS: *m/z*, 280.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.23 (t, *J* = 4.8 Hz, 1H), 7.15 (q, *J* = 8.0 Hz, 1H), 6.42-6.43 (m, 1H), 6.32 (d, *J* = 8.4 Hz, 1H), 6.26 (dd, *J* = 14.0, 2.4 Hz, 1H), 3.78 (d, *J* = 9.2 Hz, 1H), 3.56 (d, *J* = 9.2 Hz, 1H), 3.49 (d, *J* = 9.2 Hz, 1H), 3.38-3.41 (m, 1H), 2.21-2.26 (m, 1H), 1.44-1.47 (m, 1H), 1.11 (t, *J* = 4.8 Hz, 1H).

Example Compound 47

Preparation of 3-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile :



59 **Compound 47**

Experimental section:

Procedure for preparation of Compound 47:

To a mixture of **59** (300 mg, 1.47 mmol) in anhydrous dioxane (10 mL) was added Cs_2CO_3 (1.44 g, 4.41 mmol), Xtanphos (85.1 mg, 147 μmol), **60** (337 mg, 1.47 mmol) and $Pd_2(dba)_3$ (135 mg, 147 μmol) at 5-10°C. The mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hr. TLC showed the starting material was consumed completely. The mixture was poured into H_2O (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 3) and the combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give the crude product. The crude product

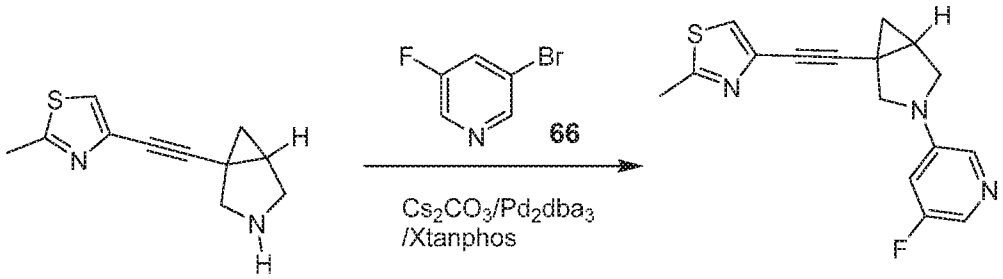
was purified by prep-HPLC to give the desired product **Compound 47** (42.54 mg, yield: 9%) as a yellow solid.

LCMS: *m/z*, 306.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) :δ 7.27-7.29 (m, 1H), 7.25 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.73-6.75 (m, 2H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.55 (d, *J* = 9.2 Hz, 1H), 3.41-3.46 (m, 2H), 2.71 (s, 3H), 2.13-2.17 (m, 1H), 1.36-1.39 (m, 1H), 1.00 (t, *J* = 4.8 Hz, 1H).

Example Compound 48

Preparation of 4-((3-(5-fluoropyridin-3-yl)-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)-2-methylthiazole :



59 **Compound 48**

Experimental section:

Procedure for preparation of Compound 48:

To a solution of **59** (300 mg, 1.47 mmol) in anhydrous dioxane (2.00 mL) was added Cs_2CO_3 (1.44 g, 4.41 mmol), Xtanphos (85.0 mg, 147 μmol), **66** (258 mg, 1.47 mmol) and $Pd_2(dba)_3$ (134 mg, 147 μmol) at 5-10°C. The mixture was degessed with N_2 for 3 times and stirred at 80°C for 16 hr. TLC showed the starting material was consumed completely and the main spot was detected. The mixture was cooled to 15°C. The mixture was poured into H_2O (50 mL) at 0-5°C. The aqueous layer ware extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give

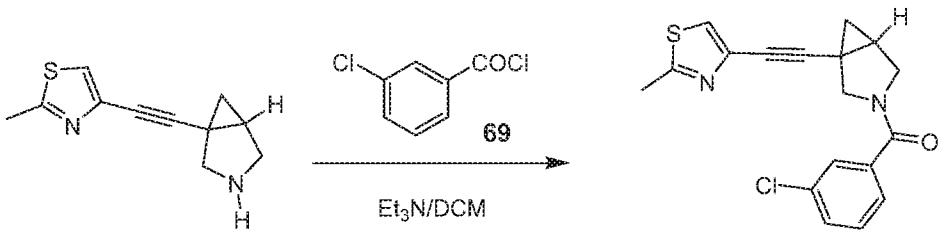
the crude product. The crude product was purified by prep-HPLC to give the desired product **Compound 48** (23.06 mg, yield: 5%) as a yellow solid.

LCMS: *m/z*, 300.0 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 7.85 (d, *J* = 2.0 Hz, 1H), 7.80 (s, 1H), 7.25 (s, 1H), 6.51-6.55 (m, 1H), 3.76 (d, *J* = 8.8 Hz, 1H), 3.56 (d, *J* = 9.2 Hz, 1H), 3.44-3.49 (m, 2H), 2.71 (s, 3H), 2.14-2.18 (m, 1H), 1.37-1.41 (m, 1H), 1.01 (t, *J* = 4.8 Hz, 1H).

Example Compound 49

Preparation of (3-chlorophenyl)-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



59 **Compound 49**

Experimental section:

Procedure for preparation of Compound 49:

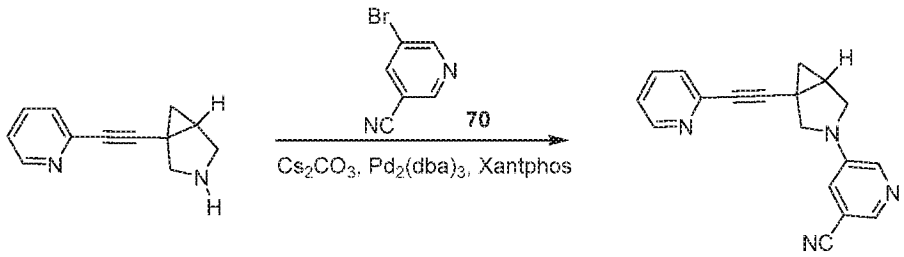
To a solution of **59** (250 mg, 1.22 mmol) in DCM (3.00 mL) was added Et_3N (1.23 g, 12.2 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 mins. **69** (256 mg, 1.46 mmol) was added to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hr. TLC showed the starting material was consumed completely. The mixture was poured into ice-water (5 mL), the aqueous layer was extracted with DCM (5 mL x 2), the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 49** (42.34 mg, yield: 10%) as yellow oil.

LCMS: *m/z*, 343.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$) : δ 7.37-7.43 (m, 2H), 7.31-7.37 (m, 2H), 7.21 (s, 1H), 4.23-4.45 (m, 1H), 3.50-3.81 (m, 3H), 2.70 (d, *J* = 6.8 Hz, 3H), 1.95-2.06 (m, 1H), 1.30-1.33 (m, 1H), 0.81 (t, *J* = 4.8 Hz, 1H).

Example Compound 50

Preparation of 5-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)nicotinonitrile :



6 **Compound 50**

Experimental section:

Procedure for preparation of Compound 50:

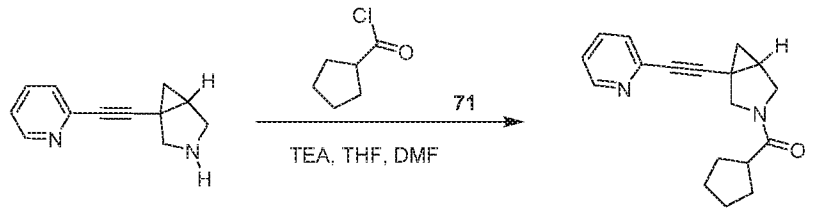
A mixture of **6** (150 mg, 814 μmol), **70** (149 mg, 814 μmol), Cs_2CO_3 (796 mg, 2.44 mmol), $Pd_2(dba)_3$ (74.6 mg, 81.4 μmol) and Xantphos (47.1 mg, 81.4 μmol) in dioxane (5.00 mL) was stirred under N_2 at 45°C for 16 hrs. TLC and LCMS showed the reaction was complete. The mixture was cooled to 25°C and filtered. The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 50** (18.0 mg, yield: 7.7%) as a yellow solid.

LCMS: *m/z*, 287.1 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.53 (dd, *J* = 4.8, 0.8 Hz, 1H), 8.25 (dd, *J* = 4.8, 2.0 Hz, 2H), 7.79 (td, *J* = 7.6, 1.6 Hz, 1H), 7.48 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.44 (dd, *J* = 2.8, 1.6 Hz, 1H), 7.33-7.39 (m, 1H), 3.92 (d, *J* = 9.6 Hz, 1H), 3.68 (d, *J* = 9.6 Hz, 1H), 3.39-3.46 (m, 2H), 2.25-2.32 (m, 1H), 1.34 (dd, *J* = 8.0, 4.8 Hz, 1H), 1.00 (t, *J* = 4.8 Hz, 1H).

Example Compound 51

Preparation of cyclopentyl((1R,5S)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



6 Compound 51

Experimental section:

Procedure for preparation of Compound 51:

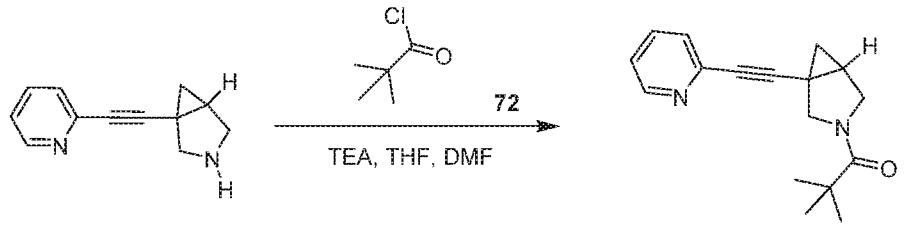
To a mixture of **6** (150 mg, 680 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (550 mg, 5.44 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **71** (108 mg, 816 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired procuct **Compound 51** (35.0 mg, yield: 18%) as a yellow oil.

LCMS: *m/z*, 281.1 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO): δ 8.49-8.55 (m, 1H), 7.77 (tt, *J* = 7.6, 2.0 Hz, 1H), 7.44-7.50 (m, 1H), 7.35 (br. dd, *J* = 6.8, 5.6 Hz, 1H), 3.88-4.01 (m, 1H), 3.63-3.75 (m, 1H), 3.63 - 3.75 (m, 2H), 3.34-3.40 (m, 1H), 2.71-2.84 (m, 1H), 2.03-2.18 (m, 1H), 1.69-1.82 (m, 2H), 1.44-1.68 (m, 6H), 1.24-1.31 (m, 1H), 0.81 (t, *J* = 4.8 Hz, 1H).

Example Compound 52

Preparation of 2,2-dimethyl-1-((1R,5S)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one :



6 Compound 52

Experimental section:

Procedure for preparation of Compound 52:

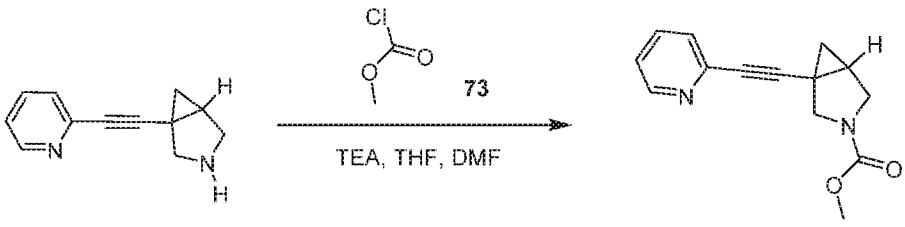
To a mixture of **6** (150 mg, 680 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (550 mg, 5.44 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **52** (98.34 mg, 816 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compund 52** (38.0 mg, yield: 21%) as a yellow oil.

LCMS: *m/z*, 269.1 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.49-8.54 (m, 1H), 7.77 (td, *J* = 7.6, 1.6 Hz, 1H), 7.44-7.51 (m, 1H), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.08 (br. d, *J* = 9.2 Hz, 1H), 3.86 (br. d, *J* = 10.4 Hz, 1H), 3.39-3.67 (m, 2H), 2.08 (br. s, 1H), 1.23 (dd, *J* = 8.0, 4.8 Hz, 1H), 1.14 (s, 9H), 0.77 (t, *J* = 4.8 Hz, 1H).

Example Compound 53

Preparation of methyl 1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate :



6 Compound 53

Experimental section:

Procedure for preparation of Compound 53:

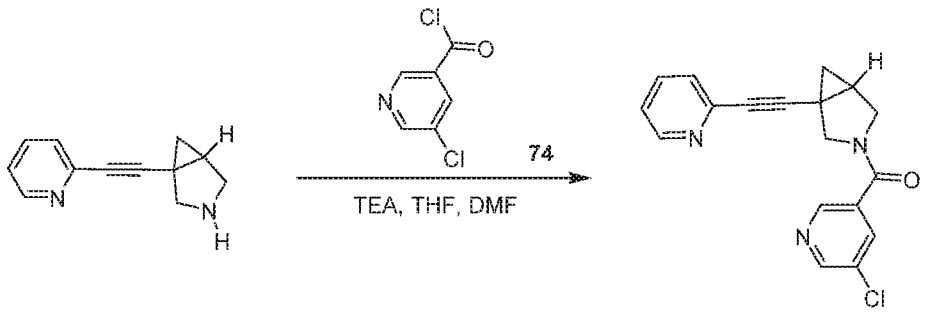
To a mixture of **6** (150 mg, 680 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (550 mg, 5.44 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **73** (77.1 mg, 816 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 53** (40.0 mg, yield: 24%) as a yellow solid.

LCMS: *m/z*, 243.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO): δ 8.49-8.54 (m, 1H), 7.77 (td, *J* = 7.6, 2.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 3.74 (br. d, *J* = 9.6 Hz, 1H), 3.58 (s, 3H), 3.41-3.53 (m, 3H), 2.08 (br. s, 1H), 1.28 (dd, *J* = 7.6, 5.2 Hz, 1H), 0.86 (t, *J* = 5.2 Hz, 1H).

Example Compound 54

Preparation of (5-chloropyridin-3-yl)((1R,5S)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



6 Compound 54

Experimental section:

Procedure for preparation of Compound 54:

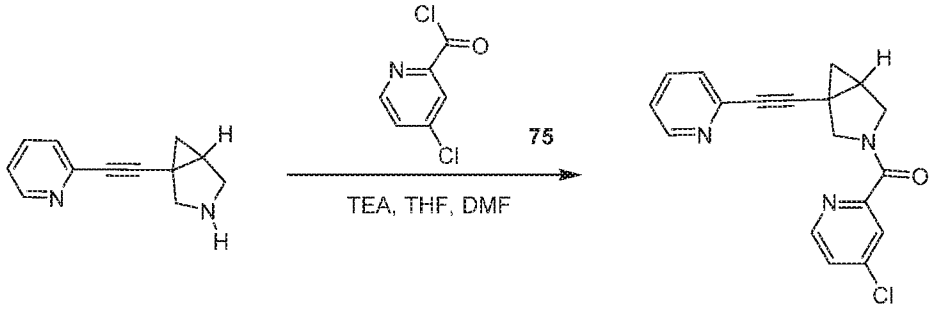
To a mixture of **6** (150 mg, 814 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (659 mg, 6.51 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **74** (143 mg, 814 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 54** (34.0 mg, yield: 13%) as a yellow oil.

LCMS: *m/z*, 324.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.73 (d, *J* = 2.4 Hz, 1H), 8.64 (dd, *J* = 5.2, 1.6 Hz, 1H), 8.52 (br. dd, *J* = 9.6, 4.8 Hz, 1H), 8.05 - 8.12 (m, 1H), 7.72-7.83 (m, 1H), 7.42-7.51 (m, 1H), 7.31-7.39 (m, 1H), 4.21 (d, *J* = 11.6 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.91 (br. d, *J* = 10.2 Hz, 1H), 3.35-3.66 (m, 1H), 3.38 (d, *J* = 10.6 Hz, 1H), 2.06-2.20 (m, 1H), 1.28 (br. t, *J* = 6.0 Hz, 1H), 0.96-1.05 (m, 1H).

Example Compound 55

Preparation of (4-chloropyridin-2-yl)-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



6 **Compound 55**

Experimental section:

Procedure for preparation of Compound 55:

To a mixture of **6** (150 mg, 814 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (659 mg, 6.51 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **75** (143

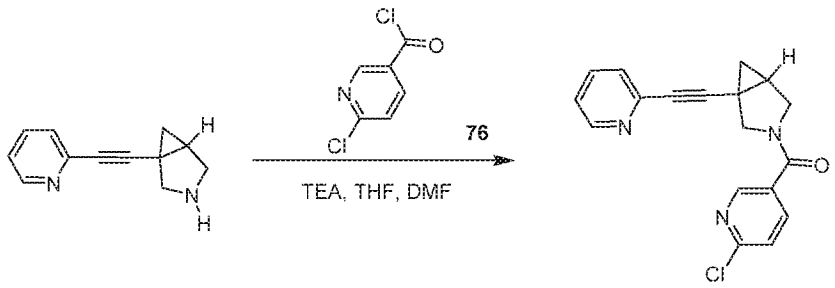
mg, 814 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 55** (50.0 mg, yield: 19%) as a yellow oil.

LCMS: *m/z*, 324.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) :δ 8.60 (dd, *J* = 8.0, 5.2 Hz, 1H), 8.49 - 8.55 (m, 1H), 7.74-7.82 (m, 2H), 7.66-7.71 (m, 1H), 7.44-7.51 (m, 1H), 7.35 (dddd, *J* = 7.6, 6.4, 4.8, 1.2 Hz, 1H), 4.01-4.23 (m, 1H), 3.74-4.01 (m, 2H), 3.57-3.68 (m, 1H), 2.10-2.18 (m, 1H), 1.29 (dd, *J* = 8.0, 4.8 Hz, 1H), 0.89-0.95 (m, 1H).

Example Compound 56

Preparation of (6-chloropyridin-3-yl)-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



6 Compound 56

Experimental section:

Procedure for preparation of Compound 56:

To a mixture of **6** (150 mg, 680 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (550.19 mg, 5.44 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **76** (144 mg, 816 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40

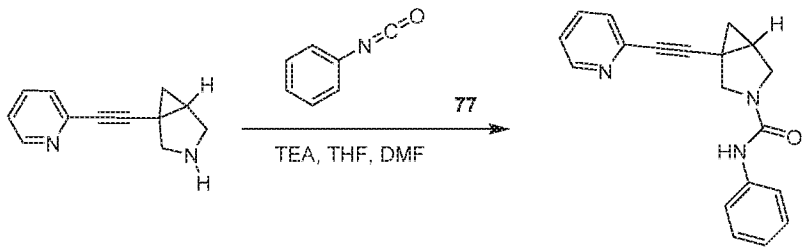
mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 56** (40.0 mg, yield: 18 %) as a yellow oil.

LCMS: *m/z*, 324.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.48-8.57 (m, 2H), 7.99 (br. t, *J* = 7.6 Hz, 1H), 7.73-7.82 (m, 1H), 7.60 (br. d, *J* = 8.0 Hz, 1H), 7.41-7.52 (m, 1H), 7.31-7.39 (m, 1H), 3.96-4.26 (m, 1H), 3.90 (br. d, *J* = 10.0 Hz, 1H), 3.37-3.66 (m, 2H), 2.06-2.19 (m, 1H), 1.28 (br. t, *J* = 6.0 Hz, 1H), 0.97 (br. d, *J* = 4.4 Hz, 1H).

Example Compound 57

Preparation of N-phenyl-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane-3-carboxamide :



6 Compound 57

Experimental section:

Procedure for preparation of Compound 57:

To a mixture of **6** (150 mg, 680 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (550 mg, 5.44 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **77** (97.2 mg, 816 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 57** (45.0 mg, yield: 22%) as a yellow solid.

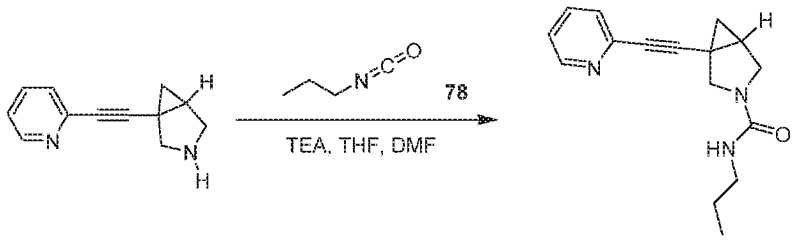
LCMS: *m/z*, 304.1 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.51-8.56 (m, 1H), 8.20 (s, 1H), 7.78 (td, *J* = 7.6, 1.6 Hz, 1H), 7.44-7.52 (m, 3H), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.18-7.26 (m, 2H), 6.90-6.97 (m, 1H),

3.95 (d, J = 10.0 Hz, 1H), 3.73 (d, J = 10.4 Hz, 1H), 3.49-3.56 (m, 2H), 2.09-2.17 (m, 1H), 1.29 (dd, J = 8.0, 4.8 Hz, 1H), 0.91 (t, J = 4.8 Hz, 1H).

Example Compound 58

Preparation of (1R,5S)-N-propyl-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane-3-carboxamide :



6 Compound 58

Experimental section:

Procedure for preparation of Compound 58:

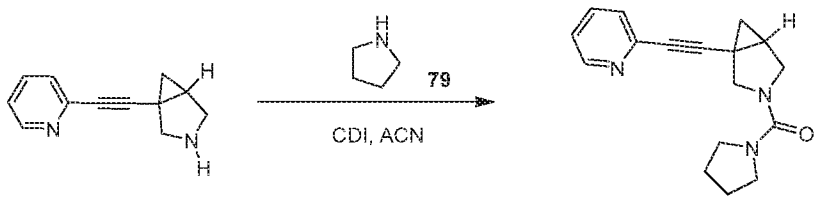
To a mixture of **6** (150 mg, 680 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (550 mg, 5.44 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **78** (69.4 mg, 816 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 58** (28.0 mg, yield: 15%) as a yellow oil.

LCMS: *m/z*, 270.1 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.48-8.54 (m, 1H), 7.77 (td, J = 7.6, 1.6 Hz, 1H), 7.46 (dt, J = 8.0, 1.2 Hz, 1H), 7.34 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 6.21 (t, J = 5.6 Hz, 1H), 3.75 (d, J = 9.6 Hz, 1H), 3.53 (d, J = 10 Hz, 1H), 3.32-3.37 (m, 2H), 2.90-2.99 (m, 2H), 2.01-2.09 (m, 1H), 1.39 (sxt, J = 7.2 Hz, 2H), 1.22 (dd, J = 8.0, 4.8 Hz, 1H), 0.78-0.85 (m, 4H).

Example Compound 59

Preparation of (1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)(pyrrolidin-1-yl)methanone :



6 Compound 59

Experimental section:

Procedure for preparation of Compound 59:

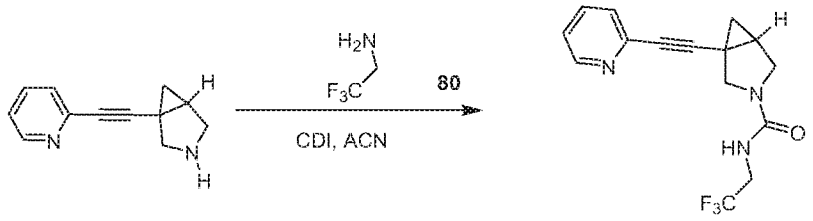
To a solution of CDI (132 mg, 814 μmol) in ACN (2.00 mL) was added a solution of **6** (150 mg, 814 μmol) in ACN (2.00 mL) dropwise under N_2 at 0°C. After stirring at 25°C for 1 hr, **79** (290 mg, 4.07 mmol) was added dropwise at 25°C. The reaction mixture was stirred at 80°C for 48 hrs. TLC showed the reaction was complete. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 59** (47.0 mg, yield: 20%) as a yellow oil.

LCMS: *m/z*, 282.1 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.48-8.54 (m, 1H), 7.77 (td, *J* = 7.6, 1.6 Hz, 1H), 7.43 - 7.49 (m, 1H), 7.34 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 3.89 (d, *J* = 10.4 Hz, 1H), 3.67 (d, *J* = 10.4 Hz, 1H), 3.40 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.36 (d, *J* = 10.4 Hz, 1H), 3.20-3.28 (m, 4H), 1.97-2.04 (m, 1H), 1.70-1.76 (m, 4H), 1.18 (dd, *J* = 8.0, 4.8 Hz, 1H), 0.68 (t, *J* = 4.8 Hz, 1H).

Example Compound 60

Preparation of 1-(pyridin-2-yl-ethynyl)-N-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane-3-carboxamide :



6 Compound 60

Experimental section:

Procedure for preparation of Compound 60:

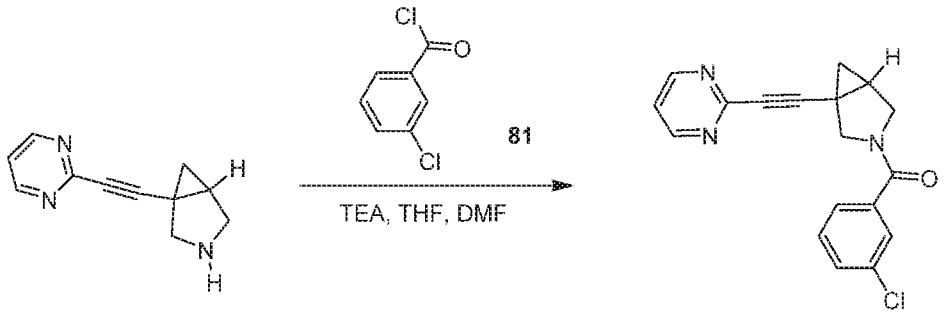
To a solution of CDI (264 mg, 1.63 mmol) in ACN (6.00 mL) was added **80** (161 mg, 1.63 mmol) dropwise under N_2 at 25°C. After stirring for 1 hr, a solution of **6** (300 mg, 1.63 mmol) in ACN (4.00 mL) was added dropwise. The reaction mixture was stirred at 25°C for 12 hrs. TLC and LCMS showed the reaction was complete. The reaction mixture was concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 60** (38.0 mg, yield: 7.5%) as a yellow oil.

LCMS: *m/z*, 310.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.77 (td, *J* = 7.6, 1.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.93 (t, *J* = 6.4 Hz, 1H), 3.72 - 3.85 (m, 3H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.36 - 3.46 (m, 2H), 2.09 (dt, *J* = 8.0, 4.4 Hz, 1H), 1.26 (dd, *J* = 8.0, 4.8 Hz, 1H), 0.80 (t, *J* = 4.8 Hz, 1H).

Example Compound 61

Preparation of (3-chlorophenyl)-(1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone :



17 Compound 61

Experimental section:

Procedure for preparation of Compound 61:

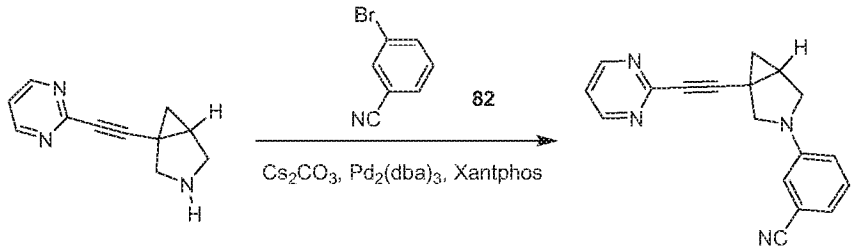
To a solution of **17** (114 mg, 615.48 μmol) in DCM (2.00 mL) was added TEA (623 mg, 6.15 mmol) at 25°C. The mixture was stirred at 25°C for 30 mins. Add **81** (129 mg, 739 μmol) to the above mixture at 25°C. The mixture was stirred at 25°C for 2 hr. TLC indicated **17** was consumed completely and one new spot formed. The mixture was poured into ice-water (50 mL), the aqueous layer was extracted with DCM (20 mL * 2), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the desired product **Compound 61** (26.0 mg, yield: 13%) as a yellow solid.

LCMS: *m/z*, 324.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.76 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.52-7.57 (m, 2H), 7.41-7.50 (m, 3H), 3.97-4.27 (m, 1H), 3.82-3.91 (m, 1H), 3.33-3.60 (m, 2H), 2.11-2.25 (m, 1H), 1.31 (dd, *J* = 8.0, 5.2 Hz, 1H), 0.98 (q, *J* = 5.2 Hz, 1H).

Example Compound 62

Preparation of 3-(1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile :



17 Compound 62

Experimental section:

Procedure for preparation of Compound 62:

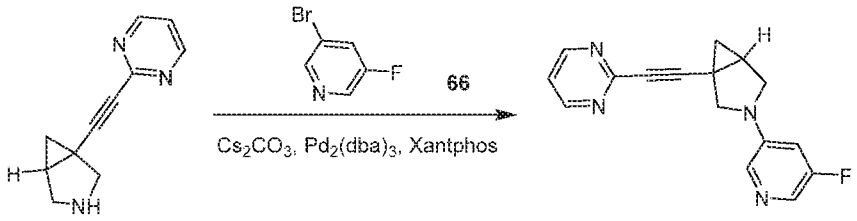
To a solution of **17** (200 mg, 1.08 mmol) in dioxane (10 mL) was added Cs_2CO_3 (1.06 g, 3.24 mmol), Xantphos (62.3 mg, 108 μmol), **82** (197 mg, 1.08 mmol) and $Pd_2(dba)_3$ (98.9 mg, 108 μmol) at 25°C. The mixture was degessed with N_2 with 3 times and the mixture was stirred at 80°C for 16 hr. TLC showed **17** was consumed completely and the main spot was detected. The mixture was cooled to 15°C. The mixture was poured into H_2O (50 mL) at 0-5°C. The aqueous layer ware extracted with EtOAc (25 mL*3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give the desired product **Compound 62** (23.0 mg, yield: 7.4%) as a yellow solid.

LCMS: *m/z*, 287.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO): δ 8.77 (d, *J* = 5.2 Hz, 2H), 7.47 (t, *J* = 4.8 Hz, 1H), 7.31-7.38 (m, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.99 - 7.02 (m, 1H), 6.94 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.90 (d, *J* = 9.2 Hz, 1H), 3.64 (d, *J* = 9.6 Hz, 1H), 3.33-3.39 (m, 2H), 2.29-2.35 (m, 1H), 1.37 (dd, *J* = 8.4, 4.4 Hz, 1H), 1.05 (t, *J* = 4.8 Hz, 1H).

Example Compound 63

Preparation of 3-(5-fluoropyridin-3-yl)-1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane :



17 Compound 63

Experimental section:

Procedure for preparation of Compound 63:

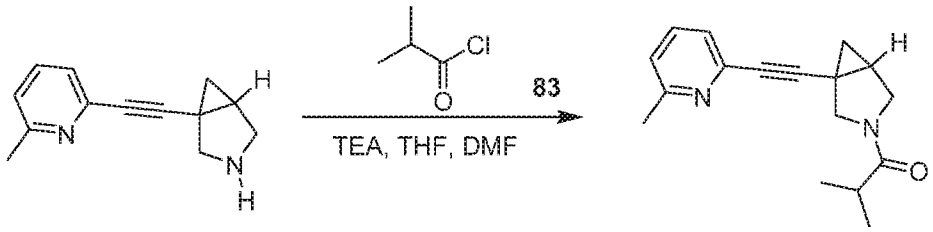
To a solution of **17** (200 mg, 1.08 mmol) in dioxane (10 mL) was added Cs_2CO_3 (1.06 g, 3.24 mmol), Xantphos (62.3 mg, 108 μmol), **66** (190 mg, 1.08 mmol) and $Pd_2(dba)_3$ (98.9 mg, 108 μmol) at 25°C. The mixture was degassed with N_2 with 3 times and the mixture was stirred at 80°C for 16 hr. TLC showed **17** was consumed completely. The mixture was cooled to 25°C. The mixture was poured into H_2O (50 mL) at 0-5°C. The aqueous layer ware extracted with EtOAc (25 mL*3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to get the desired product **Compound 63**(23.0 mg, yield: 7.6%) was obtained as a yellow solid.

LCMS: *m/z*, 281.0 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 8.77 (br. d, *J* = 4.8 Hz, 2H), 7.86 (br. d, *J* = 13.2 Hz, 2H), 7.47 (br. s, 1H), 6.92 (br. d, *J* = 11.6 Hz, 1H), 3.90 (br. d, *J* = 9.2 Hz, 1H), 3.65 (br. d, *J* = 9.2 Hz, 1H), 3.39 (br. d, *J* = 9.2 Hz, 2H), 2.33 (br. s, 1H), 1.38 (br. s, 1H), 1.05 (br. s, 1H).

Example Compound 64

Preparation of 2-methyl-1-(1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one :



65 Compound 64

Experimental section:

Procedure for preparation of Compound 64:

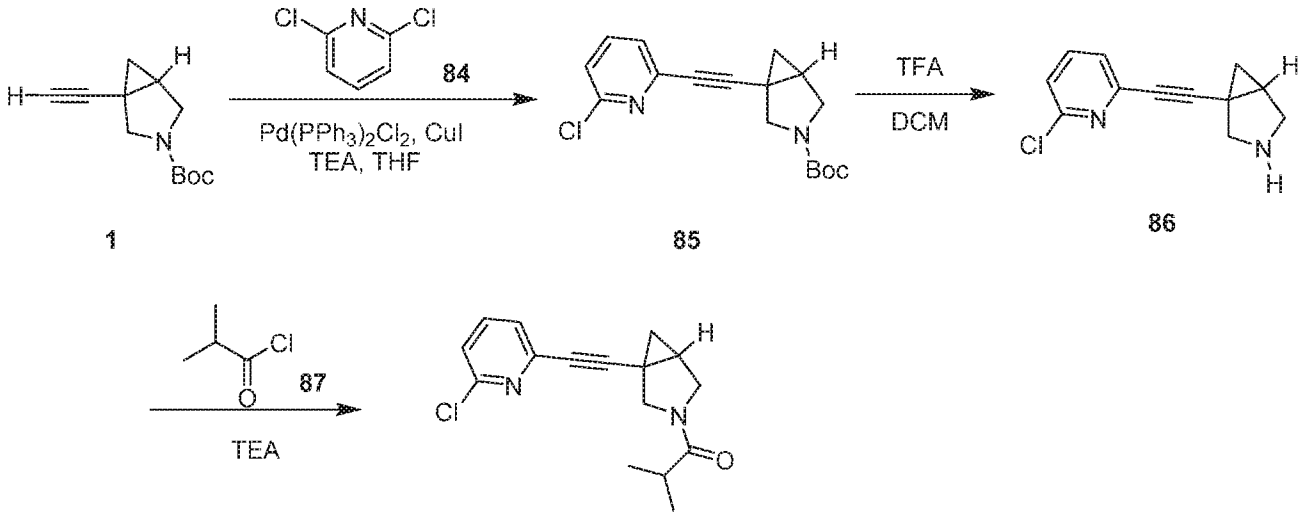
To a mixture of **65** (200 mg, 640 μmol) in THF (6.00 mL) and DMF (2.00 mL) was added TEA (518 mg, 5.12 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 10 min, then **83** (81.9 mg, 769 μmol) was added dropwise at 0°C. The mixture was warmed to 25°C and stirred for 2 hrs. TLC and LCMS showed the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to give the desired product **Compound 64** (56.0 mg, yield: 33%) as a yellow oil.

LCMS: *m/z*, 269.1 $(M+H)^+$;

^{1}H NMR (400 MHz DMSO) : δ 7.62-7.68 (m, 1H), 7.65 (td, *J* = 7.6, 1.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.86-3.98 (m, 1H), 3.65-3.72 (m, 2H), 3.33-3.39 (m, 1H), 2.55-2.65 (m, 1H), 2.42 (s, 3H), 2.02-2.17 (m, 1H), 1.24-1.31 (m, 1H), 0.94 - 1.00 (m, 6H), 0.80 (t, *J* = 4.8 Hz, 1H).

Example Compound 65

Preparation of 1-(1-((6-chloropyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methylpropan-1-one :

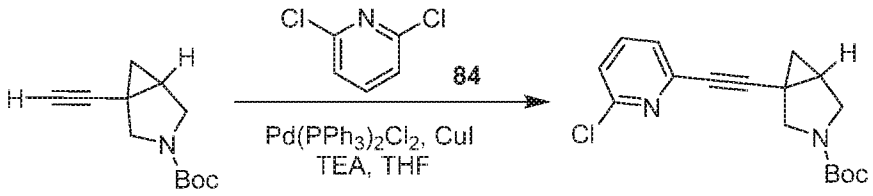


1 85 86

Compound 65

Experimental section:

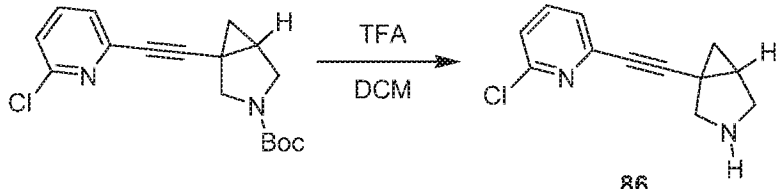
Procedure for preparation of 85:



1 85

To a solution of **1** (500 mg, 2.41 mmol) in THF (5.00 mL) was added $Pd(PPh_3)_2Cl_2$ (84.7 mg, 120 μmol), **84** (355 mg, 2.41 mmol) and CuI (45.9 mg, 241μmol) PPh_3 (63.2 mg, 241 μmol, 0.10 *eq*) at 15°C. The mixture was bubbling with N_2 at 15°C. Then the mixture was stirred at 40°C for 16 hrs. TLC showed the starting material was consumed completely and a main spot was detected. The mixture was poured into H_2O (10mL*3) at 5-10°C. The aqueous layer was extracted with Ethyl acetate (15 mL*3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give the desired product **85** (350 mg, yield: 45%) as yellow oil.

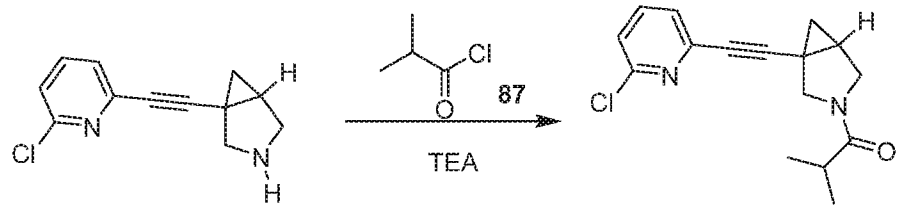
Procedure for preparation of 86:



85 86

To a mixture of **85** (300 mg, 941μmol) in DCM (10.0 mL) was added TFA (1.93 g, 16.9 mmol) in one portion at15°C under N_2 for 2 hours. TLC showed the starting material was consumed completely. The reaction mixture was extracted with ethyl acetate **30** mL (**10** mL *3). The combined organic layers were washed with H_2O (10mL*3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The mixture was concentrated to give the desired product **86** (310 mg, crude, TFA) as yellow oil.

Procedure for preparation of Compound 65:



86 Compound 65

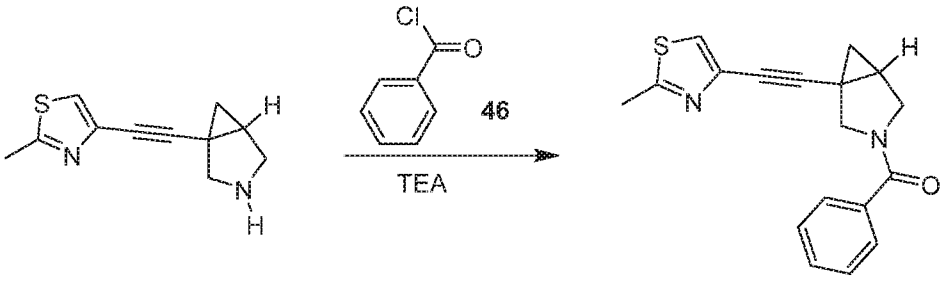
To a solution of **86** (310 mg, 1.42 mmol) in DCM (2.00 mL) was added Et_3N (1.44 g, 14.2 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 min. **87** was added (181 mg, 1.70 mmol) to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hrs. TLC showed the starting material was consumed completely. The mixture was poured into ice-water (5 mL), the aqueous layer was extracted with DCM (5 mL*2), and the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC and lyophilized to give the desired product **Compound 65** (33.0 mg, yield: 8.0%) as white oil.

LCMS: *m/z*, 275.0 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 7.57-7.62 (m, 1H), 7.30-7.32 (m, 1H), 7.25-7.28 (m, 1H), 3.70-4.13 (m, 3H), 3.46-3.53(m, *m*,1H), 2.53-2.57 (m, 1H), 2.02-2.07 (m, 1H), 1.35-1.37 (t, *J* = 8.0 Hz, 1H), 1.09-1.11 (d, *J* = 7.2 Hz, 6H), 0.82-0.85 (t, *J* = 8.6Hz, 1H).

Example Compound 66

Preparation of (1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)(phenyl)methanone :



59 **Compound 66**

Experimental section:

Procedure for preparation of Compound 66:

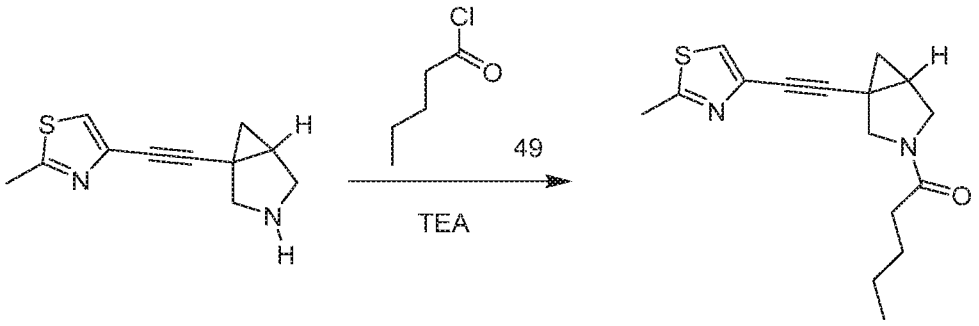
To a solution of **59** (150 mg, 734 μmol) in DCM (10.00 mL) was added Et_3N (742.99 mg, 7.34 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 mins. **46** (123 mg, 881μmol) was added to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hr. LCMS showed compound **59** was consumed completely and one main peak with desired MS was detected. The mixture was poured into ice-water (5 mL), the aqueous layer was extracted with DCM (5 mL*2), the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC and lyophilized to give the desired product **Compound 66** (35.0 mg, yield: 15%) as white oil.

LCMS: *m/z*, 309.1 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 7.13 (s, 5H), 7.19 (s, 1H), 4.25-4.47 (m, 1H), 3.50-3.80 (m, 3H), 2.70 (s, 3H), 1.94-2.02 (m, 1H), 1.26-1.29 (m, 1H), 0.82 (s, 1H).

Example Compound 67

Preparation of 1-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)pentan-1-one :



59 **Compound 67**

Experimental section:

Procedure for preparation of Compound 67:

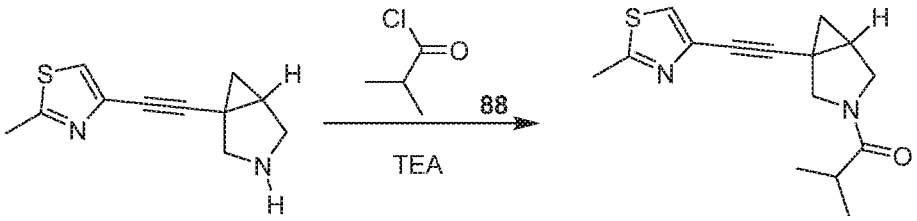
To a solution of compound **59** (150 mg, 734 μmol) in DCM (10.0 mL) was added Et_3N (743 mg, 7.34 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 mins. Add pentanoyl chloride (106 mg, 881 μmol) to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hrs. LCMS showed **59** was consumed completely and one main peak with desired MS was detected. TLC indicated **59** was consumed completely and one new spot formed. The mixture was poured into ice-water (5 mL) and the aqueous layer was extracted with DCM (5 mL*2), the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC and lyophilized to give the desired product **Compound 67** (27.0 mg, yield: 13%) as a white solid.

LCMS: *m/z*, 289.0 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 7.23 (s, 1H), 3.87-4.10 (m, 1H) , 3.57-3.78 (m, 2H), 3.48-3.51 (m, 1H), 2.70 (s, 3H), 2.19-2.24 (m, 2H), 1.99 (s, 1H), 1.58-1.62 (m, 2H), 1.32-1.38 (m, 3H), 0.92 (t, *J* = 14.4 Hz, 3H) ,0.79 (t, *J* = 9.6 Hz, 1H).

Example Compound 68

Preparation of 2-methyl-1-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one :



59 Compound 68

Experimental section:

Procedure for preparation of Compound 68:

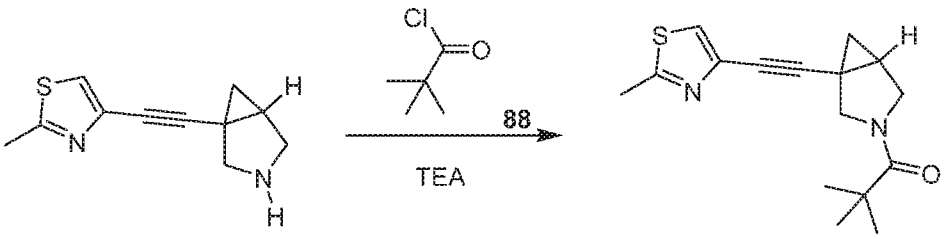
To a solution of **59** (150 mg, 734 μmol) in DCM (10.0 mL) was added Et_3N (743 mg, 7.34 mmol) at 5-10°C. The mixture was stirred at 15°C for 15 mins. **88** (93.9 mg, 881 μmol) was added to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hrs. LCMS showed **59** was consumed completely and one main peak with desired MS was detected. TLC indicated **59** was consumed completely and one new spot formed. The mixture was poured into ice-water (5 mL), the aqueous layer was extracted with DCM (5 mL*2), and the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC and lyophilized to give the desired product **Compound 68** (17.0 mg, 8.4% yield) as a white solid.

LCMS: *m/z*, 275.0 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 7.23 (s, 1H), 4.10 (d, *J* = 11.6 Hz, 1H), 3.85-3.92 (m, 1H), 3.67-3.74 (m, 2H), 3.45-3.51 (m, 1H), 2.70 (s, 3 H), 2.53-2.69 (m, 1 H), 1.97-2.03 (m, 1H) ,1.32 (t, *J* = 8.8 Hz, 1H), 1.11 (d, *J* = 6.4 Hz, 6H), 0.79 (t, *J* = 6.0 Hz, 1H).

Example Compound 69

Preparation of 2,2-dimethyl-1-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one :



59 Compound 69

Experimental section:

Procedure for preparation of Compound 69:

To a solution of **59** (150 mg, 734 μmol) in DCM (10.0 mL) was added Et_3N (742.99 mg, 7.34 mmol,) at 5-10°C. The mixture was stirred at 15°C for 15 mins. **88** (106 mg, 881μmol) was added to the above mixture at 5-10°C. The mixture was stirred at 15°C for 2 hrs. LCMS showed **59** was consumed completely and one main peak with desired MS was detected. The mixture was poured into ice-water (5 mL), the aqueous layer was extracted with DCM (5 mL*2), the combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC and lyophilized to give the desired product **Compound 69** (17.0 mg, yield: 8.0%) as a white solid.

LCMS: *m/z*, 275.0 $(M+H)^+$;

^{1}H NMR (400 MHz $CDCl_3$): δ 7.23 (s, 1 H),.4.16 (d, J = 10.8 Hz, 1 H), 3.98(d, J = 11.2 Hz, 1 H), 3.63 (s, 2 H), 2.70 (s , 3H), 1.95 (s, 1H), 1.23(s, 10 H), 0.76-0.78(t, J = 4.8 Hz, 1 H).

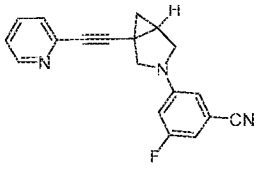
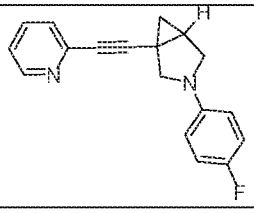
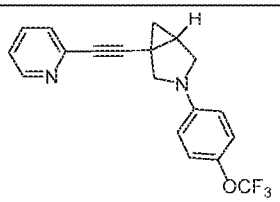
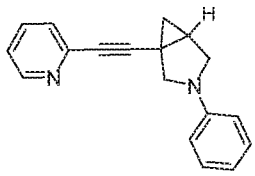
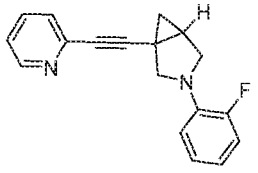
Functional Calcium Flux Assay Methodology

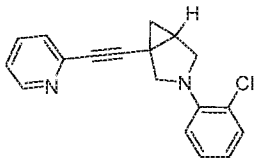
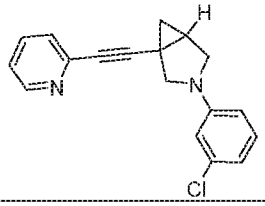
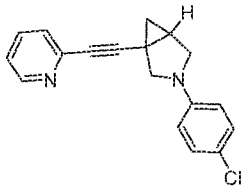
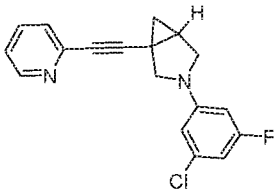
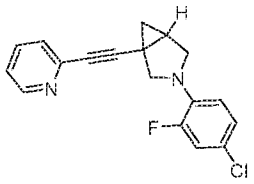
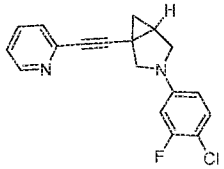
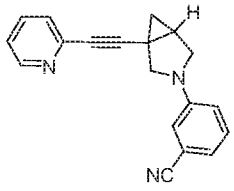
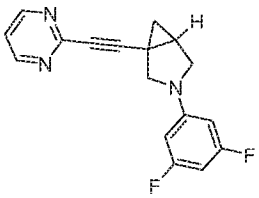
[00041] For functional assays, HEK293 cells stably expressing recombinant rat mGluR5 were seeded in 384-well plates and dye loaded using Fluo-8. Cells were then washed to remove the un-incorporated dye. Antagonist evaluation was performed following a 15 min incubation of the test compound followed by the addition of submaximal concentration of glutamate. Intracellular calcium ($[Ca^{2+}]_i$) measurements were performed using a fluorometric imaging plate reader (FLIPR, Molecular Devices). The glutamate-evoked increase in $[Ca^{2+}]_i$ in the presence of

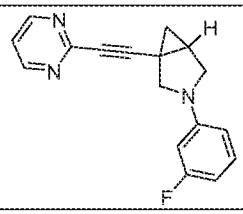
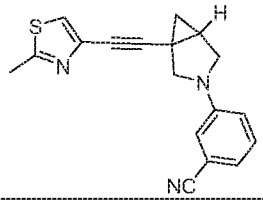
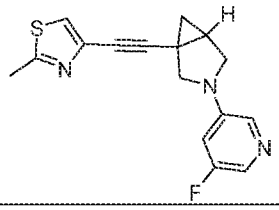
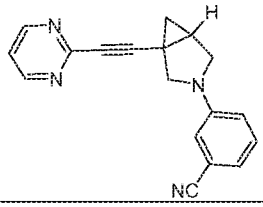
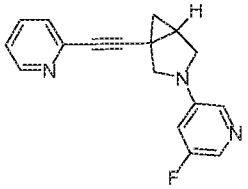
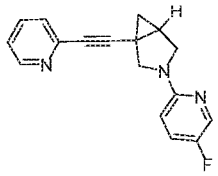
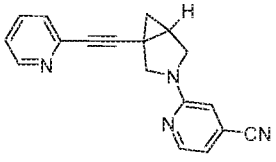
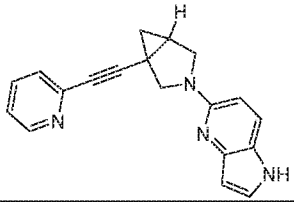
the test compounds was compared to the response to glutamate alone (the positive control). Antagonist inhibition curves were fitted with a 4-parameter logistic equation giving IC_{50} values, and Hill coefficients using an iterative nonlinear curve fitting algorithm.

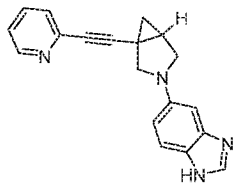
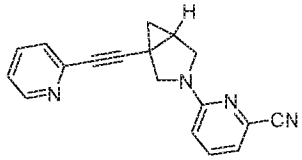
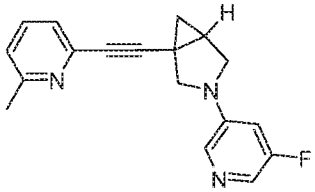
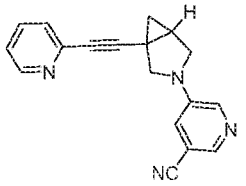
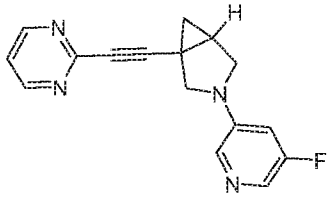
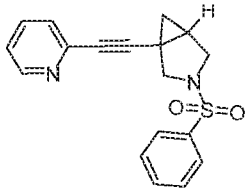
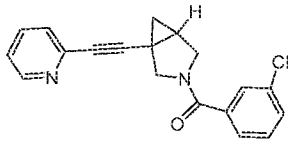
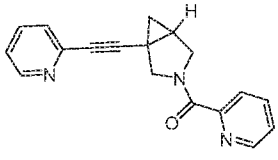
[00042] The tables below provide IC50 data in this assay. In the activity column, A = IC_{50} >1,000 and ≤ 5,000 nM; B = IC_{50} >500 and ≤1,000 nM and C = IC_{50} ≤500 nM.

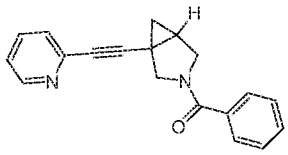
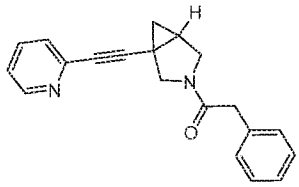
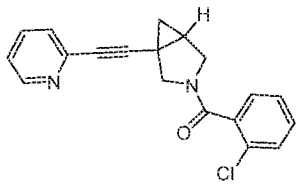
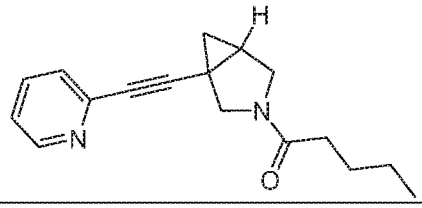
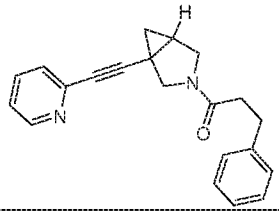
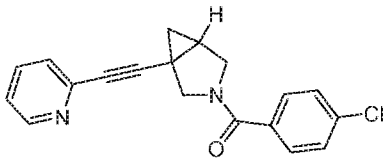
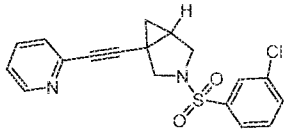
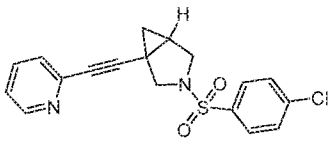
[00043] Table 1

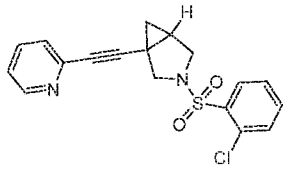
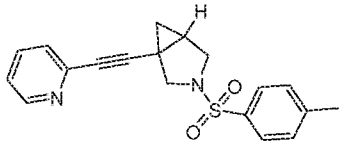
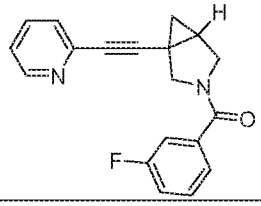
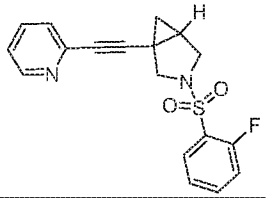
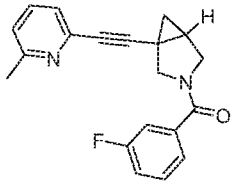
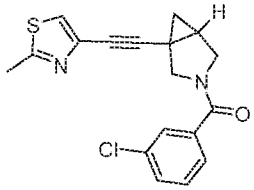
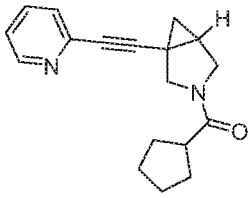
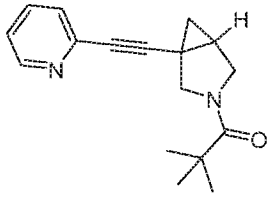
#	**Example Compound**	Structure	**IC50 value (FLIPR assay)**
1	**1**		**C**
2	**2**		**C**
3	**3**		**A**
4	**10**		**C**
5	**16**		**C**

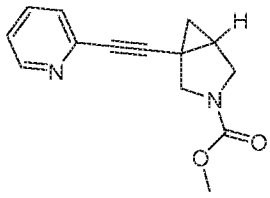
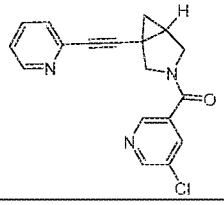
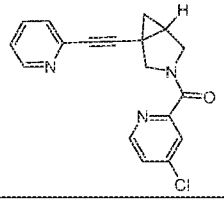
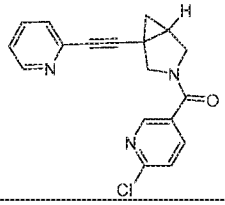
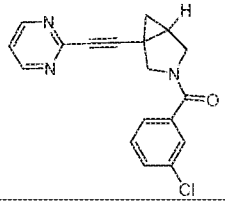
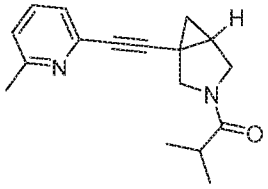
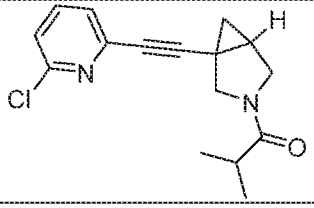
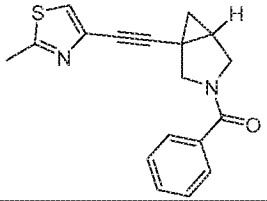
6	**17**		**C**
7	**18**		**C**
8	**19**		**B**
9	**20**		**C**
10	**21**		**B**
11	**22**		**B**
12	**40**		**C**
13	**45**		**C**

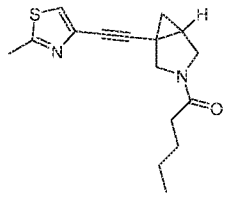
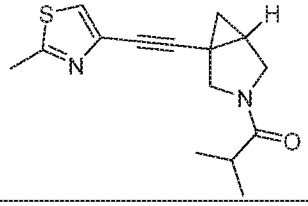
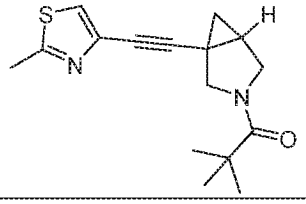
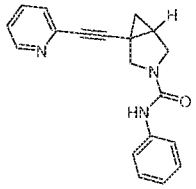
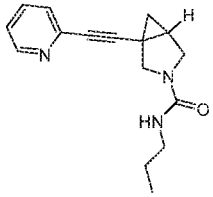
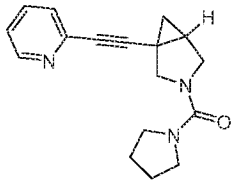
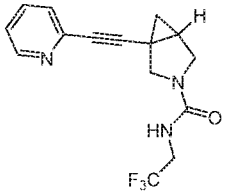
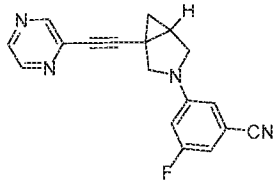
14	**46**		**C**
15	**47**		**C**
16	**48**		**C**
17	**62**		**C**
18	**4**		**C**
19	**6**		**C**
20	**23**		**C**
21	**24**		**A**

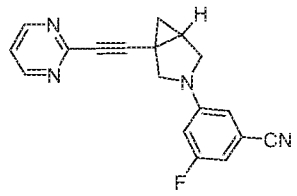
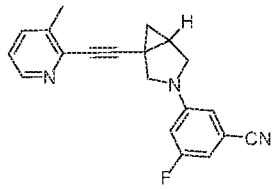
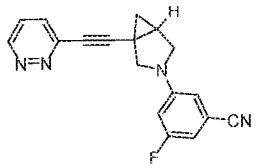
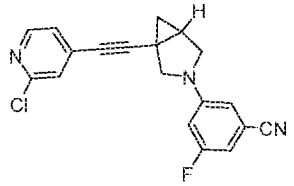
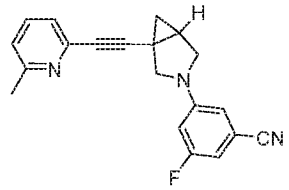
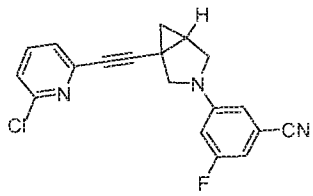
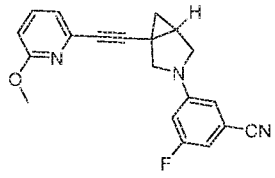
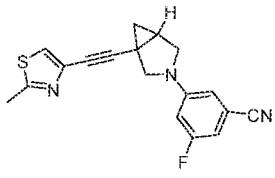
22	**25**		**A**
23	**38**		**C**
24	**43**		**C**
25	**50**		**C**
26	**63**		**C**
27	**5**		**C**
28	**26**		**C**
29	**27**		**C**

30	**28**		**C**
31	**29**		**C**
32	**30**		**C**
33	**31**		**C**
34	**32**		**C**
35	**33**		**C**
36	**34**		**C**
37	**35**		**C**

38	**36**		**C**
39	**37**		**C**
40	**41**		**C**
41	**42**		**C**
42	**44**		**C**
43	**49**		**C**
44	**51**		**C**
45	**52**		**C**

46	**53**		**C**
47	**54**		**C**
48	**55**		**C**
49	**56**		**C**
50	**61**		**B**
51	**64**		**C**
52	**65**		**C**
53	**66**		**C**

54	**67**		**C**
55	**68**		**C**
56	**69**		**C**
57	**57**		**B**
58	**58**		**C**
59	**59**		**C**
60	**60**		**C**
61	**7**		**C**

62	**8**		**C**
63	**9**		**A**
64	**11**		**C**
65	**12**		**C**
66	**13**		**C**
67	**14**		**C**
68	**15**		**C**
69	**39**		**C**

Example 11

Radioligand Binding Assay Using Membrane Preparations Expressing Rat mGluR5

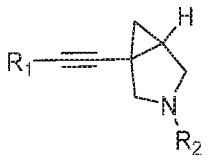
[00044] The radiolabeled allosteric antagonist [^{3}H]-2-Methyl-6-(phenylethynyl)pyridine (MPEP, American Radiolabeled Chemical) was used to evaluate the ability of test compounds to interact with the MPEP site on mGluR5 as described in Rodriguez et al. [Mol Pharmacol 78:1105-1123, 2010]. Membranes were prepared from HEK293 cells expressing rat mGluR5. Radioligand binding assays were performed in 96-well plates (Corning) containing binding buffer (15mM Tris pH 7.4, 120mM NaCl, 100mM KCl, 25mM $MgCl_2$, 25mM $CaCl_2$) with a final assay volume of 250µL and 40µg membranes/well.

[00045] Saturation isotherms were determined by incubation in presence of 12 increasing concentrations of [^{3}H]-MPEP (0.1-100 nM), while competition experiments were performed with a fixed concentration (4nM) of [^{3}H]-MPEP in presence of 12 increasing concentrations of test compound (1-30,000 nM). Incubations were performed at 4°C for 1h. Nonspecific binding was estimated using 100 µM MTEP. At the end of incubation, membranes were filtered over GF/C filter plates (Perkin Elmer) presoaked in 0.1% BSA for 2h at room temperature. Filter plates were then washed 5 times with ice cold buffer (15mM Tris, pH 7.4 plus 0.1% BSA) using the Packard Filtermate Harvester and dried overnight in a 37°C oven. Fifty µL microscint 20 (PerkinElmer) were added to each well and the plates were incubated on an orbital shaker for 15 min before counting on a Microbeta Trilux for 2 min/well.

[00046] It is to be understood that the invention is not limited to the particular embodiments of the invention described above, as variations of the particular embodiments may be made and still fall within the scope of the appended claims.

CLAIMS

1. A compound of formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is a 5- to 10-membered mono- or bicyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-O-CF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic aryl ring, wherein the 5- to 10-membered aryl ring is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form a 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring,

R_2 is alkanoyl, arylalkanoyl, herteroaryl acyl, aryl sulfonyl, heteroaryl sulfonyl, alkoxycarbonyl, -C(O)O-aryl, arylalkoxycarbonyl, acylamino, wherein the aryl or heteroaryl are optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl,, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring; or

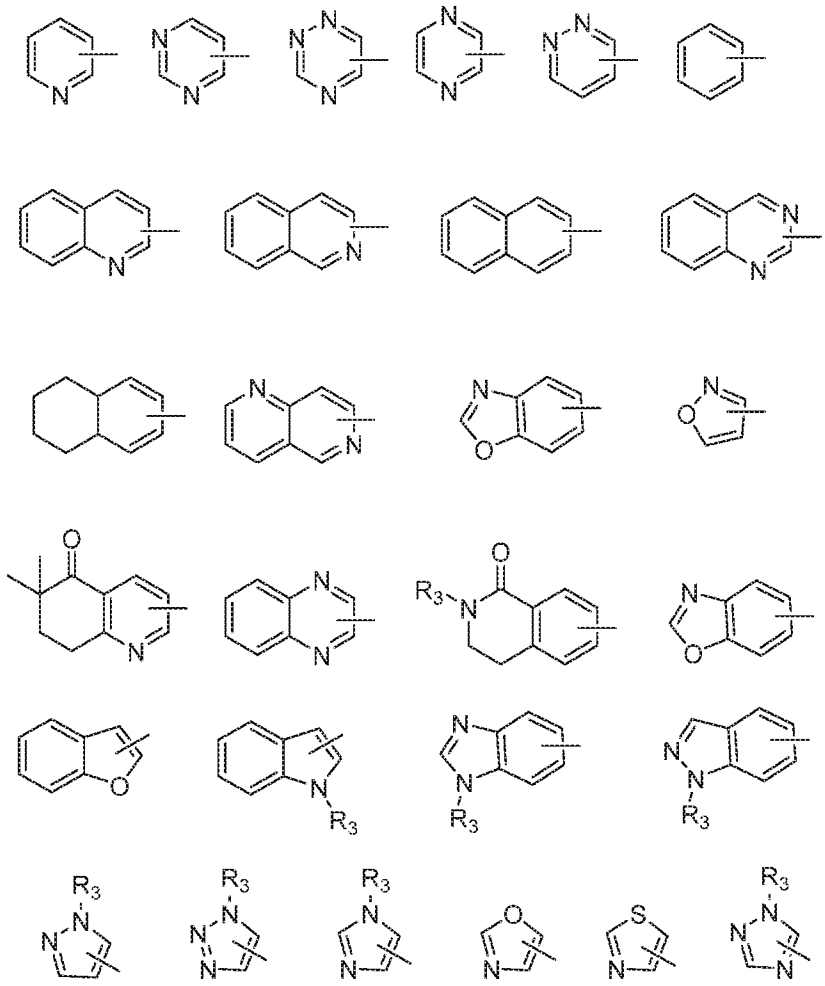
a 5- to 10-membered mono- or bicyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-O-CF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic aryl ring, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may

combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

R_1 is a substituted or unsubstituted ring selected from the following list:



Wherein the ring is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower

alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring;

R_3 where presents is -H or lower alkyl;

R_2 is alkanoyl, arylalkanoyl, herteroaryl acyl, aryl sulfonyl, heteroaryl sulfonyl, alkoxycarbonyl, -C(O)O-aryl, arylalkoxycarbonyl, acylamino, wherein the aryl or heteroaryl are optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl,, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-O-CF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$-aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused and optionally substituted carbocyclic or heterocyclic ring; or

a 5- to 10-membered mono- or bicyclic aryl ring, wherein the 5- to 10-membered ring system is optionally substituted with 0-3 substituents independently selected from alkyl, halogen, -OH, -CN, nitro, $-CF_3$, $-OCF_3$, -O-alkyl, -O-aryl, -S-alkyl, -S-aryl, -S(O)-alkyl, S(O)-aryl, $-S(O_2)$-alkyl, $-S(O_2)$aryl, $-CH_2$-aryl, aryl, heteroaryl, $-O-CH_2$-aryl, $-N(CH_3)_2$, cycloalkyl, heterocycloalkyl, -C(O)-alkyl, -C(O)cycloalkyl, -C(O)-heterocycloalkyl, -

C(O)-aryl, -C(O)-heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-heterocycloalkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)N-alkyl, -C(O)N-cycloalkyl, -C(O)N-heteroalkyl, -C(O)N-aryl, -C(O)N-heteroaryl or substituted lower alkyl, wherein the substituents may combine to form an optionally substituted 5-7 membered fused carbacyclic or heterocyclic ring.

3. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

R_1 is an optionally mono- or disubstituted 5- to 6-membered monocyclic heteroaryl ring that contains 1-3 heteroatoms selected from the group consisting of N, O and S;

R_2 is optionally mono- or disubstituted 5- to 10-membered mono- or bicyclic aryl, or optionally mono- or disubstituted mono- or bicyclic heteroaryl that contains 1-3 heteroatoms selected from the group consisting of N, O and S, or optionally substituted -C(O)-C_1-C_5-alkyl, -C(O)-C_1-C_5-alkyl-aryl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)O-C_1-C_5-alkyl, -C(O)O-C_1-C_5-alkyl-aryl or -S(O_2)-phenyl.

4. The compound according to anyone of claim 1-3 or a pharmaceutically acceptable salt thereof, wherein:

R_1 is 2-pyridinyl or substituted 2-pyridinyl.

5. The compound according to anyone of claim 1-3 or a pharmaceutically acceptable salt thereof, wherein:

R_1 is 4-pyridinyl or substituted 4-pyridinyl; or

R_1 is substituted or unsubstituted pyrimidinyl, pyrazinyl, pyridazinyl or thiazoly.

6. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein said compound is:

3-fluoro-5-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0] hexan-3-yl)benzonitrile,

3-(4-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo [3.1.0]hexane,

1-(pyridin-2-ylethynyl)-3-(4-(trifluoromethoxy)phenyl)-3-azabicyclo [3.1.0]hexane,

3-phenyl-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(2-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(2-chlorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(3-chlorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(4-chlorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(3-chloro-5-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(4-chloro-2-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(4-chloro-3-fluorophenyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile,
3-(3,5-difluorophenyl)-1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(3-fluorophenyl)-1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile,
4-(3-(5-fluoropyridin-3-yl)-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)-2-methylthiazole,
3-(1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile.

7. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein said compound is:

3-(5-fluoropyridin-3-yl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-(5-fluoropyridin-2-yl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
2-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)isonicotinonitrile,
5-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-1H-pyrrolo[3,2-b]pyridine,
5-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazole,
6-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)picolinonitrile,
3-(5-fluoropyridin-3-yl)-1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexane,
5-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)nicotinonitrile,
3-(5-fluoropyridin-3-yl)-1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane.

8. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein said compound is:

3-(phenylsulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0] hexane,
(3-chlorophenyl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,

pyridin-2-yl(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
phenyl(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
2-phenyl-1-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)ethanone,
(2-chlorophenyl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
1-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)pentan-1-one,
3-phenyl-1-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one,
(4-chlorophenyl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
3-((3-chlorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-((4-chlorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
3-((2-chlorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
1-(pyridin-2-ylethynyl)-3-tosyl-3-azabicyclo[3.1.0]hexane,
(3-fluorophenyl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
3-((2-fluorophenyl)sulfonyl)-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane,
(3-fluorophenyl)(1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
(3-chlorophenyl)(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
cyclopentyl(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
2,2-dimethyl-1-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one,
methyl-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate
(5-chloropyridin-3-yl)-(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
(4-chloropyridin-2-yl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
(6-chloropyridin-3-yl)(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
(3-chlorophenyl)(1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone,
2-methyl-1-(1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one,
1-(1-((6-chloropyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methylpropan-1-one,
(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)(phenyl)methanone,
1-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)pentan-1-one,
2-methyl-1-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one,
2,2-dimethyl-1-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)propan-1-one,
N-phenyl-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane-3-carboxamide,
N-propyl-1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexane-3-carboxamide,
(1-(pyridin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)(pyrrolidin-1-yl)methanone,

1-(pyridin-2-ylethynyl)-N-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane-3-carboxamide.

9. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein said compound is:

3-fluoro-5-(1-(pyrazin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile,
3-fluoro-5-(1-(pyrimidin-2-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile,
3-fluoro-5-(1-((3-methylpyridin-2-yl)ethynyl)-3-azabicyclo [3.1.0]hexan-3-yl)benzonitrile,
3-fluoro-5-(1-(pyridazin-3-ylethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile,
3-(1-((2-chloropyridin-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluorobenzonitrile,
3-fluoro-5-(1-((6-methylpyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile,
3-(1-(6-chloropyridin-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluorobenzonitrile,
3-fluoro-5-(1-((6-methoxypyridin-2-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile,
3-fluoro-5-(1-((2-methylthiazol-4-yl)ethynyl)-3-azabicyclo[3.1.0]hexan-3-yl)benzonitrile.

10. A pharmaceutical composition, comprising a compound of claim 1 in free base or pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent.

11. A compound according to anyone of claim 1-9 in free base or pharmaceutically acceptable salt form and the pharmaceutical compositions according to claim 10, for use in the prevention, treatment or delay of progression of disorders associated with irregularities of glutamatergic signal transmission in the digestive tract, urinary tract or central nervous system mediated in full or in part by mGluR5 receptors.

12. A pharmaceutical composition, comprising a compound of claim 1 in free base or pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent.

13. A method of treating disorders associated with irregularities of the glutamatergic signal transmission, and the nervous system disorders mediated full or in part by mGluR5 receptors, which method comprises administering to a subject in need of such treatment a

therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable salt form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/102946

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/08(2006.01)i; A61K 31/4439(2006.01)i; A61P 25/28(2006.01)i

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; A61K; A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNKI; EPODOC; STN; CNPAT; DWPI; CAPLUS; REGISTRY:azabicyclo,benzonitrile, gluamatergic signal transmission, glutamatergic, mglur, digestive, urinary, central nervous system

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOMEYAMA, Kimihiro et al. "Intramolecular Alkynylcyclopropanation of Olefins Catalyzed by Bi(OTf)3:Stereoselective Synthesis of 1-Alkynyl-3-azabicyclo[3.1.0]hexanes" *Angewandte Chemie, International Edition,* Vol. 48, No. 52, 31 December 2009 (2009-12-31), pages 9875-9878	1-2,11
A	WO 2014124560 A1 (HUA MEDICINE SHANGHAI LTD) 21 August 2014 (2014-08-21) the whole document	1-12
A	CN 101287726 A (NOVARTIS AG) 15 October 2008 (2008-10-15) the whole document	1-12

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2016	**11 January 2017**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**WANG, Bo**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10) 62086314**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/102946

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

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

1. ☑ Claims Nos.: **13**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 13 is directed to a method for the treatment of the human/animal body by therapy.Thus, the subject-matter of claim 13 is not required to be searched by this Authority. (Rule 39.1(iv) PCT).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/102946

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2014124560 A1	21 August 2014	CN 105121424 A	02 December 2015
CN 101287726 A	15 October 2008	US 2008269250 A1	30 October 2008
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		WO 2006089700 A1	31 August 2006
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