

Acylamino bridged heterocyclic compound, and composition and application thereof

TECHNICAL FIELD

[0001] The present disclosure belongs to the field of medicinal chemistry, and particularly relates to acylamino bridged heterocyclic compounds, or isomers, solvates, pharmaceutically acceptable salts or prodrugs thereof, and to pharmaceutical compositions thereof, and their use in the preparation of medicaments for the treatment of autoimmune diseases, tumors and neurodegenerative diseases related to receptor-interacting protein 1 kinase (RIPK1).

BACKGROUND OF THE INVENTION

[0002] In the early days, it was thought that there are two main ways of cell death, i.e., apoptosis and necrosis. Apoptosis is the autonomous and orderly death of cells controlled by genes in order to maintain the stability of the body's internal environment. It plays an important role in the evolution of the organism, the stability of the internal environment, and the development of the system. Cell necrosis is a pathological process in which cells are affected by physical, chemical and other environmental factors, such as mechanical damage, poisons, microorganisms, radiation, etc., causing cell death. In 2005, Degterev A et al. first discovered and reported an orderly cell necrosis process regulated by a series of biochemical molecules, and named it Necroptosis (also known as programmed necrosis). This process is a kind of programmed cell necrosis produced by stimulating death receptors with TNF- α , FasL or TRAIL. Morphologically, it is manifested as cell swelling, cell volume increasing, organelle dysfunction, damage to cell membrane integrity, release of cell contents, and mass production of ROS.

[0003] Receptor-interacting protein 1 kinase (RIPK1) belongs to the TKL family of serine/threonine protein kinases. Members of the RIPK serine/threonine kinase family have the same N-terminal kinase domain, but different binding domains. Studies have shown that receptor-interacting protein 1 can regulate the process of cell apoptosis. The death domain of RIPK-1 binds to death receptors such as TNFR1, Fas, TRAILR1, TRAILR2, etc., and they can also bind to other proteins containing death domains, such as TRADD, FADD, etc. Binding with the latter is a necessary condition for activating caspase-8 and inducing apoptosis. The intermediate structure of RIPK-1 is the RIPK isotype interaction target, through which RIPK-1 can interact with RIPK-3. Kelliher et al. found that mice with congenital defects of RIPK-1 died less than 3 days after birth due to a large number of cell apoptosis, which indicates that RIPK-1 is also involved in regulating cell apoptosis. In addition, cells with congenital RIPK-1 deficiency are quite sensitive to TNF-induced cell death, perhaps because such cells cannot effectively activate NF- κ B.

[0004] On the other hand, studies have also shown that RIPK-1 and RIPK-3 are also involved in the process of cell necroptosis. In most cell types, death receptors TNFR1, Fas and TRAILR mediate cell apoptosis.

Activating TNFR1 can trigger the ubiquitination of RIPK-1 through cIAP1 and cIAP2, and the ubiquitinated RIPK-1 determines whether the cell will continue to survive or die. When the apoptosis pathway is blocked by the pan-caspase inhibitor z-VAD-fmk, cell death will move toward to necroptosis. In this process, the activity of RIPK-1 is a key factor, which is regulated by FasL, TNF and TRAIL death receptors.

[0005] Recent studies have shown that the process of necroptosis is related to a variety of diseases, including tumors, autoimmune diseases, degenerative diseases, inflammatory diseases and the like. Based on this, it can be known that RIP family kinases are closely related to the occurrence of tumors, autoimmune diseases, degenerative diseases, inflammatory diseases and other diseases.

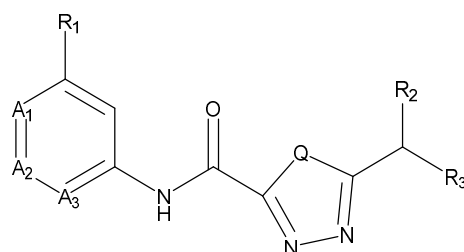
[0006] For example, in the study of Alzheimer's disease, Claudia Balducci et al. found that activated microglia plays an important role in the evolution of Alzheimer's disease (Pharmacological Research. 2018; 130: 402-413). At the same time, microglia highly expresses RIPK-1, and RIPK-1 inhibitors can protect from A β -induced neuronal death in vitro and reduce the proliferation of microglia. Moreover, in Alzheimer-like mouse brains, RIPK-1 inhibitors can improve their learning and memory abilities. In addition to Alzheimer's disease, RIPK-1 inhibitors are expected to be used in a variety of other neurodegenerative diseases including Parkinson's disease, amyotrophic lateral sclerosis, Huntington disease, etc.

[0007] At present, there are not many studies on RIPK-1 inhibitors, and only a small number of studies have entered the clinical stage. There is an urgent need for more research and development of drugs based on RIPK-1 inhibitors.

[0008] The present disclosure provides a class of acylamino bridged heterocyclic compounds, which exhibit good RIPK-1 inhibitory activity and can be used as RIPK-1 inhibitors in the preparation of a medicament for the treatment of tumors, autoimmune diseases, degenerative diseases, and inflammatory diseases.

SUMMARY OF THE INVENTION

[0009] The compound represented by formula (I) provided by the present disclosure, or pharmaceutically acceptable salts, isomers, hydrates, solvates, or prodrugs thereof, can be used to prepare medicaments for the treatment or prevention of diseases related to RIPK1.



formula (I)

[0010] In formula (I),

[0011] Q is NH, O or S;

[0012] A₁, A₂, and A₃ are each independently selected from N or CR₄ and at least one of A₁, A₂, and A₃ is N, R₄ is H, F, Cl or methyl;

[0013] R₁ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

[0014] or 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

[0015] or aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -SO₂-R₅, -SO-R₅, -CO-R₅, -CONH-R₅, -NHCO-R₅, -R'-COO-R'', -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl and/or C₁-C₆ alkoxy, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, and -O-R₆,

[0016] the aryl group is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring, the heteroaryl is a monocyclic or bicyclic group having 5 to 10 ring atoms and containing 1 to 3 heteroatoms selected from N, O, or S as ring atoms, the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1-2 atoms selected from N, O, or S as ring atoms,

[0017] R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0018] R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

[0019] R' is C₂-C₆ alkenylene, or C₁-C₆ alkylene,

[0020] R'' is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0021] R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted

with mono- or di-C₁-C₃ alkyl;

[0022] R₂ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

5 or C₇-C₁₂ bridged cyclyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

10 or C₁-C₁₀ alkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, cyano, -CONH₂, C₃-C₈ cycloalkyl, and -NR^cR^d,

or -(CH₂)_n-R^e, wherein R^e is aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, C₃-C₆ cycloalkyl, phenyl, naphthyl, C₂-C₆ alkynyl, C₂-C₆ alkenyl, and -NR^cR^d, wherein n is an integer from 0 to 3,

15 or -(CH₂)_m-R^f, wherein R^f is 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d, m is an integer from 0 to 3,

[0023] the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

20 **[0024]** the aryl group is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring, the heteroaryl is a monocyclic or bicyclic group having 5 to 10 ring atoms and containing 1 to 3 heteroatoms selected from N, O, or S as ring atoms,

[0025] R^c and R^d are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

[0026] R₃ is hydrogen, C₁-C₃ alkyl, hydroxyl, halogen, trifluoromethyl, or cyano.

[0027] In some embodiments, alternatively, Q is NH, O or S;

30 **[0028]** A₁, A₂, and A₃ are each independently selected from N or CR₄ and at least one of A₁, A₂, and A₃ is N, R₄ is H, F, Cl or methyl;

[0029] R₁ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

[0030] or 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

[0031] or aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -SO₂-R₅, -SO-R₅, -CO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, and -O-R₆,

[0032] the aryl group is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring, the heteroaryl is a monocyclic or bicyclic group having 5 to 10 ring atoms and containing 1 to 3 heteroatoms selected from N, O, or S as ring atoms, the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

[0033] R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0034] R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

[0035] R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

[0036] R₂ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

or C₇-C₁₂ bridged cyclyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

or C₁-C₁₀ alkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, cyano, -CONH₂, C₃-C₈ cycloalkyl,

and $-NR^cR^d$,

or $-(CH_2)_n-R^e$, wherein R^e is aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_3 acyl, hydroxyl, halogen, trifluoromethyl, cyano, $-CONH_2$, C_2 - C_6 alkynyl, C_2 - C_6 alkenyl, and $-NR^cR^d$, wherein n is an integer from 0 to 3,

5 or $-(CH_2)_m-R^f$, wherein R^f is 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_3 acyl, hydroxyl, halogen, trifluoromethyl, cyano, $-CONH_2$, oxo ($=O$) and $-NR^cR^d$, m is an integer from 0 to 3,

[0037] the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

10 **[0038]** the aryl group is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring, the heteroaryl is a monocyclic or bicyclic group having 5 to 10 ring atoms and containing 1 to 3 heteroatoms selected from N, O, or S as ring atoms,

[0039] R^c and R^d are each independently selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 alkyl substituted with C_1 - C_6 alkoxy, C_1 - C_6 alkyl substituted with hydroxyl, C_3 - C_8 cycloalkyl C_1 - C_6 alkyl, C_1 - C_6 alkyl substituted with 4- to 8-membered heteroalicyclic group, C_1 - C_6 alkyl substituted with C_1 - C_3 alkylthio, or C_1 - C_6 alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di- C_1 - C_3 alkyl;

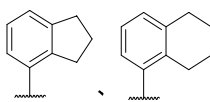
[0040] R_3 is hydrogen, C_1 - C_3 alkyl, hydroxyl, halogen, trifluoromethyl, or cyano.

[0041] In some embodiments, alternatively, A_3 is N, A_1 , and A_2 are each independently selected from N or CR_4 , R_4 is H, F, Cl or methyl; still alternatively, A_3 is N, A_1 , and A_2 are each independently CH.

20 **[0042]** In some embodiments, alternatively, A_3 is N, A_1 , A_2 are each independently selected from N or CR_4 , R_4 is H or F.

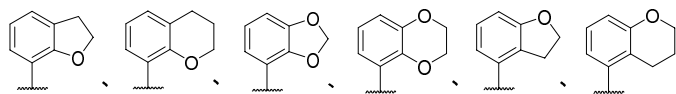
[0043] In some embodiments, still alternatively, Q is NH.

[0044] In some embodiments, alternatively, R_1 is C_3 - C_8 cycloalkyl, 4- to 8-membered heteroalicyclic group, or aryl or heteroaryl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C_1 - C_{10} alkyl, halogen, C_3 - C_8 cycloalkyl, halogenated C_1 - C_{10} alkyl, cyano, hydroxyl, C_1 - C_6 alkylthio, $-CO-R_5$, $-SO_2-R_5$, $-SO-R_5$, $-CONH-R_5$, $-NR^aR^b$, 4- to 8-membered heteroalicyclic group, C_2 - C_6 alkynyl, C_2 - C_6 alkenyl, C_1 - C_3 alkoxy C_1 - C_6 alkylthio, C_1 - C_{10} alkyl substituted with hydroxyl, C_1 - C_6 alkoxy C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl C_1 - C_6 alkyl, $(C_3$ - C_8 cycloalkyl)-O-(C_1 - C_6 alkyl), C_1 - C_6 alkyl substituted with 4- to 8-membered heteroalicyclic group, and $-O-R_6$,



25 **[0045]** the aryl group is phenyl, naphthyl, , the heteroaryl group is pyrrolyl, furyl, pyridyl, thienyl, imidazolyl, thiazolyl, isothiazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolinyl, indoliziny, isoxazolyl, 1,5-naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, oxazolyl, 1-

phenyl-1H-pyrrolyl, phenaziny, phenothiaziny, phenoxaziny, phthalaziny, pteridiny, puriny, pyranly, pyrazoly, pyrazolo[3,4-d]pyrimidiny, pyridyl, pyrido[3,2-d]pyrimidiny, pyrido[3,4-d]pyrimidiny, pyraziny, pyrimidiny, pyridaziny, quinazolinyl, quinoxaliny, quinolinyl, isoquinolinyl,



, the 4- to 8-membered heteroalicyclic group is a 4-

to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

[0046] R_5 is hydrogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy C_1 - C_6 alkyl, C_1 - C_6 alkyl substituted with hydroxyl, C_3 - C_8 cycloalkyl, or C_1 - C_6 alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0047] R_6 is C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, 4- to 8-membered heteroalicyclic group, or C_1 - C_{10} alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C_1 - C_6 alkoxy, cyano, $-NR^aR^b$, C_3 - C_8 cycloalkyloxy, $-CONH-R_5$, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl substituted with hydroxyl and/or C_1 - C_4 alkyl, carboxylic, halogen, halogenated C_1 - C_6 alkoxy, $-CO-R_5$, $-SO_2-R_5$, $-SO-R_5$, C_2 - C_6 alkynyl, C_2 - C_6 alkenyl, C_1 - C_4 alkoxy C_1 - C_6 alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C_1 - C_4 alkyl, or C_1 - C_6 alkylthio,

[0048] R^a and R^b are each independently selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 alkyl substituted with C_1 - C_6 alkoxy, C_1 - C_6 alkyl substituted with hydroxyl, C_3 - C_8 cycloalkyl C_1 - C_6 alkyl, C_1 - C_6 alkyl substituted with 4- to 8-membered heteroalicyclic group, C_1 - C_6 alkyl substituted with C_1 - C_3 alkylthio, or C_1 - C_6 alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di- C_1 - C_3 alkyl.

[0049] In some embodiments, alternatively, R_1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-3-yl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or aryl or heteroaryl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C_1 - C_{10} alkyl, halogen, C_3 - C_8 cycloalkyl, halogenated C_1 - C_{10} alkyl, cyano, hydroxyl, C_1 - C_6 alkylthio, $-SO_2-R_5$, $-SO-R_5$, $-CO-R_5$, $-CONH-R_5$, $-NR^aR^b$, 4- to 8-membered heteroalicyclic group, C_2 - C_6 alkynyl, C_2 - C_6 alkenyl, C_1 - C_3 alkoxy C_1 - C_6 alkylthio, C_1 - C_{10} alkyl substituted with hydroxyl, C_1 - C_6 alkoxy C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl C_1 - C_6 alkyl, $(C_3$ - C_8 cycloalkyl)-O-(C_1 - C_6 alkyl), C_1 - C_6 alkyl substituted with 4- to 8-membered heteroalicyclic group, and $-O-R_6$,

[0050] the aryl group is phenyl, , , the heteroaryl group is pyrazoly, pyridyl, pyrimidiny,

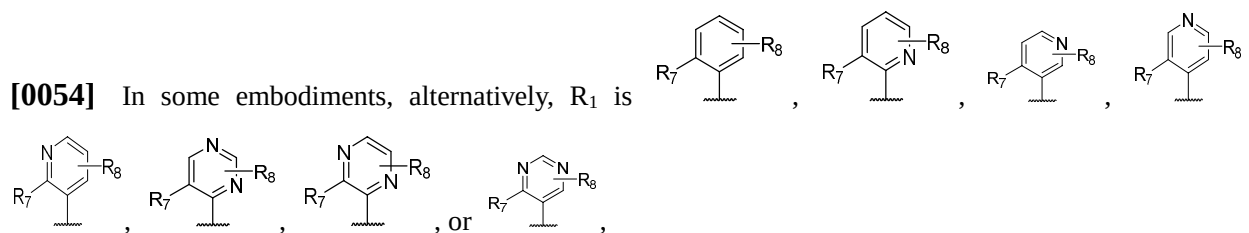
thiazoly, oxazoly, , , , , , , the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

[0051] R₅ is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0052] R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, or C₁-C₆ alkylthio,

[0053] R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl.

[0054] In some embodiments, alternatively, R₁ is



[0055] R₇ is hydrogen, C₁-C₄ alkyl, C₁-C₃ alkoxy, halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, C₂-C₄ alkynyl, C₂-C₄ alkenyl, C₃-C₄ cycloalkyl, or C₁-C₃ acyl;

[0056] R₈ is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, hydroxyl C₁-C₁₀ alkyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O-R₆,

[0057] the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

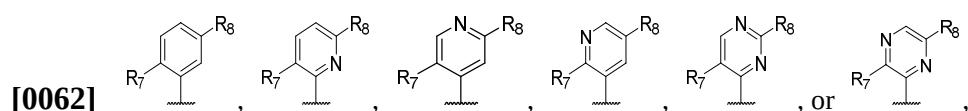
[0058] R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0059] R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered

heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

[0060] R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl.

[0061] In some embodiments, alternatively, R₁ is:



[0063] R₇ is hydrogen, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, fluorine, chlorine, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, ethynyl, propynyl, vinyl, propenyl, cyclopropyl, cyclobutyl, formyl, or acetyl;

[0064] R₈ is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O-R₆,

[0065] the 4- to 8-membered heteroalicyclic group is heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

[0066] R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

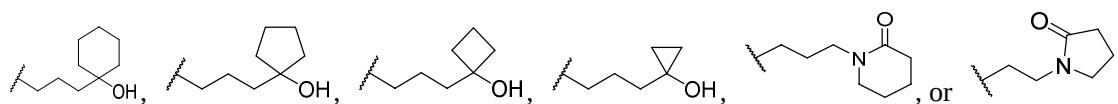
[0067] R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

[0068] R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl.

[0069] In some embodiments, alternatively, R₅ is hydrogen, hydroxyl, C₁-C₄ alkyl, C₁-C₃ alkoxy C₁-C₃ alkyl, C₁-C₃ alkyl substituted with hydroxyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or C₁-C₃ alkyl which is substituted with 4-6 membered heteroalicyclic group selected from oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydro-2H-pyranyl, tetrahydropyrrolyl, piperidiny, piperaziny, morpholiny, or thiomorpholiny,

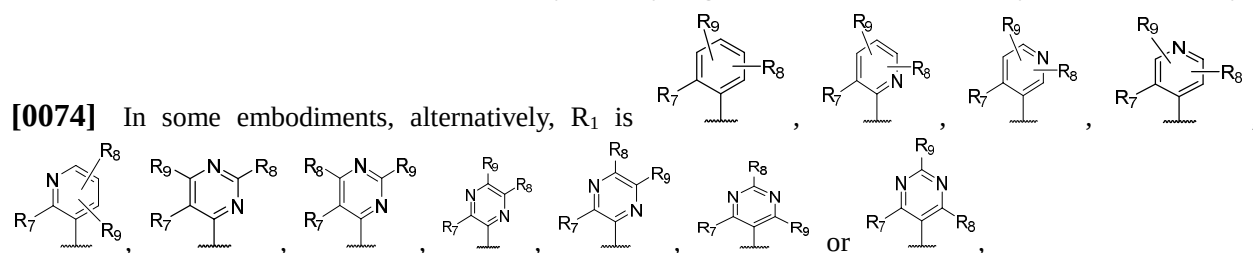
[0070] In some embodiments, alternatively, R₆ is C₁-C₈ alkyl, C₃-C₆ cycloalkyl, 4-6 membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, neopentoxy, cyano, amino, dimethylamino, diethylamino, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, -CONH-R₅, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxyl, fluorine, chlorine, trifluoromethoxy, trichloromethoxy, methylsulfone, ethylsulfone, -SO-R₅, -CO-R₅, ethynyl, vinyl, methoxyethoxy, methoxypropoxy, ethoxyethoxy, ethoxypropoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, methylthio, ethylthio, and propylthio. Still alternatively, 4- to 8-membered heteroalicyclic group described herein is oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydro-2H-pyranyl, tetrahydropyrrolyl, piperidiny, piperaziny, morpholiny, thiomorpholiny, 1,3-dioxolan-2-yl, etc.

[0071] In some embodiments, still alternatively, R₆ is 4-ethyl-4-hydroxyhexyl, 4-methyl-4-hydroxypentyl, 5-methyl-5-hydroxyhexyl, 2-methyl-2-hydroxypropyl, tetrahydro-2H-pyran-4-ylethyl, tetrahydro-2H-pyran-4-ylmethyl, tetrahydro-2H-pyran-2-ylmethyl, tetrahydro-2H-pyran-2-ylethyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, tetrahydrofuran-2-ylethyl, tetrahydrofuran-3-ylethyl, methoxypropyl, ethoxypropyl, tert-butoxypropyl, isobutoxypropyl, isopropoxypropyl, ethoxyethyl, tert-butoxyethyl, isobutoxyethyl, isopropoxyethyl, methoxyethyl, methoxybutyl, ethoxybutyl, tert-butoxybutyl, isobutoxybutyl, isopropoxybutyl, methoxyethoxyethyl, piperidin-1-ylethyl, piperidin-1-ylpropyl, 1-methylpiperidin-4-ylmethyl, 1-methylpiperidin-4-ylethyl, 1-methylpiperidin-4-ylpropyl, 1-methylpiperazin-4-ylethyl, 1-methylpiperazin-4-ylpropyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, 3,3-dimethylbutyl, octyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyoctyl, hydroxyheptyl, cyanomethyl, cyanoethyl, cyanopropyl, cyanobutyl, 4-cyanopentyl, 4,4,4-trifluorobutyl, N,N-dimethylpropyl, N,N-dimethylethyl, N,N-diethylpropyl, N,N-diethylethyl, methylthiobutyl, methylthiomethyl, methylthioethyl, methylthiopropyl, methylsulfonylbutyl, methylsulfonylmethyl, methylsulfonylethyl, methylsulfonylpropyl, cycloheptylethyl, cycloheptylpropyl, cyclohexylethyl, cyclohexylpropyl, cyclopentylethyl, cyclopentylpropyl, allyl, penten-1-yl, oxetan-3-yl, tetrahydro-2H-pyran-4-yl, oxetan-3-ylmethyl, oxetan-3-ylethyl, fluoroethyl, fluoropropyl, fluorobutyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutoxypropyl, cyclobutoxyethyl, cyclobutoxymethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, -CH₂CONH₂, -(CH₂)₂CONH₂, -(CH₂)₃CONH₂,



[0072] In some embodiments, alternatively, R^a and R^b are each independently selected from hydrogen, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₃ alkyl substituted with C₁-C₃ alkoxy, C₁-C₃ alkyl substituted with hydroxyl, C₃-C₆ cycloalkyl C₁-C₃ alkyl, C₁-C₃ alkyl substituted with 4-6 membered heteroalicyclic group, C₁-C₃ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₃ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl.

[0073] In some embodiments, still alternatively, R_7 is hydrogen, fluorine, chlorine, methyl, or trifluoromethyl.



[0075] R_7 is hydrogen, C₁-C₄ alkyl, C₁-C₃ alkoxy, halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, C₂-C₄ alkynyl, C₂-C₄ alkenyl, C₃-C₄ cycloalkyl, or C₁-C₃ acyl; still alternatively, R_7 is hydrogen, fluorine, chlorine, methyl, or trifluoromethyl.

[0076] R_8 is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO- R_5 , -SO₂- R_5 , -SO- R_5 , -CONH- R_5 , -NR^a R^b , 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O- R_6 ,

[0077] the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

[0078] R_5 is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0079] R_6 is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^a R^b , C₃-C₈ cycloalkyloxy, -CONH- R_5 , C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂- R_5 , -SO- R_5 , -CO- R_5 , C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

[0080] R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆

alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

[0081] R₉ is hydrogen, C₁-C₄ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, C₂-C₄ alkynyl, C₂-C₄ alkenyl, C₃-C₄ Cycloalkyl, or C₁-C₃ acyl.

[0082] In some embodiments, alternatively, R₂ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, oxo (=O), amino, dimethylamino, and diethylamino,

[0083] or C₇-C₁₀ bridged cyclyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, oxo (=O), amino, dimethylamino, and diethylamino,

[0084] or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, cyano, -CONH₂, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, amino, dimethylamino, and diethylamino,

[0085] or -(CH₂)_n-R^e, wherein R^e is aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, ethynyl, vinyl, amino, dimethylamino, and diethylamino, n is an integer from 0 to 3,

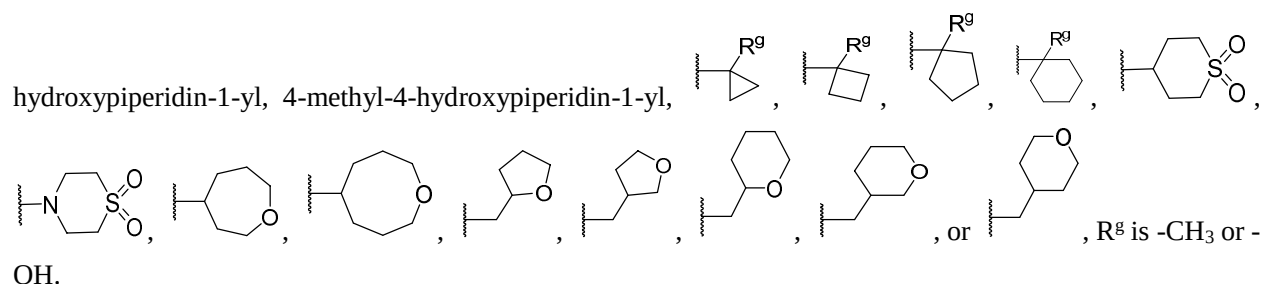
[0086] or -(CH₂)_m-R^f, wherein R^f is 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, oxo (=O), amino, dimethylamino, and diethylamino, m is an integer from 0 to 3,

[0087] the 4- to 8-membered heteroalicyclic group contains 1 to 2 atoms selected from N, O, or S as ring atoms,

[0088] the aryl group is phenyl, and the heteroaryl group is pyridyl, pyrimidinyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0089] In some embodiments, alternatively, R₂ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 4,4-difluorocyclohexyl, bicyclo[2.2.1]heptyl, adamantyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, 2-hydroxy-2-methylpropyl, 3,3-dimethylbutyl, 3-hydroxy-3-methylbutyl, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, benzyl, phenethyl, phenyl, 2-fluorophenyl, 2-

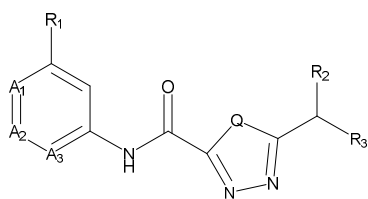
chlorophenyl, 2-methoxyphenyl, 2-cyanophenyl, 2-ethynylphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, 3-cyanophenyl, 3-ethynylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-cyanophenyl, 4-ethynylphenyl, 3,4-difluorophenyl, 3-cyano-4-methylphenyl, pyridin-2-yl, pyridin-3-yl, pyridine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydro-2H-pyran-4-yl, tetrahydropyrrolyl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, methylpiperazin-4-yl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 4-

hydroxypiperidin-1-yl, 4-methyl-4-hydroxypiperidin-1-yl, , R^g is -CH₃ or -OH.

[0090] In some embodiments, alternatively, R₂ is 2,3-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2,4-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2,4,5-trifluorophenyl, 3-chloro-2-fluorophenyl, 2-chloro-3-fluorophenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 5-chloro-3-fluorophenyl, 3-chloro-5-fluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 2-chloro-4-fluorophenyl, 4-chloro-2-fluorophenyl, 3-chloro-2,4-difluorophenyl, 5-chloro-2,4-difluorophenyl, 3-chloro-2,5-difluorophenyl, 3-chloro-2,6-difluorophenyl, 3-chloro-4,5-difluorophenyl, 2-chloro-4,5-difluorophenyl, 2-chloro-3,4-difluorophenyl, 2-chloro-3,5-difluorophenyl, 2-chloro-3,6-difluorophenyl, 4-chloro-2,3-difluorophenyl, 4-chloro-3,5-difluorophenyl, 4-chloro-2,5-difluorophenyl, 5-chloro-2,3-difluorophenyl, 5-chloro-3,4-difluorophenyl, 6-chloro-2,3-difluorophenyl, 3-fluoro-5-methylphenyl, 4-fluoro-3-methylphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluoro-5-methylphenyl, 3-fluoro-4-methylphenyl, 3-fluoro-2-methylphenyl, 3-fluoro-5-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 2-fluoro-5-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-2-methoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 3-fluoro-2-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 5-fluoro-2-trifluoromethylphenyl, 4-fluoro-3-trifluoromethylphenyl, 3-fluoro-4-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, 2-fluoro-5-ethylphenyl, 2-fluoro-5-cyclopropylphenyl, or 2-fluoro-5-phenylphenyl.

[0091] In some embodiments, alternatively, R₃ is hydrogen, methyl, ethyl, hydroxyl, cyano, trifluoromethyl, fluorine, or chlorine.

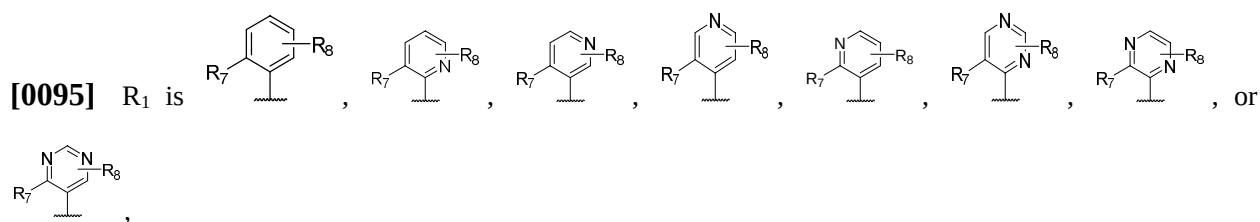
[0092] Disclosed is a compound represented by formula (I), pharmaceutically acceptable salts, isomer, solvate or prodrug thereof,



formula (I)

[0093] wherein, Q is NH;

[0094] A₃ is N, A₁, and A₂ are each independently selected from N or CR₄, R₄ is H, F, Cl or methyl, alternatively H or F;



[0096] R₇ is hydrogen, C₁-C₄ alkyl, C₁-C₃ alkoxy, halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, C₂-C₄ alkynyl, C₂-C₄ alkenyl, C₃-C₄ cycloalkyl, or C₁-C₃ acyl;

[0097] R₈ is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, hydroxyl C₁-C₁₀ alkyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O-R₆,

[0098] the 4- to 8-membered heteroalicyclic group is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

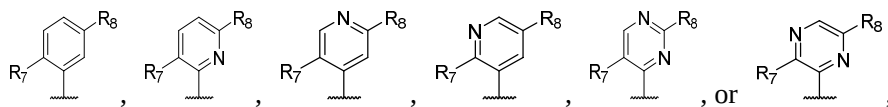
[0099] R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

[0100] R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, or C₁-C₆ alkylthio,

[0101] R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted

with mono- or di-C₁-C₃ alkyl,

[0102] still alternatively, R₁ is :



[0103] R₇ is hydrogen, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, fluorine, chlorine, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, ethynyl, propynyl, vinyl, propenyl, cyclopropyl, cyclobutyl, formyl, or acetyl; alternatively R₇ is hydrogen, fluorine, chlorine, methyl, or trifluoromethyl;

[0104] R₈ is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O-R₆,

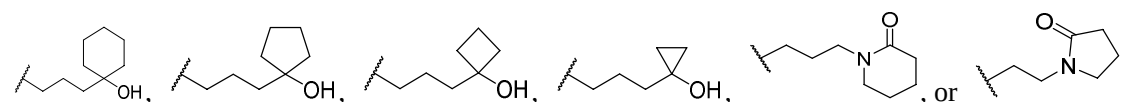
[0105] the 4- to 8-membered heteroalicyclic group is heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

[0106] R₅ is hydrogen, hydroxyl, C₁-C₄ alkyl, C₁-C₃ alkoxy C₁-C₃ alkyl, C₁-C₃ alkyl substituted with hydroxyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or C₁-C₃ alkyl which is substituted with 4-6 membered heteroalicyclic group selected from oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydro-2H-pyranyl, tetrahydropyrrolyl, piperidiny, piperaziny, morpholiny, or thiomorpholiny,

[0107] R₆ is C₁-C₈ alkyl, C₃-C₆ cycloalkyl, 4-6 membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, neopentoxy, cyano, amino, dimethylamino, diethylamino, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, -CONH-R₅, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxyl, fluorine, chlorine, trifluoromethoxy, trichloromethoxy, methylsulfone, ethylsulfone, -SO-R₅, -CO-R₅, ethynyl, vinyl, methoxyethoxy, methoxypropoxy, ethoxyethoxy, ethoxypropoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, methylthio, ethylthio, and propylthio. Still alternatively, 4- to 8-membered heteroalicyclic group described herein is oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydro-2H-pyranyl, tetrahydropyrrolyl, piperidiny, piperaziny, morpholiny, thiomorpholiny, 1,3-dioxolan-2-yl, etc.,

[0108] still alternatively, R₆ is 4-ethyl-4-hydroxyhexyl, 4-methyl-4-hydroxypentyl, 5-methyl-5-hydroxyhexyl, 2-methyl-2-hydroxypropyl, tetrahydro-2H-pyran-4-ylethyl, tetrahydro-2H-pyran-4-ylmethyl, tetrahydro-2H-pyran-2-ylmethyl, tetrahydro-2H-pyran-2-ylethyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, tetrahydrofuran-2-ylethyl, tetrahydrofuran-3-ylethyl, methoxypropyl, ethoxypropyl, tert-butoxypropyl,

isobutoxypropyl, isopropoxypropyl, ethoxyethyl, tert-butoxyethyl, isobutoxyethyl, isopropoxyethyl, methoxyethyl, methoxybutyl, ethoxybutyl, tert-butoxybutyl, isobutoxybutyl, isopropoxybutyl, methoxyethoxyethyl, piperidin-1-ylethyl, piperidin-1-ylpropyl, 1-methylpiperidin-4-ylmethyl, 1-methylpiperidin-4-ylethyl, 1-methylpiperidin-4-ylpropyl, 1-methylpiperazin-4-ylethyl, 1-methylpiperazin-4-ylpropyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, 3,3-dimethylbutyl, octyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyoctyl, hydroxyheptyl, cyanomethyl, cyanoethyl, cyanopropyl, cyanobutyl, 4-cyanopentyl, 4,4,4-trifluorobutyl, N,N-dimethylpropyl, N,N-dimethylethyl, N,N-diethylpropyl, N,N-diethylethyl, methylthiobutyl, methylthiomethyl, methylthioethyl, methylthiopropyl, methylsulfonylbutyl, methylsulfonylmethyl, methylsulfonylethyl, methylsulfonylpropyl, cycloheptylethyl, cycloheptylpropyl, cyclohexylethyl, cyclohexylpropyl, cyclopentylethyl, cyclopentylpropyl, allyl, penten-1-yl, oxetan-3-yl, tetrahydro-2H-pyran-4-yl, oxetan-3-ylmethyl, oxetan-3-ylethyl, fluoroethyl, fluoropropyl, fluorobutyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutoxypropyl, cyclobutoxyethyl, cyclobutoxymethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-\text{CH}_2\text{CONH}_2$, $-(\text{CH}_2)_2\text{CONH}_2$, $-(\text{CH}_2)_3\text{CONH}_2$,



[0109] R^a and R^b are each independently selected from hydrogen, C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_3 alkyl substituted with C_1 - C_3 alkoxy, C_1 - C_3 alkyl substituted with hydroxyl, C_3 - C_6 cycloalkyl C_1 - C_3 alkyl, C_1 - C_3 alkyl substituted with 4-6 membered heteroalicyclic group, C_1 - C_3 alkyl substituted with C_1 - C_3 alkylthio, or C_1 - C_3 alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di- C_1 - C_3 alkyl;

[0110] R_2 is C_3 - C_8 cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, $-\text{CONH}_2$, oxo ($=\text{O}$), amino, dimethylamino, and diethylamino,

[0111] or C_7 - C_{10} bridged cyclyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, $-\text{CONH}_2$, oxo ($=\text{O}$), amino, dimethylamino, and diethylamino,

[0112] or C_1 - C_{10} alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, cyano, $-\text{CONH}_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, amino, dimethylamino, and diethylamino,

[0113] or $-(\text{CH}_2)_n\text{-R}^e$, wherein R^e is aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3

substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, ethynyl, vinyl, amino, dimethylamino, and diethylamino, n is an integer from 0 to 3,

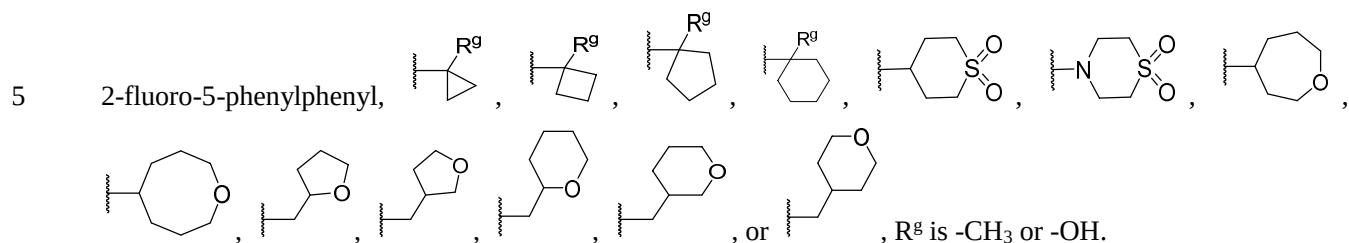
[0114] or -(CH₂)_m-R^f, wherein R^f is 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, oxo (=O), amino, dimethylamino, and diethylamino, m is an integer from 0 to 3,

[0115] the 4- to 8-membered heteroalicyclic group contains 1 to 2 atoms selected from N, O, or S as ring atoms,

[0116] the aryl group is phenyl, and the heteroaryl group is pyridyl, pyrimidinyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl;

[0117] still alternatively, R₂ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 4,4-difluorocyclohexyl, bicyclo[2.2.1]heptyl, adamantyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, 2-hydroxy-2-methylpropyl, 3,3-dimethylbutyl, 3-hydroxy-3-methylbutyl, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, benzyl, phenethyl, phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-methoxyphenyl, 2-cyanophenyl, 2-ethynylphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, 3-cyanophenyl, 3-ethynylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-cyanophenyl, 4-ethynylphenyl, 3,4-difluorophenyl, 3-cyano-4-methylphenyl, pyridin-2-yl, pyridin-3-yl, pyridine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydro-2H-pyran-4-yl, tetrahydropyrrolyl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, methylpiperazin-4-yl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 4-hydroxypiperidin-1-yl, 4-methyl-4-hydroxypiperidin-1-yl, 2,3-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2,4-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2,4,5-trifluorophenyl, 3-chloro-2-fluorophenyl, 2-chloro-3-fluorophenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 5-chloro-3-fluorophenyl, 3-chloro-5-fluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 2-chloro-4-fluorophenyl, 4-chloro-2-fluorophenyl, 3-chloro-2,4-difluorophenyl, 5-chloro-2,4-difluorophenyl, 3-chloro-2,5-difluorophenyl, 3-chloro-2,6-difluorophenyl, 3-chloro-4,5-difluorophenyl, 2-chloro-4,5-difluorophenyl, 2-chloro-3,4-difluorophenyl, 2-chloro-3,5-difluorophenyl, 2-chloro-3,6-difluorophenyl, 4-chloro-2,3-difluorophenyl, 4-chloro-3,5-difluorophenyl, 4-chloro-2,5-difluorophenyl, 5-chloro-2,3-difluorophenyl, 5-chloro-3,4-difluorophenyl, 6-chloro-2,3-difluorophenyl, 3-fluoro-5-methylphenyl, 4-fluoro-3-methylphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluoro-5-methylphenyl, 3-fluoro-4-methylphenyl, 3-fluoro-2-methylphenyl, 3-fluoro-5-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 2-fluoro-5-

methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-2-methoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 3-fluoro-2-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 5-fluoro-2-trifluoromethylphenyl, 4-fluoro-3-trifluoromethylphenyl, 3-fluoro-4-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, 2-fluoro-5-ethylphenyl, 2-fluoro-5-cyclopropylphenyl,



[0118] R₃ is hydrogen, methyl, ethyl, hydroxyl, cyano, trifluoromethyl, fluorine, or chlorine, still alternatively hydrogen, fluorine, hydroxyl, or chlorine.

[0119] According to some embodiments of the present disclosure, the pharmaceutically acceptable salt of the
 10 compound is selected from the group consisting of one or more of the following salts: hydrochloride, hydrobromide, hydroiodide, perchlorate, sulfate, nitrate, phosphate, formate, acetate, propionate, glycolate, lactate, succinate, maleate, tartrate, malate, citrate, fumarate, gluconate, benzoate, mandelate, methanesulfonate, isethionate, benzenesulfonate, oxalate, palmitate, 2-naphthalenesulfonate, p-toluenesulfonate, cyclohexylsulfamate, salicylate, hexonate, trifluoroacetate, aluminum salt, calcium salt, chloroprocaine salt,
 15 choline salt, diethanolamine salt, ethylenediamine salt, lithium salt, magnesium salt, potassium salt, sodium salt and zinc salt.

[0120] Another aspect of the present disclosure relates to the application of the compound, pharmaceutically acceptable salt(s), isomer(s), solvate(s), or prodrug(s) thereof in the preparation of a medicament for the treatment of RIP1 related diseases, Wherein, the RIP1 related disease include ocular fundus disease,
 20 xerophthalmia, psoriasis, leucoderma, dermatitis, alopecia areata, rheumatoid arthritis, colitis, multiple sclerosis, systemic lupus erythematosus, Crohn's disease, atherosclerosis, pulmonary fibrosis, liver fibrosis, myelofibrosis, non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, ovarian cancer, cervical cancer, colorectal cancer, melanoma, endometrial cancer, prostate cancer, bladder cancer, leukemia, gastric cancer, liver cancer, gastrointestinal stromal tumor, thyroid cancer, chronic myeloid leukemia,
 25 acute myeloid leukemia, non-Hodgkin's lymphoma, nasopharyngeal cancer, esophageal cancer, brain tumor, B-cell and T-cell lymphoma, lymphoma, multiple myeloma, biliary cancer and sarcoma, cholangiocarcinoma, inflammatory bowel disease, ulcerative colitis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, spondyloarthritis, gout, SoJIA, Sjogren's syndrome, systemic scleroderma, antiphospholipid syndrome, vasculitis, osteoarthritis, non-alcoholic steatohepatitis, alcoholic steatohepatitis,
 30 autoimmune hepatitis, autoimmune hepatobiliary disease, primary sclerosing cholangitis, nephritis, celiac disease, autoimmune ITP, transplant rejection, ischemia-reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial infarction, Huntington's disease,

Alzheimer's disease, Parkinson's disease, allergic diseases, asthma, atopic dermatitis, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converzyme-related fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor related periodic syndrome and periodontitis.

5 **[0121]** Another aspect of the present disclosure provides a pharmaceutical composition, which includes the acylamino bridged heterocyclic compounds of the present disclosure, or isomers, solvates, pharmaceutically acceptable salts or prodrugs thereof, and one or more pharmaceutically acceptable carriers or excipients.

[0122] According to some embodiments of the application, the pharmaceutical composition may also include one or more other therapeutic agents.

10 **[0123]** The present disclosure also relates to a method for treating diseases or disorders mediated by RIP1 kinase, which comprises administering a therapeutically effective amount of a compound of formula (I) or a salt thereof to a patient (human or other mammals, especially human) in need thereof. The RIP1 kinase-mediated diseases or disorders include those mentioned above.

15 **Description of the figures**

[0124] Figure 1 shows a Western Blot picture of the inhibition of RIPK1 phosphorylation by the compound of Example 2;

[0125] Figure 2 shows the inhibitory rate of the compound of Example 2 on the inhibition of RIPK1 phosphorylation;

20 **[0126]** Figure 3 shows the dilution flow chart for the compound of Assay Example 2.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0127] Unless otherwise stated, the following terms used in this application (including the description and claims) have the definitions given below. In this application, the use of "or" or "and" means "and/or" unless
25 stated otherwise. In addition, the use of the term "comprising" and other forms such as "including", "containing" and "having" is not limiting. The chapter headings used herein are for organizational purposes only and should not be interpreted as limitations on the topics described.

Detailed description

[0128] Unless otherwise specified, alkyl represents a saturated straight-chain, or branched-chain hydrocarbon
30 group with the specified number of carbon atoms. The term C₁-C₁₀ alkyl represents an alkyl moiety containing 1 to 10 carbon atoms, similarly C₁-C₃ alkyl represents an alkyl moiety containing 1 to 3 carbon atoms, such as, C₁-C₆ alkyl including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl etc.

[0129] When substituent terms such as "alkyl" are used in combination with other substituent terms, for
35 example in the term "C₁-C₃ alkoxy C₁-C₆ alkylthio" or "C₁-C₁₀ alkyl substituted with hydroxyl", this linking

substituent term (e.g. alkyl or alkylthio) is intended to include a divalent moiety, wherein the connection point is through the connection substituent. Examples of "C₁-C₃ alkoxy C₁-C₆ alkylthio" include, but are not limited to, methoxymethylthio, methoxyethylthio and ethoxypropylthio, etc. Examples of "C₁-C₁₀ alkyl substituted with hydroxyl" include, but are not limited to, hydroxymethyl, hydroxyethyl, and hydroxyisopropyl.

[0130] Alkoxy is an alkyl-O- group formed by the previously described linear or branched alkyl group and -O-, for example, methoxy, ethoxy, etc. Similarly, alkylthio is an alkyl-S- group formed by the previously described linear or branched alkyl group and -S-, for example, methylthio, ethylthio, etc.

[0131] Alkenyl and alkynyl include straight chain, or branched alkenyl or alkynyl, the term C₂-C₆ alkenyl or C₂-C₆ alkynyl means a straight or branched chain hydrocarbon group having at least one alkenyl or alkynyl group.

[0132] The term "halogenated C₁-C₁₀ alkyl" represents a group having one or more halogen atoms, which may be the same or different, on one or more carbon atoms of the alkyl moiety comprising 1 to 10 carbon atoms. Examples of "halogenated C₁-C₁₀ alkyl" may include, but are not limited to, -CF₃ (trifluoromethyl), -CCl₃ (trichloromethyl), 1,1-difluoroethyl, 2,2,2-trifluoroethyl and hexafluoroisopropyl, etc. Similarly, the term "halogenated C₁-C₁₀ alkoxy" represents a haloalkyl-O- group formed by the halogenated C₁-C₁₀ alkyl group and -O-, for example, trifluoromethoxy, trichloromethoxy, etc.

[0133] The term "C₁-C₃ acyl" includes formyl (-CHO), acetyl (CH₃CO-), propionyl (C₂H₅CO-).

[0134] The terms "-CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅" represent $\begin{array}{c} \text{O} \\ \parallel \\ \text{---C---R}_5 \end{array}$, $\begin{array}{c} \text{O} \\ \parallel \\ \text{---S---R}_5 \\ \parallel \\ \text{O} \end{array}$, $\begin{array}{c} \text{O} \\ \parallel \\ \text{---S---R}_5 \end{array}$, $\begin{array}{c} \text{O} \\ \parallel \\ \text{---C---NH---R}_5 \end{array}$, respectively.

[0135] "Cycloalkyl" represents a non-aromatic, saturated, cyclic hydrocarbon group containing the specified number of carbon atoms. For example, the term "(C₃-C₆) cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring with 3-6 ring carbon atoms. Exemplary "(C₃-C₆) cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0136] The term "aryl" represents a group or moiety containing an aromatic monocyclic or bicyclic hydrocarbon atom group, which contains 6 to 12 carbon ring atoms and has at least one aromatic ring. Examples of "aryl" are phenyl, naphthyl, indenyl and indanyl. Generally, in the compounds of the present disclosure, the aryl group is a phenyl group.

[0137] The term "heteroalicyclic group" as used herein, unless otherwise specified, represents an unsubstituted or substituted stable 4- to 8-membered non-aromatic monocyclic saturated ring system, which consists of carbon atoms and 1 to 3 heteroatoms selected from N, O, or S, wherein, N and S heteroatoms can be arbitrarily oxidized, and N heteroatoms can also be arbitrarily quaternized. Examples of such heterocycles include, but are not limited to, azetidiny, oxetanyl, thietanyl, pyrrolidiny, pyrroliny, pyrazolidiny, pyrazoliny,

imidazolidinyl, imidazoliny, oxazoliny, thiazoliny, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, 1,3-dioxolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, 1,4-oxathiolanyl, 1,4-oxathianyl, 1,4-dithianyl, morpholiny, and thiomorpholiny.

[0138] The term "heteroaryl" as used herein represents a group or moiety containing an aromatic monocyclic or bicyclic group (which contains 5 to 10 ring atoms), which includes 1 to 3 heteroatoms independently selected from nitrogen, oxygen and sulfur. The term also includes bicyclic heterocyclic aryl, which contains an aryl ring moiety fused to a heterocycloalkyl ring moiety, or a heteroaryl ring moiety fused to a cycloalkyl ring moiety. Unless otherwise specified, it represents an unsubstituted or substituted stable 5- or 6-membered monocyclic aromatic ring system, and can also represents an unsubstituted or substituted benzene fused heteroaromatic ring system or bicyclic heteroaromatic ring system with 9 or 10 ring atoms, which are composed of carbon atoms and 1 to 3 heteroatoms selected from N, O, or S, where N, S heteroatoms can be oxidized, and N heteroatoms can also be quaternized. Heteroaryl groups can be connected to any heteroatom or carbon atom to form a stable structure. Illustrative examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridyl, oxo-pyridyl (pyridyl-N-oxide), pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuranyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, benzothienyl, indazinyl, indolyl, isoindolyl, indoliny, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzothiazolyl, benzoisothiazolyl, dihydrobenzisothiazolyl, indazolyl, imidazopyridyl, pyrazolopyridyl, benzotriazolyl, triazolopyridyl, purinyl, quinoliny, tetrahydroquinoliny, isoquinoliny, tetrahydroisoquinoliny, quinoxaliny, cinnoliny, phthalazinyl, quinazoliny, 1,5-naphthyridiny, 1,6-naphthyridiny, 1,7-naphthyridiny, 1,8-naphthyridiny, and pteridyl.

[0139] The term "carbonyl" refers to the -C(O)- group. The terms "halogen" and "halo" represent chlorine, fluorine, bromine or iodine substituents. "Oxo" represents the oxygen moiety with double bond; for example, it forms a carbonyl moiety (C=O) when it is directly attached to a carbon atom. "Hydroxy" is intended to mean the -OH group. As used herein, the term "cyano" refers to the group -CN.

[0140] The term "each independently" means that when more than one substituents are selected from a number of possible substituents, those substituents may be the same or different.

[0141] It is clear that the compounds of formula I, or isomers, crystal forms or prodrugs and pharmaceutically acceptable salts thereof may exist in solvated and unsolvated forms. For example, the solvated form can be a hydrate form. The present disclosure includes all these solvated forms and unsolvated forms.

[0142] The compounds of the present disclosure may have asymmetric carbon atoms. According to their physical and chemical differences, such diastereomeric mixtures can be separated into single diastereomers by known, technically mature methods, such as chromatography or fractional crystallization. The separation of enantiomers can be carried out by first reacting with a suitable optically active compound, converting the

enantiomeric mixture into a diastereomeric mixture, separating the diastereoisomers, and then the single diastereomers are transformed (hydrolyzed) into the corresponding pure enantiomers. All such isomers, including diastereomeric mixtures and pure enantiomers, are considered as part of the invention.

[0143] The compound of the present disclosure as an active ingredient, and the method of preparing the same, are both included in the present disclosure. Moreover, the crystalline form of some of the compounds may exist as polymorphs, and such forms may also be included in the present disclosure. Additionally, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also included within the scope of the disclosure.

[0144] The compounds of the disclosure may be used in the free form for treatment or, when appropriate, in the form of a pharmaceutically acceptable salt or other derivative for treatment. As used herein, the term "pharmaceutically acceptable salt" refers to organic and inorganic salts of the compounds of the present disclosure which are suitable for use in human and lower animals without undue toxicity, irritation, allergic response, etc., and have reasonable benefit/risk ratio. Pharmaceutically acceptable salts of amines, carboxylic acids, phosphonates, and other types of compounds are well known in the art. The salt can be formed by reacting a compound of the disclosure with a suitable free base or acid, including, but not limited to, salts with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, malonic acid. Or the salts may be obtained by methods well known in the art, such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, besylate, benzoate, bisulfate, borate, butanoate, camphorate, camphorsulfonate, citrate, digluconate, lauryl sulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerol phosphate, glyconate, hemisulfate, hexanoate, hydroiodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, mesylate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectate, persulphate, per-3-phenylpropionate, phosphate, picrate, propionate, stearate, sulfate, thiocyanate, p-toluenesulfonate, undecanoate, and the like. Representative alkali or alkaline earth metal salts include salts of sodium, lithium, potassium, calcium, magnesium, and the like. Other pharmaceutically acceptable salts include suitable non-toxic salts of ammonium, quaternary ammonium, and amine cations formed from halides, hydroxides, carboxylates, sulfates, phosphates, nitrates, lower alkyl sulfonates and aryl sulfonates.

[0145] Further, the term "prodrug" as used herein means that a compound can be converted into the compound of the present disclosure represented by formula (I) *in vivo*. Such transformation is affected by hydrolysis of the prodrug in the blood or enzymatic conversion to the parent compound in the blood or tissue.

[0146] Pharmaceutical compositions of this disclosure comprise the compound of formula (I) described herein or a pharmaceutically acceptable salt thereof; an additional agent selected from a kinase inhibitory agent (small molecule, polypeptide, antibody, etc.), an immunosuppressant, an anticancer agent, an anti-viral agent, anti-inflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

[0147] The compounds of the present disclosure may be used alone or in combination with one or more of other compounds of the present disclosure or with one or more of other agents. When administered in combination, the therapeutic agents can be formulated for simultaneous or sequential administration at different times, or the therapeutic agents can be administered as a single composition. By "combination therapy", it refers to the use of a compound of the disclosure in combination with another agent in the form of co-administration of each agent or sequential administration of each agent, in either case, for the purpose of achieving the optimal results. Co-administration includes dosage form for simultaneous delivery, as well as separate dosage forms for each compound. Thus, administration of the compounds of the disclosure can be combined with other therapies known in the art, for example, radiation therapy or cytostatic agents, cytotoxic agents, other anticancer agents, and the like as used in the treatment of cancer, in order to improve the symptoms of cancer. The administration sequence is not limited in the present disclosure. The compounds of the present disclosure may be administered before, simultaneously, or after other anticancer or cytotoxic agents.

[0148] To prepare the pharmaceutical ingredient of the present disclosure, one or more compounds of formula (I) or salts thereof as an active ingredient can be intimately mixed with a pharmaceutical carrier, which is carried out according to a conventional pharmaceutical formulation technique. The carrier can be used in a wide variety of forms depending on the form of preparation which is designed for different administration modes (for example, oral or parenteral administration). Suitable pharmaceutically acceptable carriers are well known in the art. A description of some of these pharmaceutically acceptable carriers can be found in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

[0149] The pharmaceutical composition of the present disclosure may have the following forms, for example, those suitable for oral administration, such as tablets, capsules, pills, powders, sustained release forms, solutions or suspensions; those for parenteral injections such as clear solutions, suspensions, emulsion; or those for topical use such as ointments, creams; or as a suppository for rectal administration. The pharmaceutical ingredients may also be presented in unit dosage form for single administration in a precise dosage. The pharmaceutical ingredient will include a conventional pharmaceutical carrier or excipient and a compound as an active ingredient prepared according to the present disclosure, and may also include other medical or pharmaceutical preparations, carriers, adjuvants, and the like.

[0150] Therapeutic compounds can also be administered to mammals other than humans. The drug dosage for a mammal will depend on the species of the animal and its disease condition or its disordered condition. The therapeutic compound can be administered to the animal in the form of a capsule, a bolus, or a tablet or liquid. The therapeutic compound can also be introduced into the animal by injection or infusion. These drug forms are prepared in a traditional manner complying with standard veterinary practice. As an alternative, the therapeutic compounds can be mixed with the animal feed and fed to the animal, so that the concentrated feed additive or premix can be prepared by mixing ordinary animal feed.

[0151] It is a further object of the present disclosure to provide a method for treating cancer in a subject in need thereof, comprising a method for administering to the subject a therapeutically effective amount of a composition containing the compound of the present disclosure.

[0152] The present disclosure also includes the use of the compound of the present disclosure or a pharmaceutically acceptable derivative thereof, in the manufacture of medicaments for treating RIP1 related diseases, including ocular fundus disease, xerophthalmia, psoriasis, leucoderma, dermatitis, alopecia areata, rheumatoid arthritis, colitis, multiple sclerosis, systemic lupus erythematosus, Crohn's disease, atherosclerosis, pulmonary fibrosis, liver fibrosis, myelofibrosis, non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, ovarian cancer, cervical cancer, colorectal cancer, melanoma, endometrial cancer, prostate cancer, bladder cancer, leukemia, gastric cancer, liver cancer, gastrointestinal stromal tumor, thyroid cancer, chronic myeloid leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma, nasopharyngeal cancer, esophageal cancer, brain tumor, B-cell and T-cell lymphoma, lymphoma, multiple myeloma, biliary cancer and sarcoma, cholangiocarcinoma, inflammatory bowel disease, ulcerative colitis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, spondyloarthritis, gout, SoJIA, Sjogren's syndrome, systemic scleroderma, antiphospholipid syndrome, vasculitis, osteoarthritis, non-alcoholic steatohepatitis, alcoholic steatohepatitis, autoimmune hepatitis, autoimmune hepatobiliary disease, primary sclerosing cholangitis, nephritis, celiac disease, autoimmune ITP, transplant rejection, ischemia-reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial infarction, Huntington's disease, Alzheimer's disease, Parkinson's disease, allergic diseases, asthma, atopic dermatitis, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converzyme-related fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor related periodic syndrome and periodontitis.

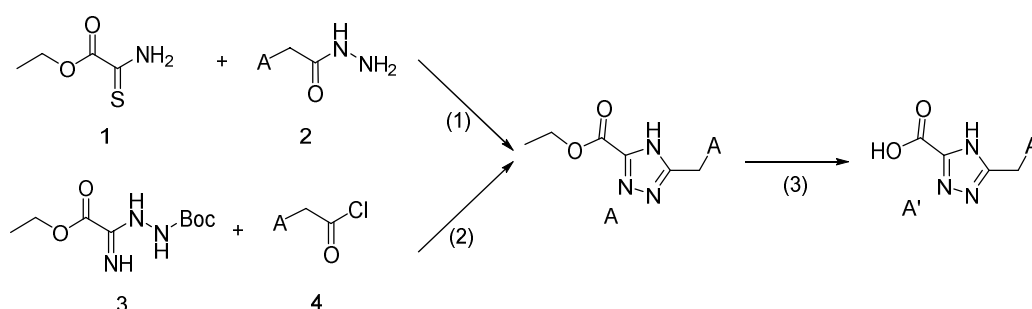
[0153] The present disclosure also provides a method for preparing the corresponding compounds. A variety of synthetic methods can be used to prepare the compounds described herein, including the method involved in the following examples. The compounds of the present disclosure, or pharmaceutically acceptable salts, isomers or hydrates thereof, can be synthesized using the following methods, synthetic methods known in the field of organic chemical synthesis, or variations of these methods understood by those skilled in the art. Preferred methods include, but are not limited to, the following methods.

[0154] In order to make the objectives, technical solutions and advantages of the present disclosure more clear, the present disclosure will be further described in detail below in conjunction with specific examples. It should be understood that the specific examples described here are only used to explain the present disclosure and are not intended to limit the present disclosure. If no specific technology or conditions are indicated in examples, the technology or conditions described in the literature in the art or the product specification shall be followed. If reagents or instruments used do not indicate manufacturers, they are all conventional products that are

commercially available. The term "and/or" as used herein includes any and all combinations of one or more related listed items. The Example provided below can better illustrate the present disclosure, unless otherwise specified, all temperatures are in °C. The names of some compounds in this disclosure are generated by Chemdraw and translated into Chinese.

Preparation of some intermediates

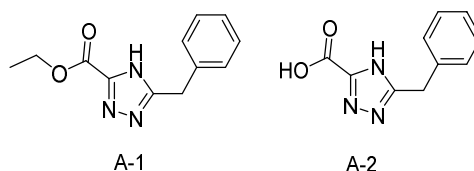
[0155] I. Preparation of A series intermediates



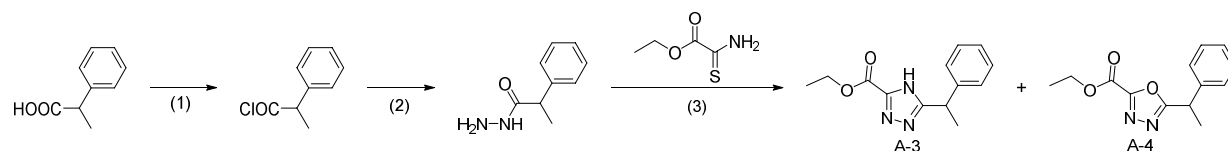
[0156] A series intermediates may include A and A', where A' can be further formed by hydrolysis of A. A can be prepared by the above two routes. In Route 2, Intermediate A is generated by the reaction of compound 3 and acid chloride 4 in a pyridine solvent at 110 degrees, and in Route 1, Intermediate A is synthesized by refluxing compound 1 and hydrazide 2.

[0157] **Synthesis of Intermediate A-1** (ethyl 5-benzyl-4H-1,2,4-triazole-3-carboxylate) and **A-2** (5-benzyl-4H-1,2,4-triazole-3-carboxylic acid)

[0158] The synthetic method refers to WO2014125444A1.



[0159] **Synthesis of Intermediate A-3** (ethyl 5-(1-phenylethyl)-4H-1,2,4-triazole-3-carboxylate) and **A-4** (ethyl 5-(1-phenylethyl)-1,3,4-oxadiazole-2-carboxylate)



[0160] Step 1: Synthesis of 2-phenylpropionyl chloride

[0161] 2-phenylpropionic acid (1g, 6.66mmol) was dissolved in thionyl chloride (10mL), and reacted at 85°C for 1 hour. The reaction solution was diluted with toluene and spin dried. The crude product was used directly in the next step.

[0162] Step 2: Synthesis of 2-phenylpropionyl hydrazide

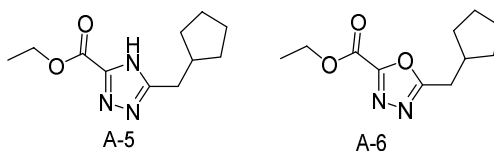
[0163] 2-phenylpropionyl chloride was dissolved in methanol (20mL), and reacted at 25°C for 2 hours. Hydrazine hydrate (10mL) was then added, and reacted at 80°C for 16 hours. The reaction solution was cooled,

extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, to afford 900mg of colorless oil. MS: 165 [M+H]⁺

[0164] Step 3: Synthesis of A-3 and A-4

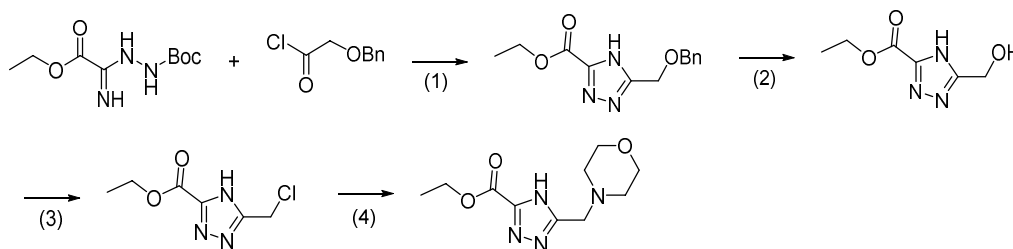
[0165] 2-phenylpropionyl hydrazide (900mg, 5.5mmol) was dissolved in ethanol (15mL), ethyl thiooxamate (805mg, 6mmol) was added, and reacted at 70°C for 3 hours. The reaction solution was cooled and filtered to afford 800mg of white solid. Xylene (20mL) was added to the solid, and reacted at 160°C under refluxing to remove water for 24 hours. The reaction solution was cooled and concentrated, the crude product was rinsed with mixture of petroleum ether/ethyl acetate (10:1), to afford 300mg of ethyl 5-(1-phenylethyl)-4H-1,2,4-triazol-3-carboxylate as white solid. MS: 246 [M+H]⁺. The mother liquor was evaporated to dryness to afford 200mg of ethyl 5-(1-phenylethyl)-1,3,4-oxadiazol-2-carboxylate as yellow solid. MS: 247 [M+H]⁺.

[0166] Synthesis of Intermediate A-5 (ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate) and A-6 (ethyl 5-(cyclopentylmethyl)-1,3,4-oxadiazol-2-carboxylate)



[0167] The preparation was carried out in a similar manner to intermediate A-3 and A-4 (step 2 to step 3), except that in step 2, cyclopentylacetyl chloride was used in place of 2-phenylpropionyl chloride.

[0168] Synthesis of Intermediate A-7 ethyl 5-(morpholinomethyl)-4H-1,2,4-triazole-3-carboxylate



[0169] Step 1: Tert-butyl 2-(2-ethoxy-1-imino-2-oxoethyl)hydrazine-1-carboxylate and 2-(benzyloxy)acetyl chloride in pyridine were reacted at 110°C to afford ethyl 5-((benzyloxy)methyl)-4H-1,2,4-triazol-3-carboxylate (see M. V. Chudinov et al./ Bioorg. Med. Chem. Lett. 26(2016) 3223-3225 for detailed operations)

[0170] Step 2: Synthesis of Ethyl 5-(hydroxymethyl)-4H-1,2,4-triazol-3-carboxylate

[0171] Ethyl 5-((benzyloxy)methyl)-4H-1,2,4-triazole-3-carboxylate (250mg, 1mmol) was dissolved in a mixture of ethanol and ethyl acetate (2:1, 3mL), palladium on carbon (10%, 25mg) was added, and was reacted for 5 hours under hydrogen atmosphere. The reaction was filtered through diatomaceous earth and the filtrate was evaporated to get 150mg of yellow solid. MS: 172 [M+H]⁺

[0172] Step 3: Synthesis of ethyl 5-(chloromethyl)-4H-1,2,4-triazole-3-carboxylate

[0173] Ethyl 5-(hydroxymethyl)-4H-1,2,4-triazole-3-carboxylate (150mg, 0.9mmol) was dissolved in thionyl chloride (2mL), and reacted at 85°C for 7 hours. The reaction was cooled and diluted with toluene, and the

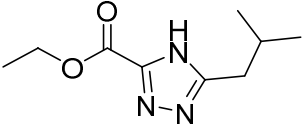
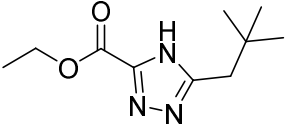
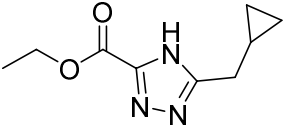
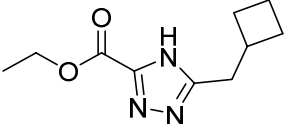
resultant was spin dried to afford 160mg of yellow oil. MS: 190 [M+H]⁺

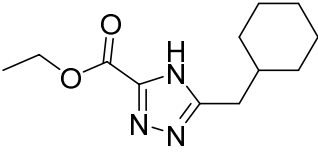
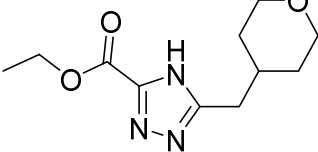
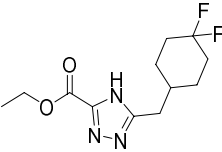
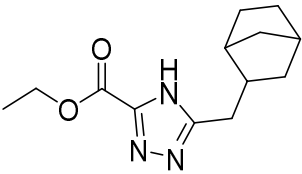
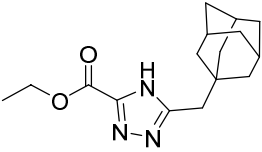
[0174] Step 4: Synthesis of ethyl 5-(morpholinomethyl)-4H-1,2,4-triazole-3-carboxylate

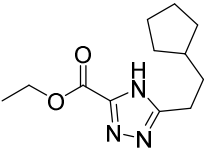
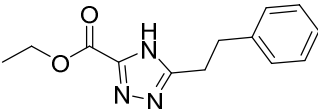
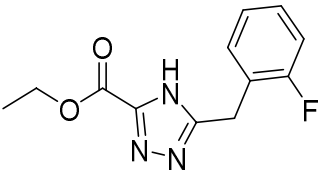
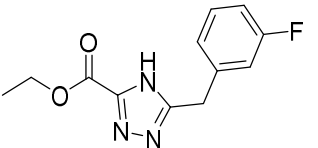
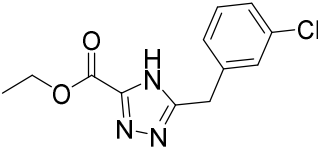
[0175] Ethyl 5-(chloromethyl)-4H-1,2,4-triazole-3-carboxylate (160mg, 0.9mmol) was dissolved in tetrahydrofuran (2mL), diisopropylethylamine (220mg, 1.7mmol) and morpholine (150mg, 1.7mmol) were added, and reacted at 25°C for 5 hours. The reaction solution was evaporated to dryness, and purified by column chromatography to get 180mg of yellow solid. MS: 241 [M+H]⁺

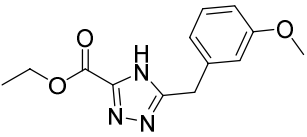
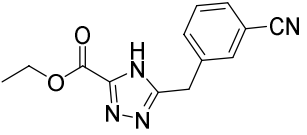
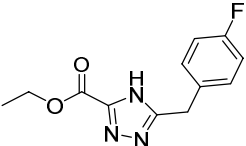
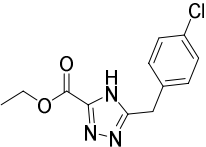
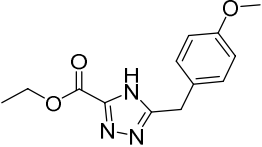
[0176] Table 1 below shows the structure and synthesis of intermediates A-8 to A-28 and mass spectral data thereof, wherein intermediates A-8 to A-12 were prepared in a similar manner to intermediate A-3, without collecting the oxadiazole by-product, and the synthesis of intermediates A-13 and A-28 were carried out in a similar manner to the first step of synthesis of intermediate A-7.

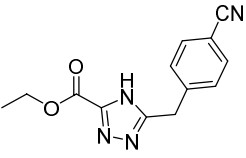
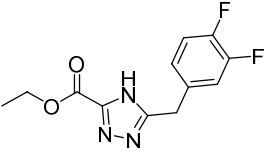
[0177] Table 1. Structures and synthesis of intermediates A-8 to A-28 and mass spectral data thereof

Intermediate	Structure	Name	Synthesis	MS: [M+H] ⁺
A-8		Ethyl 5-isobutyl-4H-1,2,4-triazol-5-carboxylate	The operation was the same as the steps 2 to 3 of the preparation of intermediate A-3, but 3-methylbutyryl chloride was used in place of 2-phenylpropionyl chloride	198
A-9		Ethyl 5-neopentyl-4H-1,2,4-triazol-5-carboxylate	The operation was the same as the steps 2 to 3 of the preparation of intermediate A-3, but 3,3-dimethylbutyryl chloride was used in place of 2-phenylpropionyl chloride	212
A-10		Ethyl 5-(cyclopropylmethyl)-4H-1,2,4-triazol-5-carboxylate	The operation was the same as the steps 1 to 3 of the preparation of intermediate A-3, but 2-cyclopropylacetic acid was used in place of 2-phenylpropionic acid	196
A-11		Ethyl 5-(cyclobutylmethyl)-4H-1,2,4-triazol-5-carboxylate	The operation was the same as the steps 1 to 3 of the preparation of intermediate A-3, but 2-cyclobutylacetic	210

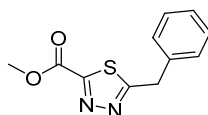
			acid was used in place of 2-phenylpropionic acid	
A-12		Ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the steps 1 to 3 of the preparation of intermediate A-3, but cyclohexylacetic acid was used in place of 2-phenylpropionic acid	238
A-13		Ethyl 5-((tetrahydro-2H-pyran-4-yl)methyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(tetrahydro-2H-pyran-4-yl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	240
A-14		Ethyl 5-((4,4-difluorocyclohexyl)methyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(4,4-difluorocyclohexyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	274
A-15		Ethyl 5-(bicyclo[2.2.1]heptan-2-ylmethyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(bicyclo[2.2.1]heptan-2-yl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	250
A-16		Ethyl 5-(adamantan-1-yl)methyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(adamantan-1-	290

			yl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	
A-17		Ethyl 5-(2-cyclopentylethyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 3-cyclopentylpropionyl chloride was used in place of 2-(benzyloxy)acetyl chloride	238
A-18		Ethyl 5-(phenethyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 3-phenylpropionyl chloride was used in place of 2-(benzyloxy)acetyl chloride	246
A-19		Ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(2-fluorophenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	250
A-20		Ethyl 5-(3-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(3-fluorophenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	250
A-21		Ethyl 5-(3-chlorobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(3-	266

			chlorophenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	
A-22		Ethyl 5-(3-methoxybenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(3-methoxyphenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	262
A-23		Ethyl 5-(3-cyanobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(3-cyanophenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	257
A-24		Ethyl 5-(4-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(4-fluorophenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	250
A-25		Ethyl 5-(4-chlorobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(4-chlorophenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	266
A-26		Ethyl 5-(4-methoxybenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate	262

			A-7, but 2-(4-methoxyphenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	
A-27		Ethyl 5-(4-cyanobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(4-cyanophenyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	257
A-28		Ethyl 5-(3,4-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate	The operation was the same as the step 1 of the preparation of intermediate A-7, but 2-(3,4-difluorobenzyl)acetyl chloride was used in place of 2-(benzyloxy)acetyl chloride	268

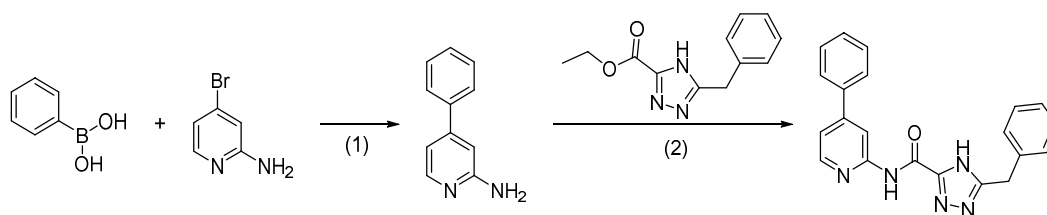
[0178] Synthesis of Intermediate A-29 methyl 5-benzyl-1,3,4-thiadiazole-2-carboxylate



[0179] Phenylacetylhydrazine (5g, 33.3mmol) was dissolved in anhydrous dichloromethane (100mL), triethylamine (6.74g, 66.7mmol) was added, and under argon protection, methyl oxalyl chloride (4.1g, 33.5mmol) was added dropwise at 0°C. The reaction solution was slowly warmed to 25°C. After 16 hours reaction, the solvent was evaporated to dryness, rinsed with mixture of petroleum ether/ethyl acetate, filtered, and the filter cake was re-dissolved in toluene (100mL), Lawson's reagent (26.9g, 66.5mmol) was added, heated to 110°C and reacted for 6 hours. The reaction was cooled and diluted with ethyl acetate, washed with water, saturated aqueous solution of sodium bicarbonate and brine, the organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and purified by column chromatography to get 4g product. MS: 235 [M+H]⁺.

Examples

[0180] Example 1: 5-benzyl-N-(4-phenylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0181] Step 1: Synthesis of 4-phenylpyridin-2-amine

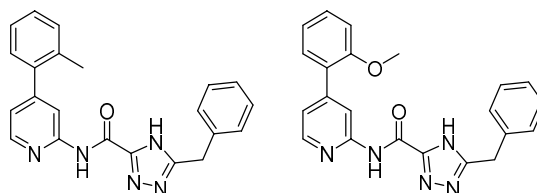
[0182] 4-Bromopyridin-2-amine (173mg, 1mmol), phenylboronic acid (146mg, 1.2mmol), Pd(dppf)Cl₂ (73mg, 0.1mmol) and sodium carbonate (160mg, 1.5mmol) were placed in a mixture of dioxane (4mL) and water (0.8mL), which was reacted at 100°C for 16 hours under argon protection. After cooling, the reaction solution was evaporated to dryness and subjected to column chromatography to afford 120mg of brown solid. MS: 171 [M+H]⁺.

[0183] Step 2: Synthesis of 5-benzyl-N-(4-phenylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0184] 4-Phenylpyridin-2-amine (120mg, 0.7mmol) was placed in dry xylene (3mL), to which trimethyl aluminum (3M, 0.7mL) was slowly added under argon protection, and reacted at 25°C for 1 hour. Then, intermediate 1 (197mg, 0.9mmol) was added, and reacted at 100°C for 16 hours. The reaction solution was cooled and diluted with methanol, evaporated to dryness and subjected to column chromatography and preparative liquid chromatography to afford 50mg of white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.90 (s, 1H), 8.49 – 8.38 (m, 2H), 7.82 – 7.71 (m, 2H), 7.62 – 7.45 (m, 4H), 7.40 – 7.30 (m, 4H), 7.30 – 7.18 (m, 1H), 4.18 (s, 2H). MS: 356 [M+H]⁺.

[0185] Example 2: 5-benzyl-N-(4-(*o*-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0186] The preparation was carried out in a similar manner to Example 1, except that in step 1, *o*-methylphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.86 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.51 – 7.34 (m, 3H), 7.34 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 7.21 (d, *J* = 5.1 Hz, 1H), 4.19 (s, 2H), 2.28 (s, 3H). MS: 370 [M+H]⁺.



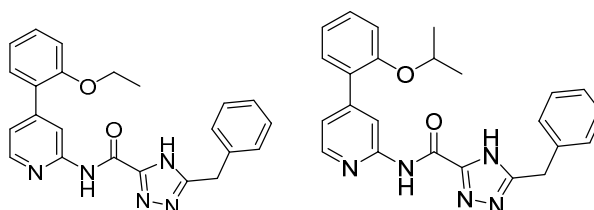
Example 2 Example 3

[0187] Example 3: 5-benzyl-N-(4-(2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0188] The preparation was carried out in a similar manner to Example 1, except that in step 1, *o*-methoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.82 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.33 – 8.17 (m, 1H), 7.60 – 6.91 (m, 10H), 4.18 (s, 2H), 3.81 (s, 3H). MS: 386 [M+H]⁺.

[0189] Example 4: 5-benzyl-N-(4-(2-ethoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0190] The preparation was carried out in a similar manner to Example 1, except that in step 1, o-ethoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.80 (s, 1H), 8.62 – 8.40 (m, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 7.60 – 6.94 (m, 10H), 4.18 (s, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 1.32 (t, *J* = 6.9 Hz, 3H). MS: 400 [M+H]⁺.



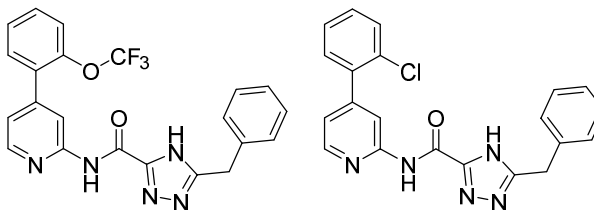
Example 4 Example 5

[0191] Example 5: 5-benzyl-N-(4-(2-isopropoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0192] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-isopropoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.74 (s, 1H), 8.56 – 8.26 (m, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.29 (m, 5H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.09 – 7.02 (m, 1H), 4.69 (p, *J* = 6.0 Hz, 1H), 4.19 (s, 2H), 1.27 (d, *J* = 6.0 Hz, 6H). MS: 414 [M+H]⁺.

[0193] Example 6: 5-benzyl-N-(4-(2-(trifluoromethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0194] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-(trifluoromethoxy)phenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 9.96 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.30 (d, *J* = 1.5 Hz, 1H), 7.70-7.51 (m, 4H), 7.41-7.18 (m, 6H), 4.18 (s, 2H). MS: 440 [M+H]⁺.



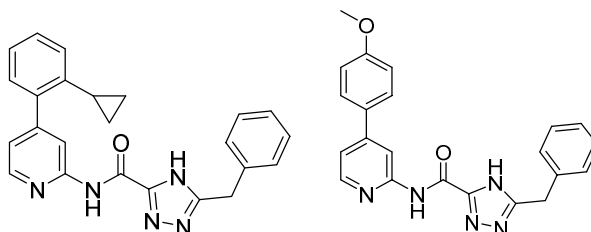
Example 6 Example 7

[0195] Example 7: 5-benzyl-N-(4-(2-chlorophenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0196] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-chlorophenylboronic acid was used in place of phenylboronic acid. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.95 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.23 (d, *J* = 1.5 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.56 – 7.46 (m, 3H), 7.39 – 7.30 (m, 4H), 7.30 – 7.21 (m, 2H), 4.18 (s, 2H). MS: 390 [M+H]⁺.

[0197] Example 8: 5-benzyl-N-(4-(2-cyclopropylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0198] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-cyclopropylphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.87 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.27 (s, 1H), 7.42 – 7.30 (m, 5H), 7.30 – 7.20 (m, 4H), 7.10 – 7.01 (m, 1H), 4.18 (s, 2H), 1.91 – 1.77 (m, 1H), 0.95 – 0.81 (m, 2H), 0.79 – 0.63 (m, 2H). MS: 396 [M+H]⁺.



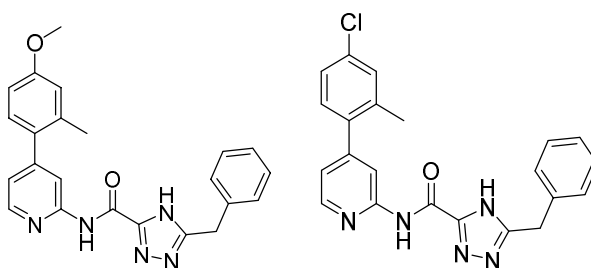
Example 8 Example 9

[0199] Example 9: 5-benzyl-N-(4-(4-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0200] The preparation was carried out in a similar manner to Example 1, except that in step 1, 4-methoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.82 (s, 1H), 8.48 – 8.29 (m, 2H), 7.80 – 7.66 (m, 2H), 7.47 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.42 – 7.18 (m, 5H), 7.18 – 6.98 (m, 2H), 4.18 (s, 2H), 3.83 (s, 3H). MS: 386 [M+H]⁺.

[0201] Example 10: 5-benzyl-N-(4-(4-methoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0202] The preparation was carried out in a similar manner to Example 1, except that in step 1, 4-methoxy-2-methylphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.85 (s, 1H), 8.38 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.47 – 7.02 (m, 7H), 7.04 – 6.76 (m, 2H), 4.18 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS: 400 [M+H]⁺.



Example 10 Example 11

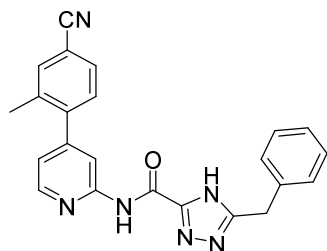
[0203] Example 11: 5-benzyl-N-(4-(4-chloro-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0204] The preparation was carried out in a similar manner to Example 1, except that in step 1, 4-chloro-2-methylphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.93 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.43-7.11 (m, 8H), 4.18 (s,

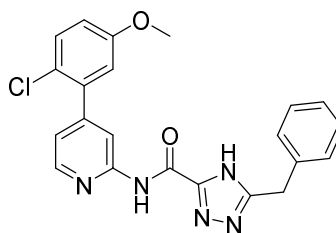
2H), 2.28 (s, 3H). MS: 404 [M+H]⁺.

[0205] Example 12: 5-benzyl-N-(4-(4-cyano-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0206] The preparation was carried out in a similar manner to Example 1, except that in step 1, 4-cyano-2-methylphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 10.00 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.89 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.15 (m, 2H), 4.18 (s, 2H), 2.30 (s, 3H). MS: 395 [M+H]⁺.



Example 12



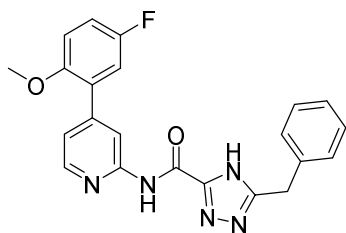
Example 13

[0207] Example 13: Synthesis of 5-benzyl-N-(4-(2-chloro-5-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

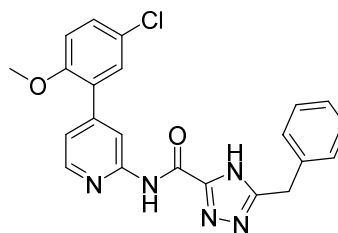
[0208] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-chloro-5-methoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.91 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.23 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.30 (m, 4H), 7.30 – 7.19 (m, 2H), 7.08 (dd, *J* = 8.8, 3.1 Hz, 1H), 7.03 (d, *J* = 3.0 Hz, 1H), 4.18 (s, 2H), 3.81 (s, 3H). MS: 420 [M+H]⁺.

[0209] Example 14: 5-benzyl-N-(4-(5-fluoro-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0210] The preparation was carried out in a similar manner to Example 1, except that in step 1, 5-fluoro-2-methoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.87 (s, 1H), 8.40 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 7.51 – 7.03 (m, 9H), 4.18 (s, 2H), 3.80 (s, 3H). MS: 404 [M+H]⁺.



Example 14



Example 15

[0211] Example 15: 5-benzyl-N-(4-(5-chloro-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

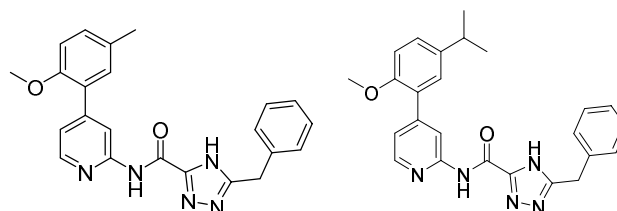
[0212] The preparation was carried out in a similar manner to Example 1, except that in step 1, 5-chloro-2-methoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.86 (s, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 8.28 (s, 1H), 7.50 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.43 (d, *J* = 2.7 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.29 – 7.15 (m, 2H), 4.18 (s, 2H), 3.81 (s, 3H). MS: 420 [M+H]⁺.

5

[0213] Example 16: 5-benzyl-N-(4-(2-methoxy-5-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0214] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-methoxy-5-methylphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.79 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.28 (s, 1H), 7.38 – 7.29 (m, 5H), 7.29 – 7.21 (m, 2H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.18 (s, 2H), 3.77 (s, 3H), 2.31 (s, 3H). MS: 400 [M+H]⁺.

10



Example 16

Example 17

[0215] Example 17: 5-benzyl-N-(4-(5-isopropyl-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

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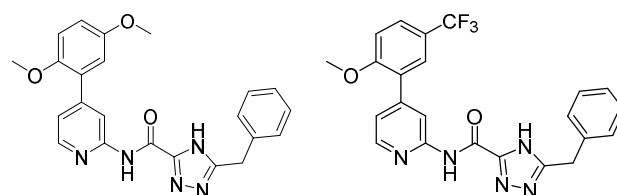
[0216] The preparation was carried out in a similar manner to Example 1, except that in step 1, 5-isopropyl-2-methoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.84 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.29 (d, *J* = 1.5 Hz, 1H), 7.41 – 7.19 (m, 8H), 7.09 (d, *J* = 8.5 Hz, 1H), 4.18 (s, 2H), 3.78 (s, 3H), 2.91 (p, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H). MS: 428 [M+H]⁺.

20

[0217] Example 18: 5-benzyl-N-(4-(2,5-dimethoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0218] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2,5-dimethoxyphenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.83 (s, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.29 (d, *J* = 1.5 Hz, 1H), 7.45 – 7.29 (m, 5H), 7.29 – 7.22 (m, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.02 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.95 (d, *J* = 3.1 Hz, 1H), 4.18 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H). MS: 416 [M+H]⁺.

25



Example 18

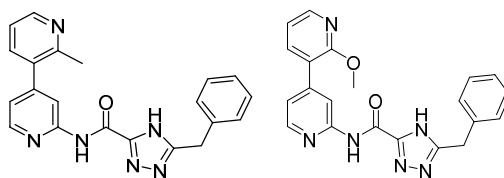
Example 19

[0219] Example 19: 5-benzyl-N-(4-(2-methoxy-5-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0220] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-methoxy-5-(trifluoromethyl)phenylboronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.86 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H), 7.83 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.46 – 7.18 (m, 7H), 4.19 (s, 2H), 3.90 (s, 3H). MS: 454 [M+H]⁺.

[0221] Example 20: 5-benzyl-N-(2-methyl-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0222] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.99 (s, 1H), 8.57 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.48 (d, *J* = 5.1 Hz, 1H), 8.18 (d, *J* = 1.5 Hz, 1H), 7.73 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 – 7.32 (m, 5H), 7.32 – 7.24 (m, 2H), 4.21 (s, 2H), 2.50 (s, 3H). MS: 371 [M+H]⁺.



Example 20

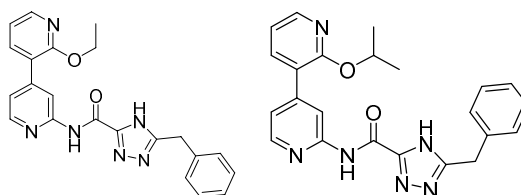
Example 21

[0223] Example 21: 5-benzyl-N-(2-methoxy-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0224] The preparation was carried out in a similar manner to Example 1, except that in step 1, (2-methoxypyridin-3-yl)boronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.88 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.37 (d, *J* = 1.5 Hz, 1H), 8.28 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.88 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.40 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 7.17 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.18 (s, 2H), 3.92 (s, 3H). MS: 387 [M+H]⁺.

[0225] Example 22: 5-benzyl-N-(2-ethoxy-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0226] The preparation was carried out in a similar manner to Example 1, except that in step 1, (2-ethoxypyridin-3-yl)boronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.83 (s, 1H), 8.48 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.26 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.90 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.42 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.39 – 7.30 (m, 4H), 7.30 – 7.21 (m, 1H), 7.15 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 4.18 (s, 2H), 1.34 (t, *J* = 7.0 Hz, 3H). MS: 401 [M+H]⁺.



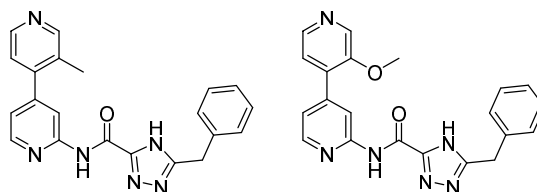
Example 22 Example 23

[0227] Example 23: 5-benzyl-N-(2-isopropoxy-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0228] The preparation was carried out in a similar manner to Example 1, except that in step 1, (2-isopropoxy-4-pyridin-3-yl)boronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.81 (s, 1H), 8.52 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.25 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.89 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.40 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.29 – 7.21 (m, 1H), 7.12 (dd, *J* = 7.4, 4.9 Hz, 1H), 5.39 (p, *J* = 6.2 Hz, 1H), 4.18 (s, 2H), 1.33 (d, *J* = 6.2 Hz, 6H). MS: 415 [M+H]⁺.

[0229] Example 24: 5-benzyl-N-(3'-methyl-[4,4'-bipyridin]-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0230] The preparation was carried out in a similar manner to Example 1, except that in step 1, (3-methylpyridin-4-yl)boronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.97 (s, 1H), 8.58 (s, 1H), 8.53 (d, *J* = 5.0 Hz, 1H), 8.49 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.39 – 7.30 (m, 5H), 7.30 – 7.22 (m, 2H), 4.18 (s, 2H), 2.28 (s, 3H). MS: 371 [M+H]⁺.



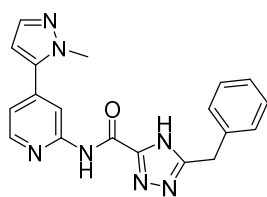
Example 24 Example 25

[0231] Example 25: 5-benzyl-N-(3'-methoxy-[4,4'-bipyridin]-2-yl)-4H-1,2,4-triazole-3-carboxamide

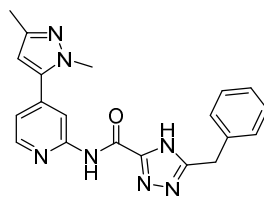
[0232] The preparation was carried out in a similar manner to Example 1, except that in step 1, (3-methoxypyridin-4-yl)boronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.91 (s, 1H), 8.56 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.38 – 8.33 (m, 2H), 7.44 (d, *J* = 4.8 Hz, 1H), 7.39 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.37 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 4.18 (s, 2H), 3.94 (s, 3H). MS: 387 [M+H]⁺.

[0233] Example 26: 5-benzyl-N-(4-(1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0234] The preparation was carried out in a similar manner to Example 1, except that in step 1, 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 10.00 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.28 (d, *J* = 1.4 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.40 (dd, *J* = 5.2, 1.5 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 6.63 (d, *J* = 1.9 Hz, 1H), 4.18 (s, 2H), 3.96 (s, 3H). MS: 360 [M+H]⁺.



Example 26



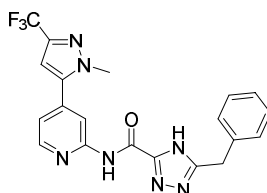
Example 27

[0235] Example 27: 5-benzyl-N-(4-(1,3-dimethyl-1H-pyrazol-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

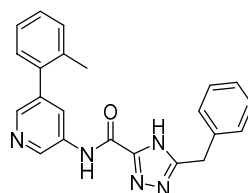
[0236] The preparation was carried out in a similar manner to Example 1, except that in step 1, 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.97 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.25 (s, 1H), 7.42 – 7.29 (m, 5H), 7.29 – 7.20 (m, 1H), 6.40 (s, 1H), 4.18 (s, 2H), 3.87 (s, 3H), 2.19 (s, 3H). MS: 374 [M+H]⁺.

[0237] Example 28: 5-benzyl-N-(4-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0238] The preparation was carried out in a similar manner to Example 1, except that in step 1, 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.08 (s, 1H), 8.65 – 8.41 (m, 1H), 8.31 (d, *J* = 3.7 Hz, 1H), 7.63 – 7.41 (m, 1H), 7.41 – 7.19 (m, 5H), 7.15 (d, *J* = 3.8 Hz, 1H), 4.19 (s, 2H), 4.04 (s, 3H). MS: 428 [M+H]⁺.



Example 28



Example 29

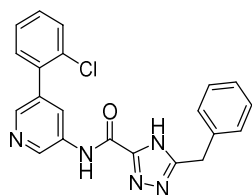
[0239] Example 29: 5-benzyl-N-(5-(o-methylphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

[0240] The preparation was carried out in a similar manner to Example 1, except that in step 1, o-methylphenylboronic acid was used in place of phenylboronic acid, and 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 10.80 (s, 1H), 9.02 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.27 – 8.11 (m, 1H), 7.57 – 7.12 (m, 9H), 4.17 (s, 2H), 2.27 (s, 3H). MS: 370 [M+H]⁺.

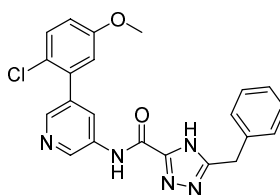
[0241] Example 30: 5-benzyl-N-(5-(2-chlorophenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

[0242] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-chlorophenylboronic acid was used in place of phenylboronic acid, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.84 (s, 1H), 9.04 (s, 1H), 8.53 –

8.23 (m, 2H), 7.66 – 7.58 (m, 1H), 7.54 – 7.45 (m, 3H), 7.37 – 7.31 (m, 2H), 7.31 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 4.18 (s, 2H). MS: 390 [M+H]⁺.



Example 30

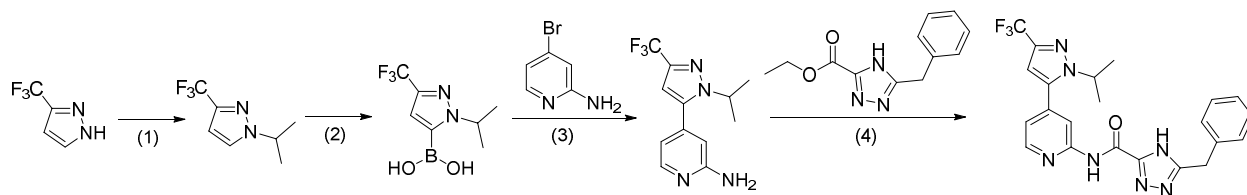


Example 31

[0243] Example 31: 5-benzyl-N-(5-(2-chloro-5-methoxyphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

[0244] The preparation was carried out in a similar manner to Example 1, except that in step 1, 2-chloro-5-methoxyphenylboronic acid was used in place of phenylboronic acid, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.82 (s, 1H), 9.04 (d, *J* = 2.4 Hz, 1H), 8.49 – 8.23 (m, 2H), 7.59 – 7.44 (m, 1H), 7.37 – 7.31 (m, 2H), 7.31 – 7.27 (m, 2H), 7.27 – 7.22 (m, 1H), 7.07 – 7.02 (m, 2H), 4.18 (s, 2H), 3.81 (s, 3H). MS: 420 [M+H]⁺.

[0245] Example 32: 5-benzyl-N-(4-(1-isopropyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0246] Step 1: Synthesis of 1-isopropyl-3-(trifluoromethyl)-1H-pyrazole

[0247] 3-(Trifluoromethyl)-1H-pyrazole (1.09g, 8mmol) was dissolved in anhydrous tetrahydrofuran (24mL), and under argon protection at 0°C, sodium hydride was added in batches (60%, 385mg, 9.6mmol). After reacting for 40 minutes, 2-bromopropane (1.28g, 10.4mmol) was added dropwise, and the reaction was warmed to 25°C and reacted for 16 hours. The reaction solution was quenched with saturated aqueous solution of ammonium chloride, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and purified by column chromatography to afford 300 mg of product, MS: 179 [M+H]⁺.

[0248] Step 2: Synthesis of (1-isopropyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)boronic acid

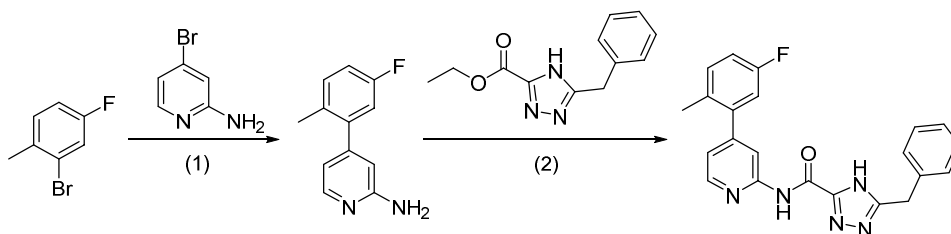
[0249] 1-Isopropyl-3-(trifluoromethyl)-1H-pyrazole (300mg, 1.7mmol) was dissolved in anhydrous tetrahydrofuran (6mL), and under argon protection at -78°C, *n*-butyllithium (2.5M, 1mL, 2.5mmol) was added dropwise. After reacting at this temperature for 1 hour, trimethyl borate (351mg, 3.4mmol) was added, and slowly warmed up overnight. The reaction solution was quenched with saturated aqueous solution of ammonium chloride, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over

anhydrous sodium sulfate, filtered and evaporated to dryness, and purified by column chromatography to afford 70 mg of product, MS: 223 [M+H]⁺.

[0250] Step 3 to Step 4: 5-benzyl-N-(4-(1-isopropyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0251] The preparation was carried out in a similar manner to Example 1, except that in step 1, (1-isopropyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)boronic acid was used in place of phenylboronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 10.08 (s, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 8.26 (s, 1H), 7.41 – 7.29 (m, 5H), 7.29 – 7.21 (m, 1H), 7.04 (s, 1H), 4.86 – 4.60 (m, 1H), 4.18 (s, 2H), 1.45 (d, *J* = 6.5 Hz, 6H). MS: 456 [M+H]⁺.

[0252] Example 33: 5-benzyl-N-(4-(5-fluoro-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0253] Step 1: Synthesis of 4-(5-fluoro-2-methylphenyl)pyridin-2-amine

[0254] 4-Bromopyridin-2-amine (400mg, 2.3mmol), pinacol diborate (645mg, 2.5mmol), Pd(dppf)Cl₂ (170mg, 0.2mmol) and potassium acetate (564mg, 5.8mmol) were placed in dioxane (12mL), and reacted at 85°C for 16 hours under argon protection. The reaction solution was cooled to 25°C, and 2-bromo-4-fluoro-1-methylbenzene (321mg, 1.7mmol), Pd(dppf)Cl₂ (150mg, 0.2mmol) and an aqueous solution (1mL) of sodium carbonate (360mg, 3.4mmol) was added, and continued to react under argon protection at 100°C for 5 hours. The reaction solution was cooled and evaporated to dryness, and subjected to column chromatography to afford 240 mg of brown solid. MS: 203 [M+H]⁺.

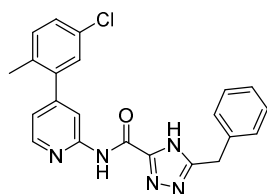
[0255] Step 2: Synthesis of 5-benzyl-N-(4-(5-fluoro-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0256] 4-(5-Fluoro-2-methylphenyl)pyridin-2-amine (0.7mmol) was placed in dry xylene (3mL), and trimethyl aluminum (3M, 0.7mL) was slowly added under argon protection. After reacting at 25°C for 1 hour, intermediate 1 (197mg, 0.9mmol) was added, and reacted at 100°C for 16 hours. The reaction solution was cooled and diluted with methanol, evaporated to dryness and subjected to column chromatography and preparative liquid chromatography to prepare the product. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.96 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.12 (d, *J* = 1.5 Hz, 1H), 7.54 – 7.00 (m, 9H), 4.18 (s, 2H), 2.24 (s, 3H). MS: 388 [M+H]⁺.

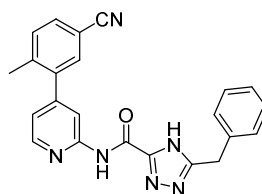
[0257] Example 34: 5-benzyl-N-(4-(5-chloro-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-

carboxamide

[0258] The preparation was carried out in a similar manner to Example 33, except that in step 1, 2-bromo-4-chloro-1-methylbenzene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.50 (s, 1H), 9.96 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.57 – 7.06 (m, 9H), 4.17 (s, 2H), 2.24 (s, 3H). MS: 404 [M+H]⁺.



Example 34



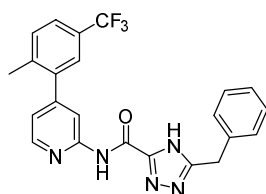
Example 35

[0259] Example 35: 5-benzyl-N-(4-(5-cyano-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

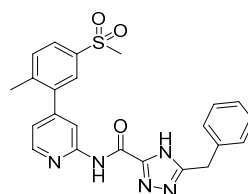
[0260] The preparation was carried out in a similar manner to Example 33, except that in step 1, 2-bromo-4-cyano-1-methylbenzene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.93 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.74 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.68 – 7.53 (m, 2H), 7.38 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 4.20 (s, 2H), 2.35 (s, 3H). MS: 395 [M+H]⁺.

[0261] Example 36: 5-benzyl-N-(4-(2-methyl-5-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0262] The preparation was carried out in a similar manner to Example 33, except that in step 1, 2-bromo-4-trifluoromethyl-1-methylbenzene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.93 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.74 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.39 – 7.23 (m, 6H), 4.20 (s, 2H), 2.35 (s, 3H). MS: 438 [M+H]⁺.



Example 36



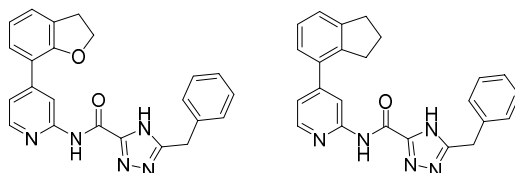
Example 37

[0263] Example 37: 5-benzyl-N-(4-(2-methyl-5-(methylsulfonyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0264] The preparation was carried out in a similar manner to Example 33, except that in step 1, 2-bromo-4-methylsulfonyl-1-methylbenzene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 10.00 (s, 1H), 8.48 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.91 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.21 (m, 6H), 4.18 (s, 2H), 3.26 (s, 3H), 2.37 (s, 3H). MS: 448 [M+H]⁺.

[0265] Example 38: 5-benzyl-N-(4-(2,3-dihydrobenzofuran-7-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0266] The preparation was carried out in a similar manner to Example 33, except that in step 1, 7-bromo-2,3-dihydrobenzofuran was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.78 (s, 1H), 8.53 (s, 1H), 8.39 (d, *J* = 5.3 Hz, 1H), 7.52 (d, *J* = 5.3 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.03 – 6.98 (m, 1H), 4.63 (t, *J* = 8.7 Hz, 2H), 4.18 (s, 2H), 3.27 (t, *J* = 8.7 Hz, 2H). MS: 398 [M+H]⁺.



Example 38

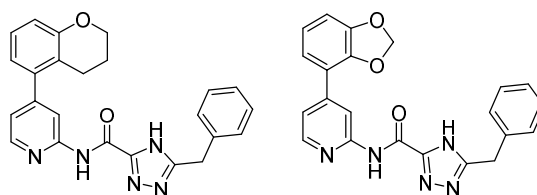
Example 39

[0267] Example 39: 5-benzyl-N-(4-(2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0268] The preparation was carried out in a similar manner to Example 33, except that in step 1, 4-bromo-2,3-dihydro-1H-indene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.27 (d, *J* = 1.5 Hz, 1H), 7.60 – 7.12 (m, 9H), 4.18 (s, 2H), 3.04 – 2.88 (m, 4H), 2.11 – 1.95 (m, 2H). MS: 396 [M+H]⁺.

[0269] Example 40: 5-benzyl-N-(4-(chroman-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0270] The preparation was carried out in a similar manner to Example 33, except that in step 1, 5-bromochroman was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.44 – 7.30 (m, 4H), 7.30 – 7.14 (m, 3H), 6.91 – 6.76 (m, 2H), 4.27 – 4.09 (m, 4H), 2.61 (t, *J* = 6.5 Hz, 2H), 1.95 – 1.78 (m, 2H). MS: 412 [M+H]⁺.



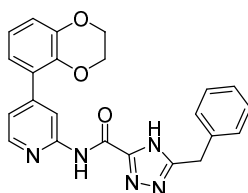
Example 40

Example 41

[0271] Example 41: N-(4-(benzo[d][1,3]dioxol-4-yl)pyridin-2-yl)-5-benzyl-4H-1,2,4-triazole-3-carboxamide

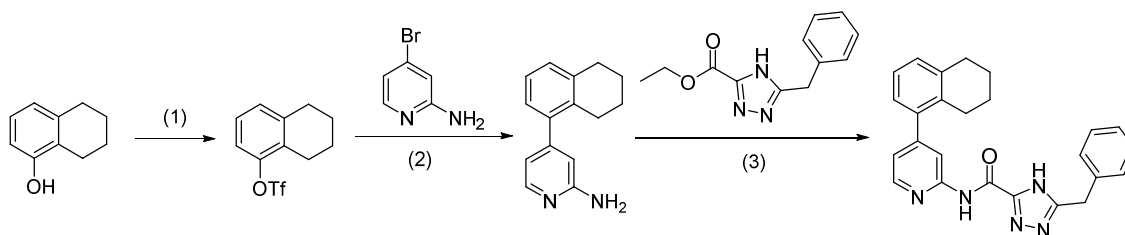
[0272] The preparation was carried out in a similar manner to Example 33, except that in step 1, 4-bromobenzo[d][1,3]dioxole was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.85 (s, 1H), 8.57 (s, 1H), 8.44 (d, *J* = 5.3 Hz, 1H), 7.55 (d, *J* = 5.3 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.19 (m, 2H), 7.08 – 6.97 (m, 2H), 6.15 (s, 2H), 4.18 (s, 2H). MS: 400 [M+H]⁺.

[0273] Example 42: 5-benzyl-N-(4-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0274] The preparation was carried out in a similar manner to Example 33, except that in step 1, 5-bromo-2,3-dihydrobenzo[b][1,4]dioxine was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.84 (s, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H), 7.39 – 7.29 (m, 5H), 7.29 – 7.21 (m, 1H), 7.02 – 6.92 (m, 3H), 4.34 – 4.25 (m, 4H), 4.17 (s, 2H). MS: 414 [M+H]⁺.

[0275] Example 43: 5-benzyl-N-(4-(5,6,7,8-tetrahydronaphthalen-1-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

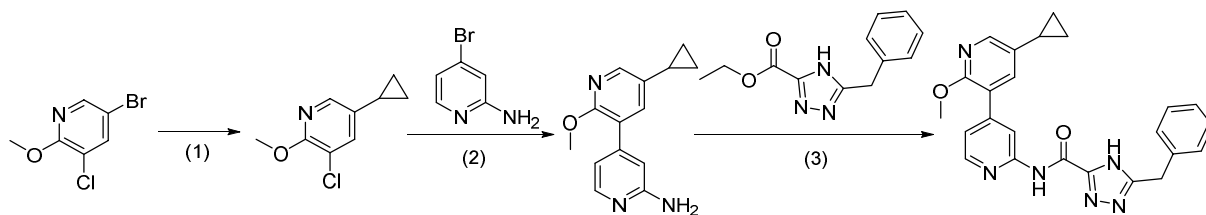


[0276] Step 1: Synthesis of 5,6,7,8-tetrahydronaphthalen-1-yl trifluoromethanesulfonate

[0277] 5,6,7,8-tetrahydronaphthalen-1-ol was dissolved in dichloromethane (600mg, 4mmol) and pyridine (480mg, 6.1mmol), trifluoromethanesulfonic anhydride (1.37g, 4.8mmol) was added dropwise under argon protection at 0°C, and the reaction was warmed to 25°C and reacted for 5 hours. The reaction solution was diluted with dichloromethane, washed with 1M HCl, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford 444mg of colorless oil. MS: 281 [M+H]⁺.

[0278] Step 2 to Step 3: The preparation was carried out in a similar manner to Example 33, except that in step 1, 5,6,7,8-tetrahydronaphthalen-1-yl trifluoromethanesulfonate was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.88 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.07 (s, 1H), 7.40 – 7.29 (m, 4H), 7.29 – 7.12 (m, 4H), 7.03 (dd, *J* = 7.3, 1.6 Hz, 1H), 4.17 (s, 2H), 2.81 (t, *J* = 6.4 Hz, 2H), 2.56 (t, *J* = 6.2 Hz, 2H), 1.81 – 1.71 (m, 2H), 1.71 – 1.59 (m, 2H). MS: 410 [M+H]⁺.

[0279] Example 44: 5-benzyl-N-(5-cyclopropyl-2-methoxy-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

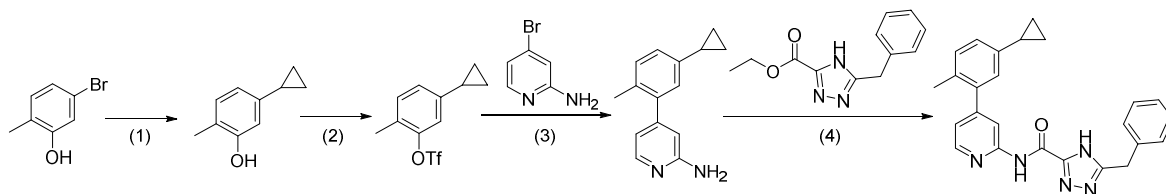


[0280] Step 1: Synthesis of 3-chloro-5-cyclopropyl-2-methoxypyridine

[0281] 5-bromo-3-chloro-2-methoxypyridine (500mg, 2.2mmol), cyclopropylboronic acid (212mg, 2.5mmol), Pd(dppf)Cl₂ (145mg, 0.2mmol) and potassium carbonate (930mg, 6.7 mmol) were placed in a mixture of dioxane (8mL) and water (2mL), and reacted for 16 hours under argon protection at 80°C. The reaction solution was evaporated to dryness and subjected to column chromatography to afford 165 mg of product, MS: 184 [M+H]⁺.

[0282] Step 2 to Step 3: The preparation was carried out in a similar manner to Example 33, except that in step 1, 3-chloro-5-cyclopropyl-2-methoxypyridine was used in place of 2-bromo-4-fluoro-1-methylbenzene, and reacted at 120°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.87 (s, 1H), 8.40 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 8.09 (d, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.43 – 7.30 (m, 5H), 7.30 – 7.21 (m, 1H), 4.18 (s, 2H), 3.88 (s, 3H), 2.05 – 1.90 (m, 1H), 1.04 – 0.88 (m, 2H), 0.82 – 0.67 (m, 2H). MS: 427 [M+H]⁺.

[0283] Example 45: 5-benzyl-N-(4-(5-cyclopropyl-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



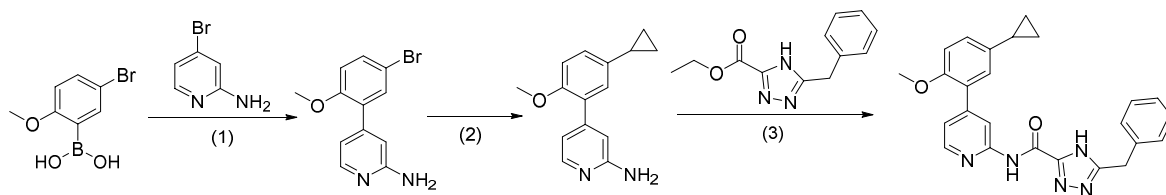
[0284] Step 1: Synthesis of 5-cyclopropyl-2-methylphenol

[0285] The operation is the same as step 1 of Example 44, but 5-bromo-2-methylphenol was used in place of 5-bromo-3-chloro-2-methoxypyridine. MS: 149 [M+H]⁺.

[0286] Step 2 to Step 4:

[0287] The preparation was carried out in a similar manner to Example 43, except that in step 1, but 5-cyclopropyl-2-methylphenol was used in place of 5,6,7,8-tetrahydronaphthalen-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.46 – 7.11 (m, 7H), 7.11 – 6.87 (m, 2H), 4.17 (s, 2H), 2.21 (s, 3H), 2.02 – 1.84 (m, 1H), 1.00 – 0.87 (m, 2H), 0.76 – 0.56 (m, 2H). MS: 410 [M+H]⁺.

[0288] Example 46: 5-benzyl-N-(4-(5-cyclopropyl-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0289] Step 1: Synthesis of 4-(5-bromo-2-methoxyphenyl)pyridin-2-amine

[0290] The operation is the same as step 1 of Example 1, but (5-bromo-2-methoxyphenyl)boronic acid was used in place of phenylboronic acid. MS: 279 [M+H]⁺.

5 **[0291]** Step 2: Synthesis of 4-(5-cyclopropyl-2-methoxyphenyl)pyridin-2-amine

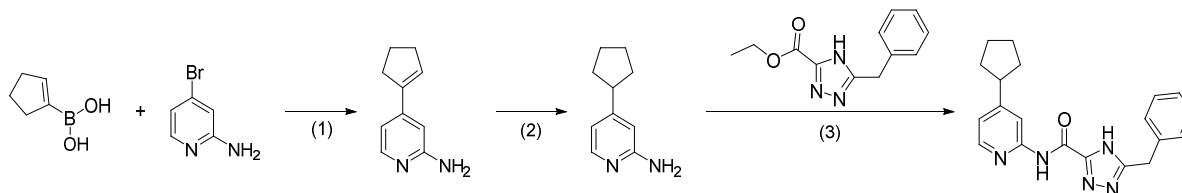
[0292] The operation is the same as step 1 of Example 44, but 4-(5-bromo-2-methoxyphenyl)pyridin-2-amine was used in place of 5-bromo-3-chloro-2-methoxypyridine. MS: 241 [M+H]⁺.

[0293] Step 3: Synthesis of 5-benzyl-N-(4-(5-cyclopropyl-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

10 **[0294]** The operation is the same as step 2 of Example 1, but 4-(5-cyclopropyl-2-methoxyphenyl)pyridin-2-amine was used in place of 4-phenylpyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.79 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.27 (s, 1H), 7.40-7.29 (m, 5H), 7.29-7.21 (m, 1H), 7.14 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.11-7.03 (m, 2H), 4.18 (s, 2H), 3.76 (s, 3H), 2.00-1.88 (m, 1H), 0.97-0.86 (m, 2H), 0.70-0.58 (m, 2H). MS: 426 [M+H]⁺.

15

[0295] Example 47: 5-benzyl-N-(4-cyclopentylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0296] Step 1: Synthesis of 4-(cyclopent-1-en-1-yl)pyridin-2-amine

20 **[0297]** The operation is the same as step 1 of Example 1, but cyclopent-1-en-1-ylboronic acid was used in place of phenylboronic acid. MS: 161 [M+H]⁺.

[0298] Step 2: Synthesis of 4-cyclopentylpyridin-2-amine

25 **[0299]** 4-(Cyclopent-1-en-1-yl)pyridin-2-amine (160mg, 1mmol) was dissolved in a mixture of ethanol (2mL) and ethyl acetate (1mL), to which a drop of hydrochloric acid and palladium on carbon (10%, 10mg) was added, and reacted for 16 hours under hydrogen atmosphere. The reaction solution was filtered through diatomaceous earth. The filtrate was evaporated to dryness, diluted with dichloromethane, washed with saturated aqueous solution of sodium carbonate, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford 140 mg of yellow oil. MS: 163 [M+H]⁺.

[0300] Step 3: Synthesis of 5-benzyl-N-(4-cyclopentylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0301] The operation is the same as step 2 of Example 1, but 4-cyclopentylpyridin-2-amine was used in place

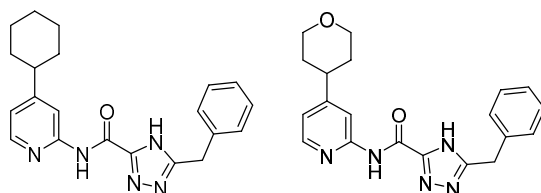
of 4-phenylpyridin-2-amine. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.61 (s, 1H), 9.70 (s, 1H), 8.23 (d, $J = 5.1$ Hz, 1H), 8.06 (d, $J = 1.5$ Hz, 1H), 7.42-7.29 (m, 4H), 7.29-7.18 (m, 1H), 7.09 (dd, $J = 5.1, 1.5$ Hz, 1H), 4.16 (s, 2H), 3.11-2.95 (m, 1H), 2.15-1.97 (m, 2H), 1.86-1.73 (m, 2H), 1.73-1.60 (m, 2H), 1.60-1.44 (m, 2H). MS: 348 $[\text{M}+\text{H}]^+$.

5

[0302] Example 48: 5-benzyl-N-(4-cyclohexylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0303] The preparation was carried out in a similar manner to Example 47, except that in step 1, cyclohex-1-en-1-ylboronic acid was used in place of cyclopent-1-en-1-ylboronic acid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.58 (s, 1H), 9.68 (s, 1H), 8.23 (d, $J = 5.2$ Hz, 1H), 8.04 (s, 1H), 7.39 – 7.28 (m, 4H), 7.28 – 7.19 (m, 1H), 7.12 – 7.03 (m, 1H), 4.15 (s, 2H), 2.64 – 2.53 (m, 1H), 1.89 – 1.74 (m, 4H), 1.75 – 1.64 (m, 1H), 1.48 – 1.31 (m, 4H), 1.30 – 1.18 (m, 1H). MS: 362 $[\text{M}+\text{H}]^+$.

10



Example 48

Example 49

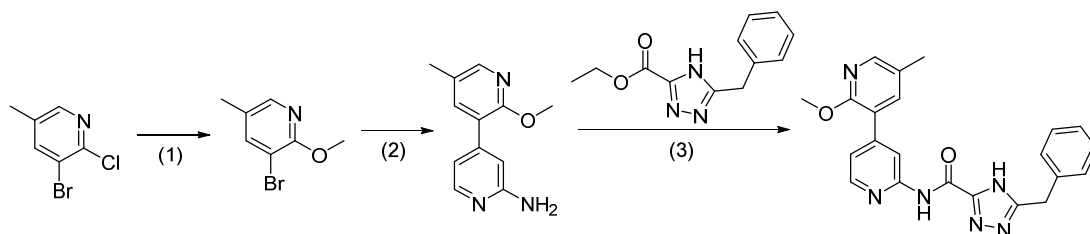
[0304] Example 49: 5-benzyl-N-(4-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

15

[0305] The preparation was carried out in a similar manner to Example 47, except that in step 1, (3,6-dihydro-2H-pyran-4-yl)boronic acid was used in place of cyclopent-1-en-1-ylboronic acid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.53 (s, 1H), 9.69 (s, 1H), 8.27 (d, $J = 5.2$ Hz, 1H), 8.08 (s, 1H), 7.42-7.18 (m, 5H), 7.12 (d, $J = 5.3$ Hz, 1H), 4.19 (s, 2H), 4.02-3.86 (m, 2H), 3.53-3.37 (m, 2H), 2.95-2.78 (m, 1H), 1.81-1.52 (m, 4H). MS: 364 $[\text{M}+\text{H}]^+$.

20

[0306] Example 50: 5-benzyl-N-(2-methoxy-5-methyl-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide



[0307] Step 1: Synthesis of 3-bromo-2-methoxy-5-methylpyridine

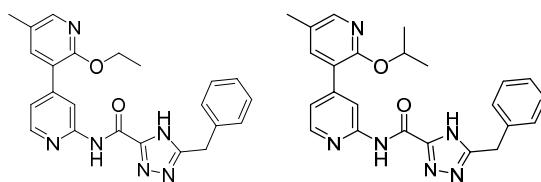
25

[0308] Anhydrous methanol (100mg, 3.1mmol) was dissolved in anhydrous DMF (3mL), and sodium hydride (60%, 115mg, 2.9mmol) was added under argon protection at 0°C. After reacting for 1 hour, 3-bromo-2-chloro-5-methylpyridine (400mg, 1.9mmol) in DMF (1mL) was added dropwise, and reacted at 60°C for 16 hours. MS: 202 $[\text{M}+\text{H}]^+$.

[0309] Step 2 to Step 3: The preparation was carried out in a similar manner to Example 33, except that in step 1, 3-bromo-2-methoxy-5-methylpyridine was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.86 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.36 (d, *J* = 1.5 Hz, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.39 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 4.18 (s, 2H), 3.88 (s, 3H), 2.30 (s, 3H). MS: 401 [M+H]⁺.

[0310] Example 51: 5-benzyl-N-(2-ethoxy-5-methyl-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0311] The preparation was carried out in a similar manner to Example 50, except that in step 1, anhydrous ethanol was used in place of anhydrous methanol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.80 (s, 1H), 8.47 (s, 1H), 8.40 (d, *J* = 5.2 Hz, 1H), 8.07 (dd, *J* = 2.3, 1.0 Hz, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.41 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.18 (s, 2H), 2.29 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H). MS: 415 [M+H]⁺.



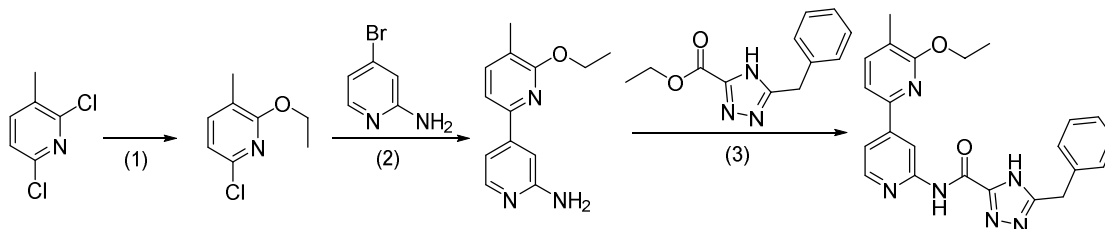
Example 51

Example 52

[0312] Example 52: 5-benzyl-N-(2-isopropoxy-5-methyl-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0313] The preparation was carried out in a similar manner to Example 50, except that in step 1, anhydrous isopropanol was used in place of anhydrous methanol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.91 – 9.71 (m, 1H), 8.51 (s, 1H), 8.40 (d, *J* = 5.2 Hz, 1H), 8.06 (d, *J* = 2.3 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.44 – 7.18 (m, 6H), 5.34 (p, *J* = 6.2 Hz, 1H), 4.18 (s, 2H), 2.28 (s, 3H), 1.31 (d, *J* = 6.2 Hz, 6H). MS: 429 [M+H]⁺.

[0314] Example 53: 5-benzyl-N-(6-ethoxy-5-methyl-[2,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide



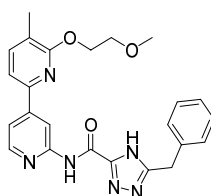
[0315] Step 1: Synthesis of 6-chloro-2-ethoxy-3-methylpyridine

[0316] Anhydrous ethanol (830mg, 18mmol) was dissolved in anhydrous tetrahydrofuran (10mL), and sodium hydride (60%, 600mg, 15mmol) was added at 0°C. After reacting for 30 minutes, 2,6-dichloro-3-

methylpyridine (810mg, 5mmol) in tetrahydrofuran (5mL) was added, and reacted at 40°C for 24 hours. The reaction solution was quenched with saturated ammonium chloride, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and purified by column chromatography to afford 300 mg of product. MS: 172 [M+H]⁺.

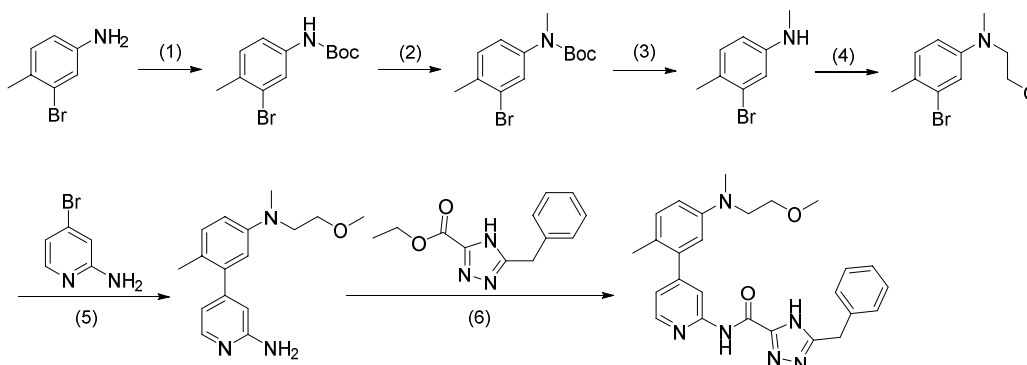
[0317] Step 2 to Step 3: The preparation was carried out in a similar manner to Example 33, except that in step 1, 6-chloro-2-ethoxy-3-methylpyridine was used in place of 2-bromo-4-fluoro-1-methylbenzene, and reacted at 120°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.21 (s, 1H), 9.86 (s, 1H), 8.86 (d, *J* = 3.6 Hz, 1H), 8.53-8.32 (m, 1H), 7.84-7.77 (m, 1H), 7.71 (dd, *J* = 7.8, 3.6 Hz, 1H), 7.59 (dd, *J* = 7.8, 3.8 Hz, 1H), 7.40-7.30 (m, 4H), 7.27 (d, *J* = 7.0 Hz, 1H), 4.56-4.43 (m, 2H), 4.18 (s, 2H), 2.21 (s, 3H), 1.52-1.36 (m, 3H). MS: 415 [M+H]⁺.

[0318] Example 54: 5-benzyl-N-(6-(2-methoxyethoxy)-5-methyl-[2,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide



[0319] The preparation was carried out in a similar manner to Example 53, except that in step 1, 2-methoxyethanol was used in place of anhydrous ethanol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.87 (s, 1H), 8.85 (d, *J* = 1.3 Hz, 1H), 8.44 (d, *J* = 5.3 Hz, 1H), 7.81 (dd, *J* = 5.3, 1.6 Hz, 1H), 7.76 – 7.69 (m, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.29 (m, 4H), 7.29 – 7.20 (m, 1H), 4.64 – 4.51 (m, 2H), 4.18 (s, 2H), 3.82 – 3.73 (m, 2H), 3.45 (s, 3H), 2.22 (s, 3H). MS: 445 [M+H]⁺.

[0320] Example 55: 5-benzyl-N-(4-(5-((2-methoxyethyl)(methyl)amino)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0321] Step 1: Synthesis of tert-butyl (3-bromo-4-methylphenyl)carbamate

[0322] 3-Bromo-4-methylaniline (1.86g, 10mmol) was placed in dichloromethane (25mL), 4-dimethylaminopyridine (120mg, 1mmol) and triethylamine (2g, 20mmol) were added, a solution of di-tert-butyl dicarbonate (2.4g, 11mmol) in dichloromethane (5mL) was added dropwise under argon protection at 0°C, and

reacted at 25°C for 4 hours after the addition. The reaction solution was diluted with dichloromethane, washed with saturated aqueous solution of ammonium chloride, washed with brine, dried over anhydrous sodium sulfate, evaporated to dryness and filtered to afford 2.84g crude product.

[0323] Step 2: Synthesis of tert-butyl (3-bromo-4-methylphenyl)(methyl)carbamate

[0324] Tert-butyl (3-bromo-4-methylphenyl)carbamate (2.84 g, 9.9mmol) was dissolved in DMF, and sodium hydride (60%, 475mg, 11.9mmol) was added in batches at 0°C. After reacting at 0°C for 30minutes, iodomethane (2.1g, 14.8mmol) was added dropwise, and reacted at 25°C for 3 hours. The reaction solution was quenched with saturated aqueous solution of ammonium chloride, diluted with ethyl acetate, washed with saturated aqueous solution of ammonium chloride and brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, purified by column chromatography to afford 2.5 g.

[0325] Step 3: Synthesis of 3-bromo-N,4-dimethylaniline

[0326] Tert-butyl (3-bromo-4-methylphenyl)(methyl)carbamate (2.5g, 8.3mmol) was dissolved in dichloromethane (25mL), trifluoroacetic acid (10mL) was added dropwise at 0°C, and reacted at 25°C for 3 hours. The reaction solution was concentrated, an aqueous solution of sodium carbonate was added dropwise to adjust the pH to 9, extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford 1.5g of crude product. MS: 200 [M+H]⁺.

[0327] Step 4: Synthesis of 3-bromo-N-(2-methoxyethyl)-N,4-dimethylaniline

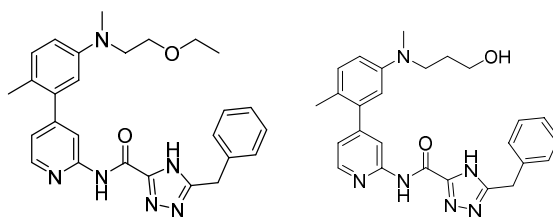
[0328] 3-Bromo-N,4-dimethylaniline (200mg, 1mmol) was dissolved in DMF, potassium carbonate (275mg, 1.5mmol) and 1-bromo-2-methoxyethane (180mg, 1.3mmol) were added, and reacted for 24 hours at 70°C in sealed tube. The reaction solution was cooled, diluted with ethyl acetate, washed with saturated ammonium chloride and brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford 180 mg of the product. MS: 258 [M+H]⁺.

[0329] Step 5 to Step 6: The preparation was carried out in a similar manner to Example 33, except that in step 1, 3-bromo-N-(2-methoxyethyl)-N,4-dimethylaniline was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.86 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.38 – 7.29 (m, 4H), 7.27 (dd, *J* = 6.1, 2.5 Hz, 1H), 7.19 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 4.17 (s, 2H), 3.54 – 3.43 (m, 4H), 3.24 (s, 3H), 2.90 (s, 3H), 2.13 (s, 3H). MS: 457 [M+H]⁺.

[0330] Example 56: 5-benzyl-N-(4-(5-((2-ethoxyethyl)(methyl)amino)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0331] The operation is the same as Example 55, but 1-bromo-2-ethoxyethane was used in place of 1-bromo-2-methoxyethane in step 4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.85 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.46 – 7.29 (m, 4H), 7.27 (d, *J* = 6.5 Hz, 1H), 7.19 (dd, *J* = 5.2, 1.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 4.18 (s, 2H), 3.56 – 3.45 (m, 4H), 3.41 (q, *J* =

7.0 Hz, 2H), 2.90 (s, 3H), 2.13 (s, 3H), 1.07 (t, $J = 7.0$ Hz, 3H). MS: 471 $[M+H]^+$.



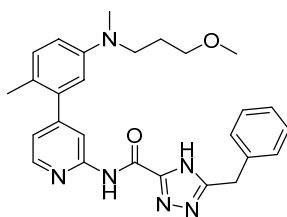
Example 56

Example 57

[0332] Example 57: 5-benzyl-N-(4-(5-((3-hydroxypropyl)(methyl)amino)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

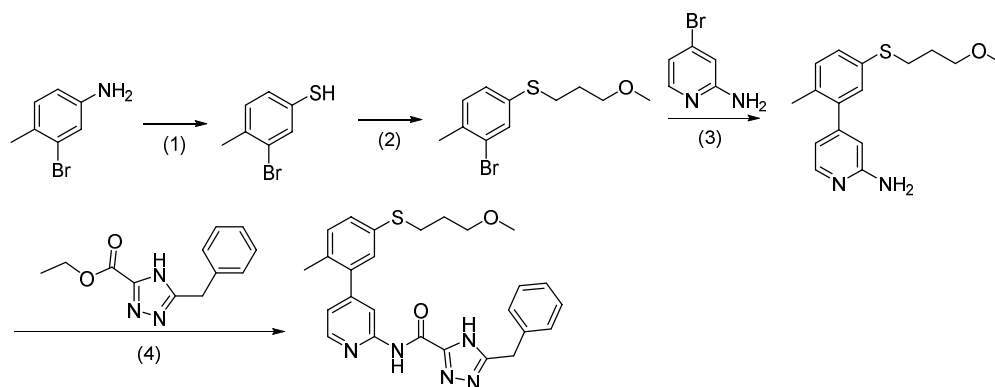
[0333] The operation is the same as Example 55, but 3-bromo-1-propanol was used in place of 1-bromo-2-methoxyethane in step 4. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.58 (s, 1H), 9.88 (s, 1H), 8.40 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.42 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.19 (dd, $J = 5.1, 1.5$ Hz, 1H), 7.12 (d, $J = 8.5$ Hz, 1H), 6.72 (dd, $J = 8.5, 2.7$ Hz, 1H), 6.54 (d, $J = 2.7$ Hz, 1H), 4.49 (t, $J = 5.0$ Hz, 1H), 4.17 (s, 2H), 3.51 – 3.36 (m, 4H), 2.86 (s, 3H), 2.13 (s, 3H), 1.73 – 1.55 (m, 2H). MS: 457 $[M+H]^+$.

[0334] Example 58: 5-benzyl-N-(4-(5-((3-methoxypropyl)(methyl)amino)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0335] The operation is the same as Example 55, but 1-bromo-3-methoxypropane was used in place of 1-bromo-2-methoxyethane in step 4. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.56 (s, 1H), 9.88 (s, 1H), 8.40 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.43 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.19 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.13 (d, $J = 8.5$ Hz, 1H), 6.70 (dd, $J = 8.5, 2.8$ Hz, 1H), 6.54 (d, $J = 2.8$ Hz, 1H), 4.17 (s, 2H), 3.40 – 3.34 (m, 4H), 3.19 (s, 3H), 2.86 (s, 3H), 2.13 (s, 3H), 1.77 – 1.63 (m, 2H). MS: 471 $[M+H]^+$.

[0336] Example 59: 5-benzyl-N-(4-(5-(3-methoxypropylthio)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



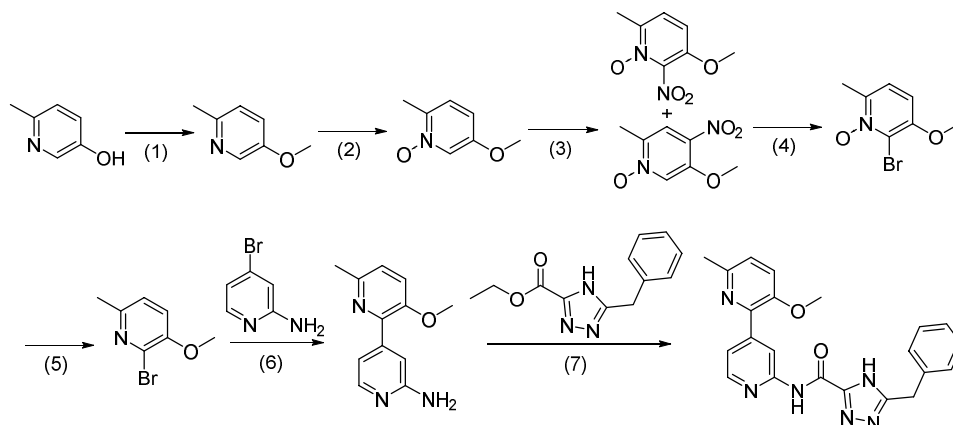
[0337] Step 1: Synthesis of 3-bromo-4-methylbenzenethiol

[0338] 3-bromo-4-methylaniline (1.12g, 6mmol) was dissolved in 6M hydrochloric acid solution, and at -10°C, an aqueous solution (6mL) of sodium nitrite (1.04g, 15mmol) was slowly added dropwise. After reacting for 30 minutes, this mixture was added dropwise to an aqueous solution (15 mL) of potassium ethylxanthate (3.36g, 21mmol), reacted at 80°C for 20 minutes, and then cooled. The reaction solution was diluted with water, extracted with ether, the organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was dissolved in ethanol (30mL), and potassium hydroxide (3.36g, 60mmol) in water (10mL) was added dropwise at 0°C, and reacted at 50 °C for 3 hours. The reaction solution was concentrated, diluted with water, adjusted to pH 4 with 6M hydrochloric acid, and extracted with ether. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford 1g of crude product. MS: 203 [M+H]⁺.

[0339] Step 2 to Step 4: Synthesis of 5-benzyl-N-(4-(5-((3-methoxypropyl)thio)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0340] The operation is the same as steps 4 to 6 of Example 55, but 3-bromo-4-methylbenzenethiol was used in place of 3-bromo-N,4-dimethylaniline in the fourth step, and 1-bromo-3-methoxypropane was used in place of 1-bromo-2-methoxyethane in the fourth step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.92 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.41 – 7.29 (m, 6H), 7.29 – 7.13 (m, 3H), 4.18 (s, 2H), 3.40 (t, *J* = 6.1 Hz, 2H), 3.19 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.84 – 1.72 (m, 2H). MS: 474 [M+H]⁺.

[0341] Example 60: 5-benzyl-N-(3-methoxy-6-methyl-[2,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide



[0342] Step 1: Synthesis of 5-methoxy-2-methylpyridine

[0343] The operation is the same as step 4 of Example 55, but iodomethane was used in place of 1-bromo-2-methoxyethane, and reacted at 50°C in sealed tube. MS: 124 [M+H]⁺.

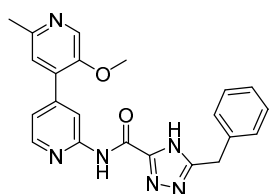
5 **[0344]** Step 2 to Step 5: Synthesis of 2-bromo-3-methoxy-6-methylpyridine

[0345] Synthesis was made with reference to the method in Gonzalez, Javier et al/ PCT Int. Appl., 2006018725, 23 Feb 2006. In the third step, the separated 3-methoxy-6-methyl-2-nitropyridine N-oxide was used for the subsequent reaction.

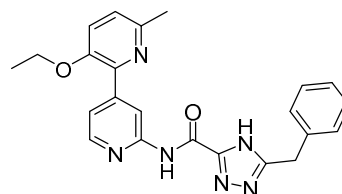
10 **[0346]** Step 6 and 7: The preparation was carried out in a similar manner to Example 33, except that in step 1, 2-bromo-3-methoxy-6-methylpyridine was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.82 (s, 1H), 8.71 (s, 1H), 8.41 (d, *J* = 5.3 Hz, 1H), 7.68 (dd, *J* = 5.3, 1.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.29 – 7.22 (m, 1H), 4.18 (s, 2H), 3.87 (s, 3H), 3.33 (s, 3H). MS: 401 [M+H]⁺.

15 **[0347]** Example 61: 5-benzyl-N-(5'-methoxy-2'-methyl-[4,4'-bipyridin]-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0348] The operation is the same as step of Example 60, but 5-methoxy-2-methyl-4-nitropyridine N-oxide separated in the third step was used for the subsequent reaction. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.93 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.41 (s, 1H), 8.36 (s, 1H), 7.43 – 7.33 (m, 5H), 7.33 – 7.26 (m, 2H), 4.21 (s, 2H), 3.92 (s, 3H), 2.50 (s, 3H). MS: 401 [M+H]⁺.



Example 61



Example 62

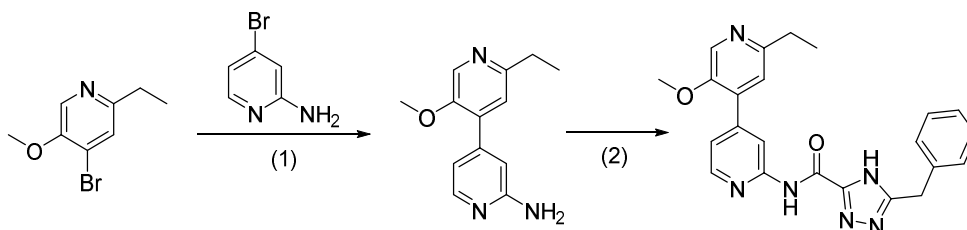
[0349] Example 62: 5-benzyl-N-(3-ethoxy-6-methyl-[2,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

25 **[0350]** The operation is the same as Example 60, but bromoethane was used in place of iodomethane in the

first step, and in the third step, the nitration process only gets 3-ethoxy-6-methyl-2-nitropyridine N-oxide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.70 (s, 1H), 9.80 (s, 1H), 8.84 (s, 1H), 8.41 (d, *J* = 5.3 Hz, 1H), 7.74 (dd, *J* = 5.3, 1.5 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.39-7.29 (m, 5H), 7.29-7.22 (m, 1H), 4.25-4.08 (m, 4H), 2.48 (s, 3H), 1.39 (t, *J* = 6.9 Hz, 3H). MS: 415 [M+H]⁺.

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[0351] Example 63: 5-benzyl-N-(2'-ethyl-5'-methoxy-[4,4'-bipyridin]-2-yl)-4H-1,2,4-triazole-3-carboxamide

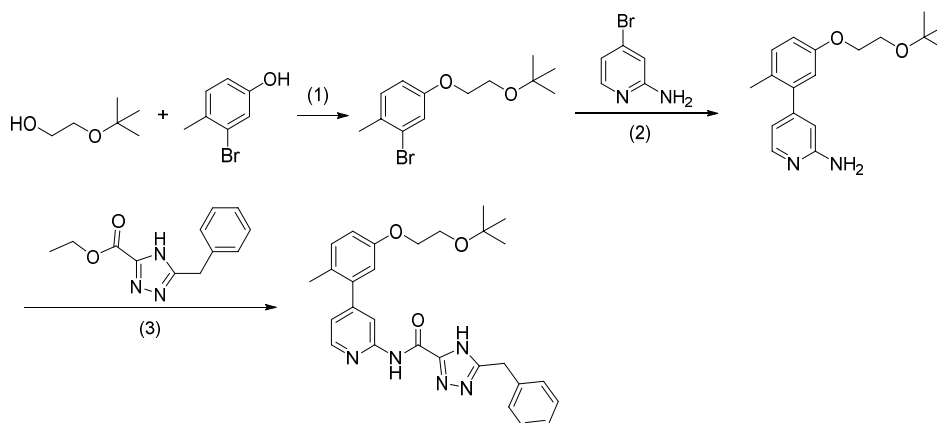


[0352] The preparation was carried out in a similar manner to Example 33, except that in step 1, 4-bromo-2-ethyl-5-methoxypyridine (see Gonzalez, Javier et al/PCT Int. Appl., 2006018725, 23 Feb 2006 for its synthetic method) was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.93 (s, 1H), 8.50 – 8.38 (m, 2H), 8.33 (d, *J* = 1.4 Hz, 1H), 7.43 – 7.30 (m, 5H), 7.30 – 7.21 (m, 2H), 4.18 (s, 2H), 3.90 (s, 3H), 2.76 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). MS: 415 [M+H]⁺.

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15

[0353] Example 64: 5-benzyl-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0354] Step 1: Synthesis of 2-bromo-4-(2-(tert-butoxy)ethoxy)-1-methylbenzene

[0355] 3-Bromo-4-methylphenol (187mg, 1mmol), 2-(tert-butoxy)ethan-1-ol (142mg, 1.2mmol) and triphenylphosphine (393mg, 1.5mmol) were placed in anhydrous tetrahydrofuran (3mL), diisopropyl azodicarboxylate (303mg, 1.5mmol) was added dropwise under argon protection at 0°C, and after the addition, reacted at 25°C for 16 hours. The reaction solution was evaporated to dryness and purified by column chromatography to afford 230 mg of colorless oil. MS: 287 [M+H]⁺.

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[0356] Step 2 to Step 3: The preparation was carried out in a similar manner to Example 33, except that in

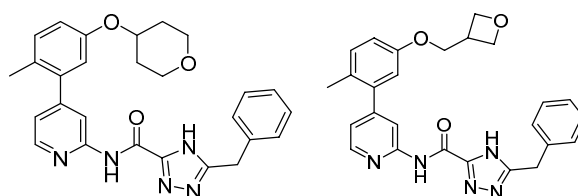
step 1, 2-bromo-4-(2-(tert-butoxy)ethoxy)-1-methylbenzene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.90 (s, 1H), 8.48 – 8.37 (m, 1H), 8.12 (s, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.18 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.12 – 3.99 (m, 2H), 3.69 – 3.58 (m, 2H), 2.19 (s, 3H), 1.15 (s, 9H). MS: 486 [M+H]⁺.

5

[0357] Example 65: 5-benzyl-N-(4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0358] The preparation was carried out in a similar manner to Example 64, except that in step 1, tetrahydro-2H-pyran-4-ol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.40 – 7.29 (m, 4H), 7.29 – 7.14 (m, 3H), 6.99 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 4.65 – 4.54 (m, 1H), 4.20 (s, 2H), 3.89 – 3.76 (m, 2H), 3.52 – 3.41 (m, 2H), 2.18 (s, 3H), 2.02 – 1.88 (m, 2H), 1.66 – 1.50 (m, 2H). MS: 470 [M+H]⁺.

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Example 65

Example 66

[0359] Example 66: 5-benzyl-N-(4-(2-methyl-5-(oxetan-3-ylmethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

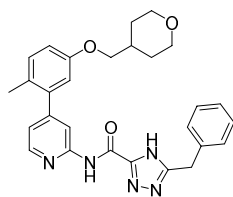
[0360] The preparation was carried out in a similar manner to Example 64, except that in step 1, oxetan-3-yl methanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.45 – 7.14 (m, 7H), 6.97 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.86 (d, *J* = 2.7 Hz, 1H), 4.78 – 4.64 (m, 2H), 4.48 – 4.36 (m, 2H), 4.22 (d, *J* = 6.8 Hz, 2H), 4.18 (s, 2H), 3.46 – 3.34 (m, 1H), 2.20 (s, 3H). MS: 456 [M+H]⁺.

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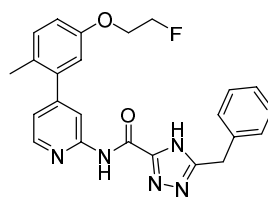
[0361] Example 67: 5-benzyl-N-(4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0362] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.42 – 7.29 (m, 4H), 7.29 – 7.12 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 3.92 – 3.79 (m, 4H), 3.33 – 3.27 (m, 2H), 2.19 (s, 3H), 2.05 – 1.90 (m, 1H), 1.72 – 1.62 (m, 2H), 1.38 – 1.23 (m, 2H). MS: 484 [M+H]⁺.

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Example 67



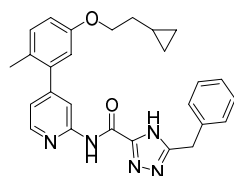
Example 68

[0363] Example 68: 5-benzyl-N-(4-(5-(2-fluoroethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

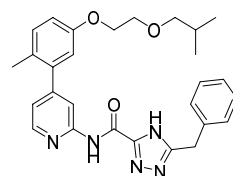
[0364] The preparation was carried out in a similar manner to Example 64, except that in step 1, 2-fluoro-1-ethanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 9.93 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (d, *J* = 1.5 Hz, 1H), 7.44 – 7.14 (m, 7H), 6.98 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.87 (d, *J* = 2.7 Hz, 1H), 4.84 – 4.75 (m, 1H), 4.72 – 4.61 (m, 1H), 4.33 – 4.26 (m, 1H), 4.26 – 4.20 (m, 1H), 4.18 (s, 2H), 2.20 (s, 3H). MS: 432 [M+H]⁺.

[0365] Example 69: 5-benzyl-N-(4-(5-(2-cyclopropylethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0366] The preparation was carried out in a similar manner to Example 64, except that in step 1, 2-cyclopropyl-1-ethanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.90 (s, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 8.12 (s, 1H), 7.39 – 7.30 (m, 4H), 7.30 – 7.19 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.03 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.69 – 1.55 (m, 2H), 0.89 – 0.75 (m, 1H), 0.50 – 0.37 (m, 2H), 0.20 – 0.06 (m, 2H). MS: 454 [M+H]⁺.



Example 69



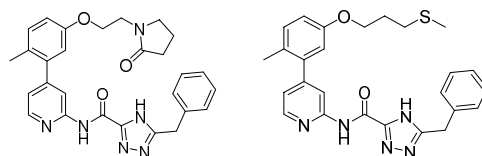
Example 70

[0367] Example 70: 5-benzyl-N-(4-(5-(2-isobutoxyethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0368] The preparation was carried out in a similar manner to Example 64, except that in step 1, 2-isobutoxy-1-ethanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.45 – 7.15 (m, 7H), 6.95 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.15 – 4.06 (m, 2H), 3.74 – 3.61 (m, 2H), 3.21 (d, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.88 – 1.68 (m, 1H), 0.84 (d, *J* = 6.7, 2.5 Hz, 6H). MS: 486 [M+H]⁺.

[0369] Example 71: 5-benzyl-N-(4-(2-methyl-5-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0370] The preparation was carried out in a similar manner to Example 64, except that in step 1, 1-(2-hydroxyethyl)pyrrolidin-2-one was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.0, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.09 (t, *J* = 5.5 Hz, 2H), 3.53 (t, *J* = 5.5 Hz, 2H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.26 – 2.13 (m, 5H), 1.95 – 1.83 (m, 2H). MS: 497 [M+H]⁺.



Example 71

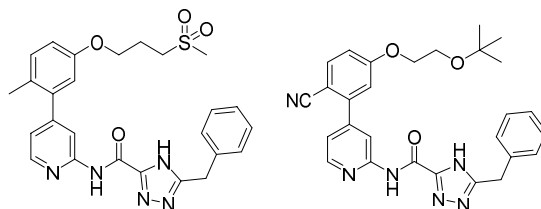
Example 72

[0371] Example 72: 5-benzyl-N-(4-(2-methyl-5-(3-(methylthio)propoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0372] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-(methylthio)-1-propanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.90 (s, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 8.11 (s, 1H), 7.42 – 7.29 (m, 4H), 7.29 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.19 (s, 3H), 2.05 (s, 3H), 2.02 – 1.90 (m, 2H). MS: 474 [M+H]⁺.

[0373] Example 73: 5-benzyl-N-(4-(2-methyl-5-(3-(methylsulfonyl)propoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0374] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-(methylsulfonyl)-1-propanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.88 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.41 – 7.15 (m, 7H), 6.96 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.11 (t, *J* = 6.2 Hz, 2H), 3.31 – 3.23 (m, 2H), 3.01 (s, 3H), 2.20 (s, 3H), 2.17 – 2.05 (m, 2H). MS: 506 [M+H]⁺.



Example 73

Example 74

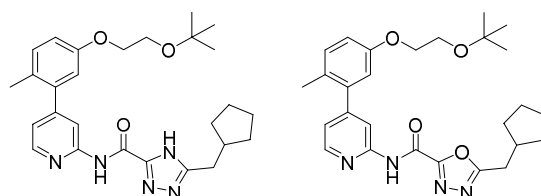
[0375] Example 74: 5-benzyl-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-cyanophenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0376] The preparation was carried out in a similar manner to Example 64, except that in step 1, 2-chloro-4-hydroxybenzonitrile was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s,

1H), 10.02 (s, 1H), 8.52 (d, $J = 5.1$ Hz, 1H), 8.34 (s, 1H), 7.94 (d, $J = 9.2$ Hz, 1H), 7.42 (d, $J = 4.9$ Hz, 1H), 7.39 – 7.30 (m, 4H), 7.30 – 7.18 (m, 3H), 4.23 (t, $J = 4.6$ Hz, 2H), 4.18 (s, 2H), 3.67 (t, $J = 4.7$ Hz, 2H), 1.15 (s, 9H). MS: 497 [M+H]⁺.

[0377] Example 75: N-(4-(5-(2-(tert-butoxy)ethoxy)-2-methylphenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0378] The preparation was carried out in a similar manner to Example 64, except that in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.86 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.14 (s, 1H), 7.32 – 7.13 (m, 2H), 6.95 (dd, $J = 8.4, 2.8$ Hz, 1H), 6.84 (d, $J = 2.7$ Hz, 1H), 4.09 – 4.00 (m, 2H), 3.67 – 3.57 (m, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.39 – 2.22 (m, 1H), 2.20 (s, 3H), 1.80 – 1.66 (m, 2H), 1.66 – 1.44 (m, 4H), 1.29 – 1.17 (m, 2H), 1.15 (s, 9H). MS: 478 [M+H]⁺.



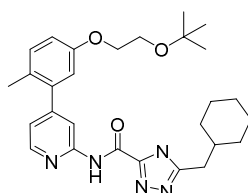
Example 75

Example 76

[0379] Example 76: N-(4-(5-(2-(tert-butoxy)ethoxy)-2-methylphenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-1,3,4-oxadiazol-2-carboxamide

[0380] The preparation was carried out in a similar manner to Example 64, except that in step 3, ethyl 5-(cyclohexylmethyl)-1,3,4-oxadiazol-2-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.24 (s, 1H), 8.48 (d, $J = 5.0$ Hz, 1H), 7.99 (s, 1H), 7.33 – 7.20 (m, 2H), 6.95 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.83 (d, $J = 2.7$ Hz, 1H), 4.10 – 3.99 (m, 2H), 3.67 – 3.58 (m, 2H), 2.97 (d, $J = 7.4$ Hz, 2H), 2.37 – 2.24 (m, 1H), 2.20 (s, 3H), 1.86 – 1.73 (m, 2H), 1.70 – 1.44 (m, 4H), 1.33 – 1.18 (m, 2H), 1.15 (s, 9H). MS: 479 [M+H]⁺.

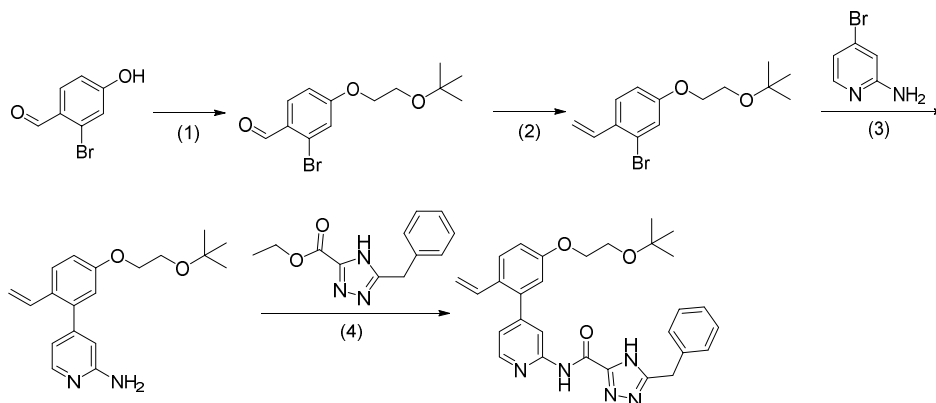
[0381] Example 77: N-(4-(5-(2-(tert-butoxy)ethoxy)-2-methylphenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide



[0382] The preparation was carried out in a similar manner to Example 64, except that in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.93 – 9.76 (m, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.14

(s, 1H), 7.32 – 7.15 (m, 2H), 6.94 (dd, $J = 8.5, 2.7$ Hz, 1H), 6.83 (d, $J = 2.7$ Hz, 1H), 4.04 (t, $J = 4.8$ Hz, 2H), 3.63 (t, $J = 4.9$ Hz, 2H), 2.66 (d, $J = 7.0$ Hz, 2H), 2.20 (s, 3H), 1.83 – 1.53 (m, 6H), 1.30 – 1.06 (m, 12H), 1.06 – 0.88 (m, 2H). MS: 492 $[M+H]^+$.

5 **[0383]** Example 78: 5-benzyl-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-vinylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0384] Step 1: Synthesis of 2-bromo-4-(2-(tert-butoxy)ethoxy)benzaldehyde

[0385] The operation is the same as step 1 of Example 64, but 2-bromo-4-hydroxybenzaldehyde was used in place of 2-bromo-3-methylphenol in step 1.

[0386] Step 2: Synthesis of 2-bromo-4-(2-(tert-butoxy)ethoxy)-1-vinylbenzene

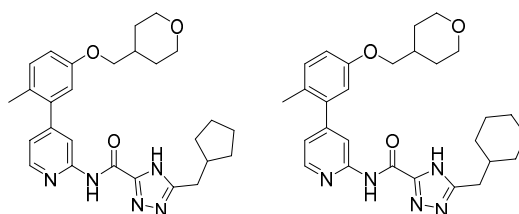
[0387] Methyltriphenylphosphonium bromide (1.25g, 3.5mmol) was placed in anhydrous tetrahydrofuran (7mL), and n-butyl lithium was added dropwise at -20°C under argon protection. After reacting at 0°C for 1 hour, 2-bromo-4-(2-(tert-butoxy)ethoxy)benzaldehyde (700mg, 2.3mmol) in anhydrous tetrahydrofuran (2.5mL) solution was added, heated to 25°C and reacted for 5 hours. The reaction solution was quenched with saturated ammonium chloride, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and the crude product was directly used in the next step.

[0388] Step 3 to Step 4: The preparation was carried out in a similar manner to Example 33, except that in step 1, 2-bromo-4-(2-(tert-butoxy)ethoxy)-1-vinylbenzene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.54 (s, 1H), 9.92 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.69 (d, $J = 8.7$ Hz, 1H), 7.38 – 7.30 (m, 4H), 7.29 – 7.22 (m, 1H), 7.17 (dd, $J = 5.0, 1.5$ Hz, 1H), 7.06 (dd, $J = 8.7, 2.6$ Hz, 1H), 6.88 (d, $J = 2.6$ Hz, 1H), 6.55 (dd, $J = 17.4, 11.0$ Hz, 1H), 5.71 (d, $J = 17.4$ Hz, 1H), 5.15 (d, $J = 11.1$ Hz, 1H), 4.17 (s, 2H), 4.10 (t, $J = 4.8$ Hz, 2H), 3.64 (dd, $J = 5.6, 4.0$ Hz, 2H), 1.15 (s, 9H). MS: 498 $[M+H]^+$.

[0389] Example 79: 5-(cyclopentylmethyl)-N-(4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0390] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-

2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.86 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.86 – 3.78 (m, 3H), 3.32 – 3.23 (m, 2H), 2.77 (d, *J* = 7.4 Hz, 2H), 2.35 – 2.22 (m, 1H), 2.19 (s, 3H), 2.06 – 1.92 (m, 1H), 1.79 – 1.44 (m, 8H), 1.40 – 1.12 (m, 4H). MS: 476 [M+H]⁺.



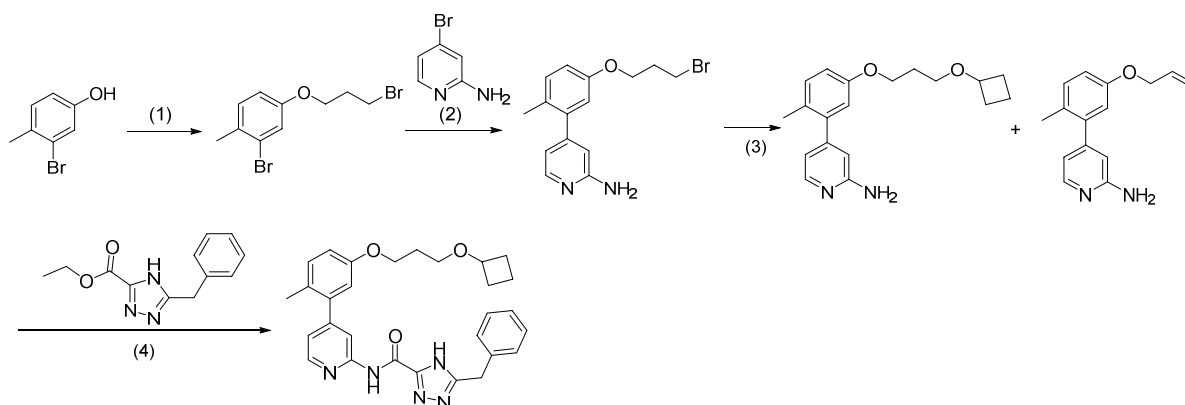
Example 79

Example 80

[0391] Example 80: 5-(cyclohexylmethyl)-N-(4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0392] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.36 (s, 1H), 9.84 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.34 – 7.12 (m, 2H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 3.93 – 3.79 (m, 4H), 3.40 – 3.31 (m, 3H), 2.72 – 2.62 (m, 2H), 2.19 (s, 3H), 2.07 – 1.92 (m, 1H), 1.84 – 1.70 (m, 1H), 1.70 – 1.53 (m, 6H), 1.41 – 1.05 (m, 5H), 1.05 – 0.90 (m, 2H). MS: 490 [M+H]⁺.

[0393] Example 81: 5-benzyl-N-(4-(5-(3-cyclobutoxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0394] Step 1 to Step 2: Synthesis of 4-(5-(3-bromopropoxy)-2-methylphenyl)pyridin-2-amine

[0395] The operation is the same as steps 1 to 2 of Example 64, but 3-bromopropyl-1-ol was used in place of 2-(tert-butoxy)ethan-1-ol in step 1.

[0396] Step 3: Synthesis of 4-(5-(3-cyclobutoxypropoxy)-2-methylphenyl)pyridin-2-amine

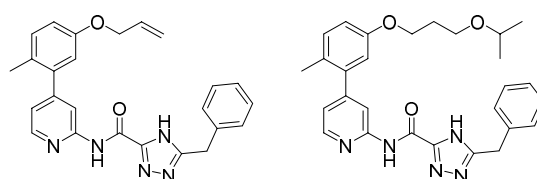
[0397] Cyclobutanol (115mg, 1.6mmol) was dissolved in anhydrous tetrahydrofuran (3mL), and sodium hydride (60%, 65mg, 1.6mmol) was added under argon protection at 0°C. After 30 minutes of reaction, 4-(5-(3-bromopropoxy)-2-methylphenyl)pyridin-2-amine (200mg, 0.6mmol) in tetrahydrofuran was added dropwise, and reacted at 50°C for 4 hours. The reaction was cooled, quenched with saturated ammonium chloride, the reaction solution was evaporated, and purified by column chromatography to afford 40mg of product and 20mg of by-product 4-(5-allyloxy)-2-methylphenylpyridin-2-amine. MS: 313 [M+H]⁺ and MS: 241 [M+H]⁺

[0398] Step 4: Synthesis of 5-benzyl-N-(4-(5-(3-cyclobutoxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0399] The operation is the same as step 2 of Example 1, but 4-(5-(3-cyclobutoxypropoxy)-2-methylphenyl)pyridin-2-amine was used in place of 4-phenylpyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.88 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.49 – 7.30 (m, 4H), 7.30 – 7.17 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.93 – 3.81 (m, 1H), 3.42 – 3.39 (m, 2H), 2.19 (s, 3H), 2.16 – 2.06 (m, 2H), 1.96 – 1.85 (m, 2H), 1.85 – 1.71 (m, 2H), 1.66 – 1.53 (m, 1H), 1.50 – 1.36 (m, 1H). MS: 498 [M+H]⁺.

[0400] Example 82: N-(4-(5-(allyloxy)-2-methylphenyl)pyridin-2-yl)-5-benzyl-4H-1,2,4-triazole-3-carboxamide

[0401] The operation is the same as Example 81, but the by-product 4-(5-allyloxy)-2-methylphenylpyridin-2-amine obtained in the third step was used for the subsequent reaction. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.92 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (d, *J* = 1.5 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 6.11 – 5.96 (m, 1H), 5.45 – 5.32 (m, 1H), 5.32 – 5.19 (m, 1H), 4.64 – 4.53 (m, 2H), 4.17 (s, 2H), 2.19 (s, 3H). MS: 426 [M+H]⁺.



Example 82

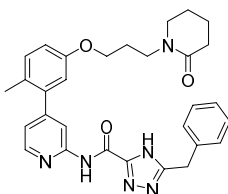
Example 83

[0402] Example 83: 5-benzyl-N-(4-(5-(3-isopropoxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0403] The operation is the same as Example 81, but isopropanol was used in place of cyclobutanol in the third step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.89 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.48 – 7.10 (m, 7H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.58 – 3.44 (m, 3H), 2.19 (s, 3H), 1.95 – 1.80 (m, 2H), 1.06 (d, *J* = 6.1 Hz, 6H). MS: 486 [M+H]⁺.

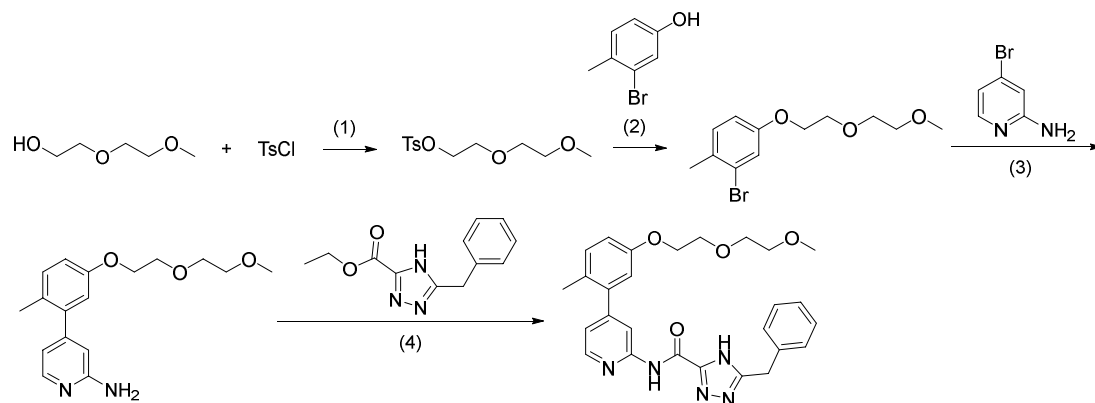
[0404] Example 84: 5-benzyl-N-(4-(5-(2-methyl-5-(3-(2-oxopiperidin-1-yl)propoxy)phenyl)pyridin-2-yl)-

4H-1,2,4-triazole-3-carboxamide



[0405] The operation is the same as Example 81, but piperidin-2-one was used in place of cyclobutanol in the third step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.46 – 7.11 (m, 7H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 3.98 (t, *J* = 6.3 Hz, 2H), 3.28 – 3.20 (m, 4H), 2.26 – 2.13 (m, 5H), 1.91 (t, *J* = 6.8 Hz, 2H), 1.77 – 1.61 (m, 4H). MS: 525 [M+H]⁺.

[0406] Example 85: 5-benzyl-N-(4-(5-(2-(2-methoxyethoxy)ethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0407] Step 1: Synthesis of 2-(2-methoxyethoxy)ethyl 4-methylbenzenesulfonate

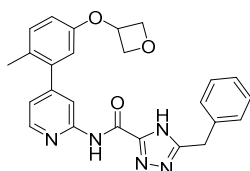
[0408] 2-(2-methoxyethoxy)ethan-1-ol (1g, 8.3mmol) and triethylamine (2.1g, 20.8mmol) were dissolved in dichloromethane (30mL), *p*-toluenesulfonyl chloride (1.75g, 9.2mmol) was added at 0°C, and reacted at 25°C for 2 hours. Saturated aqueous solution of sodium bicarbonate was added, extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford 1.8g of yellow oil.

[0409] Step 2 to Step 4: 5-benzyl-N-(4-(5-(2-(2-methoxyethoxy)ethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

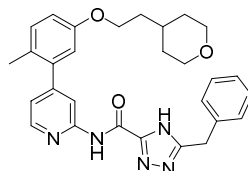
[0410] The operation is the same as steps 4 to 6 of Example 55, but 3-bromo-4-methylphenol was used in place of 3-bromo-N,4-dimethylaniline in the fourth step, 2-(2-methoxyethoxy)ethyl 4-methylbenzenesulfonate was used in place of 1-bromo-2-methoxyethane in the fourth step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (d, *J* = 1.4 Hz, 1H), 7.37 – 7.29 (m, 4H), 7.29 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.14 – 4.05 (m, 2H), 3.76 – 3.67 (m, 2H), 3.61 – 3.53 (m, 2H), 3.47 – 3.41 (m, 2H), 3.23 (s, 3H), 2.19 (s, 3H). MS: 488 [M+H]⁺.

[0411] Example 86: 5-benzyl-N-(4-(2-methyl-5-(oxetan-3-yloxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0412] The preparation was carried out in a similar manner to Example 85, except that in step 1, oxetan-3-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.92 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.43 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 7.20 (dd, *J* = 5.1, 1.5 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.69 (d, *J* = 2.7 Hz, 1H), 5.36 – 5.26 (m, 1H), 4.96 – 4.86 (m, 2H), 4.61 – 4.50 (m, 2H), 4.18 (s, 2H), 2.19 (s, 3H). MS: 442 [M+H]⁺.



Example 86



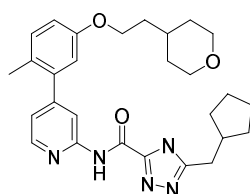
Example 87

[0413] Example 87: 5-benzyl-N-(4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

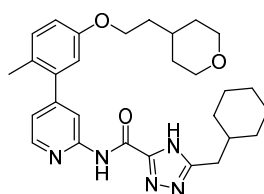
[0414] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.89 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.49 – 7.14 (m, 7H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.89 – 3.75 (m, 2H), 3.30 – 3.19 (m, 2H), 2.19 (s, 3H), 1.77 – 1.55 (m, 5H), 1.26 – 1.12 (m, 2H). MS: 498 [M+H]⁺.

[0415] Example 88: 5-(cyclopentylmethyl)-N-(4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0416] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.84 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.30 – 7.16 (m, 2H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.09 – 3.98 (m, 2H), 3.88 – 3.76 (m, 2H), 3.32 – 3.21 (m, 2H), 2.85 – 2.72 (m, 2H), 2.36 – 2.22 (m, 1H), 2.19 (s, 3H), 1.79 – 1.45 (m, 11H), 1.31 – 1.14 (m, 4H). MS: 490 [M+H]⁺.



Example 88



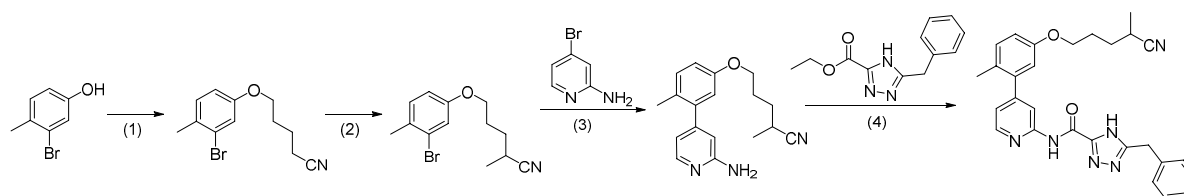
Example 89

[0417] Example 89: 5-(cyclohexylmethyl)-N-(4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-

yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0418] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.85 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.31 – 7.15 (m, 2H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.87 – 3.75 (m, 2H), 3.32 – 3.21 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 1.83 – 1.72 (m, 1H), 1.71 – 1.54 (m, 9H), 1.31 – 1.09 (m, 6H), 1.05 – 0.88 (m, 2H). MS: 504 [M+H]⁺.

[0419] Example 90: 5-benzyl-N-(4-(5-((4-cyanopentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0420] Step 1: Synthesis of 5-(3-bromo-4-methylphenoxy)valeronitrile

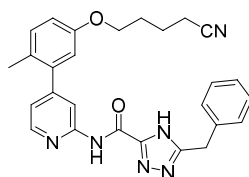
[0421] The operation is the same as step 4 of Example 55, but 3-bromo-4-methylphenol was used in place of 3-bromo-N,4-dimethylaniline in the fourth step, and 5-chlorovaleronitrile was used in place of 1-bromo-2-methoxyethane in the fourth step.

[0422] Step 2: Synthesis of 5-(3-bromo-4-methylphenoxy)-2-methylvaleronitrile

[0423] 5-(3-Bromo-4-methylphenoxy)valeronitrile (268mg, 1mmol) was dissolved in anhydrous tetrahydrofuran (2mL), and LDA (2M, 0.8mL, 1.6mmol) was added dropwise at -78°C under argon protection. After reacting for 1 hour, iodomethane (215mg, 1.5mmol) was added dropwise at the same temperature, the reaction was gradually warmed to 25°C, and reacted for 16 hours. The reaction was quenched with saturated ammonium chloride, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and dried, and purified by column chromatography to afford 210 mg of product.

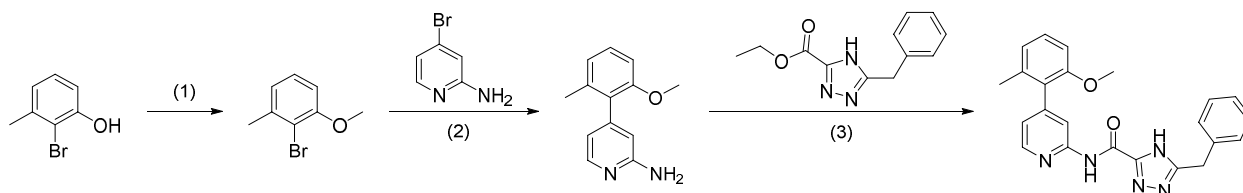
[0424] Step 3 to Step 4: The preparation was carried out in a similar manner to Example 33, except that in step 1, 5-(3-bromo-4-methylphenoxy)-2-methylvaleronitrile was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.47 – 7.16 (m, 7H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.02 (t, *J* = 6.2 Hz, 2H), 2.99 – 2.84 (m, 1H), 2.19 (s, 3H), 1.93 – 1.74 (m, 2H), 1.74 – 1.60 (m, 2H), 1.24 (d, *J* = 7.0 Hz, 3H). MS: 481 [M+H]⁺.

[0425] Example 91: 5-benzyl-N-(4-(5-(4-cyanobutoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0426] The operation is the same as step of Example 90, but the product of the first step 5-(3-bromo-4-methylphenoxy)valeronitrile was used directly to carry out the third to fourth step reaction. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 8.11 (d, *J* = 1.4 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.29 – 7.18 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.02 (t, *J* = 6.1 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 1.93 – 1.59 (m, 4H). MS: 467 [M+H]⁺.

[0427] Example 92: 5-benzyl-N-(4-(2-methoxy-6-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



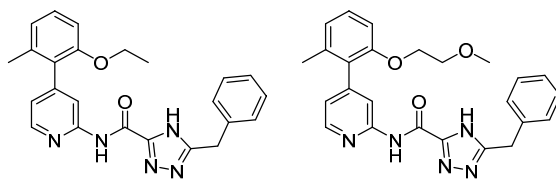
[0428] Step 1: Synthesis of 2-bromo-1-methoxy-3-methylbenzene

[0429] 2-Bromo-3-methylphenol (374mg, 2mmol) was placed in acetonitrile (6mL), potassium carbonate (553mg, 4mmol) was added and stirred at 25°C for 1 hour. Iodomethane (426mg, 3mmol) was added, and reacted at 80°C for 16 hours in sealed tube. The reaction solution was diluted with ethyl acetate, and filtered. The filtrate was evaporated to dryness, and subjected to column chromatography to afford 340 mg of yellow oil. MS: 201 [M+H]⁺

[0430] Step 2 to Step 3: The preparation was carried out in a similar manner to Example 33, except that in step 1, 2-bromo-1-methoxy-3-methylbenzene was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.84 (s, 1H), 8.40 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.96 (s, 1H), 7.46-7.30 (m, 5H), 7.30-7.17 (m, 1H), 7.04 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.01-6.85 (m, 2H), 4.18 (s, 2H), 3.67 (s, 3H), 2.04 (s, 3H). MS: 400 [M+H]⁺.

[0431] Example 93: 5-benzyl-N-(4-(2-ethoxy-6-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0432] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromoethane was used in place of iodomethane. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.83 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 7.99 (s, 1H), 7.43 – 7.29 (m, 4H), 7.29 – 7.16 (m, 2H), 7.05 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.01 – 6.89 (m, 2H), 4.18 (s, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 2.05 (s, 3H), 1.13 (t, *J* = 7.0 Hz, 3H). MS: 414 [M+H]⁺.



Example 93

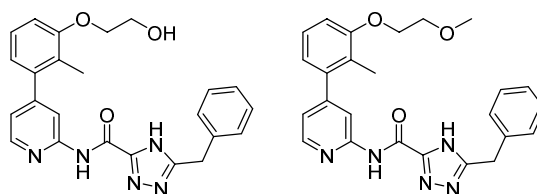
Example 94

[0433] Example 94: 5-benzyl-N-(4-(2-(2-methoxyethoxy)-6-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0434] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.52 (s, 1H), 9.80 (s, 1H), 8.39 (d, $J = 5.1$ Hz, 1H), 8.00 (s, 1H), 7.39-7.30 (m, 4H), 7.30-7.20 (m, 2H), 7.06 (d, $J = 5.1$ Hz, 1H), 7.01-6.87 (m, 2H), 4.19 (s, 2H), 4.09-3.98 (m, 2H), 3.52-3.41 (m, 2H), 3.10 (s, 3H), 2.07 (s, 3H). MS: 444 $[\text{M}+\text{H}]^+$.

[0435] Example 95: 5-benzyl-N-(4-(3-(2-hydroxyethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0436] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromo-1-ethanol was used in place of iodomethane, and 3-bromo-2-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.60 (s, 1H), 9.93 (s, 1H), 8.41 (d, $J = 5.0$ Hz, 1H), 8.10 (d, $J = 1.4$ Hz, 1H), 7.50 – 7.21 (m, 6H), 7.16 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.05 (d, $J = 8.2$ Hz, 1H), 6.85 (d, $J = 7.5$ Hz, 1H), 5.16 – 4.62 (m, 1H), 4.18 (s, 2H), 4.05 (t, $J = 5.0$ Hz, 2H), 3.76 (t, $J = 5.0$ Hz, 2H), 2.11 (s, 3H). MS: 430 $[\text{M}+\text{H}]^+$.



Example 95

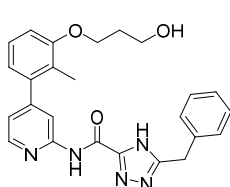
Example 96

[0437] Example 96: 5-benzyl-N-(4-(3-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

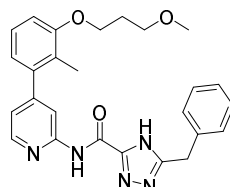
[0438] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, and 3-bromo-2-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.21 (s, 1H), 9.93 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.10 (s, 1H), 7.54 – 7.20 (m, 6H), 7.16 (dd, $J = 5.0, 1.5$ Hz, 1H), 7.05 (d, $J = 8.2$ Hz, 1H), 6.86 (d, $J = 7.6$ Hz, 1H), 4.28 – 4.06 (m, 4H), 3.75 – 3.66 (m, 2H), 3.33 (s, 3H), 2.09 (s, 3H). MS: 444 $[\text{M}+\text{H}]^+$.

[0439] Example 97: 5-benzyl-N-(4-(3-(3-hydroxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0440] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-1-propanol was used in place of iodomethane, and 3-bromo-2-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.08 (d, *J* = 1.4 Hz, 1H), 7.44-7.21 (m, 6H), 7.17 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 4.58 (t, *J* = 5.0 Hz, 1H), 4.17 (s, 2H), 4.09 (t, *J* = 6.2 Hz, 2H), 3.64-3.56 (m, 2H), 2.08 (s, 3H), 1.95-1.84 (m, 2H). MS: 444 [M+H]⁺.



Example 97

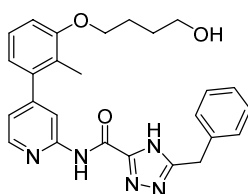


Example 98

[0441] Example 98: 5-benzyl-N-(4-(3-(3-methoxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

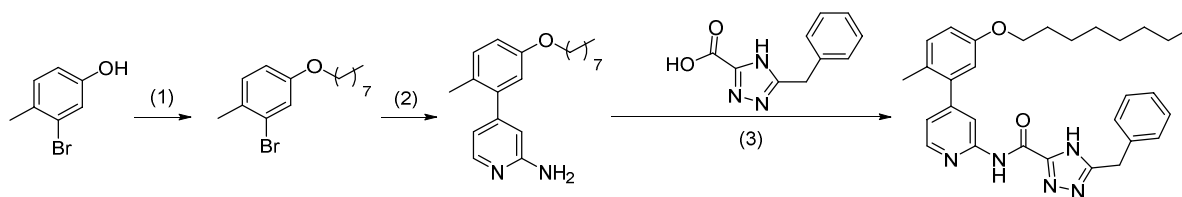
[0442] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, and 3-bromo-2-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.92 (s, 1H), 8.51 – 8.31 (m, 1H), 8.20 – 7.99 (m, 1H), 7.42 – 7.30 (m, 4H), 7.30 – 7.20 (m, 2H), 7.16 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.04 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.85 (dd, *J* = 7.7, 1.1 Hz, 1H), 4.17 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.51 (t, *J* = 6.3 Hz, 2H), 3.25 (s, 3H), 2.08 (s, 3H), 2.04 – 1.91 (m, 2H). MS: 458 [M+H]⁺.

[0443] Example 99: 5-benzyl-N-(4-(3-(4-hydroxybutoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0444] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, and 3-bromo-2-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.0 Hz, 1H), 8.09 (s, 1H), 7.40-7.21 (m, 6H), 7.17 (d, *J* = 5.1 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 4.53-4.41 (m, 1H), 4.17 (s, 2H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.51-3.44 (m, 2H), 2.09 (s, 3H), 1.87-1.73 (m, 2H), 1.68-1.55 (m, 2H). MS: 458 [M+H]⁺.

[0445] Example 100: 5-benzyl-N-(4-(2-methyl-5-(octyloxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



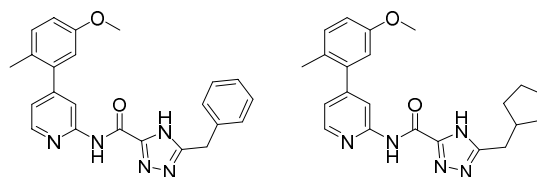
[0446] Step 1 to Step 2: Synthesis of 4-(2-methyl-5-(octyloxy)phenyl)pyridin-2-amine

[0447] The operation is the same as steps 1 to 2 of Example 92, but 3-bromo-2-methylphenol was used in place of 2-bromo-3-methylphenol in step 1, and 1-bromooctane was used in place of iodomethane in step 1. MS: 313 [M+H]⁺.

[0448] Step 3: Intermediate 2 (98mg, 0.48mmol) was dissolved in DMF (3mL), 1-propanephosphonic acid cyclic anhydride (50%, 305mg, 0.48mmol), diisopropylethylamine (124mg, 0.96mmol) and 4-(2-methyl-5-(octyloxy)phenyl)pyridin-2-amine (100mg, 0.3mmol) were added, and reacted at 25°C for 16 hours. The reaction solution was diluted with water, extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, evaporated to dryness, and subjected to column chromatography and preparative liquid chromatography to afford 30mg of white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.74 (s, 1H), 9.92 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.12 (d, *J* = 1.4 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.13 (m, 3H), 6.91 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 4.17 (s, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.18 (s, 3H), 1.76 – 1.57 (m, 2H), 1.45 – 1.33 (m, 2H), 1.33 – 1.14 (m, 8H), 0.91 – 0.76 (m, 3H). MS: 498 [M+H]⁺.

[0449] Example 101: 5-benzyl-N-(4-(5-methoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0450] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.42 – 7.31 (m, 4H), 7.31 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.0, 1.5 Hz, 1H), 6.94 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.82 (d, *J* = 2.8 Hz, 1H), 4.18 (s, 2H), 3.77 (s, 3H), 2.19 (s, 3H). MS: 400 [M+H]⁺.



Example 101

Example 102

[0451] Example 102: 5-(cyclopentylmethyl)-N-(4-(5-methoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0452] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400

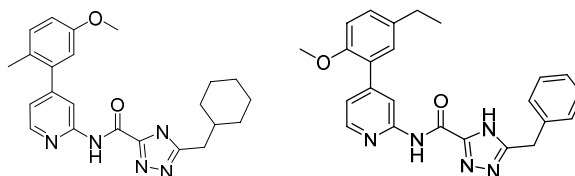
MHz, DMSO- d_6) δ 14.37 (s, 1H), 9.85 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.14 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 5.1 Hz, 1H), 6.95 (dd, J = 8.5, 2.8 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 3.77 (s, 3H), 2.78 (d, J = 7.5 Hz, 2H), 2.34 – 2.22 (m, 1H), 2.20 (s, 3H), 1.80 – 1.66 (m, 2H), 1.66 – 1.43 (m, 4H), 1.30 – 1.13 (m, 2H). MS: 392 $[M+H]^+$.

5

[0453] Example 103: 5-(cyclohexylmethyl)-N-(4-(5-methoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0454] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.38 (s, 1H), 9.86 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.14 (s, 1H), 7.34 – 7.16 (m, 2H), 7.03 – 6.88 (m, 1H), 6.83 (d, J = 2.9 Hz, 1H), 3.77 (s, 3H), 2.66 (d, J = 7.0 Hz, 2H), 2.19 (s, 3H), 1.83-1.52 (m, 6H), 1.30-1.06 (m, 3H), 1.06-0.86 (m, 2H). MS: 406 $[M+H]^+$.

10



Example 103

Example 104

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[0455] Example 104: 5-benzyl-N-(4-(5-ethyl-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0456] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromo-4-ethylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, DMSO- d_6) δ 14.59 (s, 1H), 9.83 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 1.4 Hz, 1H), 7.54 – 7.16 (m, 8H), 7.09 (d, J = 8.4 Hz, 1H), 4.17 (s, 2H), 3.78 (s, 3H), 2.61 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.5 Hz, 3H). MS: 414 $[M+H]^+$.

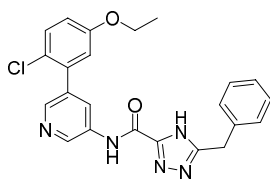
20

[0457] Example 105: 5-benzyl-N-(5-(2-chloro-5-ethoxyphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

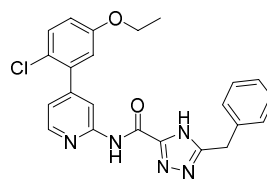
[0458] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromoethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 2, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ^1H NMR (400 MHz, DMSO- d_6) δ 14.60 (s, 1H), 10.82 (s, 1H), 9.03 (d, J = 2.3 Hz, 1H), 8.44 – 8.29 (m, 2H), 7.49 (d, J = 8.7 Hz, 1H), 7.39 – 7.20 (m, 5H), 7.08 – 6.97 (m, 2H), 4.17 (s, 2H), 4.08 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 6.9 Hz, 3H). MS: 434 $[M+H]^+$.

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Example 105



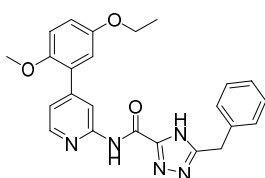
Example 106

[0459] Example 106: 5-benzyl-N-(4-(2-chloro-5-ethoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

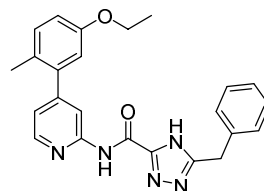
[0460] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromoethane was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.65 (s, 1H), 9.94 (s, 1H), 8.45 (d, $J = 5.2$ Hz, 1H), 8.23 (d, $J = 1.5$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.40 – 7.30 (m, 4H), 7.30 – 7.20 (m, 2H), 7.06 (dd, $J = 8.8, 3.1$ Hz, 1H), 7.01 (d, $J = 3.0$ Hz, 1H), 4.18 (s, 2H), 4.08 (q, $J = 7.0$ Hz, 2H), 1.33 (t, $J = 7.0$ Hz, 3H). MS: 434 $[\text{M}+\text{H}]^+$.

[0461] Example 107: 5-benzyl-N-(4-(5-ethoxy-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0462] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromoethane was used in place of iodomethane, and 3-bromo-4-methoxyphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 14.54 (s, 1H), 9.79 (s, 1H), 8.43 – 8.24 (m, 2H), 7.47 – 7.29 (m, 5H), 7.27 (d, $J = 6.5$ Hz, 1H), 7.10 (d, $J = 9.0$ Hz, 1H), 7.01 (dd, $J = 9.0, 3.1$ Hz, 1H), 6.94 (d, $J = 3.1$ Hz, 1H), 4.19 (s, 2H), 4.03 (q, $J = 6.9$ Hz, 2H), 3.75 (s, 3H), 1.32 (t, $J = 6.9$ Hz, 3H). MS: 430 $[\text{M}+\text{H}]^+$.



Example 107



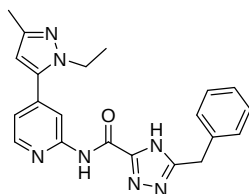
Example 108

[0463] Example 108: 5-benzyl-N-(4-(5-ethoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

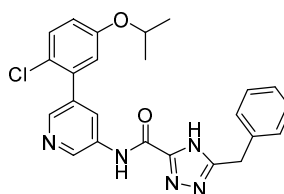
[0464] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromoethane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 14.62 (s, 1H), 9.90 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.22 (m, 2H), 7.20 (dd, $J = 5.1, 1.5$ Hz, 1H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.17 (s, 2H), 4.04 (q, $J = 7.0$ Hz, 2H), 2.19 (s, 3H), 1.32 (t, $J = 7.0$ Hz, 3H). MS: 414 $[\text{M}+\text{H}]^+$.

[0465] Example 109: 5-benzyl-N-(4-(1-ethyl-3-methyl-1H-pyrazol-5-yl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0466] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromoethane was used in place of iodomethane, and 5-bromo-3-methyl-1H-pyrazole was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.98 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.35 – 8.14 (m, 1H), 7.51 – 7.15 (m, 6H), 6.35 (s, 1H), 4.29 – 3.95 (m, 4H), 2.21 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H). MS: 388 [M+H]⁺.



Example 109



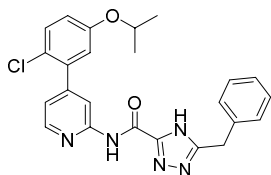
Example 110

[0467] Example 110: 5-benzyl-N-(5-(2-chloro-5-isopropoxyphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

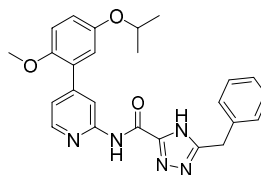
[0468] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromopropane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 2, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 10.83 (s, 1H), 9.04 (d, *J* = 2.2 Hz, 1H), 8.49 – 8.20 (m, 2H), 7.48 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.31 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 7.07 – 6.98 (m, 2H), 4.74 – 4.64 (m, 1H), 4.18 (s, 2H), 1.28 (dd, *J* = 6.1, 1.9 Hz, 6H). MS: 448 [M+H]⁺.

[0469] Example 111: 5-benzyl-N-(4-(2-chloro-5-isopropoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0470] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromopropane was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.94 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.50 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.22 (m, 2H), 7.09 – 7.02 (m, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 4.69 (p, *J* = 6.0 Hz, 1H), 4.17 (s, 2H), 1.28 (d, *J* = 6.1, 2.7 Hz, 6H). MS: 448 [M+H]⁺.



Example 111



Example 112

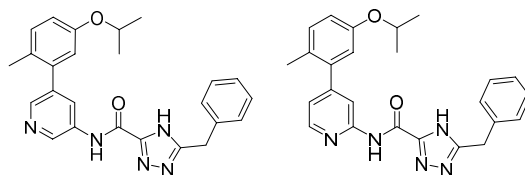
[0471] Example 112: 5-benzyl-N-(4-(5-isopropoxy-2-methoxyphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0472] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromopropane was used in place of iodomethane, and 3-bromo-4-methoxyphenol was used in place of 2-bromo-

3-methylphenol. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 14.59 (s, 1H), 9.84 (s, 1H), 8.37 (d, $J = 5.2$ Hz, 1H), 8.30 (s, 1H), 7.40 – 7.29 (m, 5H), 7.29 – 7.22 (m, 1H), 7.09 (d, $J = 9.0$ Hz, 1H), 7.00 (dd, $J = 8.9, 3.0$ Hz, 1H), 6.93 (d, $J = 3.0$ Hz, 1H), 4.56 (p, $J = 6.0$ Hz, 1H), 4.18 (s, 2H), 3.75 (s, 3H), 1.25 (d, $J = 6.0$ Hz, 6H). MS: 444 $[\text{M}+\text{H}]^+$.

[0473] Example 113: 5-benzyl-N-(5-(5-isopropoxy-2-methylphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

[0474] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromopropane was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 2, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.62 (s, 1H), 10.79 (s, 1H), 9.02 (d, $J = 2.3$ Hz, 1H), 8.31 (d, $J = 2.0$ Hz, 1H), 8.25 – 8.08 (m, 1H), 7.42 – 7.16 (m, 6H), 6.88 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.79 (d, $J = 2.7$ Hz, 1H), 4.62 (p, $J = 6.0$ Hz, 1H), 4.17 (s, 2H), 2.17 (s, 3H), 1.26 (d, $J = 6.0$ Hz, 6H). MS: 428 $[\text{M}+\text{H}]^+$.



Example 113

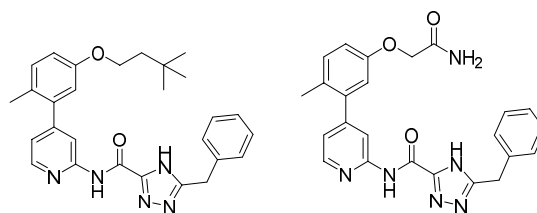
Example 114

[0475] Example 114: 5-benzyl-N-(4-(5-isopropoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0476] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromopropane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 14.57 (s, 1H), 9.90 (s, 1H), 8.58 – 8.29 (m, 1H), 8.11 (s, 1H), 7.63 – 7.29 (m, 4H), 7.29 – 7.06 (m, 3H), 6.92 (d, $J = 8.0$ Hz, 1H), 6.78 (d, $J = 3.5$ Hz, 1H), 4.67 – 4.54 (m, 1H), 4.17 (s, 2H), 2.18 (s, 3H), 1.26 (d, $J = 6.3, 3.3$ Hz, 6H). MS: 428 $[\text{M}+\text{H}]^+$.

[0477] Example 115: 5-benzyl-N-(4-(5-(3,3-dimethylbutoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0478] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3,3-dimethylbutane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.62 (s, 1H), 9.91 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.48 – 7.13 (m, 7H), 6.94 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.82 (d, $J = 2.7$ Hz, 1H), 4.17 (s, 2H), 4.02 (t, $J = 7.2$ Hz, 2H), 2.18 (s, 3H), 1.65 (t, $J = 7.2$ Hz, 2H), 0.95 (s, 9H). MS: 470 $[\text{M}+\text{H}]^+$.



Example 115

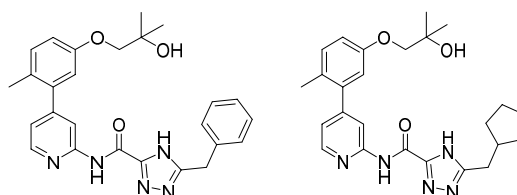
Example 116

[0479] Example 116: N-(4-(5-(2-amino-2-oxoethoxy)-2-methylphenyl)pyridin-2-yl)-5-benzyl-4H-1,2,4-triazole-3-carboxamide

[0480] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-chloroacetamide was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.91 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.54 (s, 1H), 7.42 – 7.30 (m, 5H), 7.30 – 7.22 (m, 2H), 7.20 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.88 (d, *J* = 2.8 Hz, 1H), 4.44 (s, 2H), 4.18 (s, 2H), 2.20 (s, 3H). MS: 443 [M+H]⁺.

[0481] Example 117: 5-benzyl-N-(4-(5-(2-hydroxyl-2-methylpropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0482] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-chloro-2-methylpropyl-2-ol was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.91 – 14.25 (m, 1H), 9.90 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.45 – 7.13 (m, 7H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.61 (s, 1H), 4.18 (s, 2H), 3.73 (s, 2H), 2.19 (s, 3H), 1.19 (s, 6H). MS: 458 [M+H]⁺.



Example 117

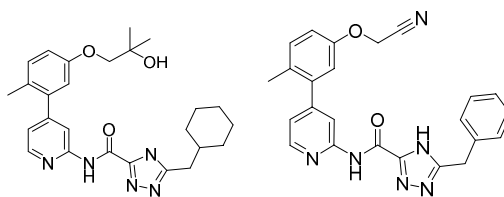
Example 118

[0483] Example 118: 5-(cyclopentylmethyl)-N-(4-(5-(2-hydroxyl-2-methylpropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0484] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-chloro-2-methylpropyl-2-ol was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.87 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.14 (d, *J* = 1.4 Hz, 1H), 7.32 – 7.17 (m, 2H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.63 (s, 1H), 3.73 (s, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.33 – 2.22 (m, 1H), 2.20 (s, 3H), 1.80 – 1.66 (m, 2H), 1.66 – 1.42 (m, 4H), 1.30 – 1.10 (m, 8H). MS: 450 [M+H]⁺.

[0485] Example 119: 5-(cyclohexylmethyl)-N-(4-(5-(2-hydroxy-2-methylpropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0486] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-chloro-2-methylpropyl-2-ol was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.85 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.34-7.14 (m, 2H), 6.95 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 4.63 (s, 1H), 3.73 (s, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.20 (s, 3H), 1.84-1.53 (m, 6H), 1.31-1.05 (m, 9H), 1.05-0.88 (m, 2H). MS: 464 [M+H]⁺.



Example 119

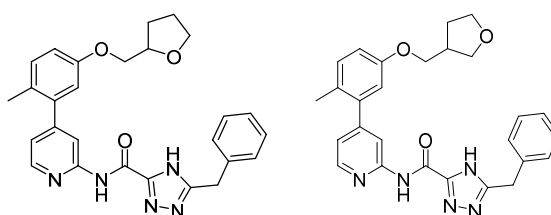
Example 120

[0487] Example 120: 5-benzyl-N-(4-(5-(cyanomethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0488] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromoacetonitrile was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.91 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.41-7.29 (m, 5H), 7.29-7.18 (m, 2H), 7.08 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.99 (d, *J* = 2.8 Hz, 1H), 5.20 (s, 2H), 4.18 (s, 2H), 2.22 (s, 3H). MS: 425 [M+H]⁺.

[0489] Example 121: 5-benzyl-N-(4-(2-methyl-5-((tetrahydrofuran-2-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0490] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-(bromomethyl)tetrahydrofuran was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.44-7.29 (m, 4H), 7.29-7.12 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.26-4.07 (m, 3H), 4.02-3.86 (m, 2H), 3.82-3.72 (m, 1H), 3.72-3.61 (m, 1H), 2.19 (s, 3H), 2.06-1.92 (m, 1H), 1.92-1.73 (m, 2H), 1.73 – 1.58 (m, 1H). MS: 470 [M+H]⁺.



Example 121

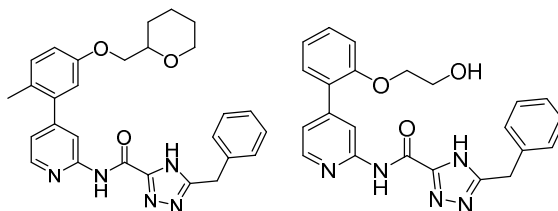
Example 122

[0491] Example 122: 5-benzyl-N-(4-(2-methyl-5-((tetrahydrofuran-3-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0492] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-(bromomethyl)tetrahydrofuran was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.00 – 3.84 (m, 2H), 3.83 – 3.70 (m, 2H), 3.70 – 3.58 (m, 1H), 3.57 – 3.47 (m, 1H), 2.71 – 2.57 (m, 1H), 2.19 (s, 3H), 2.07 – 1.92 (m, 1H), 1.72 – 1.57 (m, 1H). MS: 470 [M+H]⁺.

[0493] Example 123: 5-benzyl-N-(4-(2-methyl-5-((tetrahydro-2H-pyran-2-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0494] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-(bromomethyl)tetrahydro-2H-pyran was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.94 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.11 (s, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.15 (m, 3H), 6.93 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 3.97 – 3.81 (m, 3H), 3.63 – 3.56 (m, 2H), 2.18 (s, 3H), 1.85 – 1.73 (m, 1H), 1.68 – 1.57 (m, 1H), 1.55 – 1.39 (m, 3H), 1.37 – 1.16 (m, 1H). MS: 484 [M+H]⁺.



Example 123

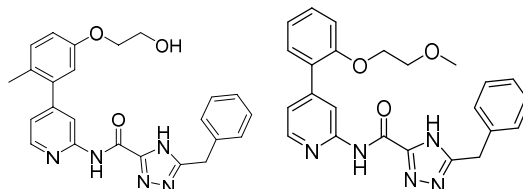
Example 124

[0495] Example 124: 5-benzyl-N-(4-(2-(2-hydroxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0496] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromo-1-ethanol was used in place of iodomethane, and 2-bromophenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.78 (s, 1H), 8.47 – 8.26 (m, 2H), 7.46 – 7.39 (m, 3H), 7.37 – 7.31 (m, 4H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.12 – 7.07 (m, 1H), 4.76 (t, *J* = 5.5 Hz, 1H), 4.18 (s, 2H), 4.08 (t, *J* = 5.2 Hz, 2H), 3.78 – 3.67 (m, 2H). MS: 416 [M+H]⁺.

[0497] Example 125: 5-benzyl-N-(4-(5-(2-hydroxyethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0498] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromo-1-ethanol was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.85 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.44 – 7.14 (m, 7H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.19 (s, 2H), 4.00 (t, *J* = 5.0 Hz, 2H), 3.77 – 3.62 (m, 2H), 2.19 (s, 3H). MS: 430 [M+H]⁺.



Example 125

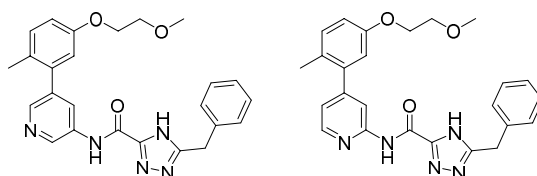
Example 126

[0499] Example 126: 5-benzyl-N-(4-(2-(2-methoxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0500] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, and 2-bromophenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.81 (s, 1H), 8.42 – 8.32 (m, 2H), 7.46 – 7.40 (m, 2H), 7.39 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.12 – 7.08 (m, 1H), 4.22 – 4.14 (m, 4H), 3.69 – 3.63 (m, 2H), 3.22 (s, 3H). MS: 430 [M+H]⁺.

[0501] Example 127: 5-benzyl-N-(5-(5-(2-methoxyethoxy)-2-methylphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

[0502] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 2, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.49 (s, 1H), 10.72 (s, 1H), 9.02 (d, *J* = 2.3 Hz, 1H), 8.31 (d, *J* = 1.9 Hz, 1H), 8.25 – 8.16 (m, 1H), 7.39 – 7.19 (m, 6H), 6.92 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.13 – 4.05 (m, 2H), 3.69 – 3.61 (m, 2H), 3.30 (s, 3H), 2.18 (s, 3H). MS: 444 [M+H]⁺.



Example 127

Example 128

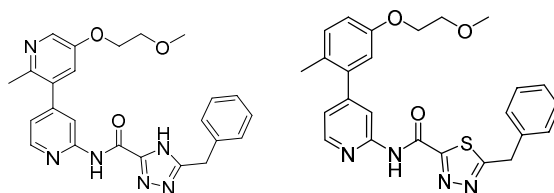
[0503] Example 128: 5-benzyl-N-(4-(5-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0504] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-

3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.55 (s, 1H), 9.85 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.13 (s, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.16 (m, 3H), 6.95 (dd, $J = 8.4, 2.8$ Hz, 1H), 6.83 (d, $J = 2.8$ Hz, 1H), 4.19 (s, 2H), 4.11 (t, $J = 4.6$ Hz, 2H), 3.65 (t, $J = 4.6$ Hz, 2H), 3.30 (s, 3H), 2.19 (s, 3H). MS: 444 $[\text{M}+\text{H}]^+$.

[0505] Example 129: 5-benzyl-N-(5-(2-methoxyethoxy)-2-methyl-[3,4'-bipyridin]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0506] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, and 5-bromo-6-methylpyridin-3-ol (for the synthetic method refers to Lin, Nan-Horng et al/ U.S., 6437138, 20 Aug 2002) was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.62 (s, 1H), 9.97 (s, 1H), 8.46 (d, $J = 5.1$ Hz, 1H), 8.28 (d, $J = 2.9$ Hz, 1H), 8.16 (s, 1H), 7.42 – 7.20 (m, 7H), 4.28 – 4.11 (m, 4H), 3.66 (s, 2H), 3.30 (s, 3H), 2.39 (s, 3H). MS: 445 $[\text{M}+\text{H}]^+$.



Example 129

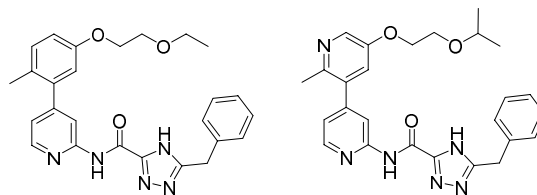
Example 130

[0507] Example 130: 5-benzyl-N-(4-(5-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)-1,3,4-thiodiazol-2-carboxamide

[0508] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, methyl 5-benzyl-1,3,4-thiodiazol-2-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.84 (s, 1H), 8.47 (dd, $J = 5.1, 0.7$ Hz, 1H), 8.00 (dd, $J = 1.6, 0.8$ Hz, 1H), 7.44 – 7.20 (m, 7H), 6.94 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.83 (d, $J = 2.8$ Hz, 1H), 4.58 (s, 2H), 4.14 – 4.05 (m, 2H), 3.69 – 3.60 (m, 2H), 3.30 (s, 3H), 2.19 (s, 3H). MS: 461 $[\text{M}+\text{H}]^+$.

[0509] Example 131: 5-benzyl-N-(4-(5-(2-ethoxyethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0510] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.62 (s, 1H), 9.91 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.12 (s, 1H), 7.45 – 7.13 (m, 7H), 6.95 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.84 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 2H), 4.14 – 4.02 (m, 2H), 3.76 – 3.64 (m, 2H), 3.49 (q, $J = 7.0$ Hz, 2H), 2.19 (s, 3H), 1.12 (t, $J = 7.0$ Hz, 3H). MS: 458 $[\text{M}+\text{H}]^+$.



Example 131

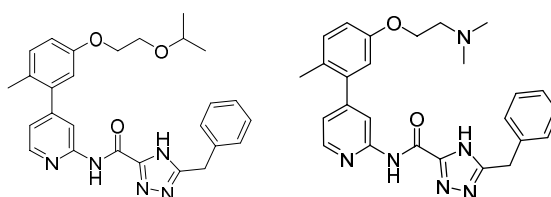
Example 132

[0511] Example 132: 5-benzyl-N-(5-(2-isopropoxyethoxy)-2-methyl-[3,4'-dipyridine]-2'-yl)-4H-1,2,4-triazole-3-carboxamide

[0512] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, and 5-bromo-6-methylpyridin-3-ol (for the synthetic method refers to Lin, Nan-Horng et al/ U.S., 6437138, 20 Aug 2002) was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 9.98 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.27 (d, *J* = 2.9 Hz, 1H), 8.16 (s, 1H), 7.41 – 7.18 (m, 7H), 4.26 – 4.07 (m, 4H), 3.69 (s, 2H), 3.61 (p, *J* = 6.1 Hz, 1H), 2.39 (s, 3H), 1.09 (d, *J* = 6.0 Hz, 6H). MS: 473 [M+H]⁺.

[0513] Example 133: 5-benzyl-N-(4-(5-(2-isopropoxyethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0514] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.90 (s, 1H), 8.42 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.12 (s, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.18 (m, 3H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 4.17 (s, 2H), 4.12 – 4.01 (m, 2H), 3.74 – 3.65 (m, 2H), 3.61 (p, *J* = 6.1 Hz, 1H), 2.19 (s, 3H), 1.10 (d, *J* = 6.1 Hz, 6H). MS: 472 [M+H]⁺.



Example 133

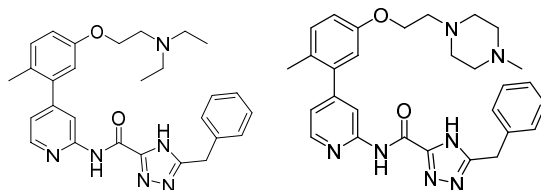
Example 134

[0515] Example 134: 5-benzyl-N-(4-(5-(2-(dimethylamino)ethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0516] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromo-N,N-dimethyl-1-ethylamine hydrochloride was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.89-14.02 (m, 1H), 9.90 (s, 1H), 8.42 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.15-8.07 (m, 1H), 7.39-7.30 (m, 4H), 7.30-7.17 (m, 3H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.06 (t, *J* = 5.8 Hz, 2H), 2.62 (t, *J* = 5.8 Hz, 2H), 2.21 (s, 6H), 2.19 (s, 3H). MS: 457 [M+H]⁺.

[0517] Example 135: 5-benzyl-N-(4-(5-(2-(diethylamino)ethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0518] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-bromo-N,N-dimethyl-1-ethylamine hydrochloride was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.20 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (d, *J* = 1.5 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.18 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 6.1 Hz, 2H), 2.60 (q, *J* = 7.1 Hz, 4H), 2.19 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 6H). MS: 485 [M+H]⁺.



Example 135

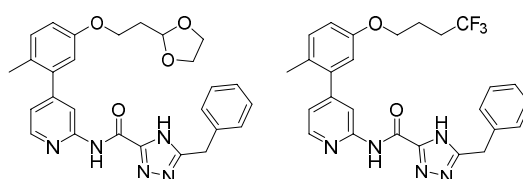
Example 136

[0519] Example 136: 5-benzyl-N-(4-(2-methyl-5-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0520] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-chloroethyl)-4-methylpiperazine dihydrochloride was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.97 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.12 (s, 1H), 7.40 – 7.15 (m, 7H), 6.94 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.84 (d, *J* = 2.8 Hz, 1H), 4.17 (s, 2H), 4.08 (t, *J* = 5.9 Hz, 2H), 2.67 (t, *J* = 5.8 Hz, 2H), 2.46 (s, 4H), 2.30 (s, 4H), 2.19 (s, 3H), 2.13 (s, 3H). MS: 512 [M+H]⁺.

[0521] Example 137: N-(4-(5-(2-(1,3-dioxolan-2-yl)ethoxy)-2-methylphenyl)pyridin-2-yl)-5-benzyl-4H-1,2,4-triazole-3-carboxamide

[0522] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-(2-bromoethyl)-1,3-dioxolane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.45 – 7.15 (m, 7H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.98 (t, *J* = 4.9 Hz, 1H), 4.18 (s, 2H), 4.08 (t, *J* = 6.6 Hz, 2H), 3.96 – 3.84 (m, 2H), 3.84 – 3.71 (m, 2H), 2.19 (s, 3H), 2.10 – 1.95 (m, 2H). MS: 486 [M+H]⁺.



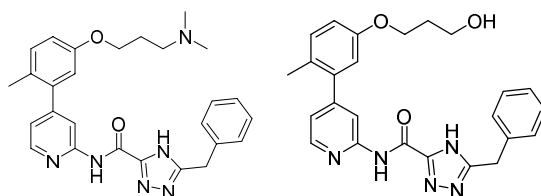
Example 137 Example 138

[0523] Example 138: 5-benzyl-N-(4-(2-methyl-5-(4,4,4-trifluorobutoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0524] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1,1,1-trifluorobutane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (d, *J* = 1.5 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 2.47 – 2.31 (m, 2H), 2.19 (s, 3H), 1.99 – 1.85 (m, 2H). MS: 496 [M+H]⁺.

[0525] Example 139: 5-benzyl-N-(4-(5-(3-(dimethylamino)propoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0526] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-N,N-dimethyl-1-propylamine hydrochloride was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.57 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.39-7.29 (m, 4H), 7.29-7.14 (m, 3H), 6.92 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 2.36 (t, *J* = 7.1 Hz, 2H), 2.18 (s, 3H), 2.14 (s, 6H), 1.89-1.77 (m, 2H). MS: 471 [M+H]⁺.



Example 139 Example 140

[0527] Example 140: 5-benzyl-N-(4-(5-(3-hydroxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

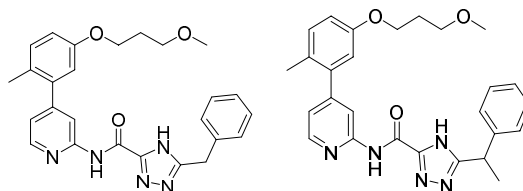
[0528] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-1-propanol was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.80 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.38 – 7.30 (m, 4H), 7.26 (dd, *J* = 7.5, 4.8 Hz, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.54 (t, *J* = 5.1 Hz, 1H), 4.17 (s, 2H), 4.04 (t, *J* = 6.4 Hz, 2H), 3.57 – 3.52 (m, 2H), 2.19 (s, 3H), 1.91 – 1.79 (m, 2H). MS: 444 [M+H]⁺.

[0529] Example 141: 5-benzyl-N-(4-(5-(3-methoxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0530] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-

methoxypropane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.90 (s, 1H), 8.41 (dd, *J* = 5.2, 2.1 Hz, 1H), 8.11 (d, *J* = 1.6 Hz, 1H), 7.45-7.15 (m, 7H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 4.17 (s, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.48-3.44 (m, 2H), 3.23 (d, *J* = 2.1 Hz, 3H), 2.19 (d, *J* = 2.1 Hz, 3H), 2.02-1.85 (m, 2H).

MS: 458 [M+H]⁺.



Example 141

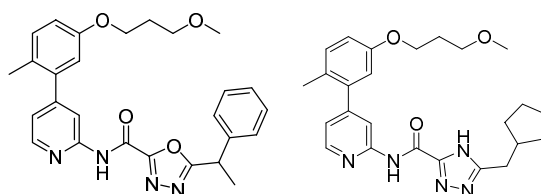
Example 142

[0531] Example 142: N-(4-(5-(3-methoxypropoxy)-2-methylphenyl)pyridin-2-yl)-5-(1-phenylethyl)-4H-1,2,4-triazole-3-carboxamide

[0532] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(1-phenylethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.44 – 7.28 (m, 4H), 7.29 – 7.17 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.24 (s, 3H), 2.19 (s, 3H), 1.98 – 1.87 (m, 2H), 1.67 (d, *J* = 7.2 Hz, 3H). MS: 472 [M+H]⁺.

[0533] Example 143: N-(4-(5-(3-methoxypropoxy)-2-methylphenyl)pyridin-2-yl)-5-(1-phenylethyl)-1,3,4-oxadiazol-2-carboxamide

[0534] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, in step 3, ethyl 5-(1-phenylethyl)-1,3,4-oxadiazol-2-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.29 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 7.96 (s, 1H), 7.43 – 7.20 (m, 7H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.63 (q, *J* = 7.2 Hz, 1H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 6.3 Hz, 2H), 3.34 (s, 3H), 2.18 (s, 3H), 1.98 – 1.87 (m, 2H), 1.71 (d, *J* = 7.2 Hz, 3H). MS: 473 [M+H]⁺.



Example 143

Example 144

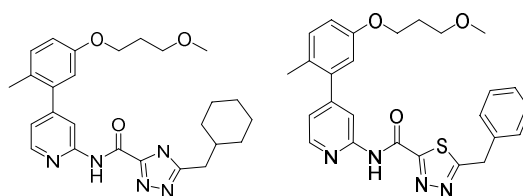
[0535] Example 144: 5-(cyclopentylmethyl)-N-(4-(5-(3-methoxypropoxy)-2-methylphenyl)pyridin-2-yl)-

4H-1,2,4-triazole-3-carboxamide

[0536] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.84 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.33 – 7.14 (m, 2H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.24 (s, 3H), 2.84-2.74 (m, 2H), 2.36-2.22 (m, 1H), 2.20 (s, 3H), 2.00-1.88 (m, 2H), 1.79-1.66 (m, 2H), 1.66-1.56 (m, 2H), 1.56-1.45 (m, 2H), 1.27-1.18 (m, 2H). MS: 450 [M+H]⁺.

[0537] Example 145: 5-(cyclohexylmethyl)-N-(4-(5-(3-methoxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0538] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.97 – 9.76 (m, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.34 – 7.12 (m, 2H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.8 Hz, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.24 (s, 3H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 2.01 – 1.86 (m, 2H), 1.84 – 1.53 (m, 6H), 1.30 – 1.06 (m, 3H), 1.06 – 0.87 (m, 2H). MS: 464 [M+H]⁺.



Example 145

Example 146

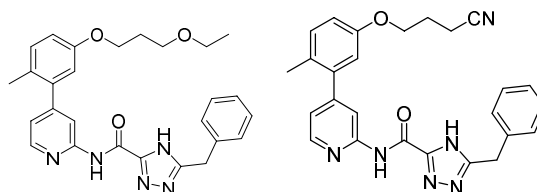
[0539] Example 146: 5-benzyl-N-(4-(5-(3-methoxypropoxy)-2-methylphenyl)pyridin-2-yl)-1,3,4-thiodiazol-2-carboxamide

[0540] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, methyl 5-benzyl-1,3,4-thiodiazol-2-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.84 (s, 1H), 8.47 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.99 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.46 – 7.17 (m, 7H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.58 (s, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.23 (s, 3H), 2.18 (s, 3H), 2.00 – 1.87 (m, 2H). MS: 475 [M+H]⁺.

[0541] Example 147: 5-benzyl-N-(4-(5-(3-ethoxypropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-

3-carboxamide

[0542] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-ethoxypropane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.92 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.46 – 7.29 (m, 4H), 7.29 – 7.14 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.49 (t, *J* = 6.3 Hz, 2H), 3.41 (q, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 2.00 – 1.86 (m, 2H), 1.08 (t, *J* = 7.0 Hz, 3H). MS: 472 [M+H]⁺.



Example 147

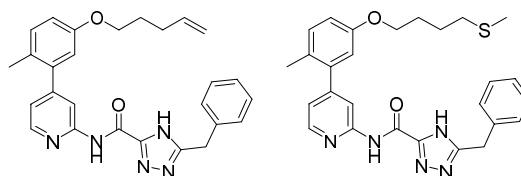
Example 148

[0543] Example 148: 5-benzyl-N-(4-(5-(3-cyanopropoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0544] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanenitrile was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.45 – 7.14 (m, 7H), 6.96 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 2.19 (s, 3H), 2.06 – 1.96 (m, 2H). MS: 453 [M+H]⁺.

[0545] Example 149: 5-benzyl-N-(4-(2-methyl-5-(pent-4-en-1-yloxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0546] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentene was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.97 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.44 – 7.16 (m, 7H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 5.94 – 5.77 (m, 1H), 5.62 – 5.40 (m, 1H), 5.12 – 4.91 (m, 1H), 4.18 (s, 2H), 4.06 – 3.91 (m, 2H), 2.44 – 2.32 (m, 1H), 2.19 (s, 3H), 1.87 – 1.72 (m, 1H), 1.69 – 1.55 (m, 2H). MS: 454 [M+H]⁺.



Example 149

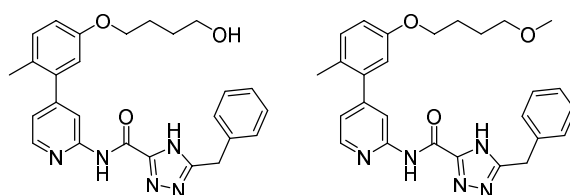
Example 150

[0547] Example 150: 5-benzyl-N-(4-(2-methyl-5-(4-(methylthio)butoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0548] The preparation was carried out in a similar manner to Example 92, except that in step 1, (4-bromobutyl)(methyl)sulfane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.23 (m, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.00 (t, *J* = 6.4 Hz, 2H), 2.58 – 2.52 (m, 2H), 2.19 (s, 3H), 2.03 (s, 3H), 1.85 – 1.73 (m, 2H), 1.73 – 1.61 (m, 2H). MS: 488 [M+H]⁺.

[0549] Example 151: 5-benzyl-N-(4-(5-(4-hydroxybutoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0550] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.22 (m, 2H), 7.21 (dd, *J* = 5.2, 1.6 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.51 – 4.35 (m, 1H), 4.17 (s, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.19 (s, 3H), 1.80 – 1.67 (m, 2H), 1.62 – 1.49 (m, 2H). MS: 458 [M+H]⁺.



Example 151

Example 152

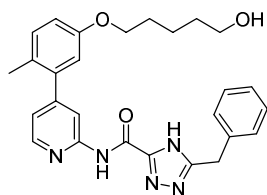
[0551] Example 152: 5-benzyl-N-(4-(5-(4-methoxybutoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0552] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-4-methoxybutane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.91 (s, 1H), 8.47 – 8.34 (m, 1H), 8.18 – 8.03 (m, 1H), 7.43 – 7.13 (m, 7H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.35 (t, *J* = 6.3 Hz, 2H), 3.22 (s, 3H), 2.19 (s, 3H), 1.81 – 1.68 (m, 2H), 1.68 – 1.56 (m, 2H). MS: 472 [M+H]⁺.

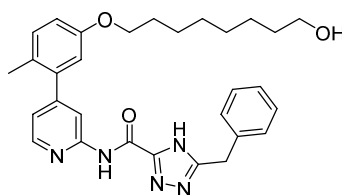
[0553] Example 153: 5-benzyl-N-(4-(5-((5-hydroxypentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0554] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.42-7.30 (m, 4H), 7.30-7.13 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.45-4.31

(m, 1H), 4.18 (s, 2H), 3.97 (t, $J = 6.5$ Hz, 2H), 3.46-3.36 (m, 2H), 2.19 (s, 3H), 1.70 (t, $J = 6.9$ Hz, 2H), 1.54-1.36 (m, 4H). MS: 472 $[M+H]^+$.



Example 153



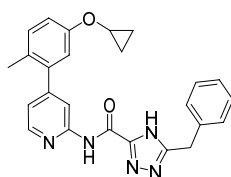
Example 154

[0555] Example 154: 5-benzyl-N-(4-(5-((8-hydroxyoctyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

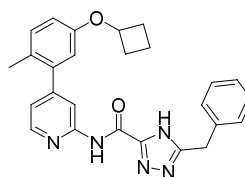
[0556] The preparation was carried out in a similar manner to Example 92, except that in step 1, 8-bromo-1-octanol was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.64 (s, 1H), 9.92 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.11 (d, $J = 1.5$ Hz, 1H), 7.42 – 7.11 (m, 7H), 6.92 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.46 – 4.24 (m, 1H), 4.17 (s, 2H), 3.96 (t, $J = 6.5$ Hz, 2H), 3.37 – 3.34 (m, 2H), 2.18 (s, 3H), 1.78 – 1.60 (m, 2H), 1.50 – 1.34 (m, 4H), 1.34 – 1.13 (m, 6H). MS: 514 $[M+H]^+$.

[0557] Example 155: 5-benzyl-N-(4-(5-cyclopropoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0558] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromocyclopropane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.54 (s, 1H), 9.85 (s, 1H), 8.42 (d, $J = 5.2$ Hz, 1H), 8.13 (s, 1H), 7.39 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 7.05 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.93 (d, $J = 2.7$ Hz, 1H), 4.19 (s, 2H), 3.91 – 3.82 (m, 1H), 2.20 (s, 3H), 0.83 – 0.71 (m, 2H), 0.71 – 0.60 (m, 2H). MS: 426 $[M+H]^+$.



Example 155



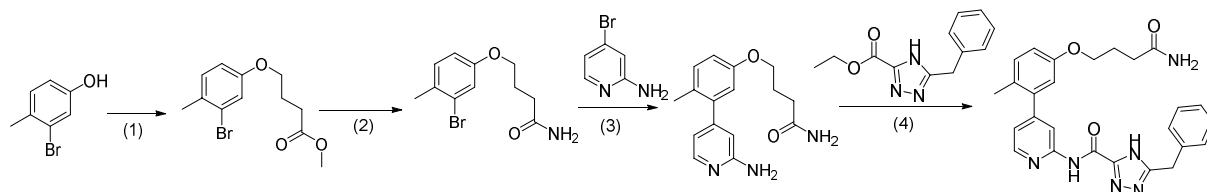
Example 156

[0559] Example 156: 5-benzyl-N-(4-(5-cyclobutoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0560] The preparation was carried out in a similar manner to Example 92, except that in step 1, bromocyclobutane was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.58 (s, 1H), 9.89 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.40 – 7.29 (m, 4H), 7.29 – 7.15 (m, 3H), 6.84 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.72 (d, $J = 2.7$ Hz, 1H),

4.77 – 4.64 (m, 1H), 4.18 (s, 2H), 2.46 – 2.35 (m, 2H), 2.18 (s, 3H), 2.11-1.94 (m, 2H), 1.83-1.70 (m, 1H), 1.70-1.54 (m, 1H). MS: 440 [M+H]⁺.

[0561] Example 157: N-(4-(5-(4-amino-4-oxobutoxy)-2-methylphenyl)pyridin-2-yl)-5-benzyl-4H-1,2,4-triazole-3-carboxamide



[0562] Step 1: Synthesis of methyl 4-(3-bromo-4-methylphenoxy)butanoate

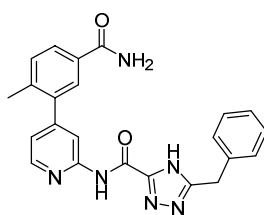
[0563] The operation is the same as step 1 of Example 92, but methyl 4-bromobutanoate was used in place of iodomethane in step 1, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol in step 1.

[0564] Step 2: Synthesis of 4-(3-bromo-4-methylphenoxy)butanamide

[0565] Methyl 4-(3-bromo-4-methylphenoxy)butanoate (287mg, 1mmol) was dissolved in 7M ammonia in methanol, and reacted at 80°C for 36 hours in sealed tube. The reaction solution was cooled, evaporated to dryness, and used directly in the next step.

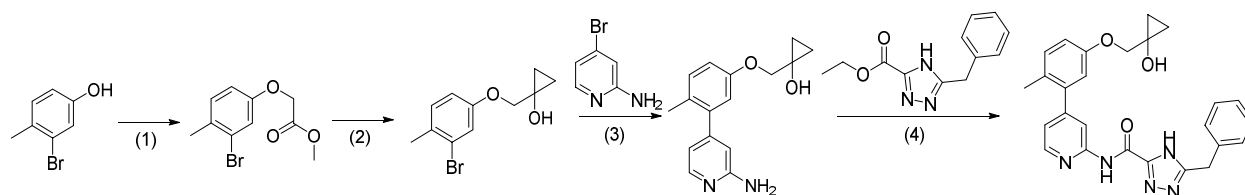
[0566] Step 3 to Step 4: The preparation was carried out in a similar manner to Example 33, except that in step 1, 4-(3-bromo-4-methylphenoxy)butanamide was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.41-7.30 (m, 5H), 7.26 (dd, *J* = 7.6, 5.2 Hz, 2H), 7.21 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.88-6.67 (m, 2H), 4.18 (s, 2H), 3.97 (t, *J* = 6.4 Hz, 2H), 2.28-2.12 (m, 5H), 1.97-1.83 (m, 2H). MS: 471 [M+H]⁺.

[0567] Example 158: 5-benzyl-N-(4-(5-carbamoyl-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0568] The operation is the same as steps 2 to 4 of Example 157, but methyl 3-bromo-4-methylbenzoate was used in place of methyl 4-(3-bromo-4-methylphenoxy)butanoate in step 2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.95 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.15 (d, *J* = 5.3 Hz, 1H), 8.04 (d, *J* = 5.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 5.4 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.42 – 7.30 (m, 5H), 7.30 – 7.18 (m, 2H), 4.18 (s, 2H), 2.33 (s, 3H). MS: 413 [M+H]⁺.

[0569] Example 159: 5-benzyl-N-(4-(5-((1-hydroxycyclopropyl)methoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0570] Step 1: Synthesis of methyl 2-(3-bromo-4-methylphenoxy)acetate

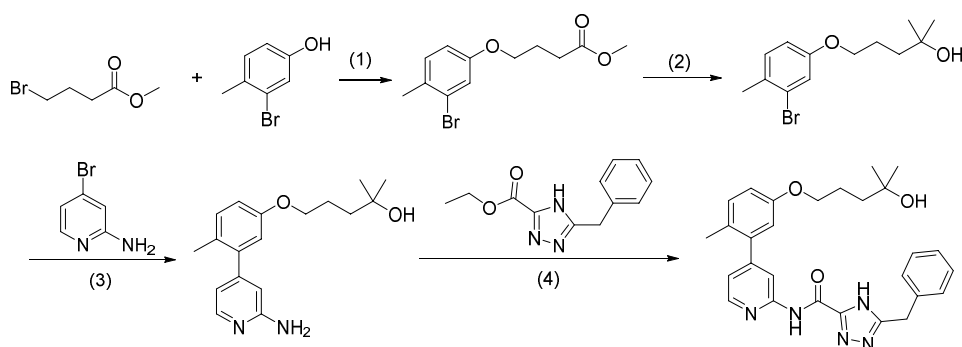
5 **[0571]** The operation is the same as step 1 of Example 92, but methyl bromoacetate was used in place of iodomethane in step 1, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol in step 1.

[0572] Step 2: Synthesis of 1-((3-bromo-4-methylphenoxy)methyl)cyclopropane-1-ol

10 **[0573]** Methyl 2-(3-bromo-4-methylphenoxy)acetate (259mg, 1mmol) and tetraisopropyl titanate (57mg, 0.2mmol) were dissolved in anhydrous tetrahydrofuran, and ethyl Grignard reagent (1M in THF, 2.5mL, 2.5mmol) slowly added at 0°C under argon protection. Then the mixture was slowly warmed to 25°C after the addition, and reacted for 4 hours. The reaction solution is quenched with saturated solution of ammonium chloride, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and used directly in the next step.

15 **[0574]** Step 3 to Step 4: The preparation was carried out in a similar manner to Example 33, except that in step 1, 1-((3-bromo-4-methylphenoxy)methyl)cyclopropan-1-ol was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.90 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.14 (m, 3H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.8 Hz, 1H), 5.59 (s, 1H), 4.18 (s, 2H), 3.97 (s, 2H), 2.19 (s, 3H), 0.73 – 0.63 (m, 2H), 0.63 – 0.53 (m, 2H). MS: 456 [M+H]⁺.

20 **[0575]** Example 160: 5-benzyl-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[0576] Step 1: Synthesis of methyl 4-(3-bromo-4-methylphenoxy)butanoate

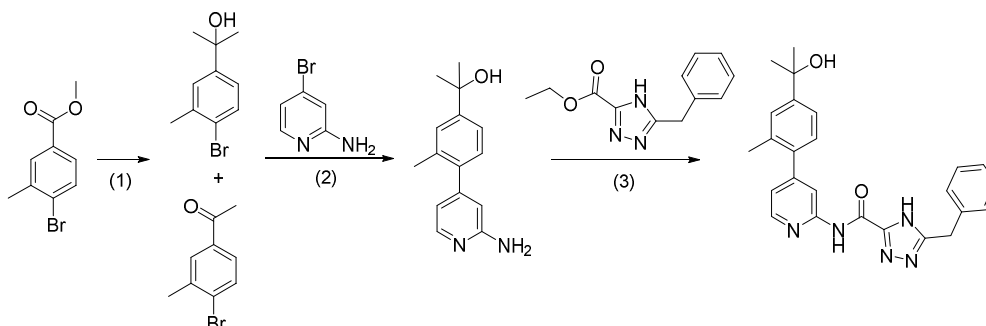
25 **[0577]** The operation is the same as step 4 of Example 55, but 3-bromo-4-methylphenol was used in place of 3-bromo-N,4-dimethylaniline in the fourth step, and methyl 4-bromobutanoate was used in place of 1-bromo-2-methoxyethane in the fourth step.

[0578] Step 2: Synthesis of 5-(3-bromo-4-methylphenoxy)-2-methylpentan-2-ol

[0579] Methyl 4-(3-bromo-4-methylphenoxy)butanoate (287mg, 1mmol) was dissolved in anhydrous tetrahydrofuran (3mL), to which methylmagnesium bromide (3M, 1mL, 3mmol) was added dropwise under argon protection at 0°C, and reacted at 25°C for 2 hours. The reaction was quenched with saturated aqueous solution of ammonium chloride, extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and subjected to column chromatography to afford 260mg of product. MS: 287 [M+H]⁺.

[0580] Step 3 to Step 4: The preparation was carried out in a similar manner to Example 33, except that in step 1, 5-(3-bromo-4-methylphenoxy)-2-methylpentan-2-ol was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.88 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.16 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.26 – 4.10 (m, 3H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.82 – 1.68 (m, 2H), 1.54 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 486 [M+H]⁺.

[0581] Example 161: 5-benzyl-N-(4-(4-(2-hydroxypropan-2-yl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

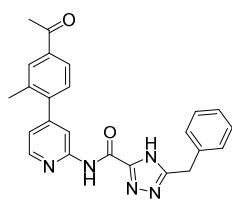


[0582] The operation is the same as steps 2 to 4 of Example 160, but methyl 4-bromo-3-methylbenzoate was used in place of methyl 4-(3-bromo-4-methylphenoxy)butanoate in step 2 of Example 160 to carry out the reaction. In this step of reaction, two products of 2-(3-bromo-4-methylphenyl)propan-2-ol and 1-(3-bromo-4-methylphenyl)ethan-1-one were obtained, and 2-(3-bromo-4-methylphenyl)propan-2-ol was used for the subsequent reactions in the present Example. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.87 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.51 – 7.14 (m, 9H), 5.07 (s, 1H), 4.18 (s, 2H), 2.29 (s, 3H), 1.45 (s, 6H). MS: 428 [M+H]⁺.

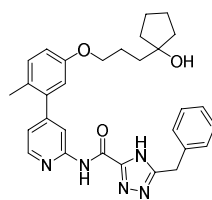
[0583] Example 162: N-(4-(4-acetyl-2-methylphenyl)pyridin-2-yl)-5-benzyl-4H-1,2,4-triazole-3-carboxamide

[0584] The operation is the same as Example 161, but the product 1-(3-bromo-4-methylphenyl)ethan-1-one obtained in the first step was used for the subsequent reactions. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.95 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.99 – 7.93 (m, 1H), 7.93 – 7.84 (m, 1H), 7.43 (d, *J* = 8.0

Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.20 (m, 2H), 4.18 (s, 2H), 2.62 (s, 3H), 2.35 (s, 3H). MS: 412 [M+H]⁺.



Example 162



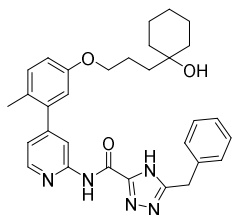
Example 163

[0585] Example 163: 5-benzyl-N-(4-(5-(3-(1-hydroxycyclopentyl)propoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

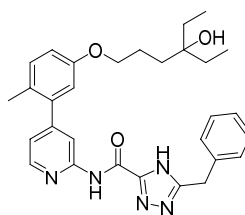
[0586] The preparation was carried out in a similar manner to Example 160, except that in step 2, (butane-1,4-diyl)dimagnesium dibromide was used in place of methylmagnesium bromide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.92 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.11 (s, 1H), 7.47 – 7.29 (m, 4H), 7.29 – 7.13 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.05 (s, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.87 – 1.33 (m, 12H). MS: 512 [M+H]⁺.

[0587] Example 164: 5-benzyl-N-(4-(5-(3-(1-hydroxycyclohexyl)propoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0588] The preparation was carried out in a similar manner to Example 160, except that in step 2, (pentane-1,5-diyl)dimagnesium dibromide was used in place of methylmagnesium bromide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.49 – 7.29 (m, 4H), 7.29 – 7.12 (m, 3H), 6.92 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.01 – 3.86 (m, 3H), 2.19 (s, 3H), 1.75 (t, *J* = 8.3 Hz, 2H), 1.63 – 1.49 (m, 2H), 1.49 – 1.38 (m, 5H), 1.38 – 1.24 (m, 5H). MS: 526 [M+H]⁺.



Example 164



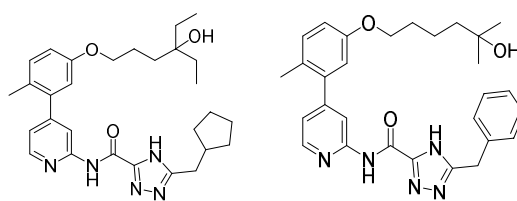
Example 165

[0589] Example 165: 5-benzyl-N-(4-(5-(4-ethyl-4-(hydroxyhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0590] The preparation was carried out in a similar manner to Example 160, except that in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.52 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.0 Hz, 1H), 8.11 (s, 1H), 7.40 – 7.28 (m, 4H), 7.28 – 7.22 (m, 2H), 7.21 (dd, *J* = 5.1, 1.5 Hz, 1H), 6.92 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 1H), 2.19 (s, 3H), 1.74 – 1.63 (m, 2H), 1.48 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 514 [M+H]⁺.

[0591] Example 166: 5-(cyclopentylmethyl)-N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0592] The preparation was carried out in a similar manner to Example 160, except that in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.85 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.32 – 7.12 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 1H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.21 (m, 1H), 2.19 (s, 3H), 1.79 – 1.47 (m, 8H), 1.47 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 1.28 – 1.11 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 506 [M+H]⁺.



Example 166

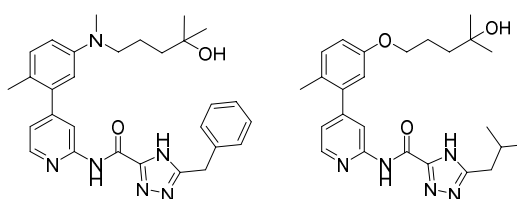
Example 167

[0593] Example 167: 5-benzyl-N-(4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0594] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.41-7.29 (m, 4H), 7.29-7.22 (m, 2H), 7.21 (dd, *J* = 5.1, 1.5 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.10 (s, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.68 (t, *J* = 6.9 Hz, 2H), 1.50-1.33 (m, 4H), 1.06 (s, 6H). MS: 500 [M+H]⁺.

[0595] Example 168: 5-benzyl-N-(4-(5-((4-hydroxy-4-(methylpentyl)(methyl)amino)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0596] The preparation was carried out in a similar manner to Example 160, except that in step 1, tert-butyl (3-bromo-4-methylphenyl)(methyl)carbamate was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.88 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.46 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.18 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.52 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 4.12 (s, 1H), 3.28 (t, *J* = 7.4 Hz, 2H), 2.86 (s, 3H), 2.13 (s, 3H), 1.63 – 1.46 (m, 2H), 1.42 – 1.27 (m, 2H), 1.05 (s, 6H). MS: 499 [M+H]⁺.



Example 168

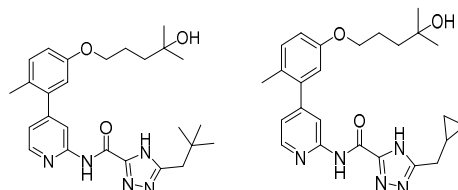
Example 169

[0597] Example 169: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-isobutyl-4H-1,2,4-triazole-3-carboxamide

[0598] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-isobutyl-4H-1,2,4-triazol-5-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 9.86 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.33 – 7.16 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.19 (s, 1H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.19 (s, 3H), 2.16 – 2.02 (m, 1H), 1.84 – 1.68 (m, 2H), 1.56 – 1.41 (m, 2H), 1.09 (s, 6H), 0.93 (d, *J* = 6.6 Hz, 6H). MS: 452 [M+H]⁺.

[0599] Example 170: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-neopentyl-4H-1,2,4-triazole-3-carboxamide

[0600] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-neopentyl-4H-1,2,4-triazol-5-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.85 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.31-7.16 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 1H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.67 (s, 2H), 2.20 (s, 3H), 1.83-1.66 (m, 2H), 1.57-1.39 (m, 2H), 1.09 (s, 6H), 0.97 (s, 9H). MS: 466 [M+H]⁺.



Example 170

Example 171

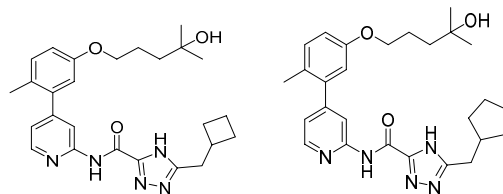
[0601] Example 171: 5-(cyclopropylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0602] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(cyclopropylmethyl)-4H-1,2,4-triazol-5-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 9.88 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.37 – 7.16 (m, 2H), 6.93 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.72 (d, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 1.83 – 1.66 (m, 2H), 1.55 – 1.39 (m, 2H), 1.18 – 1.03 (m, 7H), 0.59 – 0.46 (m, 2H), 0.33 – 0.22 (m, 2H). MS: 450 [M+H]⁺.

[0603] Example 172: 5-(cyclobutylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0604] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(cyclobutylmethyl)-4H-1,2,4-triazol-5-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-

carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.36 (s, 1H), 9.85 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.13 (s, 1H), 7.34 – 7.16 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 1H), 3.97 (t, $J = 6.5$ Hz, 2H), 2.88 (d, $J = 7.5$ Hz, 2H), 2.79 – 2.62 (m, 1H), 2.19 (s, 3H), 2.12 – 1.97 (m, 2H), 1.94 – 1.79 (m, 2H), 1.79 – 1.64 (m, 4H), 1.55 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 464 $[\text{M}+\text{H}]^+$.



Example 172

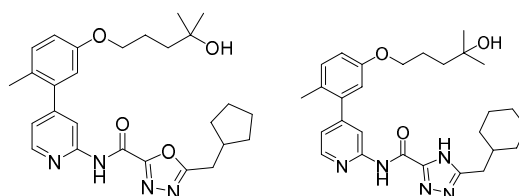
Example 173

[0605] Example 173: 5-(cyclopentylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0606] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.38 (s, 1H), 9.85 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.14 (s, 1H), 7.33 – 7.16 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.19 (s, 1H), 3.96 (t, $J = 6.6$ Hz, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.34 – 2.22 (m, 1H), 2.19 (s, 3H), 1.83 – 1.66 (m, 4H), 1.66 – 1.55 (m, 2H), 1.55 – 1.41 (m, 4H), 1.27 – 1.18 (m, 2H), 1.09 (s, 6H). MS: 478 $[\text{M}+\text{H}]^+$.

[0607] Example 174: 5-(cyclopentylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,3,4-oxadiazole-2-carboxamide

[0608] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(cyclopentylmethyl)-1,3,4-oxadiazol-2-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.23 (s, 1H), 8.47 (d, $J = 5.1$ Hz, 1H), 7.99 (s, 1H), 7.32 – 7.20 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 1H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.97 (d, $J = 7.4$ Hz, 2H), 2.38 – 2.24 (m, 1H), 2.19 (s, 3H), 1.87 – 1.69 (m, 4H), 1.69 – 1.39 (m, 6H), 1.32 – 1.20 (m, 2H), 1.09 (s, 6H). MS: 479 $[\text{M}+\text{H}]^+$.



Example 174

Example 175

[0609] Example 175: 5-(cyclohexylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0610] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-

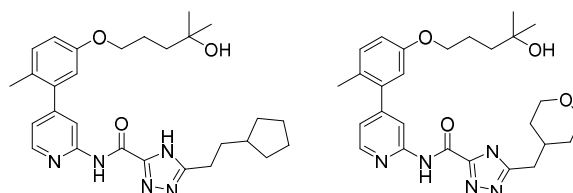
carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.37 (s, 1H), 9.85 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.13 (s, 1H), 7.31 – 7.17 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 1H), 3.97 (t, $J = 6.6$ Hz, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 2.19 (s, 3H), 1.84 – 1.70 (m, 3H), 1.70 – 1.56 (m, 5H), 1.54 – 1.41 (m, 2H), 1.29 – 1.15 (m, 3H), 1.09 (s, 6H), 1.05 – 0.89 (m, 2H). MS: 492 $[\text{M}+\text{H}]^+$.

5

[0611] Example 176: 5-(2-cyclopentylethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0612] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(2-cyclopentylethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.32 (s, 1H), 9.86 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.13 (s, 1H), 7.33 – 7.15 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 1H), 3.97 (t, $J = 6.5$ Hz, 2H), 2.79 (t, $J = 7.2$ Hz, 2H), 2.19 (s, 3H), 1.84 – 1.66 (m, 7H), 1.66 – 1.39 (m, 6H), 1.18 – 0.98 (m, 8H). MS: 492 $[\text{M}+\text{H}]^+$.

10



Example 176

Example 177

15

[0613] Example 177: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-5-((tetrahydro-2H-pyran-4-yl)methyl)-4H-1,2,4-triazole-3-carboxamide

[0614] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-((tetrahydro-2H-pyran-4-yl)methyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.41 (s, 1H), 9.87 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.13 (s, 1H), 7.34 – 7.14 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 1H), 3.97 (t, $J = 6.5$ Hz, 2H), 3.89 – 3.78 (m, 2H), 3.31 – 3.19 (m, 2H), 2.73 (d, $J = 7.1$ Hz, 2H), 2.19 (s, 3H), 2.07 – 1.92 (m, 1H), 1.81 – 1.68 (m, 2H), 1.61 – 1.51 (m, 2H), 1.51 – 1.42 (m, 2H), 1.30 – 1.22 (m, 2H), 1.09 (s, 6H). MS: 494 $[\text{M}+\text{H}]^+$.

20

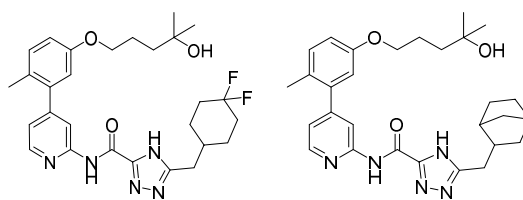
25

[0615] Example 178: 5-((4,4-difluorocyclohexyl)methyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0616] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-((4,4-difluorocyclohexyl)methyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.41 (s, 1H), 9.87 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.13 (s, 1H), 7.32 – 7.13 (m, 2H), 6.93 (dd, $J = 8.5, 2.6$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 1H), 3.97 (t, $J = 6.6$ Hz, 2H), 2.75 (d, $J = 7.0$ Hz, 2H), 2.19 (s, 3H), 2.09 – 1.64 (m, 9H), 1.55 – 1.40 (m, 2H), 1.35 – 1.23 (m,

30

2H), 1.09 (s, 6H). MS: 528 [M+H]⁺.



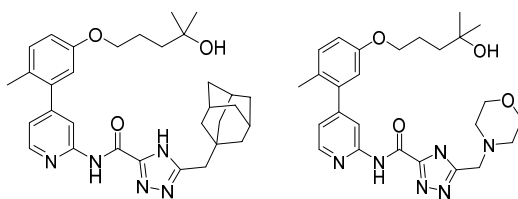
Example 178 Example 179

[0617] Example 179: 5-(bicyclo[2.2.1]heptan-2-ylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0618] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(bicyclo[2.2.1]heptan-2-ylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.32 (s, 1H), 9.86 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.35 – 7.12 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 1H), 3.97 (t, *J* = 6.6 Hz, 2H), 3.17 (d, *J* = 4.1 Hz, 1H), 2.74 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.59 (dd, *J* = 14.6, 7.7 Hz, 1H), 2.28 – 2.16 (m, 4H), 1.96 – 1.85 (m, 1H), 1.81 – 1.68 (m, 2H), 1.54 – 1.33 (m, 6H), 1.29 – 1.20 (m, 2H), 1.19 – 1.12 (m, 2H), 1.09 (s, 6H). MS: 504 [M+H]⁺.

[0619] Example 180: 5-(adamantan-1-ylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0620] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(adamantan-1-ylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.32 (s, 1H), 9.83 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.30 – 7.13 (m, 2H), 6.90 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 1H), 3.94 (t, *J* = 6.6 Hz, 2H), 2.51 (s, 2H), 2.17 (s, 3H), 1.95 – 1.83 (m, 3H), 1.79 – 1.66 (m, 2H), 1.66 – 1.57 (m, 3H), 1.57 – 1.38 (m, 11H), 1.06 (s, 6H). MS: 544 [M+H]⁺.



Example 180 Example 181

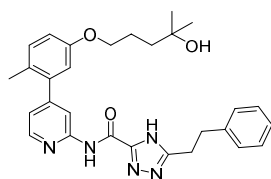
[0621] Example 181: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(morpholinomethyl)-4H-1,2,4-triazole-3-carboxamide

[0622] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(morpholinomethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.09 (s, 1H), 9.95 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.32 – 7.16 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.20 (s, 1H), 3.97 (t, *J* = 6.5 Hz,

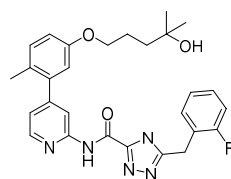
2H), 3.71 (s, 2H), 3.59 (t, $J = 4.6$ Hz, 4H), 2.49 – 2.40 (m, 4H), 2.19 (s, 3H), 1.81 – 1.67 (m, 2H), 1.52 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 495 [M+H]⁺.

[0623] Example 182: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-phenethyl-4H-1,2,4-triazole-3-carboxamide

[0624] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(phenethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.43 (s, 1H), 9.89 (s, 1H), 8.43 (d, $J = 5.2$ Hz, 1H), 8.14 (s, 1H), 7.40-7.10 (m, 7H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.18 (s, 1H), 3.97 (t, $J = 6.6$ Hz, 2H), 3.22-2.99 (m, 4H), 2.20 (s, 3H), 1.84-1.66 (m, 2H), 1.57-1.37 (m, 2H), 1.09 (s, 6H). MS: 500 [M+H]⁺.



Example 182



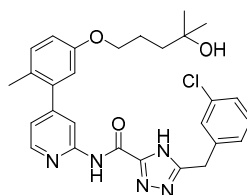
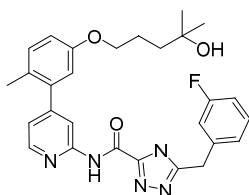
Example 183

[0625] Example 183: 5-(2-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0626] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.90 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.10 (s, 1H), 7.44 – 7.29 (m, 2H), 7.28 – 7.13 (m, 4H), 6.92 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.29 – 4.09 (m, 3H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.18 (s, 3H), 1.83 – 1.68 (m, 2H), 1.52 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 504 [M+H]⁺.

[0627] Example 184: 5-(3-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0628] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(3-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.74 (s, 1H), 9.93 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.50-7.30 (m, 2H), 7.30-7.06 (m, 4H), 6.92 (d, $J = 8.6$ Hz, 1H), 6.80 (s, 1H), 4.34-4.06 (m, 3H), 3.96 (t, $J = 6.6$ Hz, 2H), 2.19 (s, 3H), 1.84-1.66 (m, 2H), 1.47 (t, $J = 8.1$ Hz, 2H), 1.09 (s, 6H). MS: 504 [M+H]⁺.



Example 184

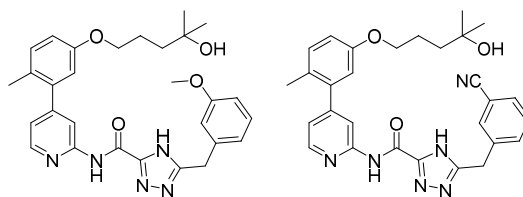
Example 185

[0629] Example 185: 5-(3-chlorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0630] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(3-chlorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.95 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.49 – 7.13 (m, 6H), 6.92 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.31 – 4.07 (m, 3H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.83 – 1.66 (m, 2H), 1.54 – 1.38 (m, 2H), 1.09 (s, 6H). MS: 520 [M+H]⁺.

[0631] Example 186: 5-(3-methoxybenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0632] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(3-methoxybenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.92 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.41 – 7.12 (m, 3H), 7.05 – 6.70 (m, 5H), 4.26 – 4.05 (m, 3H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.74 (s, 3H), 2.19 (s, 3H), 1.83 – 1.65 (m, 2H), 1.56 – 1.37 (m, 2H), 1.09 (s, 6H). MS: 516 [M+H]⁺.



Example 186

Example 187

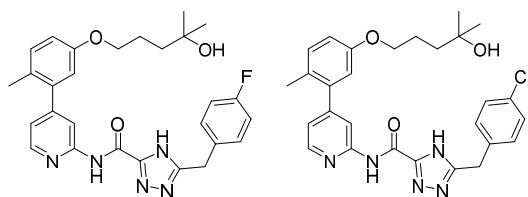
[0633] Example 187: 5-(3-cyanobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0634] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(3-cyanobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.69 (s, 1H), 9.98 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.84 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.62 – 7.51 (m, 1H), 7.30 – 7.17 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.27 (s, 2H), 4.19 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.81 – 1.68 (m, 2H), 1.53 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 511 [M+H]⁺.

[0635] Example 188: 5-(4-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0636] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(4-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.93 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H),

7.46 – 7.31 (m, 2H), 7.31 – 7.10 (m, 4H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.29 – 4.08 (m, 3H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.83 – 1.65 (m, 2H), 1.54 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 504 $[M+H]^+$.



Example 188

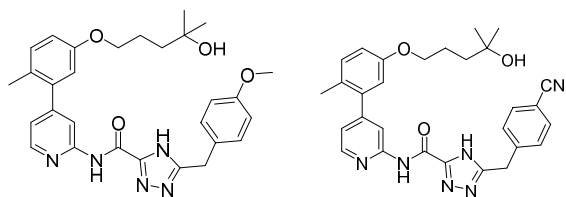
Example 189

[0637] Example 189: 5-(4-chlorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0638] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(4-chlorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.65 (s, 1H), 9.93 (s, 1H), 8.42 (d, $J = 5.2$ Hz, 1H), 8.11 (s, 1H), 7.51 – 7.29 (m, 4H), 7.29 – 7.13 (m, 2H), 6.93 (dd, $J = 8.5, 2.8$ Hz, 1H), 6.80 (d, $J = 2.8$ Hz, 1H), 4.28 – 4.07 (m, 3H), 3.96 (t, $J = 6.6$ Hz, 2H), 2.19 (s, 3H), 1.75 (t, $J = 8.2$ Hz, 2H), 1.54 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 520 $[M+H]^+$.

[0639] Example 190: 5-(4-methoxybenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0640] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(4-methoxybenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.59 (s, 1H), 9.89 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.40 – 7.09 (m, 4H), 7.04 – 6.70 (m, 4H), 4.18 (s, 1H), 4.10 (s, 2H), 3.96 (t, $J = 6.8$ Hz, 2H), 2.19 (s, 3H), 1.83 – 1.64 (m, 2H), 1.57 – 1.35 (m, 2H), 1.09 (s, 6H). MS: 516 $[M+H]^+$.



Example 190

Example 191

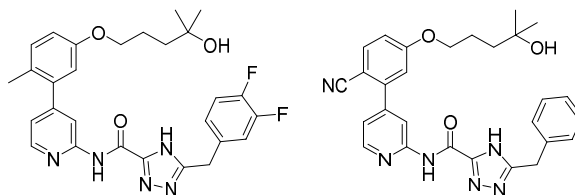
[0641] Example 191: 5-(4-cyanobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0642] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(4-cyanobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.65 (s, 1H), 9.95 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.91 – 7.76 (m, 2H), 7.62 – 7.47 (m, 2H), 7.32 – 7.13 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.29

(s, 2H), 4.18 (s, 1H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.81 – 1.67 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 511 $[M+H]^+$.

[0643] Example 192: 5-(3,4-difluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0644] The preparation was carried out in a similar manner to Example 160, except that in step 3, ethyl 5-(3,4-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.62 (s, 1H), 9.96 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.11 (d, $J = 1.4$ Hz, 1H), 7.51 – 7.32 (m, 2H), 7.32 – 7.13 (m, 3H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.25 – 4.12 (m, 3H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.82 – 1.67 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 522 $[M+H]^+$.



Example 192

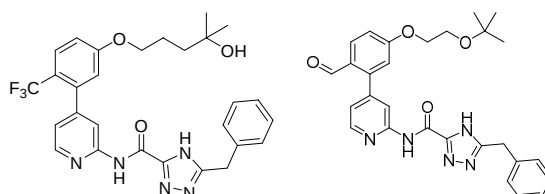
Example 193

[0645] Example 193: 5-benzyl-N-(4-(2-cyano-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0646] The preparation was carried out in a similar manner to Example 160, except that in step 1, 2-chloro-4-hydroxybenzonitrile was used in place of 3-bromo-4-methylphenol. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.54 (s, 1H), 10.04 (s, 1H), 8.52 (d, $J = 5.1$ Hz, 1H), 8.34 (d, $J = 1.4$ Hz, 1H), 7.94 (d, $J = 8.5$ Hz, 1H), 7.41 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.15 (m, 3H), 4.27 – 4.08 (m, 5H), 1.87 – 1.72 (m, 2H), 1.56 – 1.41 (m, 2H), 1.10 (s, 6H). MS: 497 $[M+H]^+$.

[0647] Example 194: 5-benzyl-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0648] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.61 (s, 1H), 9.96 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 8.16 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.43 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.22 – 7.11 (m, 2H), 6.97 (d, $J = 2.5$ Hz, 1H), 4.26 – 4.13 (m, 3H), 4.09 (t, $J = 6.6$ Hz, 2H), 1.86 – 1.69 (m, 2H), 1.54 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 540 $[M+H]^+$.



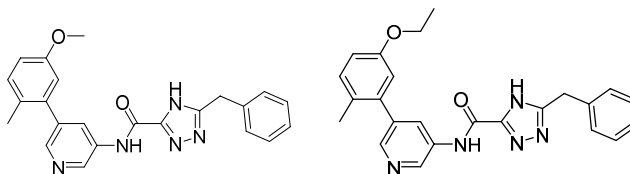
Example 194 Example 195

[0649] Example 195: 5-benzyl-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-formylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0650] The preparation was carried out in a similar manner to Example 64, except that in step 1, 2-bromo-4-hydroxybenzaldehyde was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.99 (s, 1H), 9.80 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.43 – 7.29 (m, 5H), 7.29 – 7.15 (m, 2H), 7.05 (d, *J* = 2.5 Hz, 1H), 4.28 – 4.20 (m, 2H), 4.18 (s, 2H), 3.73 – 3.61 (m, 2H), 1.15 (s, 9H). MS: 500 [M+H]⁺.

[0651] Example 196: 5-benzyl-N-(5-(5-methoxy-2-methylphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

[0652] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 2, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 10.75 (s, 1H), 9.02 (s, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 7.43-7.18 (m, 6H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.83 (s, 1H), 4.18 (s, 2H), 3.76 (s, 3H), 2.18 (s, 3H). MS: 400 [M+H]⁺.



Example 196 Example 197

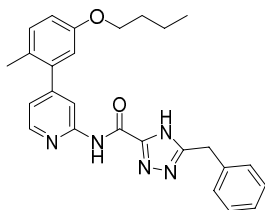
[0653] Example 197: 5-benzyl-N-(5-(5-ethoxy-2-methylphenyl)pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamide

[0654] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, bromoethane was used in place of iodomethane, and in step 2, 5-bromopyridin-3-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (600 MHz, DMSO-*d*₆) δ 14.49 (s, 1H), 10.70 (s, 1H), 9.02 (d, *J* = 2.4 Hz, 1H), 8.41 – 8.08 (m, 2H), 7.48 – 7.12 (m, 6H), 6.90 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 4.03 (q, *J* = 7.0 Hz, 2H), 2.18 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H). MS: 414 [M+H]⁺.

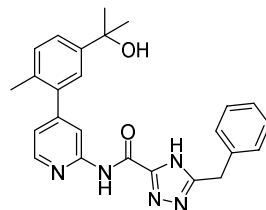
[0655] Example 198: 5-benzyl-N-(4-(5-butoxy-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0656] The preparation was carried out in a similar manner to Example 92, except that in step 1, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and 1-bromobutane was used in place of iodomethane. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.92 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (d, *J* = 1.5 Hz, 1H), 7.48 – 7.10 (m, 7H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 2H), 3.97

(t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.83 – 1.54 (m, 2H), 1.54 – 1.27 (m, 2H), 0.92 (t, $J = 7.4$ Hz, 3H). MS: 442 $[M+H]^+$.



Example 198



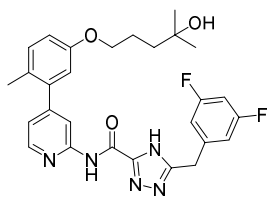
Example 199

5 **[0657]** Example 199: 5-benzyl-N-(4-(5-(2-hydroxypropan-2-yl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

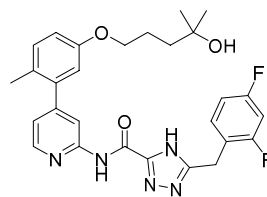
[0658] The preparation was carried out in a similar manner to Example 161, except that in step 1, methyl 3-bromo-4-methylbenzoate was used in place of methyl 4-bromo-3-methylbenzoate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.59 (s, 1H), 9.89 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.12 (d, $J = 1.3$ Hz, 1H), 7.42 (dd, $J = 7.9, 2.0$ Hz, 1H), 7.39 – 7.30 (m, 5H), 7.30 – 7.23 (m, 2H), 7.21 (dd, $J = 5.1, 1.6$ Hz, 1H), 5.05 (s, 1H), 4.17 (s, 2H), 2.25 (s, 3H), 1.43 (s, 6H). MS: 428 $[M+H]^+$.

[0659] Example 200: 5-(3,5-difluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

15 **[0660]** The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(3,5-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.56 (s, 1H), 9.91 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.12 (s, 1H), 7.29-7.03 (m, 5H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.26 (s, 2H), 4.18 (s, 1H), 3.96 (t, $J = 6.6$ Hz, 2H), 2.19 (s, 3H), 1.81-1.67 (m, 2H), 1.53-1.40 (m, 2H), 1.09 (s, 6H). MS: 522 $[M+H]^+$.



Example 200



Example 201

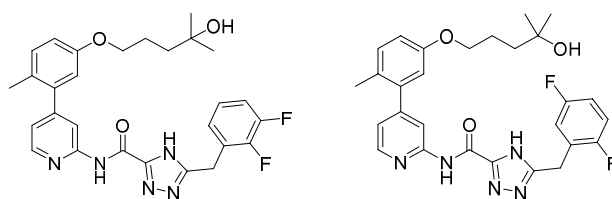
[0661] Example 201: 5-(2,4-difluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

25 **[0662]** The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2,4-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.63 (s, 1H), 9.89 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.57 – 7.38 (m, 1H), 7.38 – 7.17 (m, 3H), 7.17 – 7.01 (m, 1H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 4.28 – 4.11 (m, 3H), 3.97 (t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.83 – 1.66 (m, 2H), 1.56 – 1.40 (m, 2H),

1.10 (s, 6H). MS: 522 [M+H]⁺.

[0663] Example 202: 5-(2,3-difluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0664] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2,3-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.70 (s, 1H), 9.92 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.47 – 7.30 (m, 1H), 7.30 – 7.12 (m, 4H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.27 (s, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.82 – 1.66 (m, 2H), 1.55 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 522 [M+H]⁺.



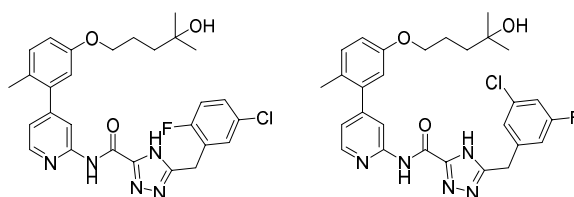
Example 202 Example 203

[0665] Example 203: 5-(2,5-difluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0666] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2,5-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.73 (s, 1H), 9.94 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.42-7.11 (m, 5H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.22 (s, 2H), 4.17 (s, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.80-1.70 (m, 2H), 1.54-1.42 (m, 2H), 1.10 (s, 6H). MS: 522 [M+H]⁺.

[0667] Example 204: 5-(5-chloro-2-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0668] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(5-chloro-2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.69 (s, 1H), 9.93 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.53 (dd, *J* = 6.6, 2.7 Hz, 1H), 7.48 – 7.36 (m, 1H), 7.36 – 7.14 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.22 (s, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.83 – 1.68 (m, 2H), 1.55 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 538 [M+H]⁺.

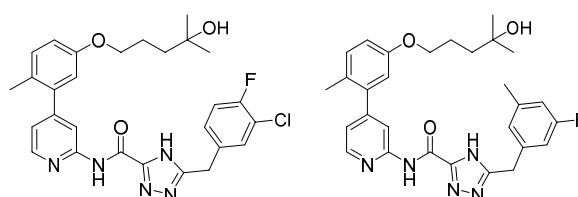


[0669] Example 205: 5-(5-chloro-3-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0670] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(5-chloro-3-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.43-7.14 (m, 5H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.24 (s, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.82-1.68 (m, 2H), 1.52-1.42 (m, 2H), 1.09 (s, 6H). MS: 538 [M+H]⁺.

[0671] Example 206: 5-(3-chloro-4-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0672] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(3-chloro-4-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.95 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.59 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.47 – 7.29 (m, 2H), 7.29 – 7.15 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.24 – 4.14 (m, 3H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.83 – 1.66 (m, 2H), 1.54 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 538 [M+H]⁺.



Example 206 Example 207

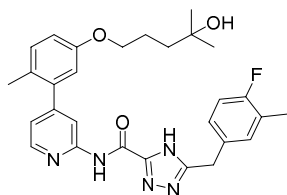
[0673] Example 207: 5-(3-fluoro-5-methylbenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0674] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(3-fluoro-5-methylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 (s, 1H), 9.90 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.32-7.14 (m, 2H), 7.03-6.86 (m, 4H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.22-4.10 (m, 3H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 1.82-1.68 (m, 2H), 1.54-1.42 (m, 2H), 1.09 (s, 6H). MS: 518 [M+H]⁺.

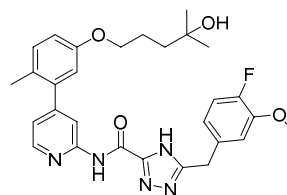
[0675] Example 208: 5-(4-fluoro-3-methylbenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0676] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(4-fluoro-3-methylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.53 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H),

7.34 – 7.00 (m, 5H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.24 – 4.04 (m, 3H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.27 – 2.12 (m, 6H), 1.83 – 1.67 (m, 2H), 1.56 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 518 [M+H]⁺.



Example 208



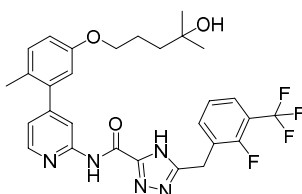
Example 209

5 **[0677]** Example 209: 5-(4-fluoro-3-methoxybenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

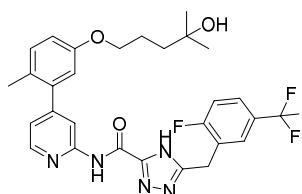
[0678] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(4-fluoro-3-methoxybenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.52 (s, 1H), 9.89 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.30 – 7.08 (m, 4H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.90 – 6.83 (m, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.22 – 4.09 (m, 3H), 3.96 (t, $J = 6.5$ Hz, 2H), 3.83 (s, 3H), 2.19 (s, 3H), 1.81 – 1.69 (m, 2H), 1.54 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 534 [M+H]⁺.

15 **[0679]** Example 210: 5-(2-fluoro-3-trifluoromethylbenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0680] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2-fluoro-3-trifluoromethylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.69 (s, 1H), 9.91 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.10 (s, 1H), 7.88 – 7.64 (m, 2H), 7.49 – 7.34 (m, 1H), 7.30 – 7.13 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.32 (s, 2H), 4.16 (s, 1H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.81 – 1.69 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 572 [M+H]⁺.



Example 210



Example 211

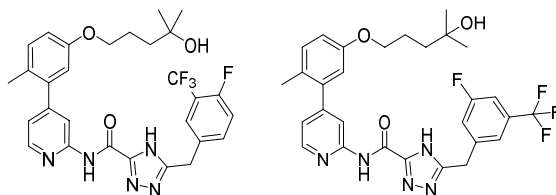
25 **[0681]** Example 211: 5-(2-fluoro-5-trifluoromethylbenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy))-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0682] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2-fluoro-5-trifluoromethylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.76 (s, 1H), 9.92 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.10 (s, 1H), 7.90 (dd, $J = 6.7, 2.4$ Hz, 1H), 7.83-7.67 (m, 1H), 7.56-7.37 (m, 1H), 7.33-7.12 (m, 2H), 6.92 (dd,

$J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.32 (s, 2H), 4.17 (s, 1H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.18 (s, 3H), 1.80-1.68 (m, 2H), 1.52-1.41 (m, 2H), 1.09 (s, 6H). MS: 572 $[M+H]^+$.

[0683] Example 212: 5-(4-fluoro-3-trifluoromethylbenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0684] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(4-fluoro-3-trifluoromethylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.55 (s, 1H), 9.90 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.11 (s, 1H), 7.84 – 7.76 (m, 1H), 7.76 – 7.67 (m, 1H), 7.50 (dd, $J = 10.6, 8.8$ Hz, 1H), 7.29 – 7.16 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.30 (s, 2H), 4.16 (s, 1H), 3.96 (t, $J = 6.6$ Hz, 2H), 2.19 (s, 3H), 1.82 – 1.66 (m, 2H), 1.52 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 572 $[M+H]^+$.



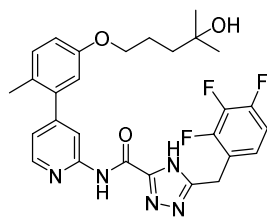
Example 212 Example 213

[0685] Example 213: 5-(3-fluoro-5-trifluoromethylbenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

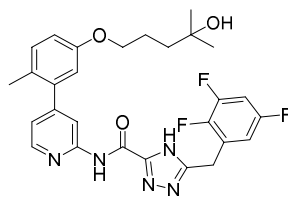
[0686] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(3-fluoro-5-trifluoromethylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.57 (s, 1H), 9.90 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.12 (s, 1H), 7.70 – 7.50 (m, 3H), 7.30 – 7.15 (m, 2H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.36 (s, 2H), 4.17 (s, 1H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.82 – 1.67 (m, 2H), 1.53 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 572 $[M+H]^+$.

[0687] Example 214: 5-(2,3,4-trifluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0688] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2,3,4-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.60 (s, 1H), 9.87 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.10 (s, 1H), 7.40 – 7.15 (m, 4H), 6.93 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 4.26 (s, 2H), 4.16 (s, 1H), 3.96 (t, $J = 6.5$ Hz, 2H), 2.19 (s, 3H), 1.80 – 1.66 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 540 $[M+H]^+$.



Example 214



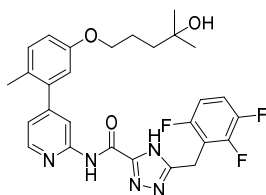
Example 215

[0689] Example 215: 5-(2,3,5-trifluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

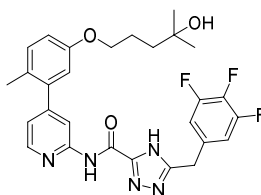
[0690] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2,3,5-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.75 (s, 1H), 9.96 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.58 – 7.41 (m, 1H), 7.33 – 7.13 (m, 3H), 7.01 – 6.87 (m, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.28 (s, 2H), 4.16 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.81 – 1.67 (m, 2H), 1.52 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 540 [M+H]⁺.

[0691] Example 216: 5-(2,3,6-trifluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0692] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2,3,6-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.75 (s, 1H), 9.89 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.08 (s, 1H), 7.59 – 7.42 (m, 1H), 7.31 – 7.12 (m, 3H), 6.92 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.25 (s, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.18 (s, 3H), 1.80 – 1.68 (m, 2H), 1.55 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 540 [M+H]⁺.



Example 216



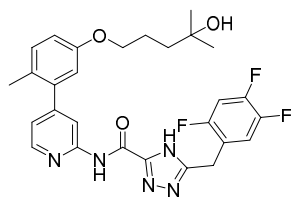
Example 217

[0693] Example 217: 5-(3,4,5-trifluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

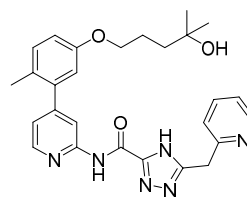
[0694] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(3,4,5-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 10.00 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.45 – 7.28 (m, 2H), 7.28 – 7.15 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.26 – 4.13 (m, 3H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.81 – 1.67 (m, 2H), 1.52 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 540 [M+H]⁺.

[0695] Example 218: 5-(2,4,5-trifluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0696] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(2,4,5-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.92 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.73 – 7.46 (m, 2H), 7.30 – 7.14 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.24 – 4.13 (m, 3H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.81 – 1.67 (m, 2H), 1.53 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 540 [M+H]⁺.



Example 218



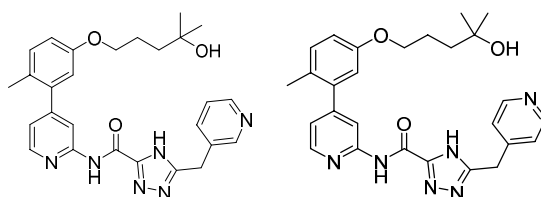
Example 219

[0697] Example 219: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(pyridin-2-ylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0698] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(pyridin-2-ylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.89 (s, 1H), 8.54 – 8.45 (m, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.84 – 7.75 (m, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.17 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.34 (s, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H), 1.82 – 1.68 (m, 2H), 1.54 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 487 [M+H]⁺.

[0699] Example 220: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(pyridin-3-ylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0700] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(pyridin-3-ylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.95 (s, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 8.48 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.13 – 8.09 (m, 1H), 7.82 – 7.70 (m, 1H), 7.43 – 7.32 (m, 1H), 7.28 – 7.17 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.8 Hz, 1H), 4.22 (s, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.81 – 1.69 (m, 2H), 1.54 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 487 [M+H]⁺.

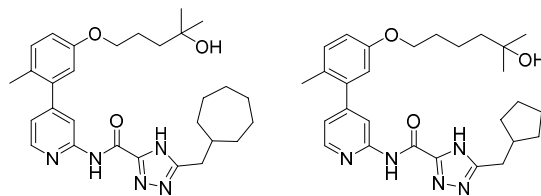


[0701] Example 221: N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(pyridin-4-ylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0702] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(pyridin-4-ylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.90 (s, 1H), 8.53 (d, *J* = 5.0 Hz, 2H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.11 (s, 1H), 7.42 – 7.29 (m, 2H), 7.29 – 7.15 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.29 – 4.20 (m, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.83 – 1.68 (m, 2H), 1.55 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 487 [M+H]⁺.

[0703] Example 222: 5-(cycloheptylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0704] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(cycloheptylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.85 (s, 1H), 8.42 (dd, *J* = 5.0, 0.8 Hz, 1H), 8.13 (s, 1H), 7.33 – 7.15 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 1H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.69 (d, *J* = 7.3 Hz, 2H), 2.19 (s, 3H), 2.07 – 1.91 (m, 1H), 1.82 – 1.70 (m, 2H), 1.70 – 1.30 (m, 12H), 1.30 – 1.15 (m, 2H), 1.09 (s, 6H). MS: 506 [M+H]⁺.



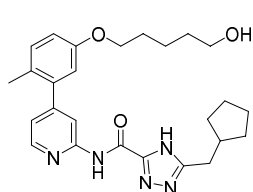
Example 222 Example 223

[0705] Example 223: 5-(cyclopentylmethyl)-N-(4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

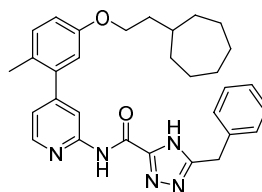
[0706] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.83 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.14 (s, 1H), 7.29 – 7.16 (m, 2H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.09 (s, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 2.79 (d, *J* = 7.5 Hz, 2H), 2.37 – 2.22 (m, 1H), 2.19 (s, 3H), 1.82 – 1.65 (m, 4H), 1.65 – 1.57 (m, 2H), 1.57 – 1.47 (m, 2H), 1.47 – 1.32 (m, 4H), 1.30 – 1.17 (m, 2H), 1.06 (s, 6H). MS: 492 [M+H]⁺.

[0707] Example 224: 5-(cyclopentylmethyl)-N-(4-(5-((5-hydroxypentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0708] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.36 (s, 1H), 9.83 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.29 – 7.16 (m, 2H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.37 (t, *J* = 5.1 Hz, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 3.51 – 3.36 (m, 2H), 2.79 (d, *J* = 7.5 Hz, 2H), 2.37 – 2.22 (m, 1H), 2.19 (s, 3H), 1.79 – 1.66 (m, 4H), 1.66 – 1.56 (m, 2H), 1.56 – 1.36 (m, 6H), 1.30 – 1.15 (m, 2H). MS: 464 [M+H]⁺.



Example 224



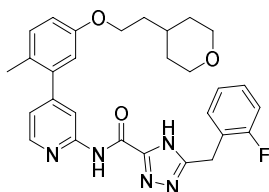
Example 225

[0709] Example 225: 5-benzyl-N-(4-(5-(2-cycloheptylethoxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

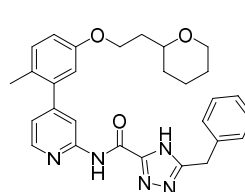
[0710] The preparation was carried out in a similar manner to Example 64, except that in step 1, 2-cycloheptyl-1-ethanol was used in place of 2-(tert-butoxy)ethan-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.88 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.44-7.30 (m, 4H), 7.30-7.14 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 3.99 (t, *J* = 6.3 Hz, 2H), 2.18 (s, 3H), 1.77-1.50 (m, 9H), 1.50 – 1.31 (m, 4H), 1.23 – 1.13 (m, 2H). MS: 510 [M+H]⁺.

[0711] Example 226: 5-(2-fluorobenzyl)-N-(4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0712] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 15.08-14.30 (m, 1H), 9.88 (s, 1H), 8.48-8.32 (m, 1H), 8.11 (s, 1H), 7.48-7.29 (m, 2H), 7.29-7.09 (m, 4H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.82 (s, 1H), 4.21 (s, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.92-3.67 (m, 2H), 3.30-3.14 (m, 2H), 2.18 (s, 3H), 1.80-1.48 (m, 5H), 1.33-1.08 (m, 2H). MS: 516 [M+H]⁺.



Example 226



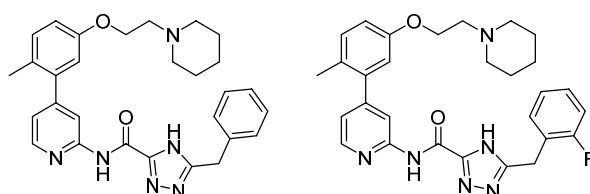
Example 227

[0713] Example 227: 5-benzyl-N-(4-(2-methyl-5-(2-(tetrahydro-2H-pyran-2-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0714] The preparation was carried out in a similar manner to Example 92, except that in step 1, 2-(2-bromoethyl)tetrahydro-2H-pyran was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.46 – 7.29 (m, 4H), 7.29 – 7.15 (m, 3H), 6.93 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.81 (d, *J* = 2.8 Hz, 1H), 4.17 (s, 2H), 4.11 – 3.95 (m, 2H), 3.90 – 3.78 (m, 1H), 3.46 – 3.19 (m, 4H), 2.19 (s, 3H), 1.87 – 1.76 (m, 2H), 1.76 – 1.68 (m, 1H), 1.65 – 1.55 (m, 1H), 1.47 – 1.39 (m, 2H). MS: 498 [M+H]⁺.

[0715] Example 228: 5-benzyl-N-(4-(2-methyl-5-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0716] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-chloroethyl)piperidine hydrochloride was used in place of iodomethane, and 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.91 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.12 (s, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.15 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 4.17 (s, 2H), 4.07 (t, *J* = 5.9 Hz, 2H), 2.64 (t, *J* = 5.9 Hz, 2H), 2.42 (t, *J* = 5.3 Hz, 4H), 2.19 (s, 3H), 1.55 – 1.41 (m, 4H), 1.41 – 1.27 (m, 2H). MS: 497 [M+H]⁺.



Example 228

Example 229

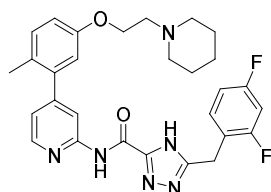
[0717] Example 229: 5-(2-fluorobenzyl)-N-(4-(2-methyl-5-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0718] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-chloroethyl)piperidine hydrochloride was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.89 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (d, *J* = 1.4 Hz, 1H), 7.36 – 7.11 (m, 6H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.33 – 4.24 (m, 2H), 4.21 (s, 2H), 4.11 (t, *J* = 5.8 Hz, 2H), 2.75 (t, *J* = 5.8 Hz, 2H), 2.19 (s, 3H), 1.56 – 1.43 (m, 4H), 1.43 – 1.32 (m, 2H), 1.31 – 1.23 (m, 2H). MS: 515 [M+H]⁺.

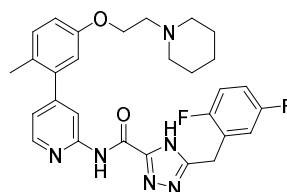
[0719] Example 230: 5-(2,4-difluorobenzyl)-N-(4-(2-methyl-5-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0720] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-

chloroethyl)piperidine hydrochloride was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2,4-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.52 – 7.40 (m, 1H), 7.31 – 7.16 (m, 3H), 7.13 – 7.04 (m, 1H), 6.94 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 4.18 (s, 2H), 4.07 (t, *J* = 5.9 Hz, 2H), 2.65 (t, *J* = 5.9 Hz, 2H), 2.47 – 2.35 (m, 4H), 2.19 (s, 3H), 1.55 – 1.41 (m, 4H), 1.41 – 1.28 (m, 2H). MS: 533 [M+H]⁺.



Example 230



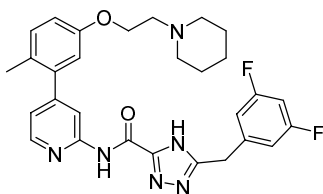
Example 231

[0721] Example 231: 5-(2,5-difluorobenzyl)-N-(4-(2-methyl-5-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

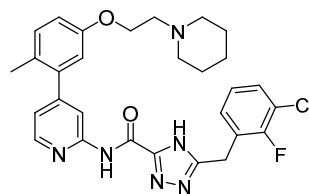
[0722] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-chloroethyl)piperidine hydrochloride was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2,5-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.93 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.45 – 7.03 (m, 5H), 7.03 – 6.67 (m, 2H), 4.20 (s, 2H), 4.07 (t, *J* = 5.9 Hz, 2H), 2.65 (t, *J* = 5.9 Hz, 2H), 2.50 – 2.33 (m, 4H), 2.18 (s, 3H), 1.62 – 1.41 (m, 4H), 1.41 – 1.21 (m, 2H). MS: 533 [M+H]⁺.

[0723] Example 232: 5-(3,5-difluorobenzyl)-N-(4-(2-methyl-5-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0724] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-chloroethyl)piperidine hydrochloride was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(3,5-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.99 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.14-8.06 (m, 1H), 7.28-7.05 (m, 5H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.22 (s, 2H), 4.08 (t, *J* = 5.9 Hz, 2H), 2.66 (t, *J* = 5.9 Hz, 2H), 2.47-2.36 (m, 4H), 2.19 (s, 3H), 1.53-1.42 (m, 4H), 1.42-1.30 (m, 2H). MS: 533 [M+H]⁺.



Example 232



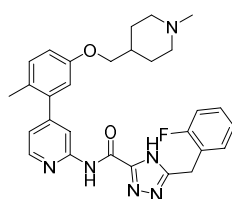
Example 233

[0725] Example 233: 5-(2-fluoro-3-chlorobenzyl)-N-(4-(2-methyl-5-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

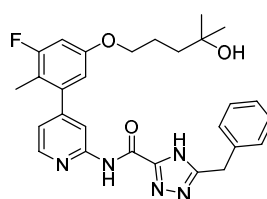
[0726] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-chloroethyl)piperidine hydrochloride was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluoro-3-chlorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.93 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.57 – 7.48 (m, 1H), 7.43 – 7.36 (m, 1H), 7.28 – 7.17 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.26 (s, 2H), 4.08 (t, *J* = 5.9 Hz, 2H), 2.66 (t, *J* = 5.8 Hz, 2H), 2.46 – 2.38 (m, 4H), 2.19 (s, 3H), 1.53 – 1.43 (m, 4H), 1.37 (t, *J* = 6.2 Hz, 2H). MS: 549 [M+H]⁺.

[0727] Example 234: 5-(2-fluorobenzyl)-N-(4-(2-methyl-5-((1-methylpiperidin-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0728] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-(chloromethyl)-1-methylpiperidine hydrochloride was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.11 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.44 – 7.30 (m, 2H), 7.28 – 7.14 (m, 4H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 4.19 (s, 2H), 3.97 (t, *J* = 6.6 Hz, 1H), 3.86 – 3.79 (m, 1H), 2.82 – 2.66 (m, 2H), 2.27 (s, 1H), 2.18 (s, 3H), 2.16 (s, 3H), 2.01 – 1.83 (m, 2H), 1.79 – 1.67 (m, 2H), 1.47 – 1.26 (m, 2H). MS: 515 [M+H]⁺.



Example 234



Example 235

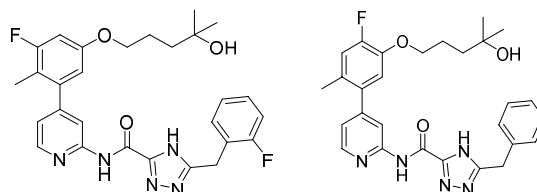
[0729] Example 235: 5-benzyl-N-(4-(3-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0730] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-5-fluoro-4-methylphenol was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.39-7.30 (m, 4H), 7.24 (dd, *J* = 20.1, 5.8 Hz, 2H), 6.91 (dd, *J* = 11.7, 2.5 Hz, 1H), 6.70 (d, *J* = 2.1 Hz, 1H), 4.18 (d, *J* = 5.4 Hz, 3H), 3.99 (t, *J* = 6.6 Hz, 2H), 2.12-2.04 (m, 3H), 1.79-1.68 (m, 2H), 1.53-1.39 (m, 2H), 1.09 (s, 6H). MS: 504 [M+H]⁺.

[0731] Example 236: 5-(2-fluorobenzyl)-N-(4-(3-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)-2-

methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0732] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-5-fluoro-4-methylphenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.67 (s, 1H), 9.92 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.09 (s, 1H), 7.52 – 7.29 (m, 2H), 7.29 – 7.14 (m, 3H), 6.90 (dd, *J* = 11.7, 2.5 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 4.21 (s, 2H), 4.17 (s, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 2.07 (d, *J* = 2.2 Hz, 3H), 1.81 – 1.70 (m, 2H), 1.51 – 1.37 (m, 2H), 1.09 (s, 6H). MS: 522 [M+H]⁺.



Example 236

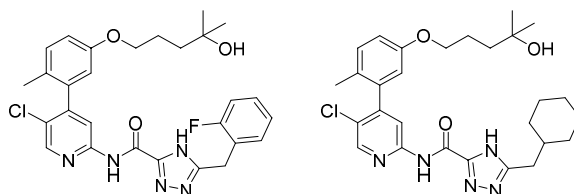
Example 237

[0733] Example 237: 5-benzyl-N-(4-(4-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0734] The preparation was carried out in a similar manner to Example 160, except that in step 1, 5-bromo-2-fluoro-4-methylphenol was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.89 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.40 – 7.29 (m, 4H), 7.29 – 7.15 (m, 3H), 7.03 (d, *J* = 8.7 Hz, 1H), 4.23 – 4.11 (m, 3H), 4.04 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.76 (dd, *J* = 10.3, 6.0 Hz, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 504 [M+H]⁺.

[0735] Example 238: N-(5-chloro-4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0736] The preparation was carried out in a similar manner to Example 160, except that in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 10.06 (s, 1H), 8.54 (s, 1H), 8.05 (s, 1H), 7.44 – 7.30 (m, 2H), 7.28 – 7.16 (m, 3H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 4.21 (s, 2H), 4.16 (s, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.01 (s, 3H), 1.80 – 1.67 (m, 2H), 1.51 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 538 [M+H]⁺.



Example 238

Example 239

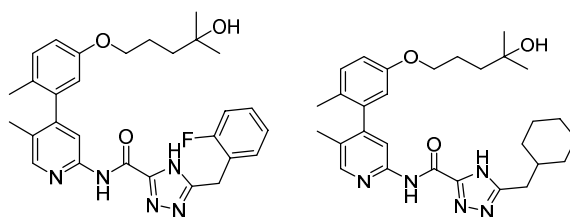
[0737] Example 239: N-(5-chloro-4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0738] The preparation was carried out in a similar manner to Example 160, except that in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 10.06 (s, 1H), 8.55 (s, 1H), 8.08 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.75 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.01 (s, 3H), 1.84 – 1.56 (m, 9H), 1.52 – 1.41 (m, 2H), 1.20 – 1.12 (m, 2H), 1.09 (s, 6H), 1.05 – 0.90 (m, 2H). MS: 526 [M+H]⁺.

[0739] Example 240: 5-(2-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)-5-methylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0740] The preparation was carried out in a similar manner to Example 160, except that in step 3, 4-bromo-5-methylpyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.75 (s, 1H), 8.30 (s, 1H), 7.87 (s, 1H), 7.44 – 7.29 (m, 2H), 7.29 – 7.14 (m, 3H), 6.90 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 4.20 (s, 2H), 4.17 (s, 1H), 3.94 (t, *J* = 6.6 Hz, 2H), 1.99 (s, 3H), 1.94 (s, 3H), 1.79 – 1.68 (m, 2H), 1.52 – 1.39 (m, 2H), 1.08 (s, 6H). MS: 518 [M+H]⁺.



Example 240

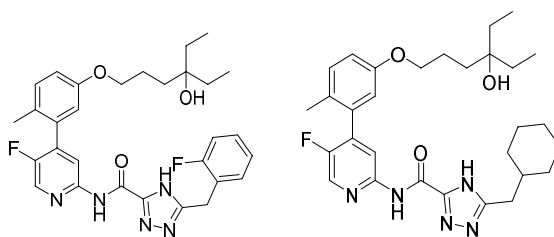
Example 241

[0741] Example 241: 5-(cyclohexylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)-5-methylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0742] The preparation was carried out in a similar manner to Example 160, except that in step 3, 4-bromo-5-methylpyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.34 (s, 1H), 9.74 (s, 1H), 8.31 (s, 1H), 7.90 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 1H), 3.94 (t, *J* = 6.6 Hz, 2H), 2.66 (d, *J* = 7.2 Hz, 2H), 2.00 (s, 3H), 1.95 (s, 3H), 1.82 – 1.57 (m, 8H), 1.52 – 1.40 (m, 2H), 1.24 – 1.13 (m, 3H), 1.08 (s, 6H), 1.05 – 0.90 (m, 2H). MS: 506 [M+H]⁺.

[0743] Example 242: N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-methylphenyl)-5-fluoropyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0744] The preparation was carried out in a similar manner to Example 160, except that in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 10.08 (s, 1H), 8.47 (s, 1H), 8.06 (d, *J* = 5.6 Hz, 1H), 7.45 – 7.30 (m, 2H), 7.30 – 7.14 (m, 3H), 6.97 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.20 (s, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 1H), 2.09 (s, 3H), 1.73 – 1.59 (m, 2H), 1.46 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 550 [M+H]⁺.



Example 242

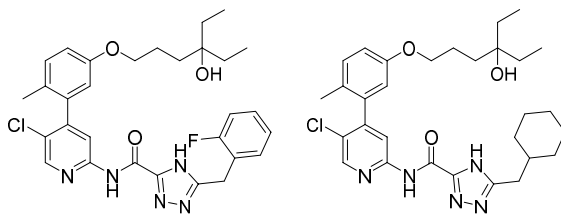
Example 243

[0745] Example 243: 5-(cyclohexylmethyl)-N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-methylphenyl)-5-fluoropyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0746] The preparation was carried out in a similar manner to Example 160, except that in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.02 (s, 1H), 8.48 (d, *J* = 1.2 Hz, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 1H), 2.66 (d, *J* = 7.0 Hz, 2H), 2.10 (s, 3H), 1.81 – 1.55 (m, 8H), 1.46 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 1.26 – 1.06 (m, 3H), 1.03 – 0.90 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 538 [M+H]⁺.

[0747] Example 244: N-(5-chloro-4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0748] The preparation was carried out in a similar manner to Example 160, except that in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 10.10 (s, 1H), 8.54 (s, 1H), 8.05 (s, 1H), 7.45 – 7.30 (m, 2H), 7.30 – 7.14 (m, 3H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 4.20 (s, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.86 (s, 1H), 2.00 (s, 3H), 1.73 – 1.60 (m, 2H), 1.46 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 566 [M+H]⁺.



Example 244

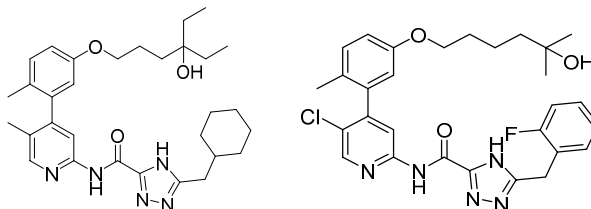
Example 245

[0749] Example 245: N-(5-chloro-4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0750] The preparation was carried out in a similar manner to Example 160, except that in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 10.03 (s, 1H), 8.55 (s, 1H), 8.08 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.95 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 3.87 (s, 1H), 2.71 – 2.62 (m, 2H), 2.01 (s, 3H), 1.81 – 1.71 (m, 1H), 1.71 – 1.56 (m, 7H), 1.46 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 1.29 – 1.14 (m, 3H), 1.03 – 0.90 (m, 2H), 0.77 (t, *J* = 7.5 Hz, 6H). MS: 554 [M+H]⁺.

[0751] Example 246: 5-(cyclohexylmethyl)-N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-methylphenyl)-5-methylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0752] The preparation was carried out in a similar manner to Example 160, except that in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.33 (s, 1H), 9.74 (s, 1H), 8.31 (s, 1H), 7.90 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 1H), 2.71 – 2.61 (m, 2H), 2.00 (s, 3H), 1.95 (s, 3H), 1.83 – 1.55 (m, 8H), 1.44 – 1.37 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 1.23 – 1.09 (m, 3H), 1.04 – 0.91 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 534 [M+H]⁺.



Example 246

Example 247

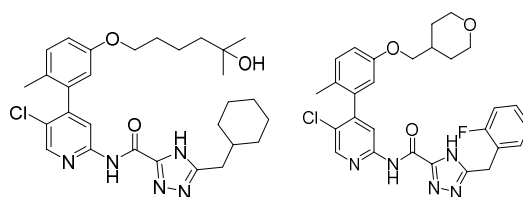
[0753] Example 247: N-(5-chloro-4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0754] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-

bromopentanoate was used in place of methyl 4-bromobutanoate, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.11 (s, 1H), 8.53 (s, 1H), 8.05 (s, 1H), 7.45 – 7.29 (m, 2H), 7.29 – 7.12 (m, 3H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 2.7 Hz, 1H), 4.19 (s, 2H), 4.09 (s, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.00 (s, 3H), 1.74 – 1.59 (m, 2H), 1.51 – 1.37 (m, 4H), 1.06 (s, 6H). MS: 552 [M+H]⁺.

[0755] Example 248: 5-(cyclohexylmethyl)-N-(5-chloro-4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0756] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 10.04 (s, 1H), 8.55 (s, 1H), 8.08 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.76 (d, *J* = 2.7 Hz, 1H), 4.09 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.66 (d, *J* = 6.9 Hz, 2H), 2.01 (s, 3H), 1.65 (dd, *J* = 13.9, 9.1 Hz, 8H), 1.49 – 1.35 (m, 4H), 1.22 – 1.10 (m, 3H), 1.06 (s, 6H), 1.04 – 0.94 (m, 2H). MS: 540 [M+H]⁺.



Example 248 Example 249

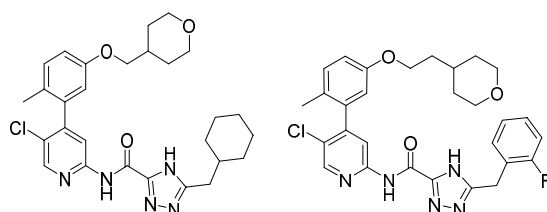
[0757] Example 249: N-(5-chloro-4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0758] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, in step 2, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 10.05 (s, 1H), 8.53 (s, 1H), 8.06 (s, 1H), 7.47 – 7.29 (m, 2H), 7.29 – 7.11 (m, 3H), 6.96 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.76 (d, *J* = 2.7 Hz, 1H), 4.23 (s, 2H), 3.92 – 3.78 (m, 4H), 3.32 – 3.26 (m, 2H), 2.01 (s, 3H), 1.99 – 1.92 (m, 1H), 1.73 – 1.59 (m, 2H), 1.37 – 1.26 (m, 2H). MS: 536 [M+H]⁺.

[0759] Example 250: N-(5-chloro-4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0760] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-

2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, in step 2, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 10.07 (s, 1H), 8.55 (s, 1H), 8.08 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.97 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 3.92 – 3.77 (m, 4H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.02 (s, 3H), 1.97 (dd, *J* = 9.5, 5.2 Hz, 1H), 1.82 – 1.56 (m, 8H), 1.39 – 1.13 (m, 7H), 1.04 – 0.91 (m, 2H). MS: 524 [M+H]⁺.



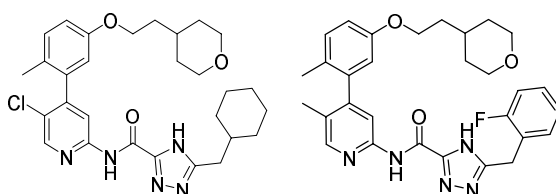
Example 250 Example 251

[0761] Example 251: N-(5-chloro-4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0762] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 10.12 (s, 1H), 8.54 (s, 1H), 8.05 (s, 1H), 7.44 – 7.29 (m, 2H), 7.28 – 7.15 (m, 3H), 6.96 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 4.20 (s, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.87 – 3.75 (m, 2H), 3.31 – 3.21 (m, 2H), 2.00 (s, 3H), 1.76 – 1.55 (m, 5H), 1.27 – 1.11 (m, 2H). MS: 550 [M+H]⁺.

[0763] Example 252: N-(5-chloro-4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0764] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 10.06 (s, 1H), 8.55 (s, 1H), 8.08 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 4.01 (t, *J* = 6.3 Hz, 2H), 3.86 – 3.76 (m, 2H), 3.30 – 3.20 (m, 2H), 2.71 – 2.61 (m, 2H), 2.01 (s, 3H), 1.82 – 1.55 (m, 11H), 1.29 – 1.08 (m, 5H), 1.05 – 0.89 (m, 2H). MS: 538 [M+H]⁺.



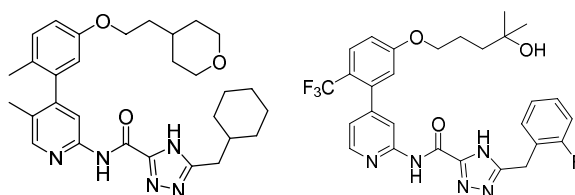
Example 252 Example 253

[0765] Example 253: 5-(2-fluorobenzyl)-N-(5-methyl-4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0766] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.76 (s, 1H), 8.30 (s, 1H), 7.87 (s, 1H), 7.46 – 7.28 (m, 2H), 7.28 – 7.12 (m, 3H), 6.91 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.68 (d, *J* = 2.7 Hz, 1H), 4.20 (s, 2H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.86 – 3.75 (m, 2H), 3.30 – 3.19 (m, 2H), 1.99 (s, 3H), 1.94 (s, 3H), 1.72 – 1.54 (m, 5H), 1.25 – 1.17 (m, 2H). MS: 530 [M+H]⁺.

[0767] Example 254: 5-(cyclohexylmethyl)-N-(5-methyl-4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0768] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.34 (s, 1H), 9.74 (s, 1H), 8.31 (s, 1H), 7.91 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.69 (d, *J* = 2.7 Hz, 1H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.81 (dd, *J* = 11.8, 4.3 Hz, 2H), 3.26 (t, *J* = 11.6 Hz, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.00 (s, 3H), 1.95 (s, 3H), 1.81 – 1.52 (m, 11H), 1.25 – 1.10 (m, 5H), 1.05 – 0.87 (m, 2H). MS: 518 [M+H]⁺.



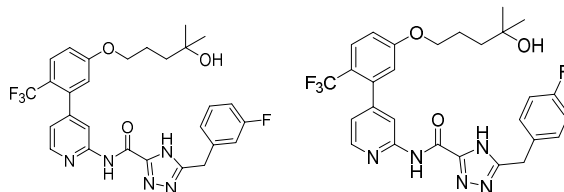
Example 254 Example 255

[0769] Example 255: 5-(2-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0770] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.94 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.29 (m, 2H), 7.26 – 7.12 (m, 4H), 6.96 (d, *J* = 2.6 Hz, 1H), 4.31 – 4.14 (m, 3H), 4.09 (t, *J* = 6.6 Hz, 2H), 1.86 – 1.67 (m, 2H), 1.53 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 558 [M+H]⁺.

[0771] Example 256: 5-(3-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0772] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(3-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 10.00 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.44 – 7.33 (m, 1H), 7.24 – 7.05 (m, 5H), 6.97 (d, *J* = 2.5 Hz, 1H), 4.20 (d, *J* = 6.3 Hz, 3H), 4.09 (t, *J* = 6.6 Hz, 2H), 1.84 – 1.69 (m, 2H), 1.55 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 558 [M+H]⁺.



Example 256

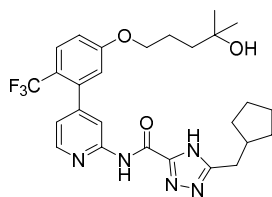
Example 257

[0773] Example 257: 5-(4-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

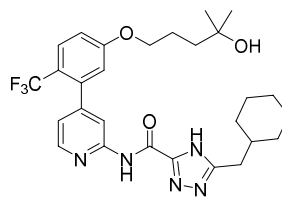
[0774] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(4-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.97 (s, 1H), 8.43 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.16 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.23 – 7.11 (m, 4H), 6.97 (d, *J* = 2.5 Hz, 1H), 4.31 – 4.13 (m, 3H), 4.09 (t, *J* = 6.5 Hz, 2H), 1.86 – 1.69 (m, 2H), 1.54 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 558 [M+H]⁺.

[0775] Example 258: 5-(cyclopentylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0776] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.26 – 7.13 (m, 2H), 6.97 (d, *J* = 2.6 Hz, 1H), 4.20 (s, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 2.78 (d, *J* = 7.4 Hz, 2H), 2.37 – 2.19 (m, 1H), 1.85 – 1.66 (m, 4H), 1.66 – 1.56 (m, 2H), 1.56 – 1.41 (m, 4H), 1.26 – 1.20 (m, 2H), 1.09 (s, 6H). MS: 532 [M+H]⁺.



Example 258



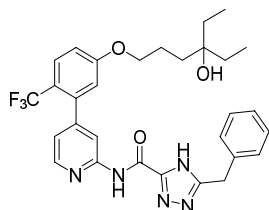
Example 259

[0777] Example 259: 5-(cyclohexylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

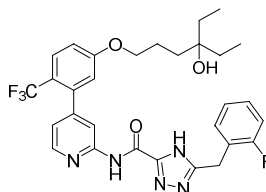
[0778] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.89 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.12 (m, 2H), 6.97 (d, *J* = 2.6 Hz, 1H), 4.19 (s, 1H), 4.09 (t, *J* = 6.6 Hz, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 1.82 – 1.55 (m, 8H), 1.52 – 1.43 (m, 2H), 1.27 – 1.13 (m, 3H), 1.10 (s, 6H), 1.05 – 0.88 (m, 2H). MS: 546 [M+H]⁺.

[0779] Example 260: 5-benzyl-N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0780] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.95 (s, 1H), 8.51 – 8.36 (m, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.43 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.22 – 7.11 (m, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 4.17 (s, 2H), 4.08 (t, *J* = 6.5 Hz, 2H), 3.89 (s, 1H), 1.78 – 1.63 (m, 2H), 1.49 – 1.38 (m, 2H), 1.34 (q, *J* = 7.5 Hz, 4H), 0.77 (t, *J* = 7.5 Hz, 6H). MS: 568 [M+H]⁺.



Example 260



Example 261

[0781] Example 261: 5-(2-fluorobenzyl)-N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0782] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆)

δ 14.64 (s, 1H), 9.88 (d, J = 46.2 Hz, 1H), 8.42 (dd, J = 12.1, 5.2 Hz, 1H), 8.15 (s, 1H), 7.80 (dd, J = 8.7, 4.7 Hz, 1H), 7.48 – 7.32 (m, 3H), 7.22 – 7.15 (m, 3H), 6.96 (d, J = 2.6 Hz, 1H), 4.21 (s, 2H), 4.16 – 4.04 (m, 2H), 3.89 (s, 1H), 1.77 – 1.60 (m, 2H), 1.48 – 1.39 (m, 2H), 1.35 (q, J = 7.5 Hz, 4H), 0.78 (t, J = 7.4 Hz, 6H). MS: 586 [M+H]⁺.

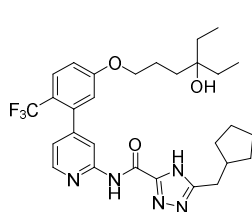
5

[0783] Example 262: 5-(cyclopentylmethyl)-N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy))-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

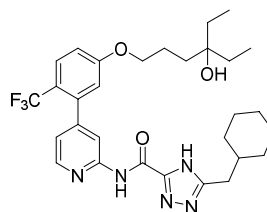
[0784] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.89 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H), 8.17 (s, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.26 – 7.11 (m, 2H), 6.97 (d, J = 2.5 Hz, 1H), 4.09 (t, J = 6.5 Hz, 2H), 3.89 (s, 1H), 2.78 (d, J = 7.5 Hz, 2H), 2.36 – 2.18 (m, 1H), 1.79 – 1.66 (m, 4H), 1.66 – 1.47 (m, 4H), 1.47 – 1.39 (m, 2H), 1.35 (q, J = 7.5 Hz, 4H), 1.29 – 1.21 (m, 2H), 0.77 (t, J = 7.4 Hz, 6H). MS: 560 [M+H]⁺.

10

15



Example 262



Example 263

[0785] Example 263: 5-(cyclohexylmethyl)-N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy))-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0786] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.89 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H), 8.17 (s, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.28 – 7.13 (m, 2H), 6.97 (d, J = 2.6 Hz, 1H), 4.09 (t, J = 6.5 Hz, 2H), 3.89 (s, 1H), 2.67 (d, J = 7.0 Hz, 2H), 1.83 – 1.56 (m, 8H), 1.51 – 1.39 (m, 2H), 1.35 (q, J = 7.5 Hz, 4H), 1.27 – 1.09 (m, 3H), 1.06 – 0.89 (m, 2H), 0.77 (t, J = 7.5 Hz, 6H). MS: 574 [M+H]⁺.

20

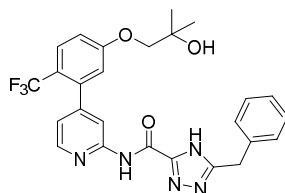
25

[0787] Example 264: 5-benzyl-N-(4-(5-(2-hydroxyl-2-methylpropoxy))-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

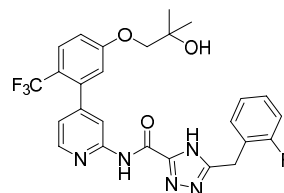
[0788] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-

30

4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and methyl bromoacetate was used in place of methyl 4-bromobutanoate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.96 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.13 (m, 3H), 6.99 (d, *J* = 2.6 Hz, 1H), 4.69 (s, 1H), 4.17 (s, 2H), 3.85 (s, 2H), 1.20 (s, 6H). MS: 512 [M+H]⁺.



Example 264



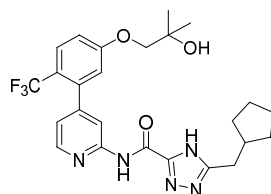
Example 265

[0789] Example 265: 5-(2-fluorobenzyl)-N-(4-(5-(2-hydroxy-2-methylpropoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

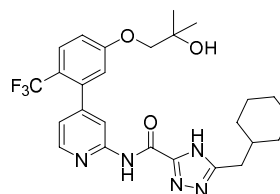
[0790] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, methyl bromoacetate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.69 (s, 1H), 9.95 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.48 – 7.29 (m, 2H), 7.29 – 7.13 (m, 4H), 6.99 (d, *J* = 2.6 Hz, 1H), 4.68 (s, 1H), 4.20 (s, 2H), 3.85 (s, 2H), 1.20 (s, 6H). MS: 530 [M+H]⁺.

[0791] Example 266: 5-(cyclopentylmethyl)-N-(4-(5-(2-hydroxy-2-methylpropoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0792] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, methyl bromoacetate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.91 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.27 – 7.14 (m, 2H), 7.00 (d, *J* = 2.6 Hz, 1H), 4.69 (s, 1H), 3.85 (s, 2H), 2.77 (d, *J* = 7.5 Hz, 2H), 2.34 – 2.20 (m, 1H), 1.79 – 1.66 (m, 2H), 1.66 – 1.56 (m, 2H), 1.56 – 1.43 (m, 2H), 1.23 – 1.14 (m, 8H). MS: 504 [M+H]⁺.



Example 266



Example 267

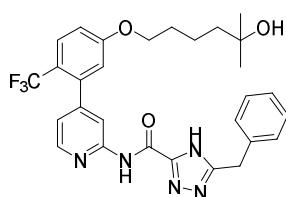
[0793] Example 267: 5-(cyclohexylmethyl)-N-(4-(5-(2-hydroxy-2-methylpropoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0794] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-

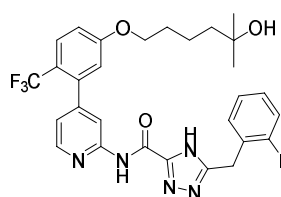
4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, methyl bromoacetate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.91 (s, 1H), 8.49-8.38 (m, 1H), 8.17 (d, *J* = 1.4 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.29-7.11 (m, 2H), 7.00 (d, *J* = 2.6 Hz, 1H), 4.69 (s, 1H), 3.85 (s, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 1.85-1.52 (m, 6H), 1.30-1.07 (m, 9H), 1.07-0.90 (m, 2H). MS: 518 [M+H]⁺.

[0795] Example 268: 5-benzyl-N-(4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0796] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.95 (s, 1H), 8.43 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.16 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.44 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.22 – 7.10 (m, 2H), 6.98 (d, *J* = 2.6 Hz, 1H), 4.17 (s, 2H), 4.14 – 4.00 (m, 3H), 1.71 (t, *J* = 6.9 Hz, 2H), 1.51 – 1.32 (m, 4H), 1.06 (s, 6H). MS: 554 [M+H]⁺.



Example 268



Example 269

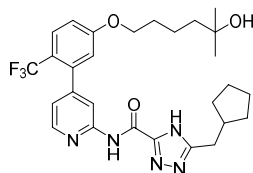
[0797] Example 269: 5-(2-fluorobenzyl)-N-(4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0798] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.93 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.46 – 7.28 (m, 2H), 7.28 – 7.12 (m, 4H), 6.97 (d, *J* = 2.5 Hz, 1H), 4.21 (s, 2H), 4.15 – 4.02 (m, 3H), 1.71 (t, *J* = 7.0 Hz, 2H), 1.52 – 1.34 (m, 4H), 1.06 (s, 6H). MS: 572 [M+H]⁺.

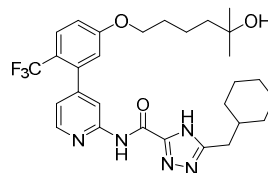
[0799] Example 270: 5-(cyclopentylmethyl)-N-(4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0800] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate

was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.90 (s, 1H), 8.44 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.27 – 7.13 (m, 2H), 6.98 (d, *J* = 2.5 Hz, 1H), 4.17 – 4.01 (m, 3H), 2.78 (d, *J* = 7.4 Hz, 2H), 2.35 – 2.19 (m, 1H), 1.81 – 1.66 (m, 4H), 1.66 – 1.33 (m, 8H), 1.29 – 1.15 (m, 2H), 1.06 (s, 6H). MS: 546 [M+H]⁺.



Example 270



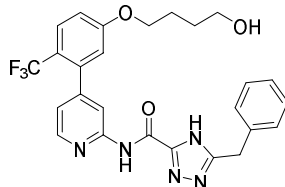
Example 271

[0801] Example 271: 5-(cyclohexylmethyl)-N-(4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

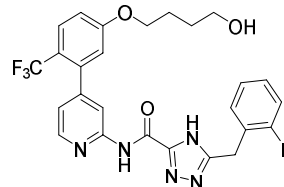
[0802] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.90 (s, 1H), 8.43 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.27 – 7.12 (m, 2H), 6.98 (d, *J* = 2.5 Hz, 1H), 4.17 – 4.01 (m, 3H), 2.66 (d, *J* = 7.1 Hz, 2H), 1.86 – 1.55 (m, 8H), 1.51 – 1.33 (m, 4H), 1.28 – 1.09 (m, 3H), 1.06 (s, 6H), 1.04 – 0.89 (m, 2H). MS: 560 [M+H]⁺.

[0803] Example 272: 5-benzyl-N-(4-(5-(4-hydroxybutoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0804] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, and 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.95 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.22 – 7.14 (m, 2H), 6.98 (d, *J* = 2.6 Hz, 1H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.17 (s, 2H), 4.11 (t, *J* = 6.5 Hz, 2H), 3.48 – 3.41 (m, 2H), 1.82 – 1.69 (m, 2H), 1.61 – 1.49 (m, 2H). MS: 512 [M+H]⁺.



Example 272



Example 273

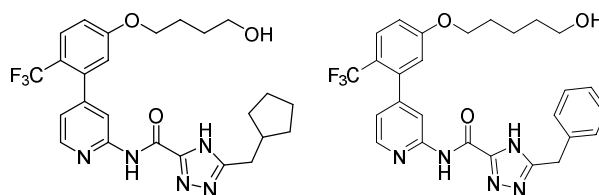
[0805] Example 273: 5-(2-fluorobenzyl)-N-(4-(5-(4-hydroxybutoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0806] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-

butanol was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.93 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.44-7.29 (m, 2H), 7.26-7.14 (m, 4H), 6.97 (d, *J* = 2.5 Hz, 1H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.21 (s, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.48-3.40 (m, 2H), 1.81-1.70 (m, 2H), 1.61-1.50 (m, 2H). MS: 530 [M+H]⁺.

[0807] Example 274: 5-(cyclopentylmethyl)-N-(4-(5-(4-hydroxybutoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0808] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.23 – 7.15 (m, 2H), 6.98 (d, *J* = 2.6 Hz, 1H), 4.45 (t, *J* = 5.2 Hz, 1H), 4.11 (t, *J* = 6.6 Hz, 2H), 3.49 – 3.39 (m, 2H), 2.77 (d, *J* = 7.5 Hz, 2H), 2.37 – 2.19 (m, 1H), 1.83 – 1.67 (m, 4H), 1.67 – 1.45 (m, 6H), 1.30 – 1.14 (m, 2H). MS: 504 [M+H]⁺.



Example 274

Example 275

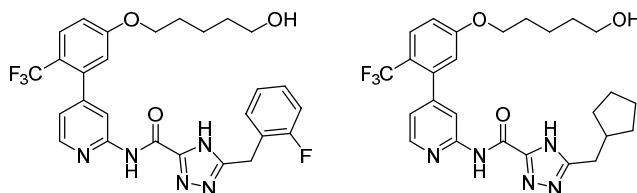
[0809] Example 275: 5-benzyl-N-(4-(5-((5-hydroxypentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0810] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, and 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.95 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.44 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 7.22 – 7.10 (m, 2H), 6.98 (d, *J* = 2.6 Hz, 1H), 4.37 (t, *J* = 5.1 Hz, 1H), 4.17 (s, 2H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.42 – 3.38 (m, 2H), 1.80 – 1.68 (m, 2H), 1.54 – 1.36 (m, 4H). MS: 526 [M+H]⁺.

[0811] Example 276: 5-(2-fluorobenzyl)-N-(4-(5-((5-hydroxypentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0812] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of

ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.67 (s, 1H), 9.94 (s, 1H), 8.43 (d, $J = 5.0$ Hz, 1H), 8.15 (s, 1H), 7.78 (d, $J = 8.8$ Hz, 1H), 7.47-7.29 (m, 2H), 7.29-7.12 (m, 4H), 6.97 (d, $J = 2.6$ Hz, 1H), 4.38 (d, $J = 5.5$ Hz, 1H), 4.20 (s, 2H), 4.09 (t, $J = 6.5$ Hz, 2H), 3.42-3.38 (m, 2H), 1.81-1.65 (m, 2H), 1.55-1.34 (m, 4H). MS: 544 $[\text{M}+\text{H}]^+$.



Example 276

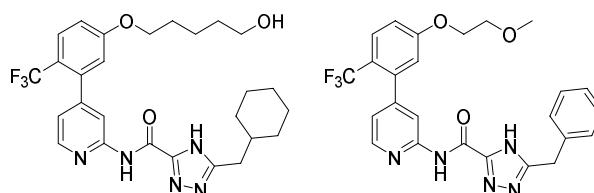
Example 277

[0813] Example 277: 5-(cyclopentylmethyl)-N-(4-(5-((5-hydroxypentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0814] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.39 (s, 1H), 9.90 (s, 1H), 8.44 (d, $J = 5.1$ Hz, 1H), 8.17 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.28 – 7.12 (m, 2H), 6.98 (d, $J = 2.6$ Hz, 1H), 4.37 (t, $J = 5.1$ Hz, 1H), 4.09 (t, $J = 6.5$ Hz, 2H), 3.45 – 3.36 (m, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.36 – 2.21 (m, 1H), 1.81 – 1.66 (m, 4H), 1.66 – 1.38 (m, 8H), 1.28 – 1.15 (m, 2H). MS: 518 $[\text{M}+\text{H}]^+$.

[0815] Example 278: 5-(cyclohexylmethyl)-N-(4-(5-((5-hydroxypentyl)oxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0816] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.36 (s, 1H), 9.89 (s, 1H), 8.44 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.17 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.28 – 7.12 (m, 2H), 6.98 (d, $J = 2.6$ Hz, 1H), 4.37 (t, $J = 5.1$ Hz, 1H), 4.09 (t, $J = 6.5$ Hz, 2H), 3.45 – 3.36 (m, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.83 – 1.53 (m, 8H), 1.53 – 1.36 (m, 4H), 1.26 – 1.15 (m, 3H), 1.03 – 0.90 (m, 2H). MS: 532 $[\text{M}+\text{H}]^+$.



Example 278

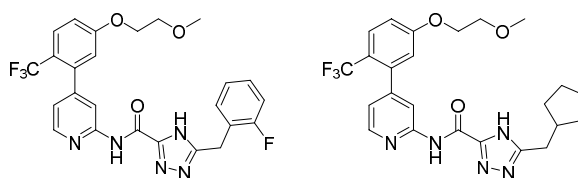
Example 279

[0817] Example 279: 5-benzyl-N-(4-(5-(2-methoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0818] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, and 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.96 (s, 1H), 8.44 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.16 (d, *J* = 1.4 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.48 – 7.29 (m, 4H), 7.29 – 7.13 (m, 3H), 7.01 (d, *J* = 2.6 Hz, 1H), 4.28 – 4.20 (m, 2H), 4.17 (s, 2H), 3.73 – 3.62 (m, 2H), 3.30 (s, 3H). MS: 498 [M+H]⁺.

[0819] Example 280: 5-(2-fluorobenzyl)-N-(4-(5-(2-methoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0820] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 9.95 (s, 1H), 8.43 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.46 – 7.28 (m, 2H), 7.28 – 7.07 (m, 4H), 7.00 (d, *J* = 2.5 Hz, 1H), 4.29 – 4.15 (m, 4H), 3.70 – 3.62 (m, 2H), 3.30 (s, 3H). MS: 516 [M+H]⁺.



Example 280

Example 281

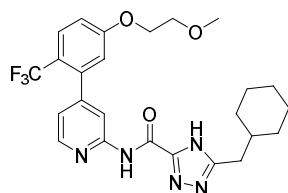
[0821] Example 281: 5-(cyclopentylmethyl)-N-(4-(5-(2-methoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0822] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.91 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.32 – 7.12 (m, 2H), 7.01 (d, *J* = 2.6 Hz, 1H), 4.31 – 4.17 (m, 2H), 3.72 – 3.62 (m, 2H), 3.30 (s, 3H), 2.77 (d, *J* = 7.4 Hz, 2H), 2.37 – 2.18 (m, 1H), 1.79 – 1.66 (m, 2H), 1.66 – 1.44 (m, 4H), 1.29 – 1.12 (m, 2H). MS: 490 [M+H]⁺.

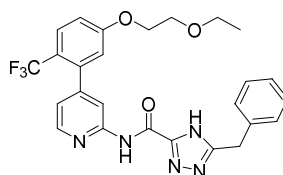
[0823] Example 282: 5-(cyclohexylmethyl)-N-(4-(5-(2-methoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0824] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.90 (s,

1H), 8.52 – 8.39 (m, 1H), 8.18 (s, 1H), 7.80 (d, $J = 8.9$ Hz, 1H), 7.30 – 7.14 (m, 2H), 7.01 (d, $J = 2.6$ Hz, 1H), 4.31 – 4.17 (m, 2H), 3.73 – 3.60 (m, 2H), 3.30 (s, 3H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.83 – 1.54 (m, 6H), 1.27 – 1.12 (m, 3H), 1.04 – 0.91 (m, 2H). MS: 504 $[M+H]^+$.



Example 282



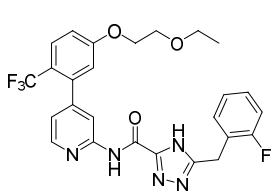
Example 283

[0825] Example 283: 5-benzyl-N-(4-(5-(2-ethoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

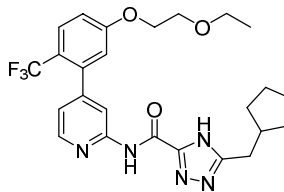
[0826] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, and 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, DMSO- d_6) δ 14.61 (s, 1H), 9.96 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 8.16 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.43 – 7.09 (m, 7H), 7.01 (d, $J = 2.6$ Hz, 1H), 4.28 – 4.20 (m, 2H), 4.17 (s, 2H), 3.75 – 3.66 (m, 2H), 3.49 (q, $J = 7.0$ Hz, 2H), 1.11 (t, $J = 7.0$ Hz, 3H). MS: 512 $[M+H]^+$.

[0827] Example 284: 5-(2-fluorobenzyl)-N-(4-(5-(2-ethoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0828] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.67 (s, 1H), 9.94 (s, 1H), 8.48-8.37 (m, 1H), 8.15 (s, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.45-7.29 (m, 2H), 7.26-7.14 (m, 4H), 7.01 (d, $J = 2.6$ Hz, 1H), 4.30 – 4.14 (m, 4H), 3.74-3.64 (m, 2H), 3.49 (q, $J = 7.0$ Hz, 2H), 1.11 (t, $J = 7.0$ Hz, 3H). MS: 530 $[M+H]^+$.



Example 284



Example 285

[0829] Example 285: 5-(cyclopentylmethyl)-N-(4-(5-(2-ethoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0830] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in

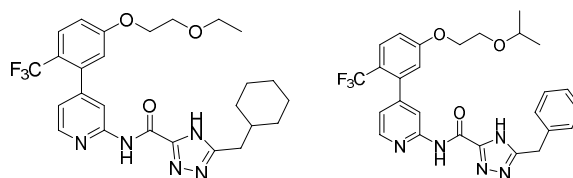
place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.29 – 7.13 (m, 2H), 7.02 (d, *J* = 2.6 Hz, 1H), 4.29 – 4.17 (m, 2H), 3.76 – 3.65 (m, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.35 – 2.18 (m, 1H), 1.79 – 1.67 (m, 2H), 1.67 – 1.44 (m, 4H), 1.30 – 1.16 (m, 2H), 1.11 (t, *J* = 7.0 Hz, 3H). MS: 504 [M+H]⁺.

5

[0831] Example 286: 5-(cyclohexylmethyl)-N-(4-(5-(2-ethoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0832] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.13 (m, 2H), 7.02 (d, *J* = 2.6 Hz, 1H), 4.28 – 4.19 (m, 2H), 3.76 – 3.66 (m, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 2.66 (d, *J* = 7.0 Hz, 2H), 1.80 – 1.57 (m, 6H), 1.25 – 1.14 (m, 3H), 1.11 (t, *J* = 7.0 Hz, 3H), 1.06 – 0.91 (m, 2H). MS: 518 [M+H]⁺.

10



15

Example 286

Example 287

[0833] Example 287: 5-benzyl-N-(4-(5-(2-isopropoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0834] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, and 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.94 (s, 1H), 8.43 (dd, *J* = 5.0, 0.8 Hz, 1H), 8.16 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.41-7.11 (m, 7H), 7.01 (d, *J* = 2.6 Hz, 1H), 4.25-4.12 (m, 4H), 3.74-3.67 (m, 2H), 3.62 (p, *J* = 6.1 Hz, 1H), 1.09 (d, *J* = 6.1 Hz, 6H). MS: 526 [M+H]⁺.

20

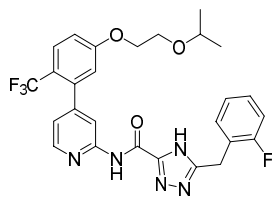
[0835] Example 288: 5-(2-fluorobenzyl)-N-(4-(5-(2-isopropoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0836] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 9.94 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.48 – 7.28 (m, 2H), 7.28 – 7.11 (m, 4H), 7.01 (d, *J* = 2.6 Hz, 1H), 4.29 – 4.13 (m, 4H), 3.76 – 3.66 (m, 2H), 3.61 (p, *J* = 6.1 Hz, 1H), 1.09 (d, *J* = 6.1 Hz, 6H).

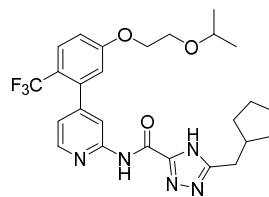
25

30

MS: 544 [M+H]⁺.



Example 288



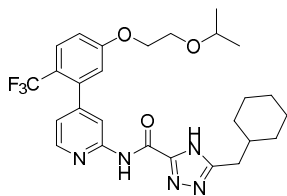
Example 289

[0837] Example 289: 5-(cyclopentylmethyl)-N-(4-(5-(2-isopropoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

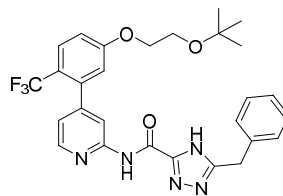
[0838] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.33 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.11 (m, 2H), 7.01 (d, *J* = 2.5 Hz, 1H), 4.26 – 4.15 (m, 2H), 3.75 – 3.67 (m, 2H), 3.62 (p, *J* = 6.1 Hz, 1H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.21 (m, 1H), 1.78 – 1.66 (m, 2H), 1.66 – 1.44 (m, 4H), 1.24 – 1.16 (m, 2H), 1.09 (d, *J* = 6.1 Hz, 6H). MS: 518 [M+H]⁺.

[0839] Example 290: 5-(cyclohexylmethyl)-N-(4-(5-(2-isopropoxyethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0840] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.36 (s, 1H), 9.88 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.14 (m, 2H), 7.01 (d, *J* = 2.6 Hz, 1H), 4.25 – 4.16 (m, 2H), 3.75 – 3.67 (m, 2H), 3.62 (p, *J* = 6.1 Hz, 1H), 2.67 (d, *J* = 6.9 Hz, 2H), 1.84 – 1.54 (m, 6H), 1.24 – 1.13 (m, 3H), 1.09 (d, *J* = 6.1 Hz, 6H), 1.05 – 0.91 (m, 2H). MS: 532 [M+H]⁺.



Example 290



Example 291

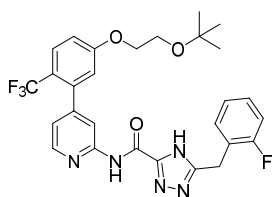
[0841] Example 291: 5-benzyl-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0842] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.53 (s, 1H), 9.95 (s, 1H), 8.43 (d, *J* = 5.0 Hz, 1H), 8.16 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.40 – 7.11 (m, 7H), 7.00

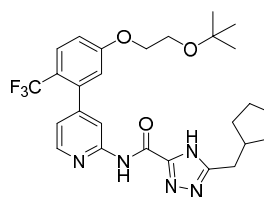
(d, $J = 2.5$ Hz, 1H), 4.22 – 4.10 (m, 4H), 3.69 – 3.59 (m, 2H), 1.14 (s, 9H). MS: 540 $[M+H]^+$.

[0843] Example 292: 5-(2-fluorobenzyl)-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0844] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.67 (s, 1H), 9.94 (s, 1H), 8.43 (d, $J = 5.2$ Hz, 1H), 8.15 (s, 1H), 7.78 (d, $J = 8.8$ Hz, 1H), 7.51 – 7.27 (m, 2H), 7.27 – 7.10 (m, 4H), 7.00 (d, $J = 2.6$ Hz, 1H), 4.28 – 4.09 (m, 4H), 3.65 (t, $J = 4.8$ Hz, 2H), 1.14 (s, 9H). MS: 558 $[M+H]^+$.



Example 292



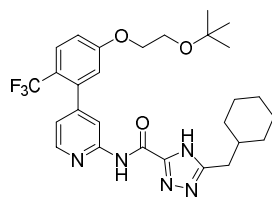
Example 293

[0845] Example 293: 5-(cyclopentylmethyl)-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

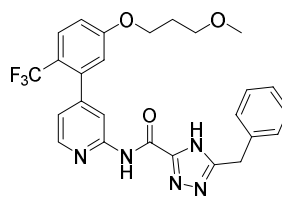
[0846] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.37 (s, 1H), 9.88 (s, 1H), 8.44 (d, $J = 5.1$ Hz, 1H), 8.18 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.28-7.11 (m, 2H), 7.01 (d, $J = 2.6$ Hz, 1H), 4.24-4.11 (m, 2H), 3.71-3.60 (m, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.28 (p, $J = 7.6$ Hz, 1H), 1.79-1.66 (m, 2H), 1.66-1.43 (m, 4H), 1.25-1.20 (m, 2H), 1.15 (s, 9H). MS: 532 $[M+H]^+$.

[0847] Example 294: 5-(cyclohexylmethyl)-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0848] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.32 (s, 1H), 9.89 (s, 1H), 8.44 (d, $J = 5.1$ Hz, 1H), 8.17 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.29 – 7.12 (m, 2H), 7.01 (d, $J = 2.6$ Hz, 1H), 4.24 – 4.13 (m, 2H), 3.66 (dd, $J = 5.5$, 4.0 Hz, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.83 – 1.56 (m, 6H), 1.23 – 1.16 (m, 3H), 1.15 (s, 9H), 1.05 – 0.93 (m, 2H). MS: 546 $[M+H]^+$.



Example 294



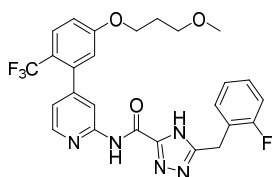
Example 295

[0849] Example 295: 5-benzyl-N-(4-(5-(3-methoxypropoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

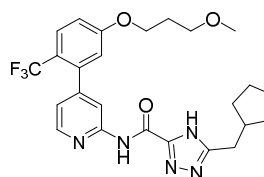
[0850] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, and 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.96 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.23 – 7.12 (m, 2H), 6.98 (d, *J* = 2.6 Hz, 1H), 4.22 – 4.08 (m, 4H), 3.46 (t, *J* = 6.2 Hz, 2H), 3.23 (s, 3H), 2.02 – 1.90 (m, 2H). MS: 512 [M+H]⁺.

[0851] Example 296: 5-(2-fluorobenzyl)-N-(4-(5-(3-methoxypropoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0852] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.67 (s, 1H), 9.94 (s, 1H), 8.43 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.46 – 7.28 (m, 2H), 7.28 – 7.12 (m, 4H), 6.98 (d, *J* = 2.6 Hz, 1H), 4.21 (s, 2H), 4.14 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.2 Hz, 2H), 3.23 (s, 3H), 2.01 – 1.91 (m, 2H). MS: 530 [M+H]⁺.



Example 296



Example 297

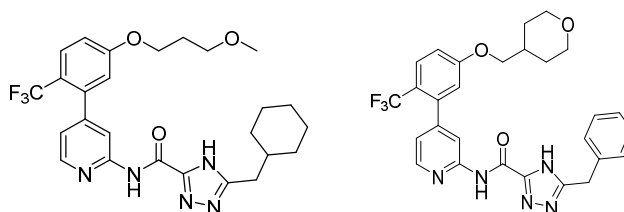
[0853] Example 297: 5-(cyclopentylmethyl)-N-(4-(5-(3-methoxypropoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0854] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.91 (s, 1H), 8.44 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.23 – 8.13 (m, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.12 (m, 2H), 6.99 (d,

$J = 2.5$ Hz, 1H), 4.15 (t, $J = 6.4$ Hz, 2H), 3.46 (t, $J = 6.2$ Hz, 2H), 3.24 (s, 3H), 2.77 (d, $J = 7.5$ Hz, 2H), 2.36 – 2.19 (m, 1H), 2.04 – 1.91 (m, 2H), 1.78 – 1.66 (m, 2H), 1.66 – 1.44 (m, 4H), 1.29 – 1.14 (m, 2H). MS: 504 $[M+H]^+$.

[0855] Example 298: 5-(cyclohexylmethyl)-N-(4-(5-(3-methoxypropoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0856] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.38 (s, 1H), 9.90 (s, 1H), 8.49 – 8.39 (m, 1H), 8.17 (s, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.29 – 7.13 (m, 2H), 6.99 (d, $J = 2.6$ Hz, 1H), 4.15 (t, $J = 6.4$ Hz, 2H), 3.47 (t, $J = 6.2$ Hz, 2H), 3.24 (s, 3H), 2.67 (d, $J = 7.0$ Hz, 2H), 2.03 – 1.90 (m, 2H), 1.81 – 1.57 (m, 6H), 1.24 – 1.10 (m, 3H), 1.03 – 0.89 (m, 2H). MS: 518 $[M+H]^+$.



Example 298

Example 299

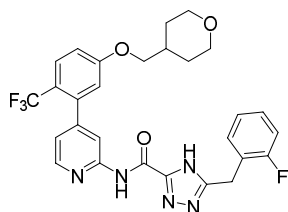
[0857] Example 299: 5-benzyl-N-(4-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0858] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, and 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, DMSO- d_6) δ 14.56 (s, 1H), 9.95 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 8.16 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.13 (m, 3H), 6.99 (d, $J = 2.6$ Hz, 1H), 4.17 (s, 2H), 3.97 (d, $J = 6.5$ Hz, 2H), 3.92 – 3.79 (m, 2H), 2.10 – 1.93 (m, 1H), 1.72 – 1.60 (m, 2H), 1.42 – 1.18 (m, 4H). MS: 538 $[M+H]^+$.

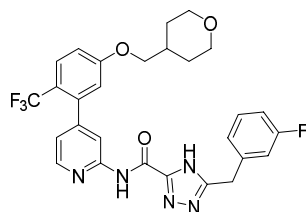
[0859] Example 300: 5-(2-fluorobenzyl)-N-(4-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0860] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.66 (s, 1H), 9.94 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 8.15 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.45 – 7.29 (m, 2H), 7.26 –

7.13 (m, 4H), 6.99 (d, $J = 2.6$ Hz, 1H), 4.21 (s, 2H), 3.96 (d, $J = 6.5$ Hz, 2H), 3.92 – 3.80 (m, 2H), 2.09 – 1.91 (m, 1H), 1.72 – 1.62 (m, 2H), 1.41 – 1.16 (m, 4H). MS: 556 $[M+H]^+$.



Example 300



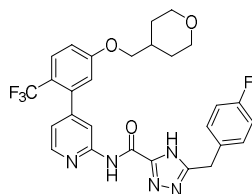
Example 301

5 **[0861]** Example 301: 5-(3-fluorobenzyl)-N-(4-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

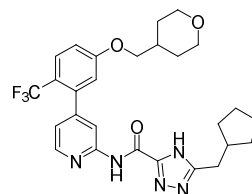
[0862] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(3-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.64 (s, 1H), 9.99 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 8.16 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.44 – 7.32 (m, 1H), 7.26 – 7.13 (m, 4H), 7.13 – 7.04 (m, 1H), 6.99 (d, $J = 2.5$ Hz, 1H), 4.21 (s, 2H), 3.96 (d, $J = 6.5$ Hz, 2H), 3.91 – 3.80 (m, 2H), 3.35 – 3.29 (m, 2H), 2.07 – 1.95 (m, 1H), 1.73 – 1.60 (m, 2H), 1.41 – 1.25 (m, 2H). MS: 556 $[M+H]^+$.

15 **[0863]** Example 302: 5-(4-fluorobenzyl)-N-(4-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0864] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(4-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.53 (s, 1H), 9.91 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 8.15 (s, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.42 – 7.31 (m, 2H), 7.26 – 7.09 (m, 4H), 6.99 (d, $J = 2.5$ Hz, 1H), 4.18 (s, 2H), 3.97 (d, $J = 6.5$ Hz, 2H), 3.92 – 3.79 (m, 2H), 3.33 – 3.31 (m, 2H), 2.13 – 1.92 (m, 1H), 1.74 – 1.60 (m, 2H), 1.42 – 1.23 (m, 2H). MS: 556 $[M+H]^+$.



Example 302



Example 303

25 **[0865]** Example 303: 5-(cyclopentylmethyl)-N-(4-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

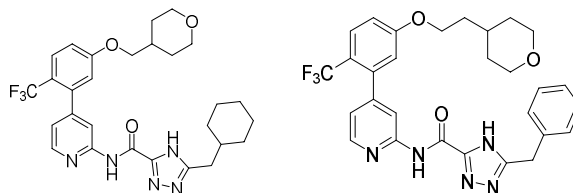
[0866] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-

2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.89 (s, 1H), 8.44 (d, *J* = 5.0 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.25 – 7.14 (m, 2H), 6.99 (d, *J* = 2.5 Hz, 1H), 3.97 (d, *J* = 6.5 Hz, 2H), 3.91 – 3.81 (m, 2H), 3.33 – 3.26 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.35 – 2.18 (m, 1H), 2.11 – 1.93 (m, 1H), 1.79 – 1.42 (m, 8H), 1.41 – 1.27 (m, 2H), 1.27 – 1.18 (m, 2H). MS: 530 [M+H]⁺.

[0867] Example 304: 5-(cyclohexylmethyl)-N-(4-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0868] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate.

[0869] ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.29 – 7.13 (m, 2H), 7.00 (d, *J* = 2.6 Hz, 1H), 3.97 (d, *J* = 6.4 Hz, 2H), 3.92 – 3.79 (m, 2H), 3.37 – 3.33 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.10 – 1.92 (m, 1H), 1.81 – 1.72 (m, 1H), 1.70 – 1.62 (m, 6H), 1.40 – 1.11 (m, 6H), 1.05 – 0.89 (m, 2H). MS: 544 [M+H]⁺.



Example 304

Example 305

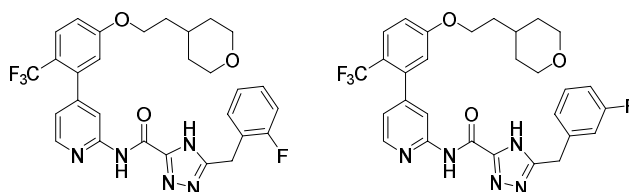
[0870] Example 305: 5-benzyl-N-(4-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0871] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, and in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.95 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.23 – 7.13 (m, 2H), 6.99 (d, *J* = 2.6 Hz, 1H), 4.25 – 4.06 (m, 4H), 3.89 – 3.71 (m, 2H), 3.29 – 3.16 (m, 2H), 1.77 – 1.65 (m, 3H), 1.65 – 1.53 (m, 2H), 1.29 – 1.18 (m, 2H). MS: 552 [M+H]⁺.

[0872] Example 306: 5-(2-fluorobenzyl)-N-(4-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0873] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-

2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.94 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.48 – 7.28 (m, 2H), 7.28 – 7.12 (m, 4H), 6.99 (d, *J* = 2.6 Hz, 1H), 4.21 (s, 2H), 4.14 (t, *J* = 6.1 Hz, 2H), 3.89 – 3.76 (m, 2H), 3.31 – 3.20 (m, 2H), 1.77 – 1.55 (m, 5H), 1.31 – 1.12 (m, 2H). MS: 570 [M+H]⁺.



Example 306

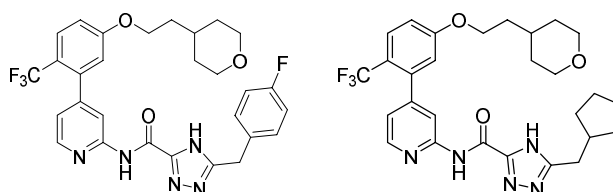
Example 307

[0874] Example 307: 5-(3-fluorobenzyl)-N-(4-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0875] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 4, ethyl 5-(3-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.97 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.32 (m, 1H), 7.23 – 7.13 (m, 4H), 7.13 – 7.05 (m, 1H), 7.00 (d, *J* = 2.6 Hz, 1H), 4.21 (s, 2H), 4.14 (t, *J* = 6.1 Hz, 2H), 3.93 – 3.72 (m, 2H), 3.32 – 3.21 (m, 2H), 1.75 – 1.57 (m, 5H), 1.29 – 1.13 (m, 2H). MS: 570 [M+H]⁺.

[0876] Example 308: 5-(4-fluorobenzyl)-N-(4-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0877] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 4, ethyl 5-(4-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.96 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.44 – 7.31 (m, 2H), 7.27 – 7.10 (m, 4H), 7.00 (d, *J* = 2.6 Hz, 1H), 4.23 – 4.10 (m, 4H), 3.87 – 3.77 (m, 2H), 3.31 – 3.20 (m, 2H), 1.79 – 1.57 (m, 5H), 1.30 – 1.14 (m, 2H). MS: 570 [M+H]⁺.



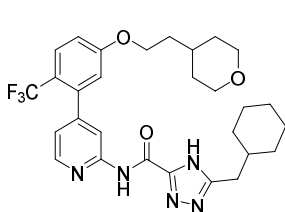
Example 308 Example 309

[0878] Example 309: 5-(cyclopentylmethyl)-N-(4-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

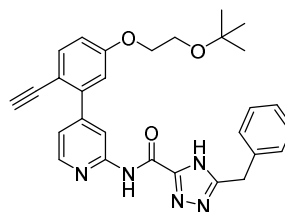
[0879] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.17 (d, *J* = 1.4 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.25 – 7.14 (m, 2H), 7.00 (d, *J* = 2.5 Hz, 1H), 4.14 (t, *J* = 6.1 Hz, 2H), 3.93 – 3.69 (m, 2H), 3.30 – 3.23 (m, 2H), 2.77 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.19 (m, 1H), 1.78 – 1.42 (m, 11H), 1.31 – 1.13 (m, 4H). MS: 544 [M+H]⁺.

[0880] Example 310: 5-(cyclohexylmethyl)-N-(4-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0881] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 2-bromo-3-methylphenol, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.90 (s, 1H), 8.44 (d, *J* = 5.0 Hz, 1H), 8.17 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.25 – 7.14 (m, 2H), 7.00 (d, *J* = 2.5 Hz, 1H), 4.15 (t, *J* = 6.1 Hz, 2H), 3.88 – 3.76 (m, 2H), 3.30 – 3.21 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 1.82 – 1.52 (m, 10H), 1.31 – 1.07 (m, 6H), 1.07 – 0.91 (m, 2H). MS: 558 [M+H]⁺.



Example 310



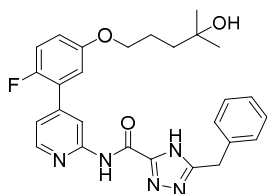
Example 311

[0882] Example 311: 5-benzyl-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-ethynylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

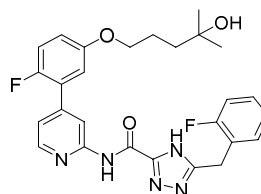
[0883] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-bromo-4-ethynylphenol was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.87 (s, 1H), 8.43 (d, *J* = 5.3 Hz, 1H), 8.37 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.42 – 7.29 (m, 5H), 7.26 (s, 1H), 7.10 – 6.97 (m, 2H), 4.18 (s, 2H), 4.16 – 4.09 (m, 2H), 4.05 (s, 1H), 3.65 (t, *J* = 4.8 Hz, 2H), 1.15 (s, 9H). MS: 496 [M+H]⁺.

[0884] Example 312: 5-benzyl-N-(4-(2-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0885] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.90 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.35 (s, 1H), 7.40 (d, *J* = 5.2 Hz, 1H), 7.38 – 7.29 (m, 5H), 7.29 – 7.19 (m, 1H), 7.16 – 6.99 (m, 2H), 4.24 – 4.11 (m, 3H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.84 – 1.69 (m, 2H), 1.55 – 1.43 (m, 2H), 1.10 (s, 6H). MS: 490 [M+H]⁺.



Example 312



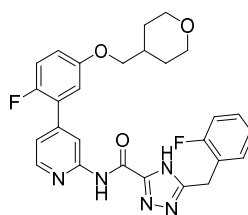
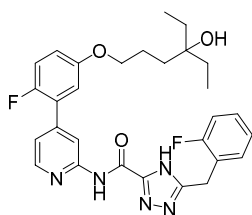
Example 313

[0886] Example 313: 5-(2-fluorobenzyl)-N-(4-(2-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0887] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.70 (s, 1H), 9.92 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 7.48 – 7.26 (m, 4H), 7.26 – 7.15 (m, 2H), 7.15 – 6.99 (m, 2H), 4.26 – 4.14 (m, 3H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.84 – 1.68 (m, 2H), 1.56 – 1.41 (m, 2H), 1.10 (s, 6H). MS: 508 [M+H]⁺.

[0888] Example 314: N-(4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-fluorophenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0889] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.21 (s, 1H), 9.91 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 7.48 – 7.26 (m, 4H), 7.26 – 7.14 (m, 2H), 7.14 – 6.97 (m, 2H), 4.21 (s, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.91 – 3.88 (m, 1H), 1.77 – 1.57 (m, 2H), 1.48 – 1.39 (m, 2H), 1.35 (q, *J* = 7.5 Hz, 4H), 0.78 (t, *J* = 7.6 Hz, 6H). MS: 536 [M+H]⁺.



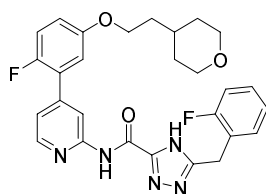
Example 314 Example 315

[0890] Example 315: 5-(2-fluorobenzyl)-N-(4-(2-fluoro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

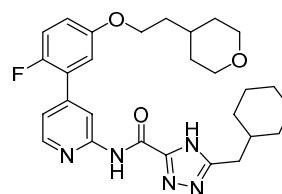
[0891] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-fluorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.89 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.33 (s, 1H), 7.48 – 7.26 (m, 4H), 7.26 – 7.15 (m, 2H), 7.15 – 7.02 (m, 2H), 4.21 (s, 2H), 3.95 – 3.81 (m, 4H), 3.40 – 3.33 (m, 2H), 2.07 – 1.93 (m, 1H), 1.75 – 1.60 (m, 2H), 1.41 – 1.25 (m, 2H). MS: 506 [M+H]⁺.

[0892] Example 316: N-(4-(2-fluoro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0893] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 0H), 9.89 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.33 (s, 1H), 7.46 – 7.26 (m, 4H), 7.26 – 7.16 (m, 2H), 7.13 (dd, *J* = 6.3, 3.1 Hz, 1H), 7.11 – 7.04 (m, 1H), 4.21 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.87 – 3.77 (m, 2H), 3.27 (dd, *J* = 11.6, 2.1 Hz, 2H), 2.09 – 1.90 (m, 1H), 1.70 – 1.59 (m, 4H), 1.23 – 1.12 (m, 2H). MS: 520 [M+H]⁺.



Example 316



Example 317

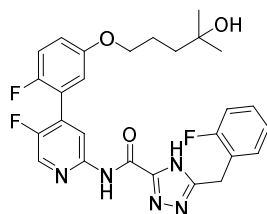
[0894] Example 317: 5-(cyclohexylmethyl)-N-(4-(2-fluoro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0895] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.36 (s, 1H), 9.85 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.37 (s, 1H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.32 (dd, *J* = 10.4, 9.0 Hz, 1H), 7.13 (dd, *J* = 6.3, 3.1 Hz, 1H), 7.11-7.04 (m, 1H), 4.08 (t, *J* = 6.3 Hz, 2H), 3.88-3.76 (m, 2H), 3.30-3.20 (m, 2H), 2.68 (d, *J* = 7.1 Hz, 2H), 1.77-1.60 (m, 10H), 1.29-1.14 (m, 6H), 1.06-0.90 (m, 2H).

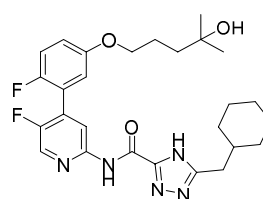
MS: 508 [M+H]⁺.

[0896] Example 318: N-(5-fluoro-4-(2-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0897] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.07 (s, 1H), 8.51 (d, *J* = 1.4 Hz, 1H), 8.20 (d, *J* = 5.4 Hz, 1H), 7.44 – 7.29 (m, 3H), 7.26 – 7.16 (m, 2H), 7.15 – 7.04 (m, 2H), 4.21 (s, 2H), 4.17 (s, 1H), 4.00 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.68 (m, 2H), 1.54 – 1.42 (m, 2H), 1.10 (s, 6H). MS: 526 [M+H]⁺.



Example 318



Example 319

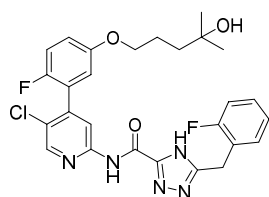
[0898] Example 319: 5-(cyclohexylmethyl)-N-(5-fluoro-4-(2-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0899] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 10.04 (s, 1H), 8.52 (d, *J* = 1.4 Hz, 1H), 8.23 (d, *J* = 5.5 Hz, 1H), 7.40 – 7.26 (m, 1H), 7.17 – 7.03 (m, 2H), 4.18 (s, 1H), 4.00 (t, *J* = 6.5 Hz, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 1.84 – 1.71 (m, 3H), 1.71 – 1.61 (m, 4H), 1.55 – 1.44 (m, 2H), 1.29 – 1.12 (m, 4H), 1.10 (s, 6H), 1.05 – 0.92 (m, 2H). MS: 514 [M+H]⁺.

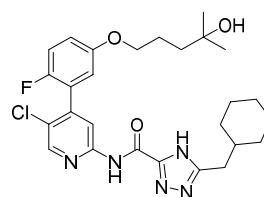
[0900] Example 320: N-(5-chloro-4-(2-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0901] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 10.10 (s, 1H), 8.56 (s, 1H), 8.18 (s, 1H), 7.51 – 7.14 (m, 5H), 7.14 – 7.04 (m, 1H), 6.99 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.26 – 4.14 (m, 3H), 3.98 (t, *J* = 6.6 Hz, 2H), 1.83 – 1.67 (m, 2H), 1.54 – 1.39 (m, 2H), 1.09 (s, 6H).

MS: 542 [M+H]⁺.



Example 320



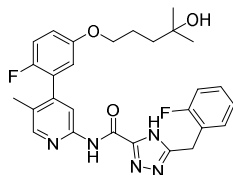
Example 321

[0902] Example 321: N-(5-chloro-4-(2-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

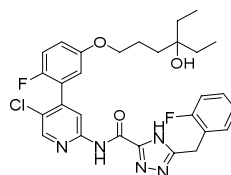
[0903] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.08 (s, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 7.37 – 7.26 (m, 1H), 7.14 – 7.06 (m, 1H), 7.00 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.18 (s, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 2.72 – 2.61 (m, 2H), 1.83 – 1.71 (m, 3H), 1.71 – 1.62 (m, 4H), 1.51 – 1.43 (m, 2H), 1.28 – 1.11 (m, 4H), 1.10 (s, 6H), 1.06 – 0.90 (m, 2H). MS: 530 [M+H]⁺.

[0904] Example 322: N-(4-(2-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)-5-methylpyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0905] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 9.83 (s, 1H), 8.33 (s, 1H), 8.00 (s, 1H), 7.49 – 7.12 (m, 5H), 7.12 – 6.97 (m, 1H), 6.90 (dd, *J* = 6.0, 3.1 Hz, 1H), 4.27 – 4.13 (m, 3H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.12 (s, 3H), 1.83 – 1.67 (m, 2H), 1.53 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 522 [M+H]⁺.



Example 322



Example 323

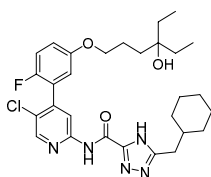
[0906] Example 323: N-(5-chloro-4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-fluorophenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0907] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-

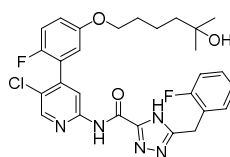
bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 10.14 (s, 1H), 8.57 (s, 1H), 8.17 (s, 1H), 7.46 – 7.25 (m, 3H), 7.25 – 7.15 (m, 2H), 7.14 – 7.05 (m, 1H), 6.99 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.21 (s, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 1H), 1.75 – 1.61 (m, 2H), 1.48 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 570 [M+H]⁺.

[0908] Example 324: 5-(cyclohexylmethyl)-N-(5-chloro-4-(5-((4-ethyl-4-hydroxyhexyl)oxy)-2-fluorophenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0909] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.08 (s, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 7.39 – 7.23 (m, 1H), 7.15 – 7.04 (m, 1H), 6.99 (dd, *J* = 5.8, 3.1 Hz, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 1H), 2.67 (d, *J* = 6.9 Hz, 2H), 1.82 – 1.57 (m, 8H), 1.49 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 1.28 – 1.09 (m, 3H), 1.06 – 0.91 (m, 2H), 0.77 (t, *J* = 7.5 Hz, 6H). MS: 558 [M+H]⁺.



Example 324



Example 325

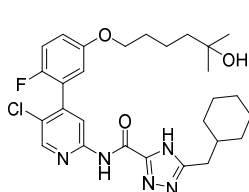
[0910] Example 325: N-(5-chloro-4-(2-fluoro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0911] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 10.16 (s, 1H), 8.57 (s, 1H), 8.17 (s, 1H), 7.45 – 7.26 (m, 3H), 7.26 – 7.15 (m, 2H), 7.15 – 7.04 (m, 1H), 7.00 (dd, *J* = 5.8, 3.1 Hz, 1H), 4.21 (s, 2H), 4.10 (s, 1H), 3.99 (t, *J* = 6.4 Hz, 2H), 1.74 – 1.63 (m, 2H), 1.51 – 1.34 (m, 4H), 1.06 (s, 6H). MS: 556 [M+H]⁺.

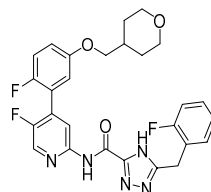
[0912] Example 326: 5-(cyclohexylmethyl)-N-(5-chloro-4-(2-fluoro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0913] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-

bromopentanoate was used in place of methyl 4-bromobutanoate, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 10.10 (s, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 7.37 – 7.26 (m, 1H), 7.16 – 7.06 (m, 1H), 7.01 (dd, *J* = 5.8, 3.1 Hz, 1H), 4.10 (s, 1H), 4.00 (t, *J* = 6.5 Hz, 2H), 2.70 – 2.61 (m, 2H), 1.81 – 1.56 (m, 8H), 1.51 – 1.34 (m, 4H), 1.28 – 1.14 (m, 3H), 1.07 (s, 6H), 1.04 – 0.89 (m, 2H). MS: 544 [M+H]⁺.



Example 326



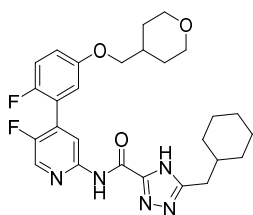
Example 327

[0914] Example 327: N-(5-fluoro-4-(2-fluoro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

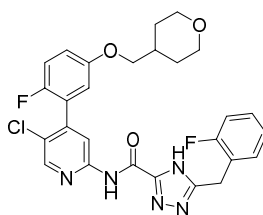
[0915] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 10.05 (s, 1H), 8.51 (s, 1H), 8.25 – 8.09 (m, 1H), 7.45 – 7.07 (m, 6H), 6.53 (s, 1H), 4.23 (s, 2H), 3.93 – 3.82 (m, 4H), 3.35 (d, *J* = 2.1 Hz, 2H), 2.05 – 1.92 (m, 1H), 1.72 – 1.61 (m, 2H), 1.39 – 1.24 (m, 2H). MS: 524 [M+H]⁺.

[0916] Example 328: 5-(cyclohexylmethyl)-N-(5-fluoro-4-(2-fluoro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0917] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 10.03 (s, 1H), 8.55 – 8.49 (m, 1H), 8.24 (d, *J* = 5.4 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.18 – 7.06 (m, 2H), 3.93 – 3.82 (m, 4H), 3.41 – 3.33 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.05 – 1.90 (m, 1H), 1.83 – 1.55 (m, 8H), 1.40 – 1.26 (m, 2H), 1.26 – 1.06 (m, 3H), 1.06 – 0.91 (m, 2H). MS: 512 [M+H]⁺.



Example 328



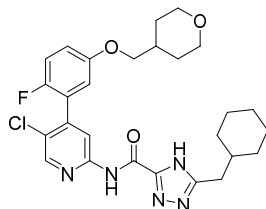
Example 329

[0918] Example 329: N-(5-chloro-4-(2-fluoro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

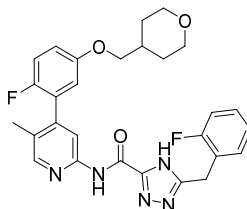
[0919] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 10.12 (s, 1H), 8.57 (s, 1H), 8.17 (s, 1H), 7.46 – 7.26 (m, 3H), 7.26 – 7.15 (m, 2H), 7.15 – 7.06 (m, 1H), 7.01 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.21 (s, 2H), 3.92 – 3.76 (m, 4H), 3.33 – 3.25 (m, 2H), 2.04 – 1.91 (m, 1H), 1.72 – 1.59 (m, 2H), 1.41 – 1.25 (m, 2H). MS: 540 [M+H]⁺.

[0920] Example 330: 5-(cyclohexylmethyl)-N-(5-chloro-4-(2-fluoro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0921] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.09 (s, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 7.37 – 7.26 (m, 1H), 7.16 – 7.07 (m, 1H), 7.02 (dd, *J* = 5.9, 3.1 Hz, 1H), 3.93 – 3.82 (m, 4H), 3.34 – 3.27 (m, 2H), 2.71 – 2.63 (m, 2H), 2.06 – 1.92 (m, 1H), 1.85 – 1.52 (m, 8H), 1.39 – 1.14 (m, 5H), 1.06 – 0.90 (m, 2H). MS: 528 [M+H]⁺.



Example 330



Example 331

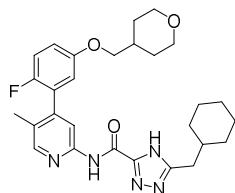
[0922] Example 331: N-(4-(2-fluoro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-5-methylpyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0923] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-

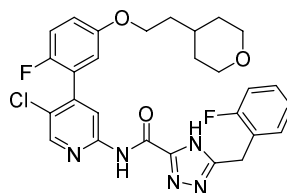
2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.83 (s, 1H), 8.33 (s, 1H), 8.00 (s, 1H), 7.46 – 7.14 (m, 5H), 7.10 – 7.01 (m, 1H), 6.92 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.20 (s, 2H), 3.95 – 3.76 (m, 4H), 3.32 – 3.24 (m, 2H), 2.12 (s, 3H), 2.05 – 1.92 (m, 1H), 1.74 – 1.61 (m, 2H), 1.39 – 1.24 (m, 2H). MS: 520 [M+H]⁺.

[0924] Example 332: 5-(cyclohexylmethyl)-N-(4-(2-fluoro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-5-methylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0925] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 9.80 (s, 1H), 8.34 (s, 1H), 8.03 (s, 1H), 7.34-7.24 (m, 1H), 7.11-7.02 (m, 1H), 6.92 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.93-3.79 (m, 4H), 3.33-3.27 (m, 2H), 2.70-2.62 (m, 2H), 2.13 (s, 3H), 2.05-1.93 (m, 1H), 1.82-1.55 (m, 8H), 1.40-1.14 (m, 5H), 1.05-0.90 (m, 2H). MS: 508 [M+H]⁺.



Example 332



Example 333

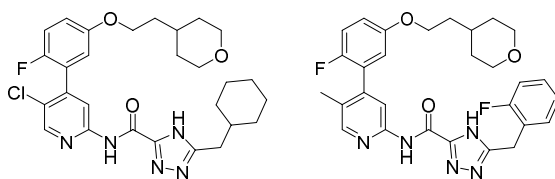
[0926] Example 333: N-(5-chloro-4-(2-fluoro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0927] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 10.11 (s, 1H), 8.57 (s, 1H), 8.18 (s, 1H), 7.50-7.27 (m, 3H), 7.27-7.15 (m, 2H), 7.15-7.06 (m, 1H), 7.02 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.22 (s, 2H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.86-3.78 (m, 2H), 3.32-3.23 (m, 2H), 1.78-1.56 (m, 5H), 1.29-1.12 (m, 2H). MS: 554 [M+H]⁺.

[0928] Example 334: N-(5-chloro-4-(2-fluoro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-

5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0929] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.08 (s, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 7.36-7.25 (m, 1H), 7.16-7.06 (m, 1H), 7.02 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.87-3.78 (m, 2H), 3.31-3.24 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 1.81-1.56 (m, 11H), 1.28-1.13 (m, 5H), 1.04-0.90 (m, 2H). MS: 542 [M+H]⁺.



Example 334

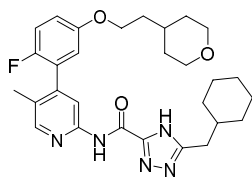
Example 335

[0930] Example 335: N-(4-(2-fluoro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)-5-methylpyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

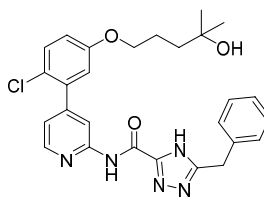
[0931] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.69 (s, 1H), 9.86 (s, 1H), 8.33 (s, 1H), 8.00 (s, 1H), 7.45 – 7.14 (m, 5H), 7.11 – 7.01 (m, 1H), 6.92 (dd, *J* = 6.0, 3.1 Hz, 1H), 4.20 (s, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.86 – 3.78 (m, 2H), 3.30 – 3.24 (m, 2H), 2.12 (s, 3H), 1.77 – 1.54 (m, 5H), 1.30 – 1.08 (m, 2H). MS: 534 [M+H]⁺.

[0932] Example 336: 5-(cyclohexylmethyl)-N-(4-(2-fluoro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)-5-methylpyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0933] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-methyl-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 9.79 (s, 1H), 8.34 (s, 1H), 8.03 (s, 1H), 7.35 – 7.22 (m, 1H), 7.11 – 7.02 (m, 1H), 6.93 (dd, *J* = 6.0, 3.1 Hz, 1H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.87 – 3.77 (m, 2H), 3.32 – 3.22 (m, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.13 (s, 3H), 1.81 – 1.55 (m, 11H), 1.30 – 1.11 (m, 5H), 1.05 – 0.89 (m, 2H). MS: 522 [M+H]⁺.



Example 336



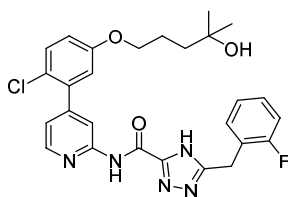
Example 337

[0934] Example 337: 5-benzyl-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-chlorophenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

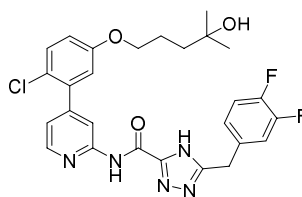
[0935] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.58 (s, 1H), 9.93 (s, 1H), 8.45 (d, $J = 5.1$ Hz, 1H), 8.23 (s, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.43 – 7.18 (m, 6H), 7.13 – 6.93 (m, 2H), 4.26 – 4.09 (m, 3H), 4.01 (t, $J = 6.6$ Hz, 2H), 1.83 – 1.69 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 506 $[\text{M}+\text{H}]^+$.

[0936] Example 338: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0937] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.66 (s, 1H), 9.95 (s, 1H), 8.45 (d, $J = 5.2$ Hz, 1H), 8.21 (s, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.45 – 7.14 (m, 5H), 7.06 (dd, $J = 8.7, 3.0$ Hz, 1H), 7.01 (d, $J = 3.0$ Hz, 1H), 4.27 – 4.16 (m, 3H), 4.01 (t, $J = 6.6$ Hz, 2H), 1.83 – 1.69 (m, 2H), 1.53 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 524 $[\text{M}+\text{H}]^+$.



Example 338



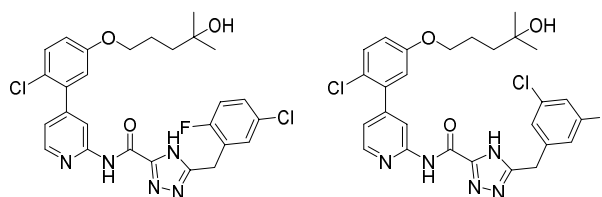
Example 339

[0938] Example 339: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(3,4-difluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0939] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(3,4-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.57 (s, 1H), 9.99 (s, 1H), 8.46 (d, $J = 5.1$ Hz, 1H), 8.22 (s, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.48 – 7.36 (m, 2H), 7.29 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.22 – 7.14 (m, 1H), 7.06 (dd, $J = 8.8, 3.0$ Hz, 1H), 7.01 (d, $J = 3.0$ Hz, 1H), 4.26 – 4.13 (m, 3H), 4.01 (t, $J = 6.6$ Hz, 2H), 1.83 – 1.69 (m, 2H), 1.52 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 542 $[\text{M}+\text{H}]^+$.

[0940] Example 340: 5-(5-chloro-2-fluorobenzyl)-N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0941] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(5-chloro-2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.94 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.21 (s, 1H), 7.60 – 7.46 (m, 2H), 7.46 – 7.36 (m, 1H), 7.36 – 7.22 (m, 2H), 7.13 – 6.95 (m, 2H), 4.27 – 4.15 (m, 3H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.52 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 558 [M+H]⁺.



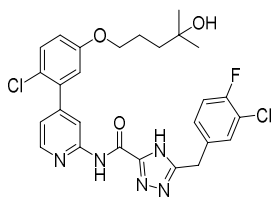
Example 340 Example 341

[0942] Example 341: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(3-chloro-5-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

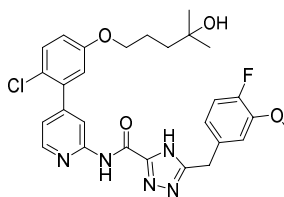
[0943] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(3-chloro-5-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 10.02 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.43 – 7.33 (m, 1H), 7.33 – 7.26 (m, 2H), 7.26 – 7.16 (m, 1H), 7.06 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 4.23 (s, 2H), 4.19 (s, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.53 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 558 [M+H]⁺.

[0944] Example 342: 5-(3-chloro-4-fluorobenzyl)-N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0945] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(3-chloro-4-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.98 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.59 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.06 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 4.28 – 4.14 (m, 3H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.70 (m, 2H), 1.52 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 558 [M+H]⁺.



Example 342



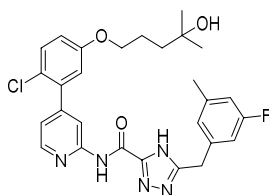
Example 343

[0946] Example 343: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(4-fluoro-3-methoxybenzyl)-4H-1,2,4-triazole-3-carboxamide

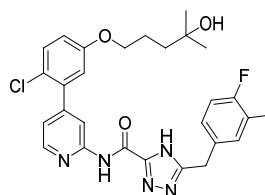
[0947] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(4-fluoro-3-methoxybenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.52 (s, 1H), 9.92 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.23 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.20 – 7.12 (m, 2H), 7.06 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 6.89 – 6.83 (m, 1H), 4.24 – 4.11 (m, 3H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 1.83 – 1.69 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 554 [M+H]⁺.

[0948] Example 344: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(3-fluoro-5-methylbenzyl)-4H-1,2,4-triazole-3-carboxamide

[0949] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(3-fluoro-5-methylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.96 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.11 – 6.85 (m, 5H), 4.23 – 4.09 (m, 3H), 4.01 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H), 1.82 – 1.70 (m, 2H), 1.55 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 538 [M+H]⁺.



Example 344



Example 345

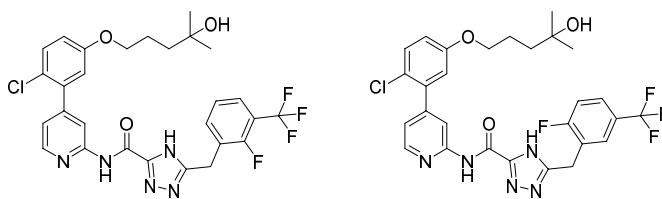
[0950] Example 345: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(4-fluoro-3-methylbenzyl)-4H-1,2,4-triazole-3-carboxamide

[0951] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(4-fluoro-3-methylbenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.52 (s, 1H), 9.91 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.36 – 6.94 (m, 6H), 4.18 (s, 1H), 4.13 (s, 2H), 4.01 (t, *J* = 6.6 Hz, 2H), 2.21 (d, *J* = 2.0 Hz, 3H), 1.83 –

1.69 (m, 2H), 1.54 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 538 [M+H]⁺.

[0952] Example 346: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluoro-3-(trifluoromethyl)benzyl)-4H-1,2,4-triazole-3-carboxamide

[0953] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluoro-3-(trifluoromethyl)benzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.76 (s, 1H), 9.98 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.21 (s, 1H), 7.86 – 7.65 (m, 2H), 7.57 – 7.34 (m, 2H), 7.28 (d, *J* = 5.1 Hz, 1H), 7.11 – 6.91 (m, 2H), 4.32 (s, 2H), 4.18 (s, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.83 – 1.66 (m, 2H), 1.55 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 592 [M+H]⁺.



Example 346

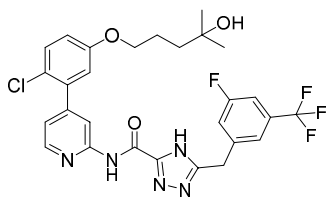
Example 347

[0954] Example 347: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluoro-5-(trifluoromethyl)benzyl)-4H-1,2,4-triazole-3-carboxamide

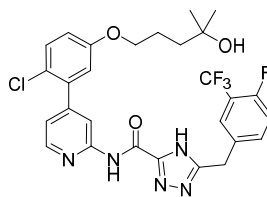
[0955] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluoro-5-(trifluoromethyl)benzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.92 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.21 (s, 1H), 7.90 (d, *J* = 6.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.56-7.41 (m, 2H), 7.28 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.11-6.93 (m, 2H), 4.32 (s, 2H), 4.18 (s, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.83-1.68 (m, 2H), 1.54-1.40 (m, 2H), 1.09 (s, 6H). MS: 592 [M+H]⁺.

[0956] Example 348: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(3-fluoro-5-(trifluoromethyl)benzyl)-4H-1,2,4-triazole-3-carboxamide

[0957] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 4, ethyl 5-(3-fluoro-5-(trifluoromethyl)benzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 10.02 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.68 – 7.45 (m, 4H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.12 – 6.94 (m, 2H), 4.34 (s, 2H), 4.19 (s, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.84 – 1.69 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 592 [M+H]⁺.



Example 348



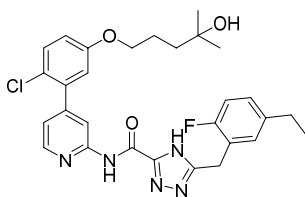
Example 349

[0958] Example 349: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(4-fluoro-3-(trifluoromethyl)benzyl)-4H-1,2,4-triazole-3-carboxamide

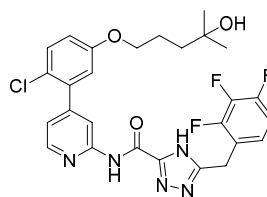
[0959] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(4-fluoro-3-(trifluoromethyl)benzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.53 (s, 1H), 9.91 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.20 (d, *J* = 20.8 Hz, 1H), 7.88-7.64 (m, 2H), 7.57-7.44 (m, 2H), 7.33-7.21 (m, 1H), 7.06 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 4.32 (s, 2H), 4.17 (s, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.82-1.70 (m, 2H), 1.52-1.41 (m, 2H), 1.09 (s, 6H). MS: 592 [M+H]⁺.

[0960] Example 350: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(5-ethyl-2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0961] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(5-ethyl-2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.88 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.35 – 6.93 (m, 6H), 4.25 – 4.09 (m, 3H), 4.09 – 3.93 (m, 2H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.82 – 1.68 (m, 2H), 1.55 – 1.38 (m, 2H), 1.16 (t, *J* = 7.6 Hz, 3H), 1.09 (s, 6H). MS: 552 [M+H]⁺.



Example 350



Example 351

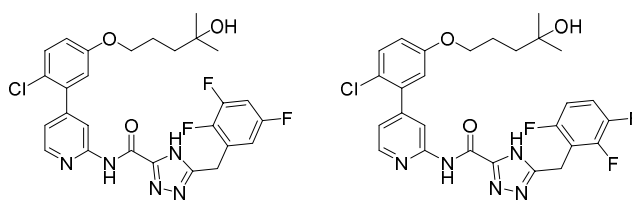
[0962] Example 351: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2,3,4-trifluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0963] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2,3,4-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.89 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.41 – 7.21 (m, 3H), 7.12 – 6.95 (m, 2H), 4.28 (s, 2H), 4.17 (s, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.84 – 1.69 (m,

2H), 1.53 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 560 [M+H]⁺.

[0964] Example 352: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2,3,5-trifluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0965] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2,3,5-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.75 (s, 1H), 10.01 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.28 – 8.13 (m, 1H), 7.56 – 7.41 (m, 2H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.25 – 7.14 (m, 1H), 7.10 – 6.95 (m, 2H), 4.28 (s, 2H), 4.17 (s, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.54 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 560 [M+H]⁺.



Example 352

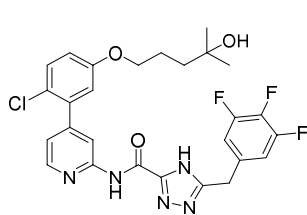
Example 353

[0966] Example 353: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2,3,6-trifluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

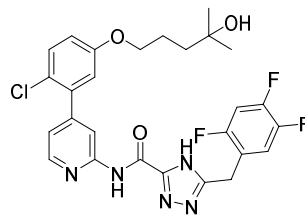
[0967] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2,3,6-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.78 (s, 1H), 9.95 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.20 (s, 1H), 7.58 – 7.42 (m, 2H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.25 – 7.14 (m, 1H), 7.10 – 6.93 (m, 2H), 4.26 (s, 2H), 4.19 (s, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.84 – 1.69 (m, 2H), 1.53 – 1.39 (m, 2H), 1.10 (s, 6H). MS: 560 [M+H]⁺.

[0968] Example 354: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(3,4,5-trifluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0969] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(3,4,5-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 10.04 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.23 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.41 – 7.23 (m, 3H), 7.08 – 6.97 (m, 2H), 4.26 – 4.15 (m, 3H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.82 – 1.70 (m, 2H), 1.53 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 560 [M+H]⁺.



Example 354



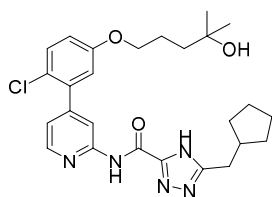
Example 355

[0970] Example 355: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2,4,5-trifluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

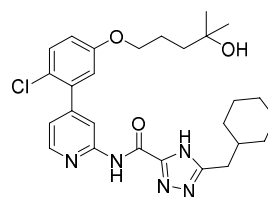
[0971] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2,4,5-trifluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.92 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.72 – 7.44 (m, 3H), 7.29 (d, *J* = 4.8 Hz, 1H), 7.12 – 6.94 (m, 2H), 4.28 – 4.07 (m, 3H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.83 – 1.66 (m, 2H), 1.55 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 560 [M+H]⁺.

[0972] Example 356: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0973] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.90 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.24 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.12 – 6.96 (m, 2H), 4.19 (s, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.20 (m, 1H), 1.82 – 1.66 (m, 4H), 1.66 – 1.57 (m, 2H), 1.57 – 1.43 (m, 4H), 1.24 – 1.20 (m, 2H), 1.09 (s, 6H). MS: 498 [M+H]⁺.



Example 356



Example 357

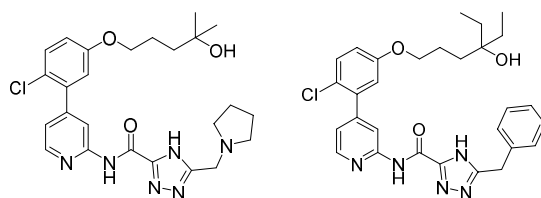
[0974] Example 357: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0975] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.92 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.30 – 8.18 (m, 1H), 7.51 (d, *J* = 8.8

Hz, 1H), 7.28 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.13 – 6.94 (m, 2H), 4.21 (s, 1H), 4.01 (t, $J = 6.5$ Hz, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.87 – 1.55 (m, 8H), 1.51 – 1.41 (m, 2H), 1.21 – 1.12 (m, 3H), 1.09 (s, 6H), 1.05 – 0.89 (m, 2H). MS: 512 [M+H]⁺.

[0976] Example 358: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(pyrrolidin-1-ylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0977] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(pyrrolidin-1-ylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.83 (s, 1H), 9.95 (s, 1H), 8.52 – 8.40 (m, 1H), 8.29 – 8.19 (m, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.27 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.13 – 6.94 (m, 2H), 4.18 (s, 1H), 4.01 (t, $J = 6.6$ Hz, 2H), 3.82 (s, 2H), 2.60 – 2.53 (m, 4H), 1.85 – 1.63 (m, 6H), 1.55 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 499 [M+H]⁺.



Example 358

Example 359

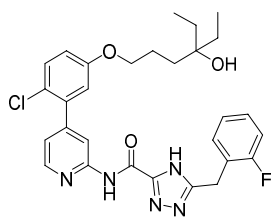
[0978] Example 359: 5-benzyl-N-(4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0979] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 9.96 (s, 1H), 8.45 (d, $J = 5.1$ Hz, 1H), 8.30 – 8.17 (m, 1H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.44 – 7.18 (m, 6H), 7.13 – 6.92 (m, 2H), 4.18 (s, 2H), 4.00 (t, $J = 6.5$ Hz, 2H), 3.89 (s, 1H), 1.78 – 1.59 (m, 2H), 1.51 – 1.38 (m, 2H), 1.34 (q, $J = 7.4$ Hz, 4H), 0.77 (t, $J = 7.4$ Hz, 6H). MS: 534 [M+H]⁺.

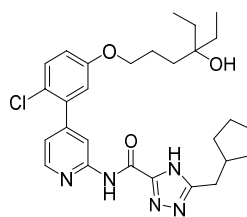
[0980] Example 360: N-(4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[0981] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 9.94 (s, 1H), 8.45 (d, $J = 5.1$ Hz, 1H), 8.21 (d, $J = 1.6$ Hz, 1H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.47 – 7.30 (m, 2H), 7.28 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.25 – 7.16 (m, 2H), 7.05 (dd, $J = 8.8, 3.0$ Hz, 1H), 7.00 (d, $J = 3.0$ Hz, 1H), 4.21 (s, 2H), 4.01 (t, $J = 6.5$ Hz, 2H), 3.89 (s, 1H), 1.76 – 1.62 (m, 2H), 1.47 – 1.38 (m, 2H), 1.34 (q, $J = 7.4$ Hz, 4H),

0.77 (t, $J = 7.5$ Hz, 6H). MS: 552 $[M+H]^+$.



Example 360



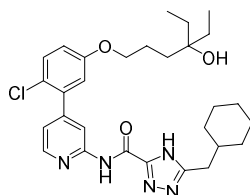
Example 361

[0982] Example 361: N-(4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

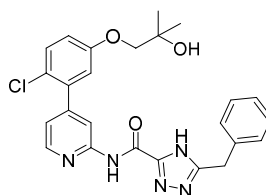
[0983] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.42 (s, 1H), 9.90 (s, 1H), 8.46 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.32-8.18 (m, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.28 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.12-6.94 (m, 2H), 4.01 (t, $J = 6.5$ Hz, 2H), 3.89 (s, 1H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.36 – 2.19 (m, 1H), 1.80-1.64 (m, 4H), 1.64 – 1.47 (m, 4H), 1.47 – 1.29 (m, 6H), 1.29-1.14 (m, 2H), 0.77 (t, $J = 7.4$ Hz, 6H). MS: 526 $[M+H]^+$.

[0984] Example 362: N-(4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0985] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.40 (s, 1H), 9.90 (s, 1H), 8.46 (d, $J = 5.1$ Hz, 1H), 8.24 (d, $J = 1.4$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.28 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.16-6.95 (m, 2H), 4.01 (t, $J = 6.5$ Hz, 2H), 3.89 (s, 1H), 2.67 (d, $J = 7.1$ Hz, 2H), 1.86-1.56 (m, 8H), 1.48-1.39 (m, 2H), 1.35 (q, $J = 7.5$ Hz, 4H), 1.25-1.12 (m, 3H), 1.05-0.92 (m, 2H), 0.78 (t, $J = 7.5$ Hz, 6H). MS: 540 $[M+H]^+$.



Example 362



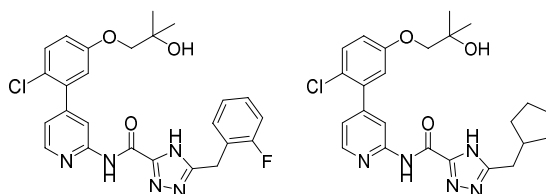
Example 363

[0986] Example 363: 5-benzyl-N-(4-(2-chloro-5-(2-hydroxyl-2-methylpropoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0987] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and methyl bromoacetate was used in place of methyl 4-bromobutanoate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.96 (s, 1H), 8.55-8.39 (m, 1H), 8.29-8.16 (m, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.41-7.19 (m, 6H), 7.13-6.99 (m, 2H), 4.66 (s, 1H), 4.18 (s, 2H), 3.77 (s, 2H), 1.19 (s, 6H). MS: 478 [M+H]⁺.

[0988] Example 364: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-(2-hydroxyl-2-methylpropoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0989] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, methyl bromoacetate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.70 (s, 1H), 9.94 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.31 – 8.12 (m, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.26 (m, 3H), 7.26 – 7.13 (m, 2H), 7.13 – 6.96 (m, 2H), 4.66 (s, 1H), 4.21 (s, 2H), 3.77 (s, 2H), 1.19 (s, 6H). MS: 496 [M+H]⁺.



Example 364 Example 365

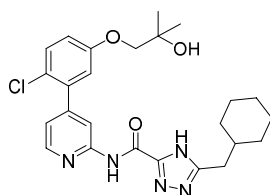
[0990] Example 365: N-(4-(2-chloro-5-(2-hydroxyl-2-methylpropoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0991] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, methyl bromoacetate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.91 (s, 1H), 8.46 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.34 – 8.19 (m, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.15 – 6.93 (m, 2H), 4.66 (s, 1H), 3.78 (s, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.37 – 2.19 (m, 1H), 1.82 – 1.66 (m, 2H), 1.66 – 1.44 (m, 4H), 1.30 – 1.12 (m, 8H). MS: 470 [M+H]⁺.

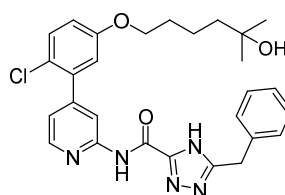
[0992] Example 366: N-(4-(2-chloro-5-(2-hydroxyl-2-methylpropoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0993] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, methyl bromoacetate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 9.90 (s, 1H),

8.46 (d, $J = 5.1$ Hz, 1H), 8.24 (d, $J = 1.4$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.29 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.16 – 6.95 (m, 2H), 4.66 (s, 1H), 3.78 (s, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.83 – 1.71 (m, 1H), 1.71 – 1.53 (m, 5H), 1.29 – 1.06 (m, 9H), 1.06 – 0.89 (m, 2H). MS: 484 $[M+H]^+$.



Example 366



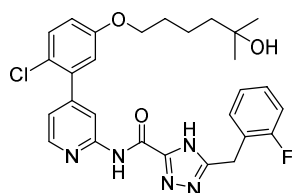
Example 367

[0994] Example 367: 5-benzyl-N-(4-(2-chloro-5-((5-hydroxy-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

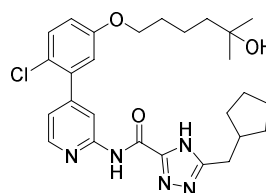
[0995] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.65 (s, 1H), 9.96 (s, 1H), 8.45 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.23 (dd, $J = 1.5, 0.8$ Hz, 1H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.45 – 7.20 (m, 6H), 7.13 – 6.97 (m, 2H), 4.18 (s, 2H), 4.10 (s, 1H), 4.02 (t, $J = 6.5$ Hz, 2H), 1.75 – 1.62 (m, 2H), 1.51 – 1.32 (m, 4H), 1.06 (s, 6H). MS: 520 $[M+H]^+$.

[0996] Example 368: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-((5-hydroxy-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[0997] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.71 (s, 1H), 9.94 (s, 1H), 8.44 (d, $J = 5.1$ Hz, 1H), 8.31 – 8.13 (m, 1H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.45 – 7.30 (m, 2H), 7.27 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.25 – 7.15 (m, 2H), 7.09 – 6.98 (m, 2H), 4.21 (s, 2H), 4.11 (s, 1H), 4.01 (t, $J = 6.4$ Hz, 2H), 1.69 (t, $J = 7.0$ Hz, 2H), 1.49 – 1.33 (m, 4H), 1.06 (s, 6H). MS: 538 $[M+H]^+$.



Example 368



Example 369

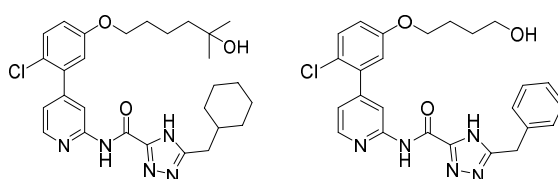
[0998] Example 369: N-(4-(2-chloro-5-((5-hydroxy-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[0999] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of

methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.90 (s, 1H), 8.46 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.25 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.11 – 6.96 (m, 2H), 4.10 (s, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.19 (m, 1H), 1.79 – 1.65 (m, 4H), 1.65 – 1.33 (m, 8H), 1.30 – 1.15 (m, 2H), 1.06 (s, 6H). MS: 512 [M+H]⁺.

[01000] Example 370: N-(4-(2-chloro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01001] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.90 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.24 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.13 – 6.97 (m, 2H), 4.10 (s, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 1.84 – 1.58 (m, 7H), 1.52 – 1.35 (m, 4H), 1.31 – 1.10 (m, 4H), 1.06 (s, 6H), 1.02 – 0.92 (m, 2H). MS: 526 [M+H]⁺.



Example 370

Example 371

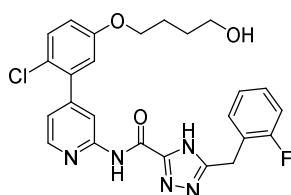
[01002] Example 371: 5-benzyl-N-(4-(2-chloro-5-(4-hydroxybutoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01003] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.92 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.40 – 7.30 (m, 4H), 7.30 – 7.21 (m, 2H), 7.06 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.02 (d, *J* = 3.0 Hz, 1H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.18 (s, 2H), 4.03 (t, *J* = 6.5 Hz, 2H), 3.47 – 3.41 (m, 2H), 1.81 – 1.69 (m, 2H), 1.61 – 1.50 (m, 2H). MS: 478 [M+H]⁺.

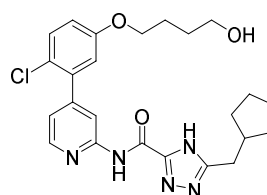
[01004] Example 372: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-(4-hydroxybutoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01005] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.91 (s, 1H), 8.45 (d,

$J = 5.1$ Hz, 1H), 8.21 (s, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.46 – 7.31 (m, 2H), 7.28 (d, $J = 5.2$ Hz, 1H), 7.26 – 7.15 (m, 2H), 7.11 – 6.98 (m, 2H), 4.45 (t, $J = 5.2$ Hz, 1H), 4.21 (s, 2H), 4.03 (t, $J = 6.5$ Hz, 2H), 3.46 – 3.42 (m, 2H), 1.80 – 1.67 (m, 2H), 1.62 – 1.49 (m, 2H). MS: 496 $[M+H]^+$.



Example 372



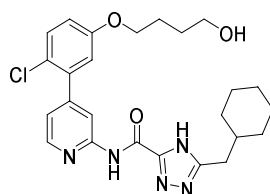
Example 373

[01006] Example 373: N-(4-(2-chloro-5-(4-hydroxybutoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

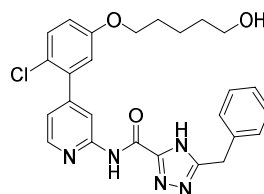
[01007] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.38 (s, 1H), 9.88 (s, 1H), 8.46 (d, $J = 5.2$ Hz, 1H), 8.24 (s, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.29 (d, $J = 5.0$ Hz, 1H), 7.12 – 6.99 (m, 2H), 4.45 (t, $J = 5.2$ Hz, 1H), 4.04 (t, $J = 6.5$ Hz, 2H), 3.46 – 3.43 (m, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.31 – 2.23 (m, 1H), 1.78 – 1.68 (m, 4H), 1.65 – 1.48 (m, 6H), 1.25 – 1.22 (m, 2H). MS: 470 $[M+H]^+$.

[01008] Example 374: N-(4-(2-chloro-5-(4-hydroxybutoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01009] The preparation was carried out in a similar manner to Example 92, except that in step 1, 4-bromo-1-butanol was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.39 (s, 1H), 9.89 (s, 1H), 8.46 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.24 (d, $J = 1.1$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.28 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.13 – 6.98 (m, 2H), 4.45 (t, $J = 5.2$ Hz, 1H), 4.04 (t, $J = 6.5$ Hz, 2H), 3.47 – 3.41 (m, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.81 – 1.52 (m, 10H), 1.22 – 0.90 (m, 5H). MS: 484 $[M+H]^+$.



Example 374



Example 375

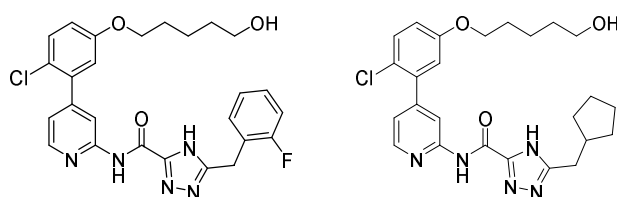
[01010] Example 375: 5-benzyl-N-(4-(2-chloro-5-((5-hydroxypentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01011] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-

pentanol was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.95 (s, 1H), 8.45 (d, *J* = 5.0 Hz, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.39 – 7.30 (m, 4H), 7.30 – 7.19 (m, 2H), 7.06 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.02 (d, *J* = 3.0 Hz, 1H), 4.44 – 4.30 (m, 1H), 4.18 (s, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.44 – 3.37 (m, 2H), 1.78 – 1.64 (m, 2H), 1.53 – 1.35 (m, 4H). MS: 492 [M+H]⁺.

[01012] Example 376: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-((5-hydroxypentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01013] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 9.94 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.31 (m, 2H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.26 – 7.13 (m, 2H), 7.11 – 6.99 (m, 2H), 4.38 (s, 1H), 4.21 (s, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.45 – 3.37 (m, 2H), 1.79 – 1.66 (m, 2H), 1.52 – 1.37 (m, 4H). MS: 510 [M+H]⁺.



Example 376

Example 377

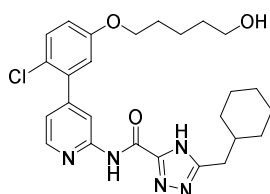
[01014] Example 377: N-(4-(2-chloro-5-((5-hydroxypentyl)oxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01015] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 9.89 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.24 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.14 – 6.96 (m, 2H), 4.38 (t, *J* = 5.2 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.46 – 3.35 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.20 (m, 1H), 1.80 – 1.67 (m, 4H), 1.67 – 1.38 (m, 8H), 1.30 – 1.15 (m, 2H). MS: 484 [M+H]⁺.

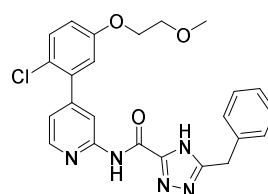
[01016] Example 378: N-(4-(2-chloro-5-((5-hydroxypentyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01017] The preparation was carried out in a similar manner to Example 92, except that in step 1, 5-bromo-1-pentanol was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of

ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.38 (s, 1H), 9.89 (s, 1H), 8.46 (d, $J = 5.1$ Hz, 1H), 8.24 (d, $J = 1.5$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.28 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.07 (dd, $J = 8.8, 3.1$ Hz, 1H), 7.02 (d, $J = 3.0$ Hz, 1H), 4.38 (t, $J = 5.2$ Hz, 1H), 4.02 (t, $J = 6.5$ Hz, 2H), 3.45-3.37 (m, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.84-1.54 (m, 8H), 1.52-1.36 (m, 4H), 1.27-1.11 (m, 3H), 1.04-0.91 (m, 2H). MS: 498 $[\text{M}+\text{H}]^+$.



Example 378



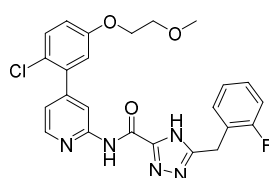
Example 379

[01018] Example 379: 5-benzyl-N-(4-(2-chloro-5-(2-methoxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

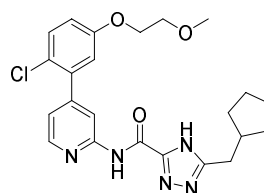
[01019] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.63 (s, 1H), 9.96 (s, 1H), 8.45 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.24 (dd, $J = 1.6, 0.8$ Hz, 1H), 7.51 (d, $J = 8.7$ Hz, 1H), 7.43 – 7.30 (m, 4H), 7.30 – 7.20 (m, 2H), 7.15 – 6.98 (m, 2H), 4.25 – 4.10 (m, 4H), 3.71 – 3.59 (m, 2H), 3.30 (s, 3H). MS: 464 $[\text{M}+\text{H}]^+$.

[01020] Example 380: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-(2-methoxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01021] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.69 (s, 1H), 9.94 (s, 1H), 8.56 – 8.38 (m, 1H), 8.31 – 8.14 (m, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.46 – 7.14 (m, 5H), 7.14 – 6.94 (m, 2H), 4.21 (s, 2H), 4.18 – 4.11 (m, 2H), 3.73 – 3.60 (m, 2H), 3.30 (s, 3H). MS: 482 $[\text{M}+\text{H}]^+$.



Example 380



Example 381

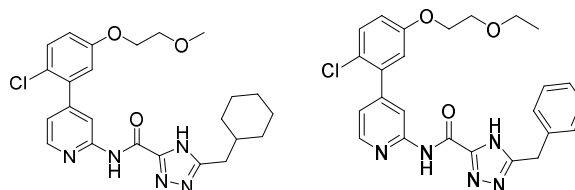
[01022] Example 381: N-(4-(2-chloro-5-(2-methoxyethoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01023] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-

methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.90 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.25 (t, *J* = 1.1 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.16 – 6.98 (m, 2H), 4.25 – 4.09 (m, 2H), 3.75 – 3.61 (m, 2H), 3.30 (s, 3H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.37 – 2.18 (m, 1H), 1.81 – 1.67 (m, 2H), 1.67 – 1.44 (m, 4H), 1.32 – 1.13 (m, 2H). MS: 456 [M+H]⁺.

[01024] Example 382: N-(4-(2-chloro-5-(2-methoxyethoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01025] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-methoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.90 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.25 (d, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.16 – 7.00 (m, 2H), 4.23 – 4.10 (m, 2H), 3.72 – 3.61 (m, 2H), 3.30 (s, 3H), 2.67 (d, *J* = 7.1 Hz, 2H), 1.85 – 1.53 (m, 6H), 1.28 – 1.11 (m, 3H), 1.03 – 0.90 (m, 2H). MS: 470 [M+H]⁺.



Example 382

Example 383

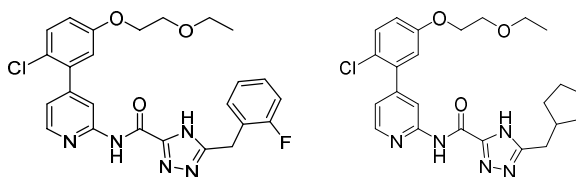
[01026] Example 383: 5-benzyl-N-(4-(2-chloro-5-(2-ethoxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01027] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.94 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.23 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.43-7.30 (m, 4H), 7.30-7.22 (m, 2H), 7.18-6.97 (m, 2H), 4.22 – 4.11 (m, 4H), 3.73 – 3.66 (m, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 1.12 (t, *J* = 7.0 Hz, 3H). MS: 478 [M+H]⁺.

[01028] Example 384: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-(2-ethoxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01029] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 9.94 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.28 – 8.16 (m, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.13 (m, 5H), 7.13 – 6.97 (m, 2H), 4.21

(s, 2H), 4.18 – 4.09 (m, 2H), 3.75 – 3.63 (m, 2H), 3.49 (q, $J = 7.0$ Hz, 2H), 1.11 (t, $J = 7.0$ Hz, 3H). MS: 496 $[M+H]^+$.



Example 384

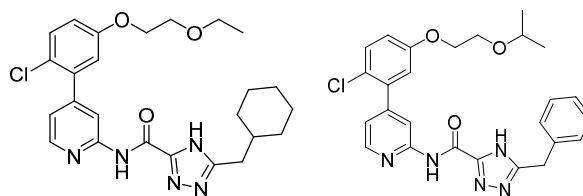
Example 385

[01030] Example 385: N-(4-(2-chloro-5-(2-ethoxyethoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01031] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.42 (s, 1H), 9.90 (s, 1H), 8.46 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.25 (t, $J = 1.1$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.29 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.17-6.96 (m, 2H), 4.23-4.09 (m, 2H), 3.75-3.65 (m, 2H), 3.49 (q, $J = 7.0$ Hz, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.36-2.18 (m, 1H), 1.80-1.67 (m, 2H), 1.67-1.57 (m, 2H), 1.57-1.44 (m, 2H), 1.25-1.16 (m, 2H), 1.12 (t, $J = 7.0$ Hz, 3H). MS: 470 $[M+H]^+$.

[01032] Example 386: N-(4-(2-chloro-5-(2-ethoxyethoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01033] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-ethoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.41 (s, 1H), 9.90 (s, 1H), 8.46 (d, $J = 5.1$ Hz, 1H), 8.25 (s, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.29 (dd, $J = 5.1, 1.7$ Hz, 1H), 7.20 – 7.00 (m, 2H), 4.16 (dd, $J = 5.6, 3.5$ Hz, 2H), 3.70 (dd, $J = 5.6, 3.4$ Hz, 2H), 3.50 (q, $J = 7.0$ Hz, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.83 – 1.53 (m, 6H), 1.25 – 1.14 (m, 3H), 1.12 (t, $J = 7.0$ Hz, 3H), 1.06 – 0.88 (m, 2H). MS: 484 $[M+H]^+$.



Example 386

Example 387

[01034] Example 387: 5-benzyl-N-(4-(2-chloro-5-(2-isopropoxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01035] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-

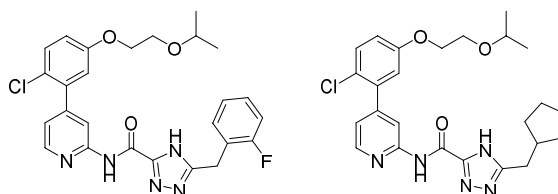
isopropoxyethane was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.96 (s, 1H), 8.46 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.29 – 8.16 (m, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.44 – 7.18 (m, 6H), 7.18 – 6.96 (m, 2H), 4.18 (s, 2H), 4.15 – 4.05 (m, 2H), 3.75 – 3.66 (m, 2H), 3.61 (p, *J* = 6.1 Hz, 1H), 1.09 (d, *J* = 6.0 Hz, 6H). MS: 492 [M+H]⁺.

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[01036] Example 388: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-(2-isopropoxyethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01037] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 9.94 (s, 1H), 8.45 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.30 – 8.14 (m, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.25 (m, 3H), 7.25 – 7.13 (m, 2H), 7.13 – 6.97 (m, 2H), 4.21 (s, 2H), 4.17 – 4.06 (m, 2H), 3.74 – 3.65 (m, 2H), 3.61 (p, *J* = 6.1 Hz, 1H), 1.09 (d, *J* = 6.1 Hz, 6H). MS: 510 [M+H]⁺.

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Example 388

Example 389

[01038] Example 389: N-(4-(2-chloro-5-(2-isopropoxyethoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01039] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.90 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.25 (d, *J* = 1.4 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.19 – 6.99 (m, 2H), 4.22 – 4.05 (m, 2H), 3.75 – 3.66 (m, 2H), 3.62 (p, *J* = 6.1 Hz, 1H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.20 (m, 1H), 1.84 – 1.66 (m, 2H), 1.66 – 1.46 (m, 4H), 1.26 – 1.18 (m, 2H), 1.10 (d, *J* = 6.1 Hz, 6H). MS: 484 [M+H]⁺.

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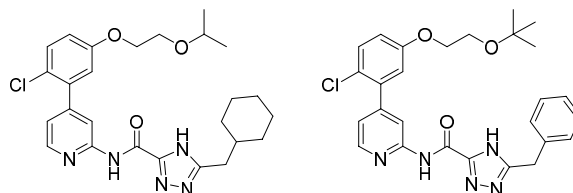
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[01040] Example 390: N-(4-(2-chloro-5-(2-isopropoxyethoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01041] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-2-isopropoxyethane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of

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ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.90 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.25 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.15 – 6.96 (m, 2H), 4.18 – 4.09 (m, 2H), 3.74 – 3.65 (m, 2H), 3.62 (p, *J* = 6.1 Hz, 1H), 2.67 (d, *J* = 7.1 Hz, 2H), 1.85 – 1.56 (m, 6H), 1.26 – 1.17 (m, 3H), 1.10 (d, *J* = 6.1 Hz, 6H), 1.05 – 0.91 (m, 2H). MS: 498 [M+H]⁺.



Example 390

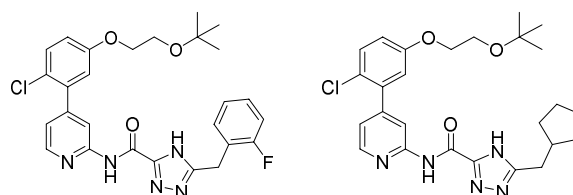
Example 391

[01042] Example 391: 5-benzyl-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-chlorophenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01043] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.93 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.23 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.43 – 7.18 (m, 6H), 7.14 – 6.97 (m, 2H), 4.18 (s, 2H), 4.13 – 4.00 (m, 2H), 3.64 (t, *J* = 4.8 Hz, 2H), 1.15 (s, 9H). MS: 506 [M+H]⁺.

[01044] Example 392: 5-(2-fluorobenzyl)-N-(4-(5-(2-(tert-butoxy)ethoxy)-2-chlorophenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01045] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 9.90 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.31 (m, 2H), 7.28 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.12 – 7.01 (m, 2H), 4.21 (s, 2H), 4.14 – 4.03 (m, 2H), 3.69 – 3.58 (m, 2H), 1.15 (s, 9H). MS: 524 [M+H]⁺.



Example 392

Example 393

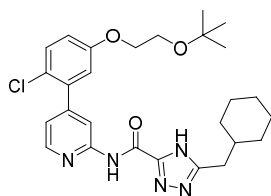
[01046] Example 393: N-(4-(5-(2-(tert-butoxy)ethoxy)-2-chlorophenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01047] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.87 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.25 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 1H),

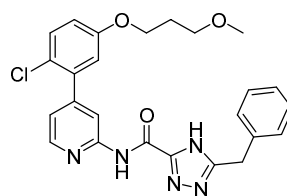
7.34 – 7.24 (m, 1H), 7.16 – 6.96 (m, 2H), 4.16 – 4.03 (m, 2H), 3.70 – 3.56 (m, 2H), 2.79 (d, $J = 7.5$ Hz, 2H), 2.37 – 2.22 (m, 1H), 1.80 – 1.66 (m, 2H), 1.66 – 1.57 (m, 2H), 1.57 – 1.41 (m, 2H), 1.29 – 1.18 (m, 2H), 1.15 (s, 9H). MS: 498 $[M+H]^+$.

[01048] Example 394: N-(4-(5-(2-(tert-butoxy)ethoxy)-2-chlorophenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01049] The preparation was carried out in a similar manner to Example 64, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.37 (s, 1H), 9.88 (s, 1H), 8.46 (d, $J = 5.1$ Hz, 1H), 8.25 (s, 1H), 7.52 (d, $J = 8.7$ Hz, 1H), 7.29 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.13 – 7.00 (m, 2H), 4.17 – 4.03 (m, 2H), 3.70 – 3.60 (m, 2H), 2.67 (d, $J = 7.0$ Hz, 2H), 1.84 – 1.57 (m, 6H), 1.28 – 1.13 (m, 12H), 1.03 – 0.91 (m, 2H). MS: 512 $[M+H]^+$.



Example 394



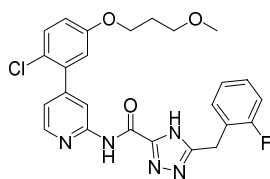
Example 395

[01050] Example 395: 5-benzyl-N-(4-(2-chloro-5-(3-methoxypropoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

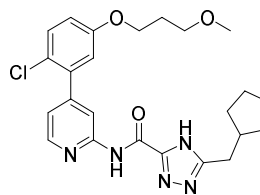
[01051] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, and 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol. ^1H NMR (400 MHz, DMSO- d_6) δ 14.63 (s, 1H), 9.96 (s, 1H), 8.45 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.22 (d, $J = 1.2$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.40-7.23 (m, 6H), 7.13-6.95 (m, 2H), 4.18 (s, 2H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.46 (t, $J = 6.2$ Hz, 2H), 3.24 (s, 3H), 2.00-1.89 (m, 2H). MS: 478 $[M+H]^+$.

[01052] Example 396: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-(3-methoxypropoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01053] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.69 (s, 1H), 9.94 (s, 1H), 8.45 (dd, $J = 5.1, 0.8$ Hz, 1H), 8.28 – 8.13 (m, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.44 – 7.31 (m, 2H), 7.28 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.26 – 7.16 (m, 2H), 7.10 – 6.95 (m, 2H), 4.21 (s, 2H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.46 (t, $J = 6.2$ Hz, 2H), 3.23 (s, 3H), 2.03 – 1.89 (m, 2H). MS: 496 $[M+H]^+$.



Example 396



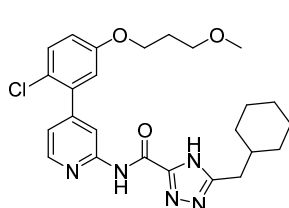
Example 397

[01054] Example 397: N-(4-(2-chloro-5-(3-methoxypropoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

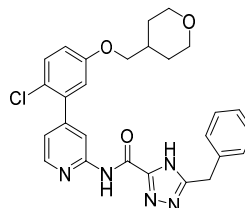
[01055] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.91 (s, 1H), 8.46 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.24 (dd, *J* = 1.5, 0.8 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.13 – 6.99 (m, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.24 (s, 3H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.18 (m, 1H), 2.00 – 1.89 (m, 2H), 1.79 – 1.67 (m, 2H), 1.67 – 1.44 (m, 4H), 1.30 – 1.15 (m, 2H). MS: 470 [M+H]⁺.

[01056] Example 398: N-(4-(2-chloro-5-(3-methoxypropoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01057] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-bromo-3-methoxypropane was used in place of iodomethane, 3-bromo-4-chlorophenol was used in place of 2-bromo-3-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.40 (s, 1H), 9.90 (s, 1H), 8.52 – 8.40 (m, 1H), 8.24 (d, *J* = 1.2 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.14 – 6.96 (m, 2H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.24 (s, 3H), 2.67 (d, *J* = 7.1 Hz, 2H), 2.02 – 1.87 (m, 2H), 1.82 – 1.58 (m, 6H), 1.28 – 1.11 (m, 3H), 1.05 – 0.89 (m, 2H). MS: 484 [M+H]⁺.



Example 398



Example 399

[01058] Example 399: 5-benzyl-N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01059] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, and 3-bromo-4-chlorophenol was used

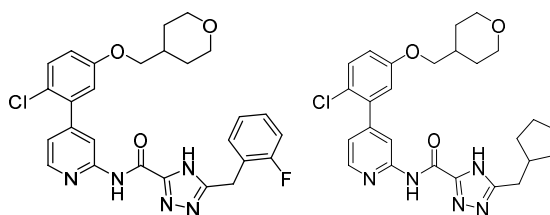
in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 9.95 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.22 (d, *J* = 1.5 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.42 – 7.30 (m, 4H), 7.30 – 7.19 (m, 2H), 7.14 – 6.97 (m, 2H), 4.18 (s, 2H), 3.96 – 3.80 (m, 4H), 3.35 – 3.26 (m, 2H), 2.05 – 1.94 (m, 1H), 1.73 – 1.61 (m, 2H), 1.40 – 1.24 (m, 2H). MS: 504 [M+H]⁺.

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[01060] Example 400: 5-(2-fluorobenzyl)-N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01061] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 9.94 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.21 (d, *J* = 1.5 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.12 (m, 5H), 7.12 – 6.95 (m, 2H), 4.21 (s, 2H), 3.95 – 3.79 (m, 4H), 3.33 – 3.26 (m, 2H), 2.06 – 1.92 (m, 1H), 1.75 – 1.62 (m, 2H), 1.41 – 1.19 (m, 2H). MS: 522 [M+H]⁺.

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Example 400 Example 401

[01062] Example 401: N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01063] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.91 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.30 – 8.19 (m, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.15 – 6.97 (m, 2H), 3.94 – 3.81 (m, 4H), 3.32 – 3.22 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.17 (m, 1H), 2.06 – 1.93 (m, 1H), 1.79 – 1.46 (m, 8H), 1.39 – 1.14 (m, 4H). MS: 496 [M+H]⁺.

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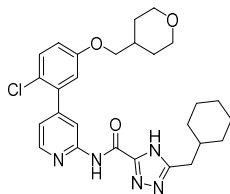
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[01064] Example 402: N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

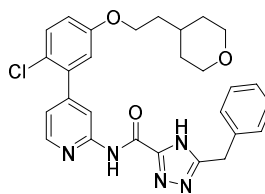
[01065] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was

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used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.91 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.24 (d, *J* = 1.6 Hz, 1H), 7.61 – 7.44 (m, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.18 – 6.96 (m, 2H), 4.00 – 3.80 (m, 4H), 3.33 – 3.23 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.10 – 1.91 (m, 1H), 1.83 – 1.54 (m, 8H), 1.38 – 1.09 (m, 5H), 1.04 – 0.90 (m, 2H). MS: 510 [M+H]⁺.



Example 402



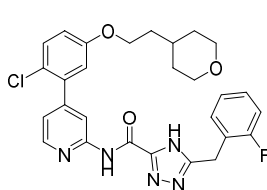
Example 403

[01066] Example 403: 5-benzyl-N-(4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

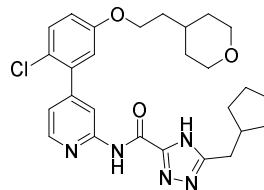
[01067] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, and in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 9.96 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.23 (d, *J* = 1.5 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.41 – 7.21 (m, 6H), 7.12 – 7.00 (m, 2H), 4.18 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.88 – 3.76 (m, 2H), 3.31 – 3.22 (m, 2H), 1.76 – 1.55 (m, 5H), 1.23 – 1.14 (m, 2H). MS: 518 [M+H]⁺.

[01068] Example 404: N-(4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01069] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.95 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.28 – 8.14 (m, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.46 – 7.30 (m, 2H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.26 – 7.12 (m, 2H), 7.12 – 7.00 (m, 2H), 4.20 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.88 – 3.76 (m, 2H), 3.30 – 3.24 (m, 2H), 1.79 – 1.56 (m, 5H), 1.22 – 1.13 (m, 2H). MS: 536 [M+H]⁺.



Example 404



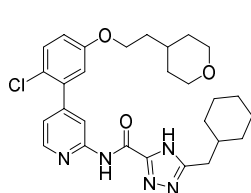
Example 405

[01070] Example 405: N-(4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

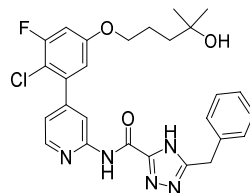
[01071] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.91 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.24 (d, *J* = 1.5 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.14 – 6.99 (m, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.88 – 3.75 (m, 2H), 3.31 – 3.21 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.19 (m, 1H), 1.78 – 1.55 (m, 9H), 1.55 – 1.46 (m, 2H), 1.26 – 1.19 (m, 4H). MS: 510 [M+H]⁺.

[01072] Example 406: N-(4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01073] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.91 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.33 – 8.17 (m, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.14 – 6.98 (m, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.87 – 3.76 (m, 2H), 3.30 – 3.21 (m, 2H), 2.67 (d, *J* = 7.1 Hz, 2H), 1.83 – 1.51 (m, 11H), 1.27 – 1.12 (m, 5H), 1.05 – 0.89 (m, 2H). MS: 524 [M+H]⁺.



Example 406



Example 407

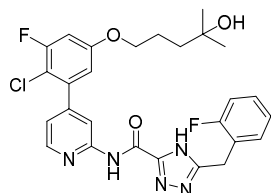
[01074] Example 407: 5-benzyl-N-(4-(2-chloro-3-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01075] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chloro-5-fluorophenol was used in place of 3-bromo-4-methylphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 9.91 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 7.46 – 7.26 (m, 4H), 7.26 – 7.15 (m, 2H), 7.15 – 7.02 (m, 2H), 4.21 (s, 2H), 4.10 (s, 1H), 4.02 (t, *J* = 6.4 Hz, 2H), 1.77 – 1.64 (m, 2H), 1.52 – 1.42 (m, 2H), 1.07 (s, 6H). MS: 524 [M+H]⁺.

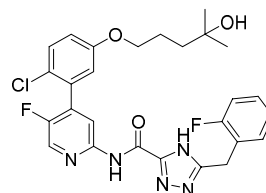
[01076] Example 408: N-(4-(2-chloro-3-fluoro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01077] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chloro-5-fluorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(2-fluorobenzyl)-

4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 9.98 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.40 (d, *J* = 1.7 Hz, 1H), 7.58 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.41 (dd, *J* = 9.8, 1.8 Hz, 1H), 7.35 – 7.31 (m, 4H), 7.29 – 7.23 (m, 1H), 4.29 – 4.20 (m, 3H), 4.18 (s, 2H), 1.89 – 1.77 (m, 2H), 1.58 – 1.47 (m, 2H), 1.12 (s, 6H). MS: 542 [M+H]⁺.



Example 408



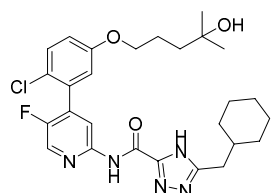
Example 409

[01078] Example 409: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)-5-fluoropyridin-2-yl)-5-(2-fluorophenyl)-4H-1,2,4-triazole-3-carboxamide

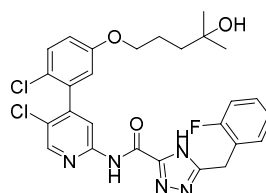
[01079] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 10.13 (s, 1H), 8.51 (d, *J* = 1.1 Hz, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.43 – 7.29 (m, 2H), 7.26 – 7.14 (m, 2H), 7.14 – 7.03 (m, 2H), 4.20 (s, 2H), 4.17 (s, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.83 – 1.69 (m, 2H), 1.52 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 542 [M+H]⁺.

[01080] Example 410: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)-5-fluoropyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01081] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 10.06 (s, 1H), 8.52 (d, *J* = 1.2 Hz, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.15 – 7.04 (m, 2H), 4.17 (s, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 1.82 – 1.56 (m, 8H), 1.52 – 1.41 (m, 2H), 1.28 – 1.12 (m, 3H), 1.09 (s, 6H), 1.05 – 0.90 (m, 2H). MS: 530 [M+H]⁺.



Example 410



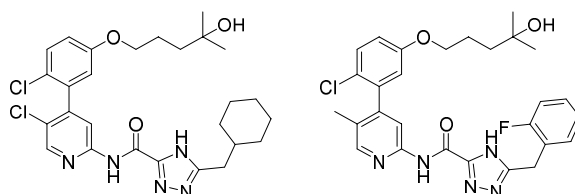
Example 411

[01082] Example 411: N-(5-chloro-4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01083] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 10.14 (s, 1H), 8.57 (s, 1H), 8.11 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.44 – 7.29 (m, 2H), 7.26 – 7.15 (m, 2H), 7.08 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 4.25 – 4.14 (m, 3H), 3.99 (t, *J* = 6.6 Hz, 2H), 1.81 – 1.69 (m, 2H), 1.52 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 558 [M+H]⁺.

[01084] Example 412: N-(5-chloro-4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01085] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.09 (s, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.09 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 4.18 (s, 1H), 4.00 (t, *J* = 6.6 Hz, 2H), 2.67 (d, *J* = 6.9 Hz, 2H), 1.82 – 1.55 (m, 8H), 1.52 – 1.42 (m, 2H), 1.28 – 1.12 (m, 3H), 1.09 (s, 6H), 1.05 – 0.87 (m, 2H). MS: 546 [M+H]⁺.



Example 412

Example 413

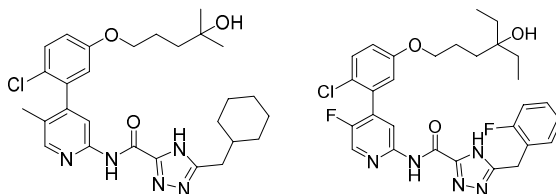
[01086] Example 413: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)-5-methylpyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01087] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-methylpyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 9.80 (s, 1H), 8.32 (s, 1H), 7.93 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.28 (m, 2H), 7.28 – 7.14 (m, 2H), 7.05 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.90 (d, *J* = 3.0 Hz, 1H), 4.26 – 4.12 (m, 3H), 3.99 (t, *J* = 6.6 Hz, 2H), 2.05 (s, 3H), 1.82 – 1.66 (m, 2H), 1.51 – 1.41 (m, 2H), 1.08 (s, 6H). MS: 538 [M+H]⁺.

[01088] Example 414: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)-5-methylpyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01089] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-

4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-methylpyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.34 (s, 1H), 9.79 (s, 1H), 8.33 (s, 1H), 7.96 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.05 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.91 (d, *J* = 3.0 Hz, 1H), 4.18 (s, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.05 (s, 3H), 1.82 – 1.56 (m, 8H), 1.52 – 1.41 (m, 2H), 1.30 – 1.12 (m, 3H), 1.09 (s, 6H), 1.04 – 0.90 (m, 2H). MS: 526 [M+H]⁺.



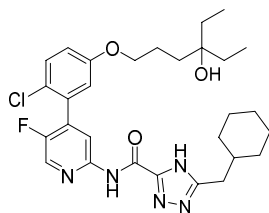
Example 414 Example 415

[01090] Example 415: N-(4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)-5-fluoropyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

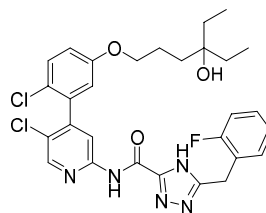
[01091] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 10.13 (s, 1H), 8.51 (d, *J* = 1.1 Hz, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.45 – 7.29 (m, 2H), 7.26 – 7.15 (m, 2H), 7.14 – 7.04 (m, 2H), 4.20 (s, 2H), 4.00 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 1H), 1.76 – 1.61 (m, 2H), 1.47 – 1.38 (m, 2H), 1.34 (q, *J* = 7.5 Hz, 4H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 570 [M+H]⁺.

[01092] Example 416: N-(4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)-5-fluoropyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01093] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 10.07 (s, 1H), 8.52 (d, *J* = 1.1 Hz, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.13 – 7.04 (m, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 1H), 2.66 (d, *J* = 7.1 Hz, 2H), 1.82 – 1.55 (m, 8H), 1.46 – 1.39 (m, 2H), 1.34 (q, *J* = 7.5 Hz, 4H), 1.28 – 1.09 (m, 3H), 1.05 – 0.91 (m, 2H), 0.77 (t, *J* = 7.5 Hz, 6H). MS: 558 [M+H]⁺.



Example 416



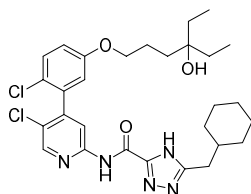
Example 417

[01094] Example 417: N-(5-chloro-4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

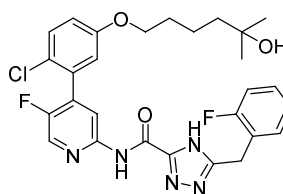
[01095] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.62 (s, 1H), 10.13 (s, 1H), 8.57 (s, 1H), 8.11 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.29 (m, 2H), 7.26 – 7.15 (m, 2H), 7.08 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 4.21 (s, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 1H), 1.74 – 1.61 (m, 2H), 1.45 – 1.37 (m, 2H), 1.34 (q, *J* = 7.5 Hz, 4H), 0.77 (t, *J* = 7.5 Hz, 6H). MS: 586 [M+H]⁺.

[01096] Example 418: N-(5-chloro-4-(2-chloro-5-((4-ethyl-4-hydroxyhexyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01097] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, ethylmagnesium bromide was used in place of methylmagnesium bromide, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.09 (s, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.09 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 4.00 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 1H), 2.67 (d, *J* = 6.8 Hz, 2H), 1.82 – 1.56 (m, 8H), 1.48 – 1.38 (m, 2H), 1.34 (q, *J* = 7.4 Hz, 4H), 1.27 – 1.09 (m, 3H), 1.05 – 0.89 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 6H). MS: 574 [M+H]⁺.



Example 418



Example 419

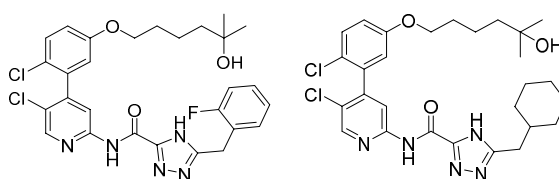
[01098] Example 419: N-(4-(2-chloro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)-5-fluoropyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01099] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-

bromopentanoate was used in place of methyl 4-bromobutanoate, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 10.05 (s, 1H), 8.52 (d, *J* = 15.7 Hz, 1H), 8.14 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.44 – 7.07 (m, 6H), 4.23 (s, 2H), 4.08 (s, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 1.76 – 1.63 (m, 2H), 1.50 – 1.33 (m, 4H), 1.06 (s, 6H). MS: 556 [M+H]⁺.

[01100] Example 420: N-(5-chloro-4-(2-chloro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01101] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 10.11 (s, 1H), 8.56 (s, 1H), 8.12 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.46 – 7.27 (m, 2H), 7.27 – 7.13 (m, 2H), 7.09 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 4.23 (s, 2H), 4.11 (s, 1H), 4.00 (t, *J* = 6.7 Hz, 2H), 1.74 – 1.62 (m, 2H), 1.48 – 1.29 (m, 4H), 1.06 (s, 6H). MS: 572 [M+H]⁺.



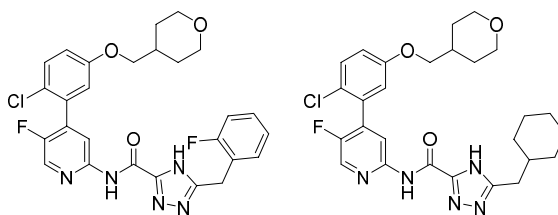
Example 420 Example 421

[01102] Example 421: N-(5-chloro-4-(2-chloro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01103] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 10.12 (s, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.10 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.02 (d, *J* = 3.0 Hz, 1H), 4.10 (s, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 2.66 (d, *J* = 7.0 Hz, 2H), 1.83 – 1.40 (m, 11H), 1.30 – 1.08 (m, 4H), 1.06 (s, 6H), 1.03 – 0.88 (m, 2H). MS: 560 [M+H]⁺.

[01104] Example 422: N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-5-fluoropyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01105] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 10.13 (s, 1H), 8.51 (d, *J* = 1.2 Hz, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.43-7.29 (m, 2H), 7.25-7.16 (m, 2H), 7.14-7.09 (m, 2H), 4.21 (s, 2H), 3.92-3.80 (m, 4H), 3.38 – 3.32 (m, 2H), 2.05 – 1.92 (m, 1H), 1.72 – 1.58 (m, 2H), 1.41 – 1.23 (m, 2H). MS: 540 [M+H]⁺.



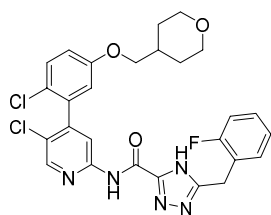
Example 422 Example 423

[01106] Example 423: N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-5-fluoropyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

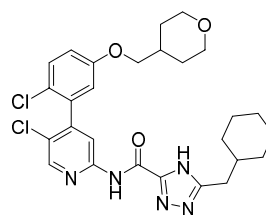
[01107] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 10.07 (s, 1H), 8.52 (s, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.17 – 7.07 (m, 2H), 3.94 – 3.82 (m, 4H), 3.37 – 3.30 (m, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.06 – 1.92 (m, 1H), 1.82 – 1.56 (m, 8H), 1.39 – 1.25 (m, 2H), 1.25 – 1.10 (m, 3H), 1.05 – 0.90 (m, 2H). MS: 528 [M+H]⁺.

[01108] Example 424: N-(5-chloro-4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01109] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.63 (s, 1H), 10.14 (s, 1H), 8.57 (s, 1H), 8.11 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.45-7.29 (m, 2H), 7.26-7.14 (m, 2H), 7.10 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.02 (d, *J* = 3.0 Hz, 1H), 4.21 (s, 2H), 3.96-3.75 (m, 4H), 3.34-3.23 (m, 2H), 2.06-1.90 (m, 1H), 1.73-1.60 (m, 2H), 1.40-1.24 (m, 2H). MS: 556 [M+H]⁺.



Example 424



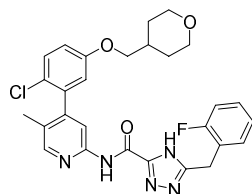
Example 425

[01110] Example 425: N-(5-chloro-4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

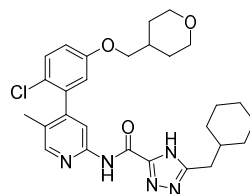
[01111] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 5-chloro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.10 (s, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.11 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.03 (d, *J* = 3.0 Hz, 1H), 3.95 – 3.81 (m, 4H), 3.34 – 3.26 (m, 2H), 2.66 (d, *J* = 7.0 Hz, 2H), 2.07 – 1.92 (m, 1H), 1.83 – 1.55 (m, 8H), 1.39 – 1.07 (m, 5H), 1.07 – 0.89 (m, 2H). MS: 544 [M+H]⁺.

[01112] Example 426: N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-5-methylpyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01113] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 4-bromo-5-methylpyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.81 (s, 1H), 8.32 (s, 1H), 7.93 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.29 (m, 2H), 7.26 – 7.15 (m, 2H), 7.06 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 4.20 (s, 2H), 3.95 – 3.78 (m, 4H), 3.38 – 3.30 (m, 2H), 2.05 (s, 3H), 2.02 – 1.92 (m, 1H), 1.66 (dd, *J* = 12.8, 3.1 Hz, 2H), 1.39 – 1.24 (m, 2H). MS: 536 [M+H]⁺.



Example 426



Example 427

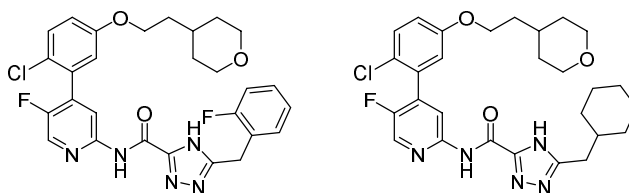
[01114] Example 427: N-(4-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-5-methylpyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01115] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-

2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 4-bromo-5-methylpyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 9.79 (s, 1H), 8.33 (s, 1H), 7.96 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.07 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.93 (d, *J* = 3.0 Hz, 1H), 3.92 – 3.81 (m, 4H), 3.38 – 3.33 (m, 2H), 2.70 – 2.62 (m, 2H), 2.05 (s, 3H), 2.04 – 1.92 (m, 1H), 1.82 – 1.58 (m, 8H), 1.38 – 1.12 (m, 5H), 1.05 – 0.89 (m, 2H). MS: 524 [M+H]⁺.

[01116] Example 428: N-(4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)-5-fluoropyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01117] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 10.14 (s, 1H), 8.51 (d, *J* = 1.1 Hz, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.45 – 7.29 (m, 2H), 7.25 – 7.15 (m, 2H), 7.15 – 7.06 (m, 2H), 4.20 (s, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.87 – 3.76 (m, 2H), 3.35 – 3.28 (m, 2H), 1.77 – 1.55 (m, 5H), 1.29 – 1.12 (m, 2H). MS: 554 [M+H]⁺.



Example 428

Example 429

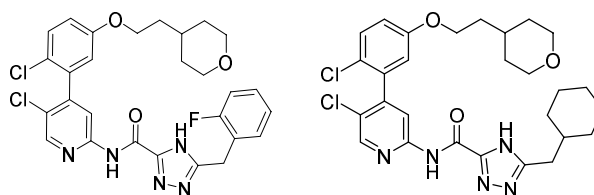
[01118] Example 429: N-(4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)-5-fluoropyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01119] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.07 (s, 1H), 8.52 (d, *J* = 1.2 Hz, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.17 – 7.08 (m, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.88 – 3.75 (m, 2H), 3.31 – 3.21 (m, 2H), 2.66 (d, *J* = 7.0 Hz, 2H), 1.83 – 1.55 (m, 12H), 1.30 – 1.12 (m, 4H), 1.05 – 0.90 (m, 2H). MS: 542 [M+H]⁺.

[01120] Example 430: N-(5-chloro-4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-

5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01121] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.64 (s, 1H), 10.15 (s, 1H), 8.57 (s, 1H), 8.10 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.29 (m, 2H), 7.26 – 7.14 (m, 2H), 7.10 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.03 (d, *J* = 3.0 Hz, 1H), 4.21 (s, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.86 – 3.74 (m, 2H), 3.31 – 3.19 (m, 2H), 1.76 – 1.54 (m, 5H), 1.27 – 1.13 (m, 2H). MS: 570 [M+H]⁺.



Example 430

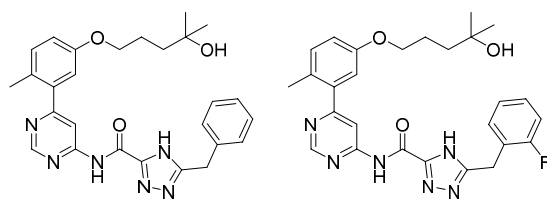
Example 431

[01122] Example 431: N-(5-chloro-4-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01123] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 4-bromo-5-chloropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38 (s, 1H), 10.09 (s, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.10 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.03 (d, *J* = 3.0 Hz, 1H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.86 – 3.75 (m, 2H), 3.31 – 3.20 (m, 2H), 2.67 (d, *J* = 6.8 Hz, 2H), 1.82 – 1.54 (m, 11H), 1.28 – 1.13 (m, 5H), 1.05 – 0.89 (m, 2H). MS: 558 [M+H]⁺.

[01124] Example 432: 5-benzyl-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01125] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 10.35 (s, 1H), 9.01 (d, *J* = 1.3 Hz, 1H), 8.24 (d, *J* = 1.3 Hz, 1H), 7.48 – 7.16 (m, 6H), 7.09 – 6.90 (m, 2H), 4.26 – 4.12 (m, 3H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.31 (s, 3H), 1.86 – 1.66 (m, 2H), 1.56 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 487 [M+H]⁺.



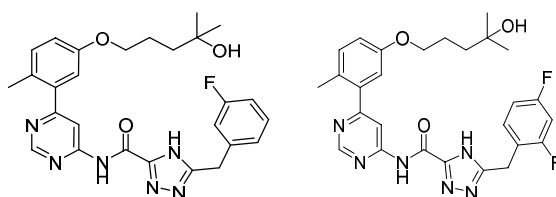
Example 432 Example 433

[01126] Example 433: 5-(2-fluorobenzyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01127] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.73 (s, 1H), 10.33 (s, 1H), 9.01 (d, *J* = 1.2 Hz, 1H), 8.23 (d, *J* = 1.3 Hz, 1H), 7.51 – 7.29 (m, 2H), 7.29 – 7.13 (m, 3H), 7.08 – 6.91 (m, 2H), 4.22 (s, 2H), 4.18 (s, 1H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.31 (s, 3H), 1.83 – 1.68 (m, 2H), 1.54 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 505 [M+H]⁺.

[01128] Example 434: 5-(3-fluorobenzyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01129] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(3-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.70 (s, 1H), 10.39 (s, 1H), 9.02 (d, *J* = 1.2 Hz, 1H), 8.24 (d, *J* = 1.2 Hz, 1H), 7.46 – 7.31 (m, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.23 – 7.14 (m, 2H), 7.14 – 7.06 (m, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.98 (dd, *J* = 8.3, 2.8 Hz, 1H), 4.22 (s, 2H), 4.18 (s, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.31 (s, 3H), 1.83 – 1.69 (m, 2H), 1.54 – 1.43 (m, 2H), 1.09 (s, 6H). MS: 505 [M+H]⁺.



Example 434 Example 435

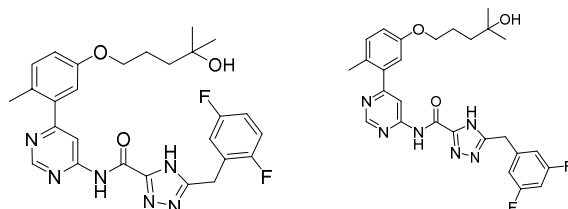
[01130] Example 435: 5-(2,4-difluorobenzyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01131] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2,4-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.72 (s, 1H), 10.35 (s, 1H), 9.01 (d, *J* = 1.2 Hz, 1H), 8.23 (d, *J* = 1.2 Hz, 1H), 7.56-7.40 (m, 1H), 7.27 (dd, *J* = 10.8, 7.8 Hz, 2H), 7.16-7.06 (m, 1H), 7.06-6.91 (m, 2H), 4.25 –

4.13 (m, 3H), 3.97 (t, $J = 6.5$ Hz, 2H), 2.31 (s, 3H), 1.82 – 1.67 (m, 2H), 1.53 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 523 $[M+H]^+$.

[01132] Example 436: 5-(2,5-difluorobenzyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01133] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2,5-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.51 (s, 1H), 10.33 (s, 1H), 9.00 (d, $J = 1.2$ Hz, 1H), 8.24 (d, $J = 1.3$ Hz, 1H), 7.39 – 7.11 (m, 4H), 7.08 – 6.90 (m, 2H), 4.24 – 4.12 (m, 3H), 3.98 (t, $J = 6.5$ Hz, 2H), 2.31 (s, 3H), 1.82 – 1.69 (m, 2H), 1.53 – 1.42 (m, 2H), 1.10 (s, 6H). MS: 523 $[M+H]^+$.



Example 436

Example 437

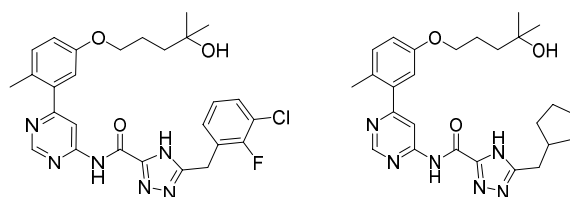
[01134] Example 437: 5-(3,5-difluorobenzyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01135] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(3,5-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.73 (s, 1H), 10.44 (s, 1H), 9.02 (d, $J = 1.2$ Hz, 1H), 8.24 (d, $J = 1.2$ Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 7.22 – 7.06 (m, 3H), 7.03 (d, $J = 2.7$ Hz, 1H), 6.98 (dd, $J = 8.4, 2.8$ Hz, 1H), 4.24 (s, 2H), 4.18 (s, 1H), 3.98 (t, $J = 6.5$ Hz, 2H), 2.31 (s, 3H), 1.82 – 1.68 (m, 2H), 1.53 – 1.43 (m, 2H), 1.09 (s, 6H). MS: 523 $[M+H]^+$.

[01136] Example 438: 5-(3-chloro-2-fluorobenzyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01137] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(3-chloro-2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.71 (s, 1H), 10.31 (s, 1H), 9.01 (d, $J = 1.2$ Hz, 1H), 8.23 (d, $J = 1.3$ Hz, 1H), 7.60 – 7.45 (m, 1H), 7.45 – 7.33 (m, 1H), 7.33 – 7.15 (m, 2H), 7.08 – 6.91 (m, 2H), 4.27 (s, 2H), 4.18 (s, 1H), 3.97 (t, $J = 6.5$ Hz, 2H), 2.31 (s, 3H), 1.83 – 1.69 (m, 2H), 1.54 – 1.40 (m, 2H), 1.09 (s, 6H). MS:

539 [M+H]⁺.



Example 438

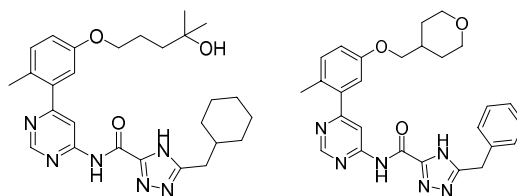
Example 439

[01138] Example 439: 5-(cyclopentylmethyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01139] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 10.27 (s, 1H), 9.02 (d, *J* = 1.2 Hz, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.09 – 6.90 (m, 2H), 4.18 (s, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 2.79 (d, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 2.30 – 2.18 (m, 1H), 1.82 – 1.67 (m, 4H), 1.67 – 1.56 (m, 2H), 1.56 – 1.43 (m, 4H), 1.25 – 1.21 (m, 2H), 1.10 (s, 6H). MS: 479 [M+H]⁺.

[01140] Example 440: 5-(cyclohexylmethyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01141] The preparation was carried out in a similar manner to Example 160, except that in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 10.28 (s, 1H), 9.02 (s, 1H), 8.26 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.99 (dd, *J* = 8.3, 2.8 Hz, 1H), 4.18 (s, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.32 (s, 3H), 1.83 – 1.55 (m, 8H), 1.52 – 1.42 (m, 2H), 1.25 – 1.14 (m, 3H), 1.10 (s, 6H), 1.04 – 0.89 (m, 2H). MS: 493 [M+H]⁺.



Example 440

Example 441

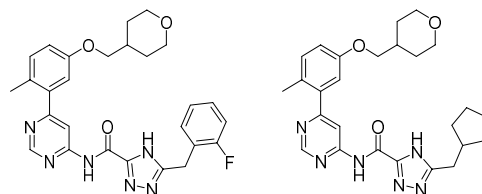
[01142] Example 441: 5-benzyl-N-(6-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01143] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, and in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 10.34 (s,

1H), 9.02 (d, $J = 1.2$ Hz, 1H), 8.24 (d, $J = 1.3$ Hz, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.22 (m, 2H), 7.04 (d, $J = 2.7$ Hz, 1H), 7.00 (dd, $J = 8.3, 2.8$ Hz, 1H), 4.19 (s, 2H), 3.92 – 3.80 (m, 4H), 3.33 – 3.28 (m, 2H), 2.31 (s, 3H), 2.05 – 1.93 (m, 1H), 1.76 – 1.62 (m, 2H), 1.39 – 1.26 (m, 2H). MS: 485 [M+H]⁺.

[01144] Example 442: 5-(2-fluorobenzyl)-N-(6-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01145] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.75 (s, 1H), 10.34 (s, 1H), 9.01 (d, $J = 1.3$ Hz, 1H), 8.23 (d, $J = 1.3$ Hz, 1H), 7.46 – 7.30 (m, 2H), 7.30 – 7.16 (m, 3H), 7.04 (d, $J = 2.8$ Hz, 1H), 6.99 (dd, $J = 8.4, 2.8$ Hz, 1H), 4.22 (s, 2H), 3.92 – 3.79 (m, 4H), 3.32 – 3.25 (m, 2H), 2.31 (s, 3H), 2.05 – 1.92 (m, 1H), 1.73 – 1.62 (m, 2H), 1.40 – 1.26 (m, 2H). MS: 503 [M+H]⁺.



Example 442

Example 443

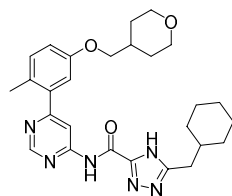
[01146] Example 443: 5-(cyclopentylmethyl)-N-(6-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01147] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.48 (s, 1H), 10.27 (s, 1H), 9.03 (d, $J = 1.3$ Hz, 1H), 8.26 (d, $J = 1.3$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.05 (d, $J = 2.8$ Hz, 1H), 7.00 (dd, $J = 8.3, 2.8$ Hz, 1H), 3.93-3.81 (m, 4H), 3.33-3.29 (m, 2H), 2.79 (d, $J = 7.5$ Hz, 2H), 2.32 (s, 3H), 2.31-2.21 (m, 1H), 2.08-1.93 (m, 1H), 1.79-1.45 (m, 8H), 1.38-1.27 (m, 2H), 1.27-1.17 (m, 2H). MS: 477 [M+H]⁺.

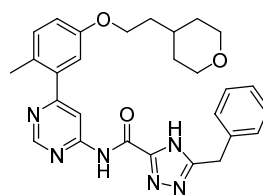
[01148] Example 444: 5-(cyclohexylmethyl)-N-(6-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01149] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆)

δ 14.47 (s, 1H), 10.26 (s, 1H), 9.02 (d, J = 1.3 Hz, 1H), 8.25 (d, J = 1.3 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 7.00 (dd, J = 8.4, 2.8 Hz, 1H), 3.92-3.81 (m, 4H), 3.37-3.32 (m, 2H), 2.67 (d, J = 7.1 Hz, 2H), 2.31 (s, 3H), 2.06-1.93 (m, 1H), 1.82-1.53 (m, 8H), 1.42-1.25 (m, 2H), 1.25-1.06 (m, 3H), 1.06-0.91 (m, 2H). MS: 491 [M+H]⁺.



Example 444



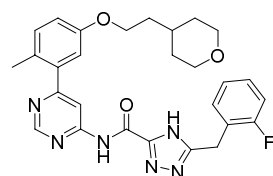
Example 445

[01150] Example 445: 5-benzyl-N-(6-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

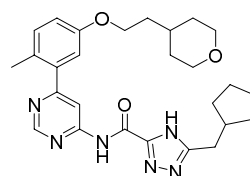
[01151] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, and in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 10.35 (s, 1H), 9.02 (d, J = 1.2 Hz, 1H), 8.24 (d, J = 1.3 Hz, 1H), 7.45 – 7.17 (m, 6H), 7.17 – 6.86 (m, 2H), 4.19 (s, 2H), 4.04 (t, J = 6.3 Hz, 2H), 3.93 – 3.66 (m, 2H), 3.30 – 3.20 (m, 2H), 2.31 (s, 3H), 1.82 – 1.56 (m, 5H), 1.28 – 1.17 (m, 2H). MS: 499 [M+H]⁺.

[01152] Example 446: 5-(2-fluorobenzyl)-N-(6-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01153] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.71 (s, 1H), 10.34 (s, 1H), 9.01 (d, J = 1.2 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 7.47 – 7.29 (m, 2H), 7.29 – 7.15 (m, 3H), 7.08 – 6.93 (m, 2H), 4.22 (s, 2H), 4.03 (t, J = 6.3 Hz, 2H), 3.91 – 3.74 (m, 2H), 3.30 – 3.18 (m, 2H), 2.30 (s, 3H), 1.83 – 1.53 (m, 5H), 1.24 – 1.13 (m, 2H). MS: 517 [M+H]⁺.



Example 446



Example 447

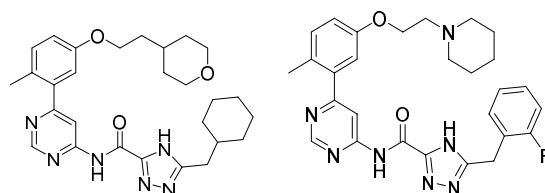
[01154] Example 447: 5-(cyclopentylmethyl)-N-(6-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01155] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-

2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.49 (s, 1H), 10.27 (s, 1H), 9.02 (d, *J* = 1.3 Hz, 1H), 8.25 (d, *J* = 1.3 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.12 – 6.83 (m, 2H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.93 – 3.66 (m, 2H), 3.30 – 3.17 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 2.29 – 2.14 (m, 1H), 1.80 – 1.43 (m, 11H), 1.26 – 1.14 (m, 4H). MS: 491 [M+H]⁺.

[01156] Example 448: 5-(cyclohexylmethyl)-N-(6-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01157] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 10.26 (s, 1H), 9.01 (s, 1H), 8.25 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 2.8 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.82 (dd, *J* = 11.2, 4.3 Hz, 2H), 3.28-3.22 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 1.83-1.55 (m, 12H), 1.25-1.17 (m, 4H), 1.04-0.89 (m, 2H). MS: 505 [M+H]⁺.



Example 448

Example 449

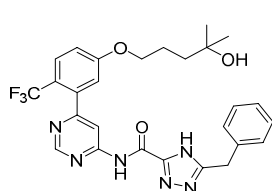
[01158] Example 449: 5-(2-fluorobenzyl)-N-(6-(2-methyl-5-(2-(piperidin-1-yl)ethoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01159] The preparation was carried out in a similar manner to Example 92, except that in step 1, 1-(2-chloroethyl)piperidine hydrochloride was used in place of iodomethane, 3-bromo-4-methylphenol was used in place of 2-bromo-3-methylphenol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.57 (s, 1H), 10.33 (s, 1H), 9.01 (d, *J* = 1.2 Hz, 1H), 8.23 (d, *J* = 1.3 Hz, 1H), 7.46-7.29 (m, 2H), 7.29-7.16 (m, 3H), 7.05 (d, *J* = 2.7 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.21 (s, 2H), 4.09 (t, *J* = 5.9 Hz, 2H), 2.67 (t, *J* = 5.9 Hz, 2H), 2.47-2.39 (m, 4H), 2.31 (s, 3H), 1.54-1.44 (m, 4H), 1.41-1.31 (m, 2H). MS: 516 [M+H]⁺.

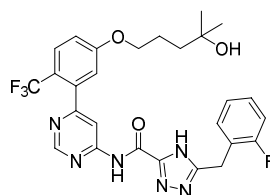
[01160] Example 450: 5-benzyl-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01161] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.68 (s, 1H), 10.45 (s,

1H), 9.02 (d, $J = 1.2$ Hz, 1H), 8.25 (d, $J = 1.2$ Hz, 1H), 7.81 (d, $J = 8.9$ Hz, 1H), 7.38 – 7.29 (m, 4H), 7.29 – 7.20 (m, 2H), 7.11 (d, $J = 2.6$ Hz, 1H), 4.24 – 4.15 (m, 3H), 4.10 (t, $J = 6.6$ Hz, 2H), 1.84 – 1.69 (m, 2H), 1.54 – 1.41 (m, 2H), 1.10 (s, 6H). MS: 541 [M+H]⁺.



Example 450



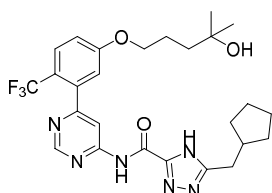
Example 451

[01162] Example 451: 5-(2-fluorobenzyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

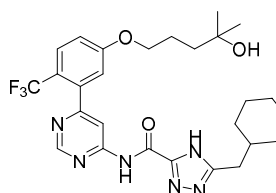
[01163] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.75 (s, 1H), 10.46 (s, 1H), 9.02 (d, $J = 1.3$ Hz, 1H), 8.24 (d, $J = 1.3$ Hz, 1H), 7.81 (d, $J = 8.9$ Hz, 1H), 7.45 – 7.30 (m, 2H), 7.27 – 7.16 (m, 3H), 7.11 (d, $J = 2.6$ Hz, 1H), 4.27 – 4.16 (m, 3H), 4.10 (t, $J = 6.6$ Hz, 2H), 1.86 – 1.71 (m, 2H), 1.55 – 1.42 (m, 2H), 1.10 (s, 6H). MS: 559 [M+H]⁺.

[01164] Example 452: 5-(cyclopentylmethyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01165] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 10.39 (s, 1H), 9.03 (d, $J = 1.3$ Hz, 1H), 8.26 (d, $J = 1.3$ Hz, 1H), 7.81 (d, $J = 8.9$ Hz, 1H), 7.24 (dd, $J = 8.7, 2.6$ Hz, 1H), 7.12 (d, $J = 2.6$ Hz, 1H), 4.20 (s, 1H), 4.10 (t, $J = 6.5$ Hz, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.36 – 2.17 (m, 1H), 1.86 – 1.66 (m, 4H), 1.66 – 1.43 (m, 6H), 1.25 – 1.18 (m, 2H), 1.10 (s, 6H). MS: 533 [M+H]⁺.



Example 452



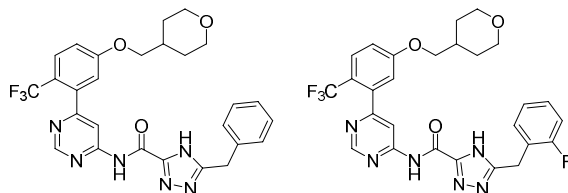
Example 453

[01166] Example 453: 5-(cyclohexylmethyl)-N-(6-(5-((4-hydroxy-4-methylpentyl)oxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01167] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 10.37 (s, 1H), 9.03 (d, *J* = 1.2 Hz, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.24 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.12 (d, *J* = 2.6 Hz, 1H), 4.20 (s, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 2.67 (d, *J* = 7.1 Hz, 2H), 1.85 – 1.54 (m, 8H), 1.54 – 1.41 (m, 2H), 1.23 – 1.16 (m, 3H), 1.10 (s, 6H), 1.05 – 0.89 (m, 2H). MS: 547 [M+H]⁺.

[01168] Example 454: 5-benzyl-N-(6-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01169] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.65 (s, 1H), 10.45 (s, 1H), 9.02 (d, *J* = 1.2 Hz, 1H), 8.25 (d, *J* = 1.2 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.19 (m, 2H), 7.13 (d, *J* = 2.6 Hz, 1H), 4.19 (s, 2H), 3.98 (d, *J* = 6.5 Hz, 2H), 3.92 – 3.81 (m, 2H), 3.37 – 3.32 (m, 2H), 2.07 – 1.94 (m, 1H), 1.74 – 1.60 (m, 2H), 1.40 – 1.26 (m, 2H). MS: 539 [M+H]⁺.



Example 454

Example 455

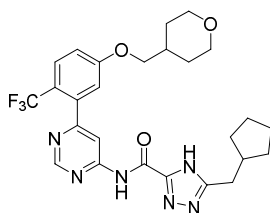
[01170] Example 455: 5-(2-fluorobenzyl)-N-(6-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01171] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.73 (s, 1H), 10.46 (s, 1H), 9.02 (d, *J* = 1.3 Hz, 1H), 8.24 (d, *J* = 1.3 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.49 – 7.28 (m, 2H), 7.28 – 7.07 (m, 4H), 4.22 (s, 2H), 3.97 (d, *J* = 6.5 Hz, 2H), 3.93 – 3.82 (m, 2H), 3.36 – 3.30 (m, 2H), 2.09 – 1.95 (m, 1H), 1.74 – 1.62 (m, 2H), 1.42 – 1.24 (m, 2H). MS: 557 [M+H]⁺.

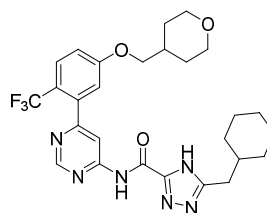
[01172] Example 456: 5-(cyclopentylmethyl)-N-(6-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-

(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01173] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 10.38 (s, 1H), 9.03 (d, *J* = 1.2 Hz, 1H), 8.26 (d, *J* = 1.2 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.26 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 3.98 (d, *J* = 6.4 Hz, 2H), 3.93 – 3.83 (m, 2H), 3.43 – 3.36 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.36 – 2.21 (m, 1H), 2.08 – 1.95 (m, 1H), 1.75 – 1.64 (m, 4H), 1.64 – 1.56 (m, 2H), 1.56 – 1.46 (m, 2H), 1.39 – 1.28 (m, 2H), 1.23 – 1.14 (m, 2H). MS: 531 [M+H]⁺.



Example 456



Example 457

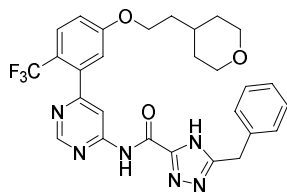
[01174] Example 457: 5-(cyclohexylmethyl)-N-(6-(5-((tetrahydro-2H-pyran-4-yl)methoxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01175] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 10.38 (s, 1H), 9.03 (d, *J* = 1.3 Hz, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.26 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 3.98 (d, *J* = 6.5 Hz, 2H), 3.93 – 3.81 (m, 2H), 3.35 – 3.30 (m, 2H), 2.67 (d, *J* = 7.1 Hz, 2H), 2.11 – 1.96 (m, 1H), 1.83 – 1.57 (m, 8H), 1.42 – 1.26 (m, 2H), 1.26 – 1.07 (m, 3H), 1.07 – 0.91 (m, 2H). MS: 545 [M+H]⁺.

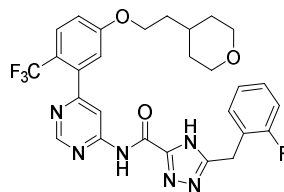
[01176] Example 458: 5-benzyl-N-(6-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01177] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, and in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.47 (s, 1H), 9.02 (d, *J* = 1.2 Hz, 1H), 8.25 (d, *J* = 1.2 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.18

(m, 2H), 7.13 (d, $J = 2.6$ Hz, 1H), 4.25 – 4.10 (m, 4H), 3.88 – 3.76 (m, 2H), 3.27 – 3.23 (m, 2H), 1.77 – 1.65 (m, 3H), 1.65 – 1.56 (m, 2H), 1.26 – 1.19 (m, 2H). MS: 553 $[M+H]^+$.



Example 458



Example 459

5 **[01178]** Example 459: 5-(2-fluorobenzyl)-N-(6-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

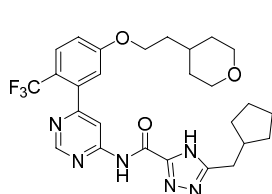
[01179] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.70 (s, 1H), 10.47 (s, 1H), 9.02 (d, $J = 1.2$ Hz, 1H), 8.24 (d, $J = 1.2$ Hz, 1H), 7.80 (d, $J = 8.9$ Hz, 1H), 7.50-7.30 (m, 2H), 7.30-7.06 (m, 4H), 4.21 (s, 2H), 4.15 (t, $J = 6.1$ Hz, 2H), 3.88-3.76 (m, 2H), 3.29-3.18 (m, 2H), 1.71-1.56 (m, 4H), 1.30-1.13 (m, 3H). MS: 571 $[M+H]^+$.

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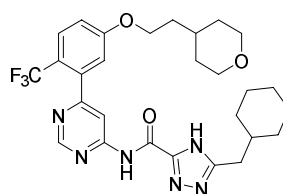
[01180] Example 460: 5-(cyclopentylmethyl)-N-(6-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01181] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.47 (s, 1H), 10.40 (s, 1H), 9.03 (s, 1H), 8.26 (s, 1H), 7.81 (d, $J = 8.9$ Hz, 1H), 7.26 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.14 (d, $J = 2.6$ Hz, 1H), 4.16 (t, $J = 6.0$ Hz, 2H), 3.82 (dd, $J = 10.8, 4.3$ Hz, 2H), 3.29 – 3.21 (m, 2H), 2.78 (d, $J = 7.5$ Hz, 2H), 2.37 – 2.18 (m, 1H), 1.82 – 1.66 (m, 5H), 1.66 – 1.57 (m, 4H), 1.57 – 1.46 (m, 2H), 1.25 – 1.14 (m, 4H). MS: 545 $[M+H]^+$.

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Example 460



Example 461

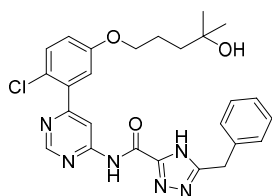
[01182] Example 461: 5-(cyclohexylmethyl)-N-(6-(5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2-

(trifluoromethyl)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

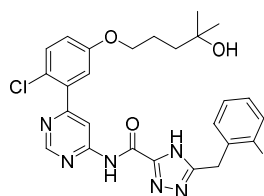
[01183] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-chloro-4-(trifluoromethyl)phenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 10.40 (s, 1H), 9.03 (d, *J* = 1.2 Hz, 1H), 8.26 (d, *J* = 1.2 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.26 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 4.16 (t, *J* = 6.1 Hz, 2H), 3.90 – 3.73 (m, 2H), 3.31 – 3.20 (m, 2H), 2.67 (d, *J* = 7.1 Hz, 2H), 1.83 – 1.54 (m, 11H), 1.24 – 1.06 (m, 5H), 1.06 – 0.89 (m, 2H). MS: 559 [M+H]⁺.

[01184] Example 462: 5-benzyl-N-(6-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01185] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.61 (s, 1H), 10.42 (s, 1H), 9.06 (d, *J* = 1.3 Hz, 1H), 8.45 (d, *J* = 1.3 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 7.20 (d, *J* = 3.0 Hz, 1H), 7.11 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.27 – 4.13 (m, 3H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.84 – 1.70 (m, 2H), 1.53 – 1.43 (m, 2H), 1.09 (s, 6H). MS: 507 [M+H]⁺.



Example 462



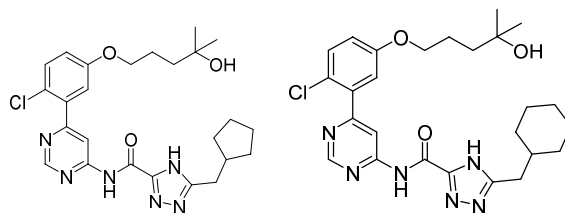
Example 463

[01186] Example 463: 5-(2-fluorobenzyl)-N-(6-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01187] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.71 (s, 1H), 10.42 (s, 1H), 9.05 (d, *J* = 1.2 Hz, 1H), 8.44 (d, *J* = 1.2 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.30 (m, 2H), 7.27 – 7.15 (m, 3H), 7.11 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.31 – 4.14 (m, 3H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.84 – 1.68 (m, 2H), 1.55 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 525 [M+H]⁺.

[01188] Example 464: 5-(cyclopentylmethyl)-N-(6-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01189] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.32 (s, 1H), 10.34 (s, 1H), 9.06 (d, *J* = 1.3 Hz, 1H), 8.46 (d, *J* = 1.2 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 3.1 Hz, 1H), 7.11 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.19 (s, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.37 – 2.20 (m, 1H), 1.85 – 1.66 (m, 4H), 1.66 – 1.42 (m, 6H), 1.25 – 1.16 (m, 2H), 1.10 (s, 6H). MS: 499 [M+H]⁺.



Example 464

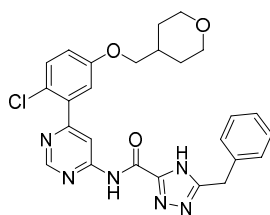
Example 465

[01190] Example 465: 5-(cyclohexylmethyl)-N-(6-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

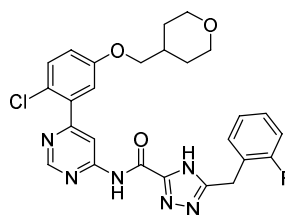
[01191] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 10.35 (s, 1H), 9.06 (s, 1H), 8.46 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 3.0 Hz, 1H), 7.11 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.19 (s, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 1.84 – 1.55 (m, 8H), 1.55 – 1.41 (m, 2H), 1.26 – 1.14 (m, 3H), 1.10 (s, 6H), 1.05 – 0.91 (m, 2H). MS: 513 [M+H]⁺.

[01192] Example 466: 5-benzyl-N-(6-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01193] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.42 (s, 1H), 9.06 (d, *J* = 1.3 Hz, 1H), 8.45 (d, *J* = 1.3 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.29 – 7.19 (m, 2H), 7.12 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.18 (s, 2H), 3.97 – 3.82 (m, 4H), 3.30 – 3.28 (m, 2H), 2.05 – 1.93 (m, 1H), 1.75 – 1.60 (m, 2H), 1.40 – 1.25 (m, 2H). MS: 505 [M+H]⁺.



Example 466



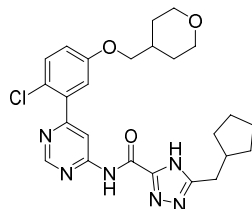
Example 467

[01194] Example 467: 5-(2-fluorobenzyl)-N-(6-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

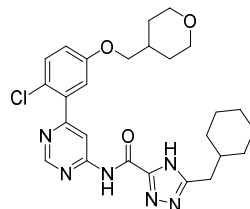
[01195] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.66 (s, 1H), 10.41 (s, 1H), 9.05 (d, *J* = 1.2 Hz, 1H), 8.44 (d, *J* = 1.3 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.30 (m, 2H), 7.28 – 7.16 (m, 3H), 7.12 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.21 (s, 2H), 3.94 – 3.81 (m, 4H), 3.31 – 3.29 (m, 2H), 2.09 – 1.92 (m, 1H), 1.73 – 1.60 (m, 2H), 1.40 – 1.25 (m, 2H). MS: 523 [M+H]⁺.

[01196] Example 468: 5-(cyclopentylmethyl)-N-(6-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01197] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.50 (s, 1H), 10.35 (s, 1H), 9.06 (d, *J* = 1.3 Hz, 1H), 8.46 (d, *J* = 1.3 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 7.23 (d, *J* = 3.1 Hz, 1H), 7.13 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.95 – 3.81 (m, 4H), 3.31 – 3.28 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.37 – 2.19 (m, 1H), 2.09 – 1.94 (m, 1H), 1.80 – 1.44 (m, 8H), 1.39 – 1.27 (m, 2H), 1.27 – 1.22 (m, 2H). MS: 497 [M+H]⁺.



Example 468



Example 469

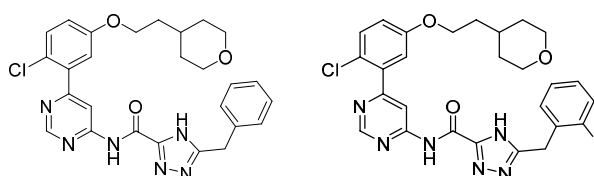
[01198] Example 469: 5-(cyclohexylmethyl)-N-(6-(2-chloro-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01199] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-

2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 2, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 10.35 (s, 1H), 9.06 (d, *J* = 1.3 Hz, 1H), 8.46 (d, *J* = 1.2 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 3.1 Hz, 1H), 7.13 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.98 – 3.82 (m, 4H), 3.31 – 3.28 (m, 2H), 2.67 (d, *J* = 7.0 Hz, 2H), 2.11 – 1.92 (m, 1H), 1.83 – 1.56 (m, 8H), 1.41 – 1.26 (m, 2H), 1.26 – 1.10 (m, 3H), 1.07 – 0.92 (m, 2H). MS: 511 [M+H]⁺.

[01200] Example 470: 5-benzyl-N-(6-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-4H-1,2,4-triazole-3-carboxamide

[01201] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.71 (s, 1H), 10.43 (s, 1H), 9.06 (d, *J* = 1.3 Hz, 1H), 8.44 (d, *J* = 1.3 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.29 – 7.21 (m, 2H), 7.12 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.18 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.90 – 3.73 (m, 2H), 3.28 – 3.20 (m, 2H), 1.77 – 1.56 (m, 5H), 1.30 – 1.15 (m, 2H). MS: 519 [M+H]⁺.



Example 470

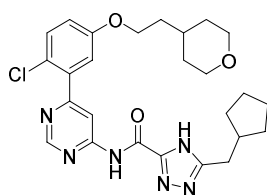
Example 471

[01202] Example 471: N-(6-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

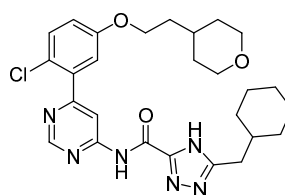
[01203] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.34 (s, 1H), 10.58 (s, 1H), 9.04 (d, *J* = 1.3 Hz, 1H), 8.44 (d, *J* = 1.3 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.43 – 7.28 (m, 2H), 7.25 – 7.15 (m, 3H), 7.12 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.19 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.86 – 3.78 (m, 2H), 3.29 – 3.27 (m, 2H), 1.74 – 1.57 (m, 5H), 1.28 – 1.19 (m, 2H). MS: 537 [M+H]⁺.

[01204] Example 472: N-(6-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01205] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.39 (s, 1H), 10.33 (s, 1H), 9.06 (d, *J* = 1.3 Hz, 1H), 8.46 (d, *J* = 1.3 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 3.1 Hz, 1H), 7.13 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.89 – 3.77 (m, 2H), 3.28 – 3.23 (m, 2H), 2.82 – 2.75 (m, 2H), 2.36 – 2.21 (m, 1H), 1.77 – 1.56 (m, 10H), 1.56 – 1.46 (m, 2H), 1.24 – 1.16 (m, 3H). MS: 511 [M+H]⁺.



Example 472

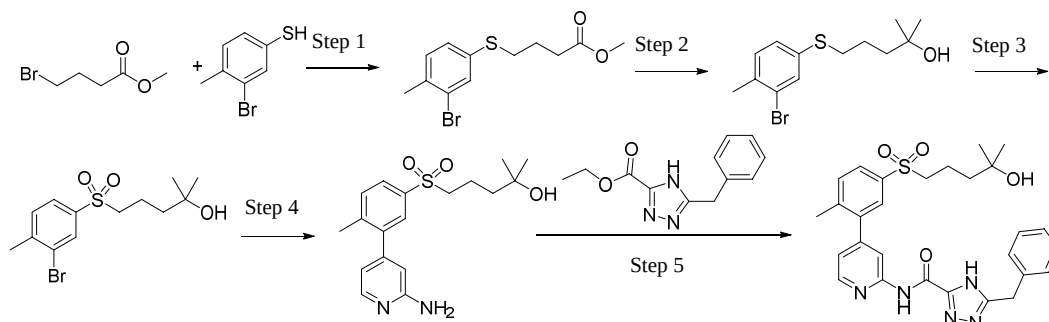


Example 473

[01206] Example 473: N-(6-(2-chloro-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyrimidin-4-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01207] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 2, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, in step 3, 6-chloropyrimidin-4-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 10.36 (s, 1H), 9.06 (s, 1H), 8.46 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 3.1 Hz, 1H), 7.12 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.86 – 3.78 (m, 2H), 3.28 – 3.23 (m, 2H), 2.67 (d, *J* = 7.1 Hz, 2H), 1.79 – 1.72 (m, 1H), 1.72 – 1.55 (m, 10H), 1.24 – 1.08 (m, 5H), 1.05 – 0.92 (m, 2H). MS: 525 [M+H]⁺.

[01208] Example 474: 5-benzyl-N-(4-(5-((4-hydroxy-4-methylpentyl)sulfonyl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[01209] Steps 1 to 2 were carried out in a similar manner to Steps 1 to 2 of Example 160, except that 3-bromo-4-methylbenzenethiol was used in place of 3-bromo-4-methylphenol.

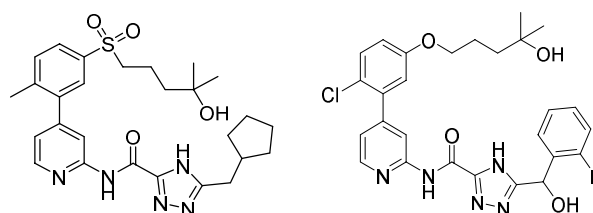
[01210] Step 3: 5-((3-bromo-4-methylphenyl)thio)-2-methylpentan-2-ol (606mg, 2mmol) was dissolved in dichloromethane (6mL), m-chloroperoxybenzoic acid (520mg, 3mmol) was added in batches at 0°C, and reacted at 25°C for 1.5 hours. The reaction solution was diluted with dichloromethane, washed with saturated aqueous solution of sodium carbonate and saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, purified by column chromatography to afford 600mg of 5-((3-bromo-4-methylphenyl)sulfonyl)-2-methylpentan-2-ol.

[01211] Steps 4 to 5 were carried out in a similar manner to Steps 3 to 4 of Example 160, except that 5-((3-bromo-4-methylphenyl)sulfonyl)-2-methylpentan-2-ol was used in place of 5-(3-bromo-4-methylphenoxy)-2-methylpentan-2-ol.

[01212] ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.00 (s, 1H), 8.48 (d, *J* = 5.1 Hz, 1H), 8.15 (d, *J* = 1.5 Hz, 1H), 7.88 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.20 (m, 6H), 4.20 (s, 1H), 4.18 (s, 2H), 3.32 – 3.23 (m, 2H), 2.38 (s, 3H), 1.71 – 1.55 (m, 2H), 1.44 – 1.32 (m, 2H), 1.02 (s, 6H). MS: 534 [M+H]⁺.

[01213] Example 475: 5-(cyclopentylmethyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)sulfonyl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01214] The preparation was carried out in a similar manner to Example 474, except that in step 5, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.41 (s, 1H), 9.94 (s, 1H), 8.49 (d, *J* = 5.1 Hz, 1H), 8.25 – 8.10 (m, 1H), 7.88 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.6 Hz, 1H), 4.20 (s, 1H), 3.39 – 3.34 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 2.35 – 2.18 (m, 1H), 1.81 – 1.67 (m, 2H), 1.67 – 1.56 (m, 4H), 1.56 – 1.45 (m, 2H), 1.44 – 1.33 (m, 2H), 1.26 – 1.18 (m, 2H), 1.03 (s, 6H). MS: 526 [M+H]⁺.



Example 475

Example 476

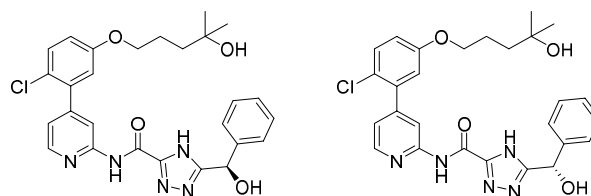
[01215] Example 476: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-((2-fluorophenyl)(hydroxyl)methyl)-4H-1,2,4-triazole-3-carboxamide

[01216] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-((2-fluorophenyl)(hydroxyl)methyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.89 (s, 1H), 9.87 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H),

8.20 (d, $J = 1.5$ Hz, 1H), 7.58 (s, 1H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.43 – 7.34 (m, 1H), 7.32 – 7.16 (m, 3H), 7.05 (dd, $J = 8.8, 3.0$ Hz, 1H), 7.00 (d, $J = 3.0$ Hz, 1H), 6.77 (s, 1H), 6.15 (d, $J = 4.9$ Hz, 1H), 4.19 (s, 1H), 4.00 (t, $J = 6.6$ Hz, 2H), 1.82 – 1.70 (m, 2H), 1.52 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 540 $[M+H]^+$.

[01217] Example 477: (R)-N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(hydroxyl(phenyl)methyl)-4H-1,2,4-triazole-3-carboxamide

[01218] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl (R)-5-(hydroxyl(phenyl)methyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.78 (s, 1H), 9.86 (s, 1H), 8.44 (d, $J = 5.2$ Hz, 1H), 8.22 (s, 1H), 7.54 – 7.44 (m, 3H), 7.44 – 7.34 (m, 2H), 7.34 – 7.23 (m, 2H), 7.06 (dd, $J = 8.8, 3.0$ Hz, 1H), 7.00 (d, $J = 3.0$ Hz, 1H), 6.71 (d, $J = 4.3$ Hz, 1H), 5.96 (d, $J = 4.3$ Hz, 1H), 4.18 (s, 1H), 4.01 (t, $J = 6.5$ Hz, 2H), 1.82 – 1.68 (m, 2H), 1.53 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 522 $[M+H]^+$.



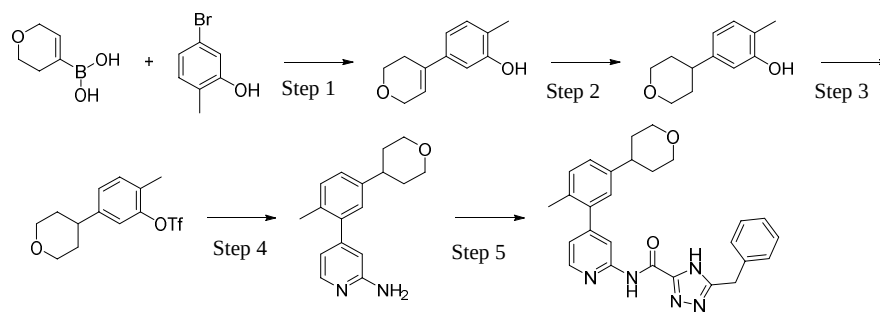
Example 477

Example 478

[01219] Example 478: (S)-N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(hydroxyl(phenyl)methyl)-4H-1,2,4-triazole-3-carboxamide

[01220] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl (S)-5-(hydroxyl(phenyl)methyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.78 (s, 1H), 9.88 (s, 1H), 8.45 (d, $J = 5.1$ Hz, 1H), 8.21 (s, 1H), 7.54 – 7.44 (m, 3H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.34 – 7.24 (m, 2H), 7.06 (dd, $J = 8.8, 3.0$ Hz, 1H), 7.00 (d, $J = 3.1$ Hz, 1H), 6.71 (s, 1H), 5.95 (s, 1H), 4.19 (s, 1H), 4.01 (t, $J = 6.6$ Hz, 2H), 1.82 – 1.69 (m, 2H), 1.51 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 522 $[M+H]^+$.

[01221] Example 479: 5-benzyl-N-(4-(2-methyl-5-(tetrahydro-2H-pyran-4-yl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

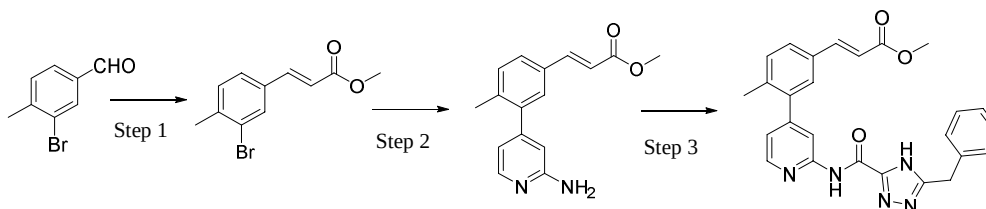


[01222] Steps 1 to 2 were carried out in a similar manner to Steps 1 to 2 of Example 47, except that (3,6-dihydro-2H-pyran-4-yl)boronic acid was used in place of cyclopent-1-en-1-ylboronic acid, and 5-bromo-2-methylphenol was used in place of 4-bromopyridin-2-amine.

5 **[01223]** Steps 3 to 5 were carried out in a similar manner to Example 43, except that 2-methyl-5-(tetrahydro-2H-pyran)-4-ylphenol was used in place of 5,6,7,8-tetrahydronaphthalen-1-ol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (d, *J* = 1.5 Hz, 1H), 7.45 – 7.29 (m, 4H), 7.29 – 7.13 (m, 5H), 4.18 (s, 2H), 4.01 – 3.91 (m, 2H), 3.50 – 3.41 (m, 2H), 2.85 – 2.71 (m, 1H), 2.28 (s, 3H), 1.81 – 1.64 (m, 4H). MS: 454 [M+H]⁺.

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[01224] Example 480: Methyl 3-(3-(2-(5-benzyl-4H-1,2,4-triazol-3-carboxamido)pyridin-4-yl)-4-methylphenyl)acrylate

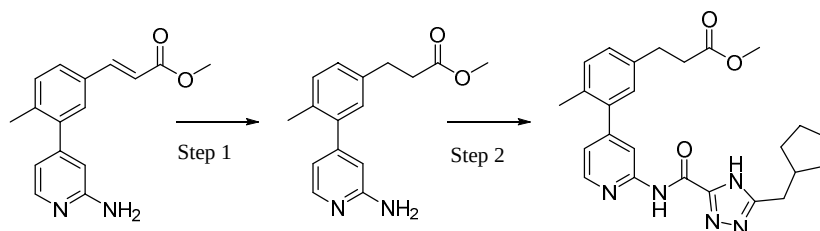


15 **[01225]** Step 1 was carried out in a similar manner to Step 2 of Example 78, except that 3-bromo-4-methylbenzaldehyde was used in place of 2-bromo-4-(2-(tert-butoxy)ethoxy)benzaldehyde, and trimethyl phosphonoacetate was used in place of methyltriphenylphosphonium bromide.

[01226] Steps 2 to 3 were carried out in a similar manner to Example 33, except that methyl 3-(3-bromo-4-methylphenyl)acrylate was used in place of 2-bromo-4-fluoro-1-methylbenzene. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 9.93 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.13 (s, 1H), 7.77 – 7.62 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.30 – 7.18 (m, 2H), 6.69 (d, *J* = 16.0 Hz, 1H), 4.18 (s, 2H), 3.72 (s, 3H), 2.29 (s, 3H). MS: 454 [M+H]⁺.

20

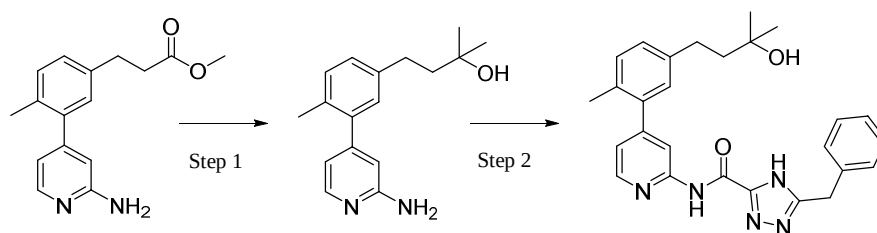
[01227] Example 481: Methyl 3-(3-(2-(5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxamido)pyridin-4-yl)-4-methylphenyl)propionate



[01228] It was carried out in a similar manner to steps 2 to 3 of Example 47, except that methyl (E)-3-(3-(2-aminopyridin-4-yl)-4-methylphenyl)acrylate (see Example 480 for the synthetic method) was used in place of 4-(cyclopent-1-en-1-yl)pyridin-2-amine, and ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate.

[01229] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.43 (s, 1H), 9.86 (s, 1H), 8.42 (d, $J = 5.1$ Hz, 1H), 8.13 (d, $J = 1.4$ Hz, 1H), 7.35 – 7.17 (m, 3H), 7.14 (d, $J = 1.8$ Hz, 1H), 3.58 (s, 3H), 2.87 (t, $J = 7.6$ Hz, 2H), 2.82 – 2.72 (m, 2H), 2.66 (t, $J = 7.6$ Hz, 2H), 2.35 – 2.25 (m, 1H), 2.24 (s, 3H), 1.79 – 1.67 (m, 2H), 1.67 – 1.56 (m, 2H), 1.56 – 1.48 (m, 2H), 1.26 – 1.21 (m, 2H). MS: 448 $[\text{M}+\text{H}]^+$.

[01230] Example 482: 5-benzyl-N-(4-(5-(3-hydroxyl-3-methylbutyl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

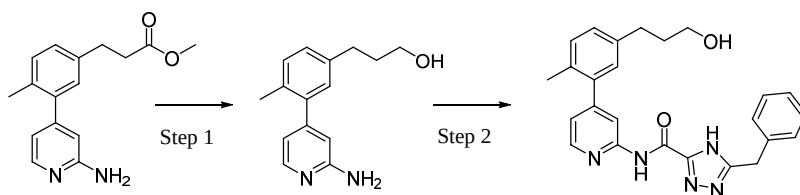


[01231] Step 1: The preparation was carried out in a similar manner to step 2 of Example 160, except that methyl 3-(3-(2-aminopyridin-4-yl)-4-methylphenyl)propionate was used in place of methyl 4-(3-bromo-4-methylphenoxy)butanoate.

[01232] Step 2: The preparation was carried out in a similar manner to step 3 of Example 100, except that 4-(3-(2-aminopyridin-4-yl)-4-methylphenyl)-2-methylbutan-2-ol was used in place of 4-(2-methyl-5-(octyloxy)phenyl)pyridin-2-amine.

[01233] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.58 (s, 1H), 9.90 (s, 1H), 8.41 (d, $J = 5.1$ Hz, 1H), 8.11 (d, $J = 1.4$ Hz, 1H), 7.39 – 7.30 (m, 4H), 7.29 – 7.23 (m, 2H), 7.23 – 7.16 (m, 2H), 7.09 (d, $J = 1.8$ Hz, 1H), 4.24 (s, 1H), 4.18 (s, 2H), 2.70 – 2.59 (m, 2H), 2.24 (s, 3H), 1.71 – 1.60 (m, 2H), 1.13 (s, 6H). MS: 456 $[\text{M}+\text{H}]^+$.

[01234] Example 483: 5-benzyl-N-(4-(5-(3-hydroxylpropyl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



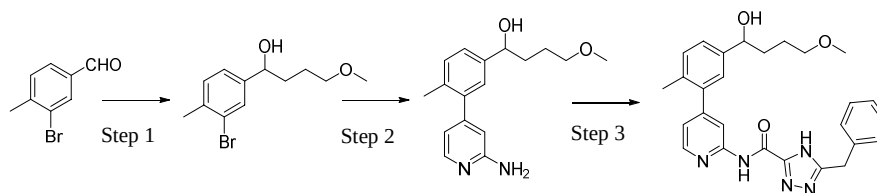
[01235] Step 1: Synthesis of 3-(3-(2-aminopyridin-4-yl)-4-methylphenyl)propanol

[01236] Methyl 3-(3-(2-aminopyridin-4-yl)-4-methylphenyl)propionate (270mg, 1mmol) was placed in anhydrous tetrahydrofuran (3mL), and lithium aluminum hydride (115mg, 3mmol) was added in batches under argon protection at 0°C. After reacting at 50°C for 2 hours, the reaction solution was quenched with saturated ammonium chloride, diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and purified by column chromatography to afford 150 mg of product.

[01237] Step 2: It was carried out in a similar manner to step 2 of Example 1, except that 3-(3-(2-aminopyridin-4-yl)-4-methylphenyl)propanol was used in place of 4-phenylpyridin-2-amine.

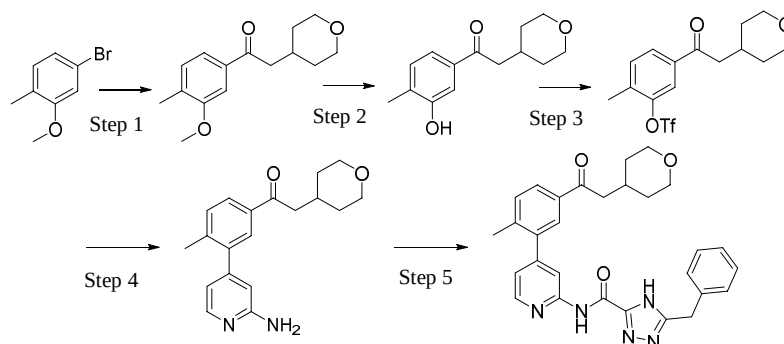
[01238] ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.47 (s, 1H), 9.90 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.15 – 8.08 (m, 1H), 7.40 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 7.23 – 7.13 (m, 2H), 7.09 (d, *J* = 1.8 Hz, 1H), 4.67 – 4.34 (m, 1H), 4.17 (s, 2H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.24 (s, 3H), 1.80 – 1.66 (m, 2H). MS: 428 [M+H]⁺.

[01239] Example 484: 5-benzyl-N-(4-(5-(1-hydroxyl-4-methoxybutyl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[01240] It was carried out in a similar manner to steps 2 to 4 of Example 160, except that 3-bromo-4-methylbenzaldehyde was used in place of methyl 4-(3-bromo-4-methylphenoxy)butanoate, and (3-methoxypropyl)magnesium bromide was used in place of methylmagnesium bromide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.48 (s, 1H), 9.90 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.38-7.22 (m, 7H), 7.22-7.17 (m, 2H), 5.19 (d, *J* = 4.5 Hz, 1H), 4.67-4.43 (m, 1H), 4.18 (s, 2H), 3.29 (t, *J* = 6.3 Hz, 2H), 3.18 (s, 3H), 2.26 (s, 3H), 1.69-1.52 (m, 3H), 1.52-1.39 (m, 1H). MS: 472 [M+H]⁺.

[01241] Example 485: 5-benzyl-N-(4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)acetyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[01242] Step 1: Synthesis of 1-(3-methoxy-4-methylphenyl)-2-(tetrahydro-2H-pyran-4-yl)ethan-1-one

[01243] 4-Bromo-2-methoxy-1-methylbenzene (500mg, 2.5mmol) was dissolved in anhydrous tetrahydrofuran (5mL), and n-butyl lithium (2.5M, 1mL, 2.5mmol) was added dropwise at -78°C under argon protection. After reacting at this temperature for 30 minutes, N-methoxy-N-methyl-2-(tetrahydro-2H-pyran-4-yl)acetamide (505mg, 2.7mmol) in anhydrous tetrahydrofuran (1mL) was added, warmed slowly, and reacted at room temperature for 2 hours. The reaction solution was quenched with saturated aqueous solution of ammonium chloride, extracted with ethyl acetate, the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and purified by column chromatography to afford 500 mg of product.

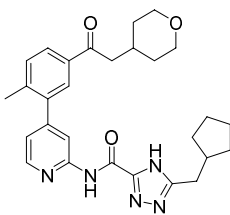
[01244] Step 2: Synthesis of 1-(3-hydroxyl-4-methylphenyl)-2-(tetrahydro-2H-pyran-4-yl)ethan-1-one

[01245] 1-(3-Methoxy-4-methylphenyl)-2-(tetrahydro-2H-pyran-4-yl)ethan-1-one (500mg, 2.0mmol) was dissolved in anhydrous dichloromethane (5mL), a solution of boron tribromide in dichloromethane (1M, 3mL, 3mmol) was added dropwise at 0°C under argon protection, and the reaction was slowly warmed to room temperature and reacted for 2 hours. The reaction solution was quenched with saturated aqueous solution of ammonium chloride, extracted with dichloromethane, and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, and purified by column chromatography to afford 350mg of product.

[01246] Steps 3 to 5 were carried out in a similar manner to Example 43, except that 1-(3-hydroxyl-4-methylphenyl)-2-(tetrahydro-2H-pyran-4-yl)ethan-1-one was used in place of 5,6,7,8-tetrahydronaphthalen-1-ol.

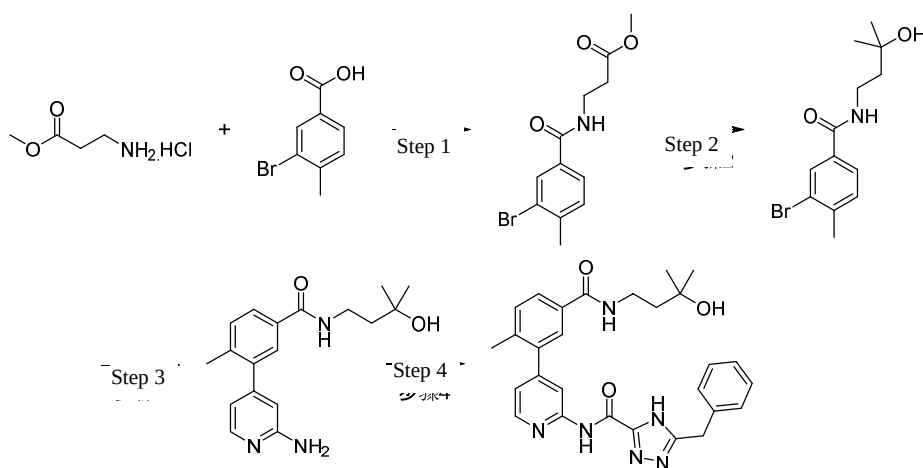
[01247] ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.96 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.96 (d, *J* = 1.7 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.39-7.29 (m, 4H), 7.29-7.21 (m, 2H), 4.18 (s, 2H), 3.88-3.75 (m, 2H), 3.32-3.25 (m, 2H), 3.00 (d, *J* = 6.7 Hz, 2H), 2.35 (s, 3H), 2.20-2.05 (m, 1H), 1.66-1.54 (m, 2H), 1.34-1.22 (m, 2H). MS: 496 [M+H]⁺.

[01248] Example 486: 5-(cyclopentylmethyl)-N-(4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)acetyl)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[01249] It was carried out in a similar manner to Example 485, except that in step 5, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.42 (s, 1H), 9.91 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.16 (d, *J* = 1.4 Hz, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 5.1, 1.6 Hz, 1H), 3.89 – 3.76 (m, 2H), 3.32 – 3.24 (m, 2H), 3.00 (d, *J* = 6.7 Hz, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.35 (s, 3H), 2.31 – 2.22 (m, 1H), 2.18 – 2.05 (m, 1H), 1.80 – 1.67 (m, 2H), 1.67 – 1.56 (m, 4H), 1.56 – 1.44 (m, 2H), 1.32 – 1.21 (m, 4H). MS: 488 [M+H]⁺.

[01250] Example 487: 5-benzyl-N-(4-(5-((3-hydroxyl-3-methylbutyl)carbamoyl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide



[01251] Step 1: Synthesis of methyl 3-(3-bromo-4-methylbenzamido)propionate

[01252] 3-Bromo-4-methylbenzoic acid (430mg, 2mmol), methyl 3-aminopropionate hydrochloride (280mg, 2mmol), T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide) (950mg, 50%, 3mmol) and DIEA (780mg, 6mmol) were dissolved in dichloromethane (6mL), and reacted at 25°C for 2 hours. The reaction solution was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, purified by column chromatography to afford 540mg of product.

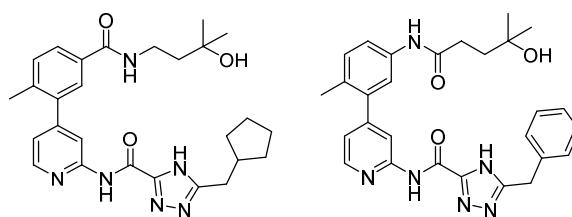
[01253] Steps 2 to 4 were carried out in a similar manner to steps 2 to 4 of Example 160, except that methyl 3-(3-bromo-4-methylbenzamido)propionate was used in place of methyl 4-(3-bromo-4-methylphenoxy)butanoate.

[01254] ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.54 (s, 1H), 9.94 (s, 1H), 8.50 – 8.38 (m, 2H), 8.14 (s, 1H), 7.82 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.17 (m, 2H), 4.33 (s, 1H), 4.18 (s, 2H), 3.38 – 3.34 (m, 2H), 2.32 (s, 3H), 1.71 – 1.58 (m, 2H), 1.12 (s, 6H). MS: 499

[M+H]⁺.

[01255] Example 488: 5-(cyclopentylmethyl)-N-(4-(5-((3-hydroxyl-3-methylbutyl)carbamoyl)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01256] The preparation was carried out in a similar manner to Example 487, except that in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.34 (s, 1H), 9.89 (s, 1H), 8.55 – 8.34 (m, 2H), 8.16 (s, 1H), 7.82 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.75 (d, *J* = 1.9 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.26 (dd, *J* = 5.1, 1.6 Hz, 1H), 4.33 (s, 1H), 3.38 – 3.35 (m, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 2.30 – 2.19 (m, 1H), 1.83 – 1.68 (m, 2H), 1.68 – 1.56 (m, 4H), 1.56 – 1.41 (m, 2H), 1.26 – 1.20 (m, 2H), 1.13 (s, 6H). MS: 491 [M+H]⁺.



Example 488

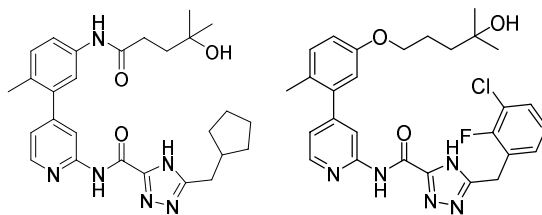
Example 489

[01257] Example 489: 5-benzyl-N-(4-(5-(4-hydroxy-4-methylvaleramido)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01258] The preparation was carried out in a similar manner to Example 487, except that in step 1, monomethyl succinate was used in place of 3-bromo-4-methylbenzoic acid, and 3-bromo-4-methylaniline was used in place of methyl 3-aminopropionate hydrochloride. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.97 (s, 1H), 9.86 (s, 1H), 8.42 (d, *J* = 5.3 Hz, 1H), 8.12 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.30 (m, 4H), 7.30 – 7.22 (m, 2H), 7.22 – 7.15 (m, 1H), 4.25 (s, 1H), 4.19 (s, 2H), 2.41 – 2.30 (m, 2H), 2.21 (s, 3H), 1.73 – 1.61 (m, 2H), 1.10 (s, 6H). MS: 499 [M+H]⁺.

[01259] Example 490: 5-(cyclopentylmethyl)-N-(4-(5-(4-hydroxy-4-methylvaleramido)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01260] The preparation was carried out in a similar manner to Example 487, except that in step 1, monomethyl succinate was used in place of 3-bromo-4-methyl benzoic acid, 3-bromo-4-methylaniline was used in place of methyl 3-aminopropionate hydrochloride, and in step 4, ethyl 5-(cyclopentylmethyl)-4H-1,2,4-triazole-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 9.98 (s, 1H), 9.83 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.14 (s, 1H), 7.63 – 7.51 (m, 2H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 5.2 Hz, 1H), 4.25 (s, 1H), 2.79 (d, *J* = 7.5 Hz, 2H), 2.41 – 2.32 (m, 2H), 2.32 – 2.24 (m, 1H), 2.22 (s, 3H), 1.79 – 1.44 (m, 8H), 1.25 – 1.19 (m, 2H), 1.10 (s, 6H). MS: 491 [M+H]⁺.



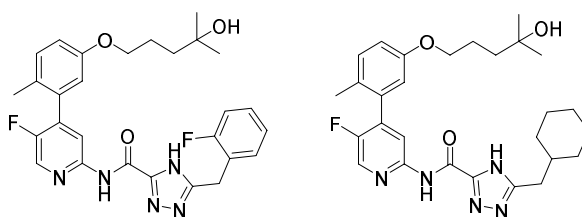
Example 490 Example 491

[01261] Example 491: 5-(3-chloro-2-fluorobenzyl)-N-(4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01262] The preparation was carried out in a similar manner to Example 160, except that in step 4, ethyl 5-(3-chloro-2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.73 (s, 1H), 9.92 (s, 1H), 8.41 (d, *J* = 5.0 Hz, 1H), 8.10 (s, 1H), 7.57 – 7.48 (m, 1H), 7.43 – 7.35 (m, 1H), 7.28 – 7.18 (m, 3H), 6.93 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 4.26 (s, 2H), 4.17 (s, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.19 (s, 3H), 1.82 – 1.65 (m, 2H), 1.54 – 1.42 (m, 2H), 1.09 (s, 6H). MS: 538 [M+H]⁺.

[01263] Example 492: N-(5-fluoro-4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01264] The preparation was carried out in a similar manner to Example 160, except that in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.70 (s, 1H), 10.09 (s, 1H), 8.47 (s, 1H), 8.06 (d, *J* = 5.6 Hz, 1H), 7.46 – 7.30 (m, 2H), 7.30 – 7.14 (m, 3H), 6.97 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.20 (s, 2H), 4.17 (s, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.09 (s, 3H), 1.81 – 1.67 (m, 2H), 1.52 – 1.41 (m, 2H), 1.09 (s, 6H). MS: 522 [M+H]⁺.



Example 492 Example 493

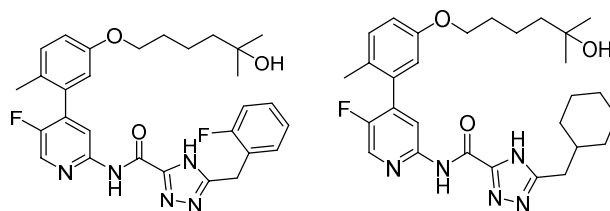
[01265] Example 493: 5-(cyclohexylmethyl)-N-(5-fluoro-4-(5-((4-hydroxy-4-methylpentyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01266] The preparation was carried out in a similar manner to Example 160, except that in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.36 (s, 1H), 10.00 (s, 1H), 8.48 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 4.17 (s, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.66 (d, *J* =

7.0 Hz, 2H), 2.10 (s, 3H), 1.82 – 1.57 (m, 8H), 1.52 – 1.41 (m, 2H), 1.24 – 1.13 (m, 3H), 1.09 (s, 6H), 1.04 – 0.91 (m, 2H). MS: 510 [M+H]⁺.

[01267] Example 494: N-(5-fluoro-4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01268] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.58 (s, 1H), 10.02 (s, 1H), 8.47 (s, 1H), 8.06 (d, *J* = 5.5 Hz, 1H), 7.46 – 7.30 (m, 2H), 7.30 – 7.15 (m, 3H), 6.97 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 4.21 (s, 2H), 4.09 (s, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.09 (s, 3H), 1.68 (t, *J* = 6.8 Hz, 2H), 1.52 – 1.30 (m, 4H), 1.06 (s, 6H). MS: 536 [M+H]⁺.



Example 494

Example 495

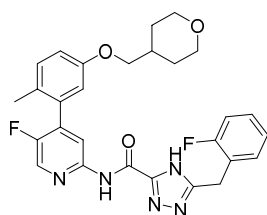
[01269] Example 495: 5-(cyclohexylmethyl)-N-(5-fluoro-4-(5-((5-hydroxyl-5-methylhexyl)oxy)-2-methylphenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01270] The preparation was carried out in a similar manner to Example 160, except that in step 1, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.34 (s, 1H), 9.99 (s, 1H), 8.48 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 4.09 (s, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.67 (d, *J* = 6.9 Hz, 2H), 2.10 (s, 3H), 1.79 – 1.57 (m, 8H), 1.47 – 1.39 (m, 3H), 1.24 – 1.10 (m, 4H), 1.06 (s, 6H), 1.02 – 0.90 (m, 2H). MS: 524 [M+H]⁺.

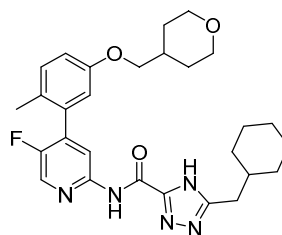
[01271] Example 496: N-(5-fluoro-4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01272] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, in step 2, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆)

δ 14.59 (s, 1H), 10.02 (s, 1H), 8.47 (s, 1H), 8.06 (d, $J = 5.4$ Hz, 1H), 7.44 – 7.29 (m, 2H), 7.29 – 7.14 (m, 3H), 6.98 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.86 (d, $J = 2.7$ Hz, 1H), 4.21 (s, 2H), 3.91 – 3.79 (m, 4H), 3.33 – 3.23 (m, 2H), 2.09 (s, 3H), 2.04 – 1.90 (m, 1H), 1.72 – 1.61 (m, 2H), 1.39 – 1.24 (m, 2H). MS: 520 $[M+H]^+$.



Example 496



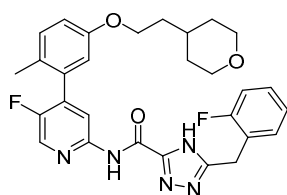
Example 497

[01273] Example 497: 5-(cyclohexylmethyl)-N-(5-fluoro-4-(2-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

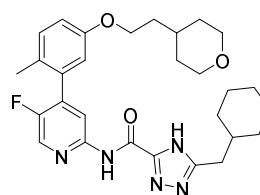
[01274] The preparation was carried out in a similar manner to Example 64, except that in step 1, (tetrahydro-2H-pyran-4-yl)methanol was used in place of 2-(tert-butoxy)ethan-1-ol, in step 2, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 3, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.35 (s, 1H), 10.00 (s, 1H), 8.48 (s, 1H), 8.09 (d, $J = 5.5$ Hz, 1H), 7.28 (d, $J = 8.5$ Hz, 1H), 6.99 (dd, $J = 8.4, 2.7$ Hz, 1H), 6.86 (d, $J = 2.7$ Hz, 1H), 3.92 – 3.78 (m, 4H), 3.32 – 3.24 (m, 2H), 2.66 (d, $J = 7.1$ Hz, 2H), 2.10 (s, 3H), 2.04 – 1.91 (m, 1H), 1.81 – 1.55 (m, 8H), 1.36 – 1.15 (m, 5H), 1.04 – 0.93 (m, 2H). MS: 508 $[M+H]^+$.

[01275] Example 498: N-(5-fluoro-4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01276] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ^1H NMR (400 MHz, DMSO- d_6) δ 14.66 (s, 1H), 10.09 (s, 1H), 8.47 (s, 1H), 8.06 (d, $J = 5.6$ Hz, 1H), 7.46 – 7.30 (m, 2H), 7.30 – 7.14 (m, 3H), 6.98 (dd, $J = 8.5, 2.7$ Hz, 1H), 6.86 (d, $J = 2.7$ Hz, 1H), 4.20 (s, 2H), 4.01 (t, $J = 6.3$ Hz, 2H), 3.81 (dd, $J = 11.6, 4.2$ Hz, 2H), 3.29 – 3.21 (m, 2H), 2.09 (s, 3H), 1.76 – 1.52 (m, 5H), 1.25 – 1.12 (m, 2H). MS: 534 $[M+H]^+$.



Example 498



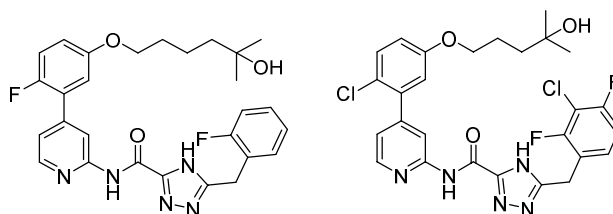
Example 499

[01277] Example 499: N-(5-fluoro-4-(2-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)phenyl)pyridin-2-yl)-5-(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01278] The preparation was carried out in a similar manner to Example 85, except that in step 1, 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol was used in place of 2-(2-methoxyethoxy)ethan-1-ol, in step 3, 5-fluoro-4-bromopyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 9.99 (s, 1H), 8.47 (s, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.87 (d, *J* = 2.7 Hz, 1H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.89 – 3.76 (m, 2H), 3.30 – 3.20 (m, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.10 (s, 3H), 1.80 – 1.55 (m, 11H), 1.30 – 1.13 (m, 5H), 1.04 – 0.92 (m, 2H). MS: 522 [M+H]⁺.

[01279] Example 500: N-(4-(2-fluoro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)pyridin-2-yl)-5-(2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01280] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-fluorophenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, and in step 4, ethyl 5-(2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.60 (s, 1H), 9.85 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.35 (s, 1H), 7.51 – 7.15 (m, 6H), 7.15 – 7.00 (m, 2H), 4.23 (s, 2H), 4.11 (s, 1H), 4.02 (t, *J* = 6.4 Hz, 2H), 1.75 – 1.64 (m, 2H), 1.52 – 1.37 (m, 4H), 1.07 (s, 6H). MS: 522 [M+H]⁺.



Example 500

Example 501

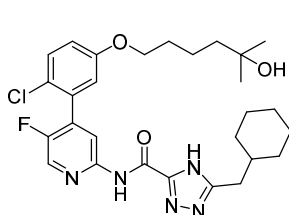
[01281] Example 501: 5-(3-chloro-2,4-difluorobenzyl)-N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide

[01282] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(3-chloro-2,4-difluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.72 (s, 1H), 9.98 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.21 (s, 1H), 7.57 – 7.44 (m, 2H), 7.38 – 7.25 (m, 2H), 7.06 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 4.26 (s, 2H), 4.18 (s, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.53 – 1.40 (m, 2H), 1.09 (s, 6H). MS: 576 [M+H]⁺.

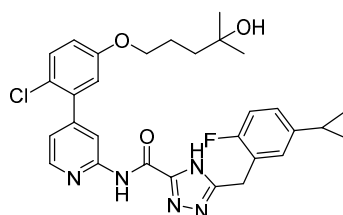
[01283] Example 502: N-(4-(2-chloro-5-((5-hydroxyl-5-methylhexyl)oxy)phenyl)-5-fluoropyridin-2-yl)-5-

(cyclohexylmethyl)-4H-1,2,4-triazole-3-carboxamide

[01284] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, methyl 5-bromopentanoate was used in place of methyl 4-bromobutanoate, in step 3, 4-bromo-5-fluoropyridin-2-amine was used in place of 4-bromopyridin-2-amine, and in step 4, ethyl 5-(cyclohexylmethyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 (s, 1H), 10.04 (s, 1H), 8.52 (d, *J* = 1.2 Hz, 1H), 8.16 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.17 – 7.05 (m, 2H), 4.09 (s, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.67 (d, *J* = 7.1 Hz, 2H), 1.82 – 1.57 (m, 8H), 1.51 – 1.33 (m, 4H), 1.28 – 1.10 (m, 3H), 1.06 (s, 6H), 1.04 – 0.88 (m, 2H). Ms: 544 [M+H]⁺.



Example 502

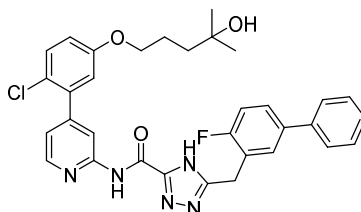


Example 503

[01285] Example 503: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-(5-cyclopropyl-2-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide

[01286] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-(5-cyclopropyl-2-fluorobenzyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 9.89 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 5.2 Hz, 1H), 7.17-6.95 (m, 5H), 4.22-4.11 (m, 3H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.95-1.85 (m, 1H), 1.82-1.69 (m, 2H), 1.53-1.41 (m, 2H), 1.09 (s, 6H), 0.97-0.88 (m, 2H), 0.68-0.57 (m, 2H). MS: 564 [M+H]⁺.

[01287] Example 504: N-(4-(2-chloro-5-((4-hydroxy-4-methylpentyl)oxy)phenyl)pyridin-2-yl)-5-((4-fluoro-[1,1'-biphenyl]-3-yl)methyl)-4H-1,2,4-triazole-3-carboxamide



[01288] The preparation was carried out in a similar manner to Example 160, except that in step 1, 3-bromo-4-chlorophenol was used in place of 3-bromo-4-methylphenol, and in step 4, ethyl 5-((4-fluoro-[1,1'-biphenyl]-3-yl)methyl)-4H-1,2,4-triazol-3-carboxylate was used in place of ethyl 5-benzyl-4H-1,2,4-triazol-3-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.70 (s, 1H), 9.94 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 8.21 (s, 1H), 7.82 – 7.68

(m, 1H), 7.68 – 7.56 (m, 3H), 7.56 – 7.41 (m, 3H), 7.41 – 7.22 (m, 3H), 7.14 – 6.89 (m, 2H), 4.29 (s, 2H), 4.17 (s, 1H), 4.00 (t, $J = 6.6$ Hz, 2H), 1.82 – 1.68 (m, 2H), 1.54 – 1.39 (m, 2H), 1.09 (s, 6H). MS: 600 $[M+H]^+$.

Assay example 1. Western Blot Determination of Inhibition of Compounds on RIPK1 Phosphorylation in HT29 Cells

[01289] Western blot was used to determine the effect of the test compounds on the phosphorylation of intracellular RIPK1 during the induction of programmed necrosis of HT29 cells, verifying the effect of compounds on RIPK1 phosphorylation, and initially estimating the IC_{50} range of compounds for RIPK1 phosphorylation.

[01290] I. Main assay reagents/instruments

Name	Item No.	Brand
McCoy's 5A	SH30200.01	Hyclone
BCA Protein concentration determination kit	P0012	Beyotime
HT29 cells	HTB-38	ATCC
Phospho-RIP (Ser166) (D1L3S) Rabbit mAb	65746s	CST
RIP (D94C ₁₂) XP Rabbit mAb	3493s	CST
Anti-rabbit IgG (H+L) (DyLight 680 Conjugate)	5366s	CST
Anti-rabbit IgG (H+L) (DyLight 800 4X PEG Conjugate)	5151s	CST
β -Actin(8H10D10)Mouse mAb	3700s	CST
Precision Plus Protein™ Dual Color Standards	1610374	Bio-Rad
10%Mini-PROTEAN® TGX Stain-Free™ Protein Gels	4568034	Bio-Rad
AT-406 (SM-406)	S2754	Selleck chem
Z-VAD-FMK	S7023	Selleck chem
Human TNF- α	300-01A-10	Peprtech
Electrophoresis power supply PowerPac™ basic electrophoresis power supply	1645050	Bio-Rad
Mini-PROTEAN® Tetra electrophoresis tank	1658004	Bio-Rad
Trans-Blot® Turbo™ Trans-Blot Turbo Transfer System	1704155	Bio-Rad
Odyssey CLXInfrared fluorescence scanning imaging system	CLX-1688	LI-COR

Table 2. Main reagents and instruments used in assay example 1

[01291] II. Experiment procedure

1. Cell collection and protein sample extraction

- a) HT29 cells in good condition were collected, resuspended in McCoy's 5A complete medium and counted, the cells were planted in a 12-well plate at a cell density of $2 \times 10^6/1$ mL/well, and placed in a 37 °C cell culture incubator overnight.

b) Z-VAD-FMK (at final concentration of 20 μ M) was added to the above 12-well plate, after 30 minutes, the inducer (where the final concentration of TNF- α is 20ng/mL, and the final concentration of AT-406 is 100nM), and test compounds of different concentrations were then added, and incubated in a cell incubator at 37°C for 7 hours.

5 c) Preparation of complete lysate: A tube of aliquoted RIPA Lysis Buffer was taken, PMSF, Phosphatase Inhibitor, and Roche Protease Inhibitor were added after thawing (volume ratio: PMSF: RIPA=1:100; phosphatase inhibitor: RIPA=1:100; Roche protease inhibitor: RIPA=4:100), and placed on ice for later use.

10 d) The cell culture medium supernatant was discarded, washed twice with PBS, 100 μ L of the prepared complete cell lysate was added to each well, the cells were lysed on ice for 15 minutes, and shaken intermittently during the lysis;

e) After the lysis is complete, the lysate was transferred to a 1.5 mL centrifuge tube labeled in advance and centrifuged at 4°C and 14000 rpm for 20 minutes;

f) The supernatant was taken, transferred to a labeled 600 μ L centrifuge tube, and placed on ice.

15 g) The BCA kit was used to detect and the protein concentration was calculated;

2. The protein sample was mixed well with 4 $\times$ loading buffer and heated in a metal bath at 100°C for 5 min to fully denature the protein and placed on ice to cool down.

3. 40-50 μ g of protein sample to be determined or pre-stained two-color protein molecular weight standard were added to each well.

20 4. Electrophoresis was carried out at a voltage of 100 V under constant voltage conditions. After 30 minutes of electrophoresis, the voltage was increased to 120V, and the electrophoresis time was set to 120 minutes or appropriately extended. The electrophoresis could be stopped when the pre-stained two-color protein molecular weight standard band on the gel run out of the lower edge of the lane.

25 5. After the electrophoresis was over, the gel holder was removed, the short glass plate was gently pried up with the peeling spatula, the upper layer of concentrated gel was discarded, the separation gel was gently peeled off and placed in the transfer buffer;

6. A moderately sized NC membrane was cut according to the size of the gel, soaked with pure water, and then immersed in the pre-cooled transfer buffer; at the same time the filter paper was soaked in the transfer buffer solution.

30 7. The transfer cartridge was assembled in the order of filter paper, NC membrane, gel, and filter paper, then

the transfer cartridge was put into the Trans-Blot® Turbo, and the "Standard SD" program that comes with the instrument was called to complete the transfer.

8. The protein-loaden NC membrane was rinsed with deionized water, blocking solution was added to immerse the membrane, and blocked with slow shaking on a shaker at room temperature for 1 hour.

9. After the blocking was completed, the NC membrane was put into the antibody incubation box, the primary antibody was diluted at a ratio of 1:1000, after adding to the antibody incubation box, the box was incubated on a shaker at room temperature for 1 hour.

10. After the incubation was completed, the membrane was washed with TBST for 3 times, 10 minutes each time.

11. The secondary antibody was selected according to the source of the primary antibody, the secondary antibody was diluted with the diluent of the secondary antibody at a ratio of 1:10000~1:15000, and added into the antibody incubation box and the membrane was immersed therein, and incubated on a shaker at room temperature for 1 hour.

12. After the incubation was completed, the membrane was washed with TBST for 3 times, with 10 minutes each time.

13. The membrane was rinsed once with pure water, Odyssey CLX infrared fluorescence scanning imaging system was used to scan the membrane to afford an image, and the fluorescence intensity value was read at the same time.

[01292] III. Typical assay results and analysis

[01293] The inhibition rate of compounds on protein phosphorylation was calculated according to the fluorescence intensity value, and the calculation method is as follows:

[01294] Inhibition rate (%) = $(1-A/B) \times 100\%$

[01295] A: Fluorescence intensity value after treatment with IL-2 and compound

[01296] B: Fluorescence intensity value after treatment with IL-2

[01297] The compound of Example 2 was tested by the above method, and the results were shown in Figure 1 and Figure 2. Figure 1 is a Western Blot picture of the inhibition of RIPK1 phosphorylation by the compound of different concentrations. Figure 2 is a quantitative calculation of the inhibition rate of RIPK1 phosphorylation based on the gray value of the band in the above picture. Therefore, it can be shown that the compound of Example 2 directly inhibit the phosphorylation activation of RIPK1.

Assay example 2. Assay method for compounds inhibiting cell necrosis (CCK8 method)

[01298] In this assay example 2, under the condition of inducing programmed cell necrosis, different concentrations of the test compounds were added to test the IC50 of the rescue effect of the test compounds on the programmed necrosis.

[01299] I. Main assay reagents, instruments and materials

Name	Brand	Item No./Name
DMSO	Sigma	D2650 (100 mL)
Trypan blue	GENIA Stock	G8003
McCOY's 5A	Hylcone	SH30200.01
CCK-8	Tongren Chemistry	CK04
GSK2982772	Selleckchem	S8484
AT-406	Selleckchem	S2754
Z-VAD-FMK	Selleckchem	S7023
TNF- α	PeptoTech	300-01A
HT29	ATCC	HTB-38
Multi-function plate reader	PerkinElmer	Envision

Table 3. Main reagents and instruments used in Assay Example 2

[01300] Compounds: Dissolved in DMSO to make a 10 mM solution;

[01301] TNF- α : The initial concentration was 100 μ g/mL;

[01302] Z-VAD-FMK: Dissolved in DMSO to make a 10 mM solution;

[01303] AT-406: Dissolved in DMSO to make a 10 mM solution.

[01304] II. Experimental steps

- 1) Compound dilution: All test compounds were dissolved in DMSO to prepare a 10 mM stock solution, and the first concentration gradient dilution of the test compounds was completed in DMSO. The gradient dilution factor was 4 times and 9 concentration gradients were made; A 40-fold overall dilution of all compounds was completed in the cell culture medium, and the resulting compound was 10 $\times$ compound, which will be added to the wells of the 96-well plate containing cells, so that the final cell culture medium was 1 $\times$ the designed final concentration.

The general drug design is 9 concentration gradients, of which the highest final concentration is 25000 nM, the lowest concentration after 4-fold dilution of 9 concentrations is 0.38 nM, and the final concentration of DMSO in all wells is 0.25%. The compound dilution process is shown in

Figure 3.

- 2) HT 29 cells in good growth condition were selected, trypsinized, the cells was collected by centrifugation, resuspended in McCoy's 5A complete medium (containing 10% FBS) and counted, and the number of cells and survival rate were recorded.
- 3) Cells were inoculated to the 60 wells in the middle of the 96-well culture plate at a density of 12000 cells/ 80 μ L/well, surrounding wells were filled with sterile water, and incubated overnight.
- 4) 10 μ L of the 10 $\times$ compound diluted with the medium was added to the assay wells, 10 μ L of McCoy's 5A complete medium containing 2.5% DMSO was added to the inducer-free wells and the control wells, mixed and shaken, and incubated for 30 minutes.
- 5) Then 10 μ L of inducer mixture (TNF- α , AT-406, Z-VAD-FMK with the final concentration of 20 ng/mL, 1 μ M, 20 μ M) was added into the assay wells and control wells. 10 μ L McCoy's 5A complete medium was added to wells without inducer. Cells were cultured in an incubator with 5% CO₂, at 37°C.
- 6) After culturing for 16-20 hours, 10 μ L of CCK-8 reagent was added to each well, and incubated for about 2 hours;
- 7) The OD value was read at 450 nm on the multi-function plate reader.
- 8) Data processing: Inhibition rate of necrosis (%) = 100* (X-B) / (A-B)

A: The OD values of the wells without inducer (containing cells, CCK-8, without compound and inducer);

X: OD values of assay wells (containing cells, CCK-8, compound, inducer);

B: OD values of control wells (containing cells, CCK-8, inducer, without compound).

Then the value were imported into Graphpad Prism5 software for curve fitting and the IC₅₀ values were calculated.

[01305] Table 4 lists the determination results of some compounds of the present disclosure in inhibiting HT29 cell necrosis, wherein A represents IC₅₀ is less than or equal to 100 nM, B represents IC₅₀ is greater than 100 nM but less than or equal to 1000 nM, C represents IC₅₀ is greater than 1000 nM but less than or equal to 10000 nM, D represents IC₅₀ is greater than 10000 nM.

Table 4. the determination results of some compounds of the present disclosure in inhibiting necrosis of HT29 cells

Example No.	HT29 IC ₅₀ (nM)	Example No.	HT29 IC ₅₀ (nM)
1	C	101	B

2	B	102	B
3	C	103	B
4	C	104	C
5	D	105	D
6	C	106	C
7	B	107	C
8	C	108	C
9	D	109	C
10	C	110	D
11	C	111	A
12	B	112	C
13	C	113	D
14	C	114	B
15	C	115	B
16	C	116	B
17	D	117	A
18	C	118	A
19	C	119	A
20	B	120	B
21	C	121	A
22	C	122	A
23	D	123	A
24	B	124	C
25	C	125	B
26	B	126	C
27	C	127	NT
28	C	128	A
29	D	129	B
30	D	130	D
31	D	131	A
32	D	132	B
33	B	133	A
34	B	134	B
35	A	135	A
36	B	136	A
37	B	137	A
38	C	138	A
39	C	139	D
40	C	140	A
41	D	141	A
42	C	142	B
43	C	143	B
44	NT	144	A
45	B	145	A
46	C	146	C

47	D	147	A
48	D	148	A
49	C	149	A
50	C	150	A
51	C	151	A
52	D	152	A
53	D	153	A
54	D	154	A
55	B	155	B
56	B	156	B
57	B	157	B
58	B	158	C
59	A	159	A
60	D	160	A
61	C	161	B
62	D	162	B
63	C	163	A
64	A	164	A
65	A	165	A
66	A	166	A
67	A	167	A
68	B	168	B
69	A	169	A
70	A	170	B
71	A	171	B
72	A	172	A
73	A	173	A
74	B	174	B
75	A	175	A
76	D	176	A
77	A	177	A
78	A	178	A
79	A	179	A
80	A	180	A
81	A	181	C
82	B	182	B
83	A	183	A
84	A	184	A
85	A	185	A
86	A	186	B
87	A	187	A
88	A	188	A
89	A	189	A
90	A	190	B
91	A	191	B

92	B	192	A
93	C	193	A
94	C	194	A
95	B	195	A
96	B	196	D
97	B	197	D
98	B	198	B
99	B	199	C
100	B	200	A
201	A	353	A
202	A	354	B
203	A	355	B
204	A	356	A
205	B	357	A
206	B	358	D
207	B	359	A
208	B	360	A
209	B	361	A
210	B	362	A
211	B	363	A
212	B	364	A
213	C	365	A
214	A	366	A
215	A	367	A
216	A	368	A
217	B	369	A
218	A	370	A
219	A	371	A
220	A	372	A
221	B	373	A
222	A	374	A
223	A	375	A
224	A	376	A
225	A	377	A
226	A	378	A
227	A	379	B
228	B	380	A
229	B	381	A
230	B	382	A
231	B	383	A
232	B	384	A
233	C	385	A
234	A	386	A
235	A	387	A
236	A	388	A

237	A	389	A
238	A	390	A
239	A	391	A
240	B	392	A
241	B	393	A
242	A	394	A
243	A	395	A
244	A	396	A
245	A	397	A
246	B	398	A
247	B	399	A
248	B	400	A
249	B	401	A
250	A	402	A
251	A	403	A
252	A	404	A
253	B	405	A
254	B	406	A
255	A	407	D
256	A	408	D
257	A	409	A
258	A	410	A
259	A	411	B
260	A	412	B
261	A	413	B
262	A	414	B
263	A	415	A
264	A	416	A
265	B	417	B
266	A	418	B
267	A	419	A
268	A	420	B
269	A	421	B
270	A	422	A
271	A	423	A
272	A	424	B
273	A	425	B
274	A	426	B
275	A	427	B
276	A	428	A
277	A	429	A
278	A	430	B
279	A	431	B
280	A	432	A
281	A	433	A

282	A	434	A
283	A	435	A
284	A	436	A
285	A	437	B
286	A	438	B
287	A	439	A
288	A	440	A
289	A	441	A
290	A	442	A
291	A	443	A
292	A	444	A
293	A	445	A
294	A	446	A
295	A	447	A
296	A	448	A
297	A	449	B
298	A	450	A
299	A	451	A
300	A	452	A
301	A	453	A
302	A	454	A
303	A	455	A
304	A	456	A
305	A	457	A
306	A	458	A
307	A	459	A
308	A	460	A
309	A	461	A
310	A	462	A
311	B	463	A
312	B	464	A
313	B	465	A
314	B	466	A
315	B	467	A
316	B	468	A
317	A	469	A
318	A	470	A
319	A	471	A
320	B	472	A
321	B	473	A
322	B	474	B
323	B	475	A
324	B	476	B
325	B	477	C
326	B	478	B

327	A	479	B
328	A	480	A
329	B	481	B
330	B	482	A
331	C	483	B
332	C	484	A
333	B	485	B
334	B	486	A
335	C	487	B
336	C	488	A
337	A	489	B
338	A	490	A
339	B	491	B
340	B	492	A
341	B	493	A
342	B	494	A
343	C	495	A
344	B	496	A
345	B	497	A
346	B	498	A
347	B	499	A
348	C	500	B
349	D	501	B
350	B	502	A
351	B	503	C
352	B	504	B

[01306] The biological data provided by the present disclosure shows that the compounds of the present disclosure are beneficial for the treatment or prevention of diseases caused by abnormal RIP1 kinase. Therefore, the compounds of the present disclosure are beneficial to the treatment of diseases related to RIP1 including ocular fundus disease, xerophthalmia, psoriasis, leucoderma, dermatitis, alopecia areata, rheumatoid arthritis, colitis, multiple sclerosis, systemic lupus erythematosus, Crohn's disease, atherosclerosis, pulmonary fibrosis, liver fibrosis, myelofibrosis, non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, ovarian cancer, cervical cancer, colorectal cancer, melanoma, endometrial cancer, prostate cancer, bladder cancer, leukemia, gastric cancer, liver cancer, gastrointestinal stromal tumor, thyroid cancer, chronic myeloid leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma, nasopharyngeal cancer, esophageal cancer, brain tumor, B-cell and T-cell lymphoma, lymphoma, multiple myeloma, biliary cancer and sarcoma, cholangiocarcinoma, inflammatory bowel disease, ulcerative colitis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, spondyloarthritis, gout, SoJIA, Sjogren's syndrome, systemic scleroderma, antiphospholipid syndrome, vasculitis, osteoarthritis, non-alcoholic steatohepatitis, alcoholic steatohepatitis, autoimmune hepatitis, autoimmune hepatobiliary disease, primary

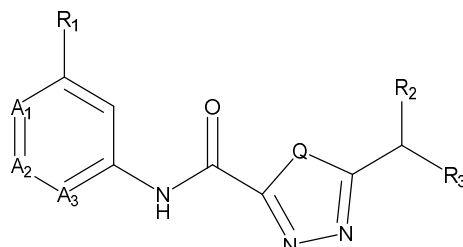
sclerosing cholangitis, nephritis, celiac disease, autoimmune ITP, transplant rejection, ischemia-reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial infarction, Huntington's disease, Alzheimer's disease, Parkinson's disease, allergic diseases, asthma, atopic dermatitis, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converzyme-related fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor related periodic syndrome and periodontitis. The compounds of the present disclosure can be used as monotherapy or combination therapy, and can be used in combination with multiple compounds of the present disclosure or in combination with other drugs that are not included in the present disclosure.

[01307] The above descriptions are only the preferred embodiments of the present disclosure and are not intended to limit the present disclosure. Any modification, equivalent replacement and improvement made within the spirit and principle of the present disclosure shall be included in the protection scope of the present disclosure.

Claims

WHAT IS CLAIMED IS:

1. A compound of formula (I), or the pharmaceutically acceptable salts, the diastereomers, the enantiomers or the solvates thereof,



formula (I)

in formula (I),

Q is NH, O or S;

A₁, A₂, and A₃ are each independently selected from N or CR₄ and at least one of A₁, A₂, and A₃ is N, R₄ is

H, F, Cl or methyl;

R₁ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

or 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

or aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -SO₂-R₅, -SO-R₅, -CO-R₅, -CONH-R₅, -NHCO-R₅, -R'-COO-R'', -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl and/or C₁-C₆ alkoxy, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, and -O-R₆,

R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group

substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

R' is C₂-C₆ alkenylene, or C₁-C₆ alkylene,

R'' is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

R₂ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

or C₇-C₁₂ bridged cyclol, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

or C₁-C₁₀ alkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, cyano, -CONH₂, C₃-C₈ cycloalkyl, and -NR^cR^d,

or -(CH₂)_n-R^e, wherein R^e is aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, C₃-C₆ cycloalkyl, phenyl, naphthyl, C₂-C₆ alkynyl, C₂-C₆ alkenyl, and -NR^cR^d, wherein n is an integer from 0 to 3,

or -(CH₂)_m-R^f, wherein R^f is 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d, m is an integer from 0 to 3,

R^e and R^d are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

R₃ is hydrogen, C₁-C₃ alkyl, hydroxyl, halogen, trifluoromethyl, or cyano;

the 4- to 8-membered heteroalicyclic group mentioned above is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

the aryl group mentioned above is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring, the heteroaryl is a monocyclic or bicyclic group having 5 to 10 ring atoms and containing 1 to 3 heteroatoms selected from N, O, or S as ring atoms.

2. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to claim 1, wherein, Q is NH, O or S;

A₁, A₂, and A₃ are each independently selected from N or CR₄ and at least one of A₁, A₂, and A₃ is N, R₄ is H, F, Cl or methyl;

R₁ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

or 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^aR^b,

or aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -SO₂-R₅, -SO-R₅, -CO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, and -O-R₆,

R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

R₂ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group

consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

or C₇-C₁₂ bridged cyclyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d,

or C₁-C₁₀ alkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, cyano, -CONH₂, C₃-C₈ cycloalkyl, and -NR^cR^d,

or -(CH₂)_nR^e, wherein R^e is aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, C₂-C₆ alkynyl, C₂-C₆ alkenyl, and -NR^cR^d, wherein n is an integer from 0 to 3,

or -(CH₂)_mR^f, wherein R^f is 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₃ acyl, hydroxyl, halogen, trifluoromethyl, cyano, -CONH₂, oxo (=O) and -NR^cR^d, m is an integer from 0 to 3,

R^c and R^d are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

R₃ is hydrogen, C₁-C₃ alkyl, hydroxyl, halogen, trifluoromethyl, or cyano;

the 4- to 8-membered heteroalicyclic group mentioned above is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms,

the aryl group mentioned above is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring, the heteroaryl is a monocyclic or bicyclic group having 5 to 10 ring atoms and containing 1 to 3 heteroatoms selected from N, O, or S as ring atoms.

3. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to claim 1 or 2, wherein, A₃ is N, A₁, and A₂ are each independently selected from N or CR₄, R₄ is H, F, Cl or methyl.

4. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to any one of claims 1-3, wherein, Q is NH.

5. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to any one of claims 1 to 4, wherein, R₁ is C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or aryl or heteroaryl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio,

-CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, and -O-R₆,

R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -CO-R₅, -SO₂-R₅, -SO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, or C₁-C₆ alkylthio,

R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

the aryl group mentioned above is phenyl, naphthyl, , , the heteroaryl group is pyrrolyl, furyl, pyridyl, thienyl, imidazolyl, thiazolyl, isothiazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolinyl, indolizynyl, isoxazolyl, 1,5-naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, oxazolyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl,

, , , , , , the 4- to 8-membered heteroalicyclic group mentioned above is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms.

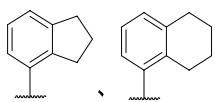
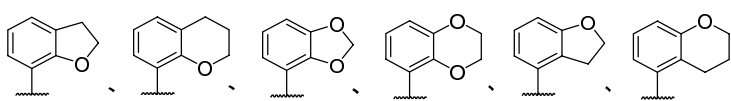
6. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to claim 5, wherein, R₁ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-3-yl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or aryl or heteroaryl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano,

hydroxyl, C₁-C₆ alkylthio, -SO₂-R₅, -SO-R₅, -CO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, and -O-R₆,

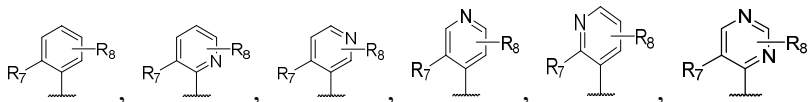
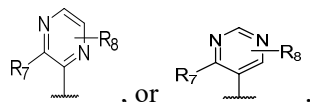
R₅ is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

the aryl group mentioned is phenyl, , the heteroaryl group is pyrazolyl, pyridyl, , the 4- to 8-membered heteroalicyclic group mentioned is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms.

7. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof

according to claim 5, wherein, R₁ is , , or

R₇ is hydrogen, C₁-C₄ alkyl, C₁-C₃ alkoxy, halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, C₂-C₄ alkynyl, C₂-C₄ alkenyl, C₃-C₄ cycloalkyl, or C₁-C₃ acyl;

R₈ is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-

C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O-R₆,

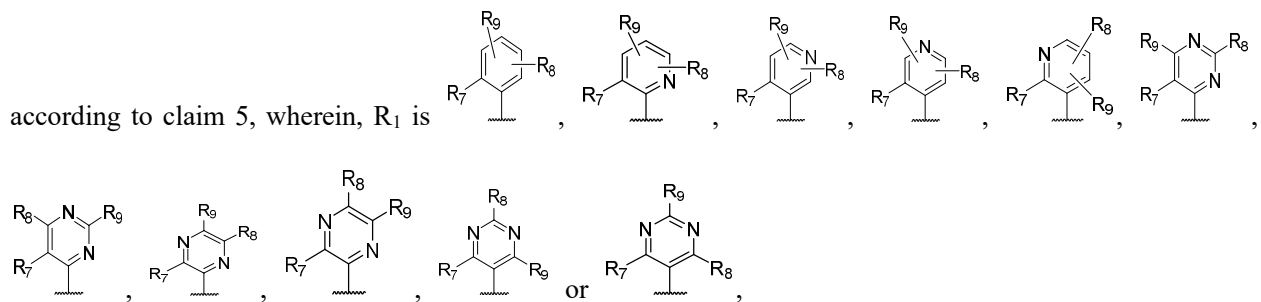
R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, C₁-C₆ alkylthio,

R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

the 4- to 8-membered heteroalicyclic group mentioned above is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms.

8. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof



R₇ is hydrogen, C₁-C₄ alkyl, C₁-C₃ alkoxy, halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, C₂-C₄ alkynyl, C₂-C₄ alkenyl, C₃-C₄ cycloalkyl, or C₁-C₃ acyl;

R₈ is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O-R₆,

R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, or C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is

unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy, 4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

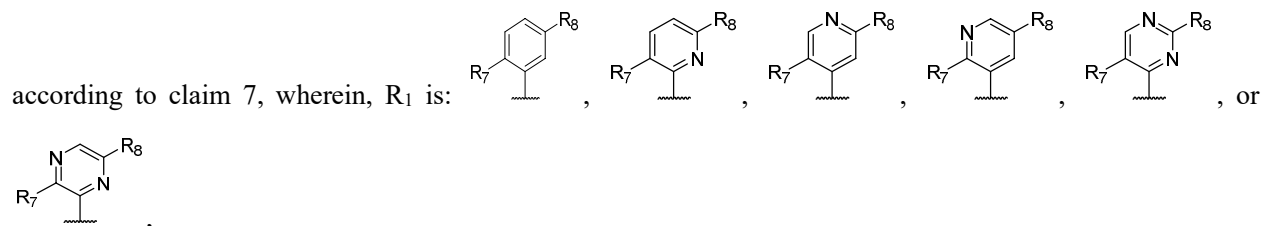
R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

R₉ is hydrogen, C₁-C₄ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, C₂-C₄ alkynyl, C₂-C₄ alkenyl, C₃-C₄ Cycloalkyl, or C₁-C₃ acyl;

the 4- to 8-membered heteroalicyclic group mentioned above is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms.

9. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof

according to claim 7, wherein, R₁ is:



R₇ is hydrogen, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, fluorine, chlorine, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, ethynyl, propynyl, vinyl, propenyl, cyclopropyl, cyclobutyl, formyl, or acetyl;

R₈ is hydrogen, C₁-C₁₀ alkyl, halogen, C₃-C₈ cycloalkyl, halogenated C₁-C₁₀ alkyl, cyano, hydroxyl, C₁-C₆ alkylthio, -CO-R₅, -SO₂-R₅, -SO-R₅, -CONH-R₅, -NR^aR^b, 4- to 8-membered heteroalicyclic group, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₃ alkoxy C₁-C₆ alkylthio, C₁-C₁₀ alkyl substituted with hydroxyl, C₁-C₆ alkoxy C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, (C₃-C₈ cycloalkyl)-O-(C₁-C₆ alkyl), C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, or -O-R₆,

R₅ is hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group,

R₆ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl substituted with 1 to 3 substituents selected from hydroxyl, C₁-C₆ alkoxy, cyano, -NR^aR^b, C₃-C₈ cycloalkyloxy, -CONH-R₅, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl substituted with hydroxyl and/or C₁-C₄ alkyl, carboxylic, halogen, halogenated C₁-C₆ alkoxy, -SO₂-R₅, -SO-R₅, -CO-R₅, C₂-C₆ alkynyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy C₁-C₆ alkoxy,

4- to 8-membered heteroalicyclic group, 4- to 8-membered heteroalicyclic group substituted with oxo, 4- to 8-membered heteroalicyclic group substituted with hydroxyl and/or C₁-C₄ alkyl, and C₁-C₆ alkylthio,

R^a and R^b are each independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl substituted with C₁-C₆ alkoxy, C₁-C₆ alkyl substituted with hydroxyl, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₁-C₆ alkyl substituted with 4- to 8-membered heteroalicyclic group, C₁-C₆ alkyl substituted with C₁-C₃ alkylthio, or C₁-C₆ alkyl substituted with substituted amino or unsubstituted amino, wherein the substituted amino is substituted with mono- or di-C₁-C₃ alkyl;

the 4- to 8-membered heteroalicyclic group mentioned above is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms.

10. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to any one of claims 1 to 9, wherein, R₂ is C₃-C₈ cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, oxo (=O), amino, dimethylamino, and diethylamino,

or C₇-C₁₀ bridged cyclyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, oxo (=O), amino, dimethylamino, and diethylamino,

or C₁-C₁₀ alkyl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, cyano, -CONH₂, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, amino, dimethylamino, and diethylamino,

or -(CH₂)_n-R^e, wherein R^e is aryl or heteroaryl, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, ethynyl, vinyl, amino, dimethylamino, and diethylamino, n is an integer from 0 to 3,

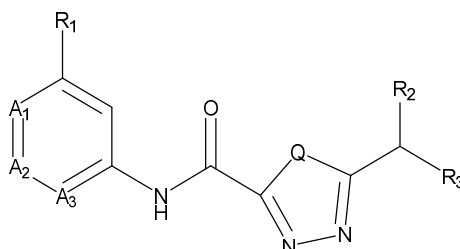
or -(CH₂)_m-R^f, wherein R^f is 4- to 8-membered heteroalicyclic group, which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylthio, ethylthio, propylthio, formyl, acetyl, hydroxyl, fluorine, chlorine, trifluoromethyl, cyano, -CONH₂, oxo (=O), amino, dimethylamino, and diethylamino, m is an integer from 0 to 3,

the 4- to 8-membered heteroalicyclic group mentioned above contains 1 to 2 atoms selected from N, O, or S as ring atoms,

the aryl group mentioned above is phenyl, and the heteroaryl group is pyridyl, pyrimidinyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl.

13. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to claim 1, wherein, R₃ is hydrogen, methyl, ethyl, hydroxyl, cyano, trifluoromethyl, fluorine, or chlorine.

14. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to claim 1,



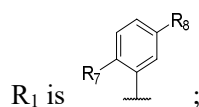
formula (I)

in formula (I),

Q is NH;

A₁, and A₂ are each CH;

A₃ is N;



R₁ is ;

R₇ is methyl, ethyl, propyl, isopropyl, fluorine, chlorine, trifluoromethyl, vinyl, or propenyl;

R₈ is cyano, C₁-C₃ alkoxy C₁-C₆ alkylthio, or -O-R₆;

R₅ is C₁-C₆ alkyl;

R₆ is 4- to 8-membered heteroalicyclic group, or C₁-C₁₀ alkyl which is substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, C₁-C₆ alkoxy, cyano, C₃-C₈ cycloalkyloxy, C₃-C₈ cycloalkyl, -SO₂-R₅, 4- to 8-membered heteroalicyclic group, and C₁-C₆ alkylthio;

R₂ is -(CH₂)_n-R^e, wherein R^e is aryl, which is unsubstituted or substituted with 1 substituent selected from the group consisting of halogen, and cyano, wherein n is an integer from 0 to 3;

the 4- to 8-membered heteroalicyclic group mentioned above is a 4- to 8-membered heteroalicyclic group containing 1 to 2 atoms selected from N, O, or S as ring atoms;

the aryl group mentioned above is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring;

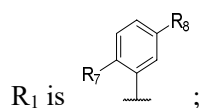
R₃ is hydrogen.

15. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to claim 14, wherein

Q is NH;

A₁, and A₂ are each CH;

A₃ is N;



R₇ is methyl, chlorine, or trifluoromethyl;

R₈ is -O-R₆;

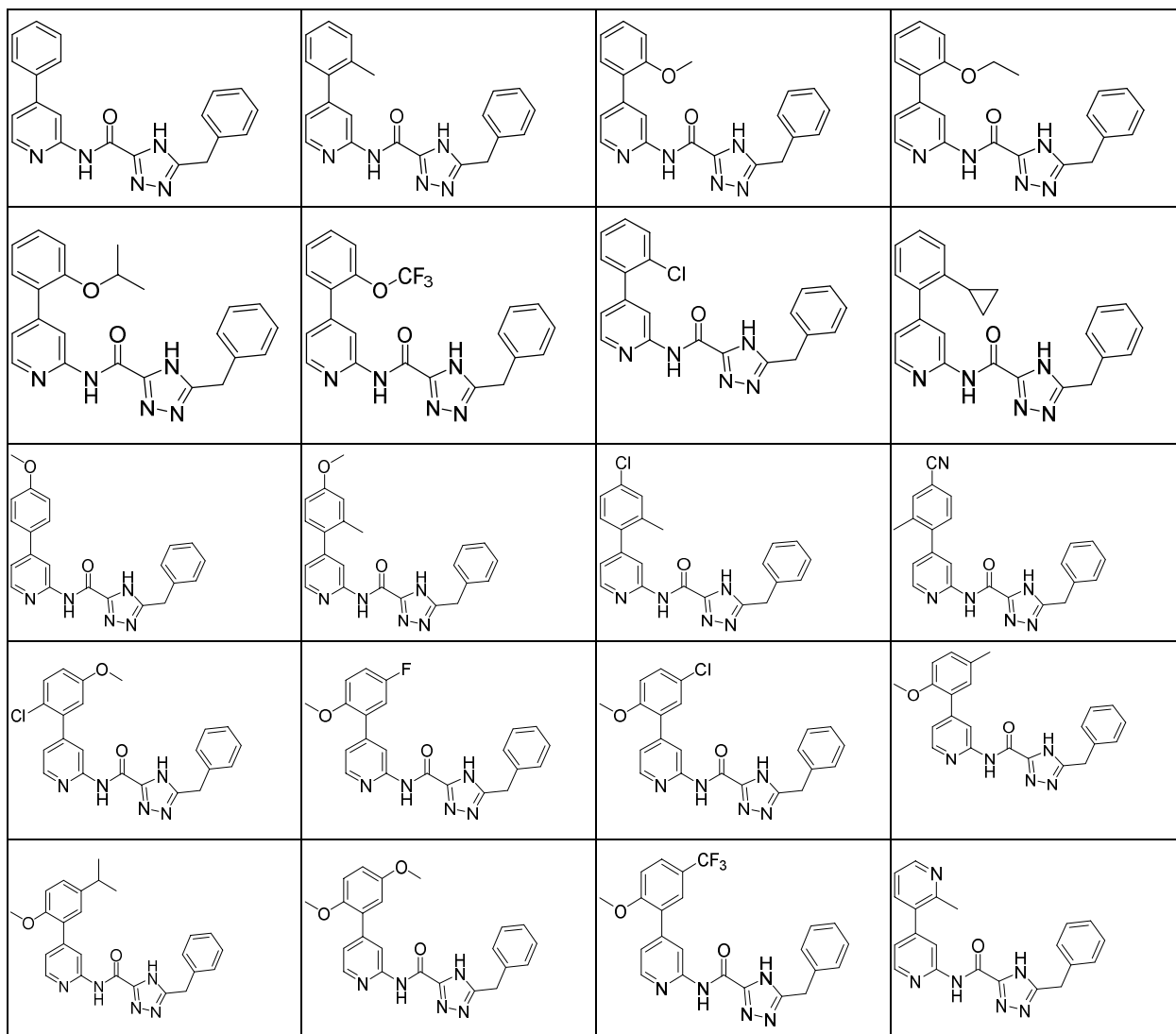
5 R₆ is C₁-C₁₀ alkyl which is substituted with 1 to 3 substituents selected from hydroxyl;

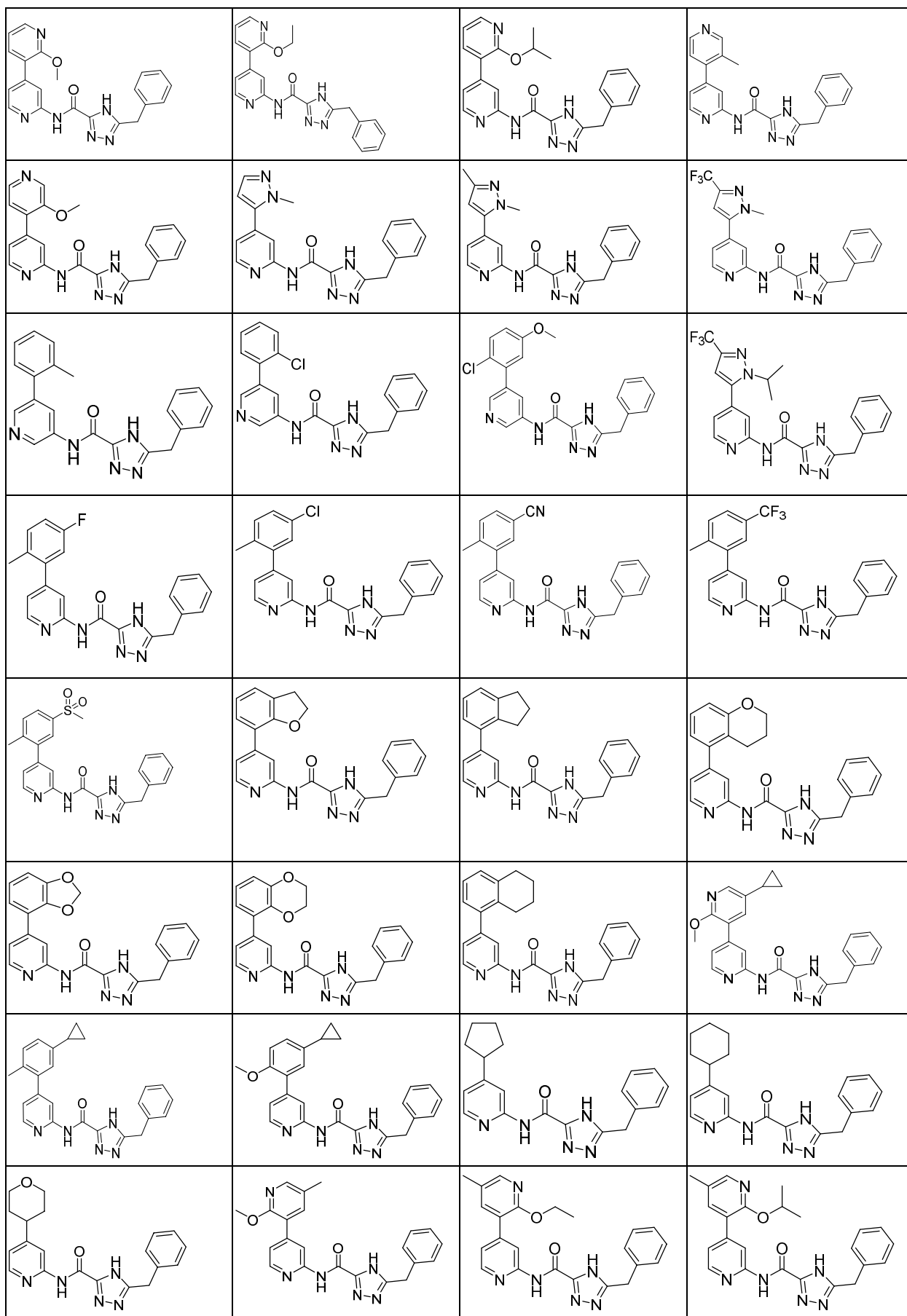
R₂ is -(CH₂)_n-R^e, wherein R^e is aryl, which is unsubstituted or substituted with 1 substituent selected from halogen, wherein n is an integer from 0;

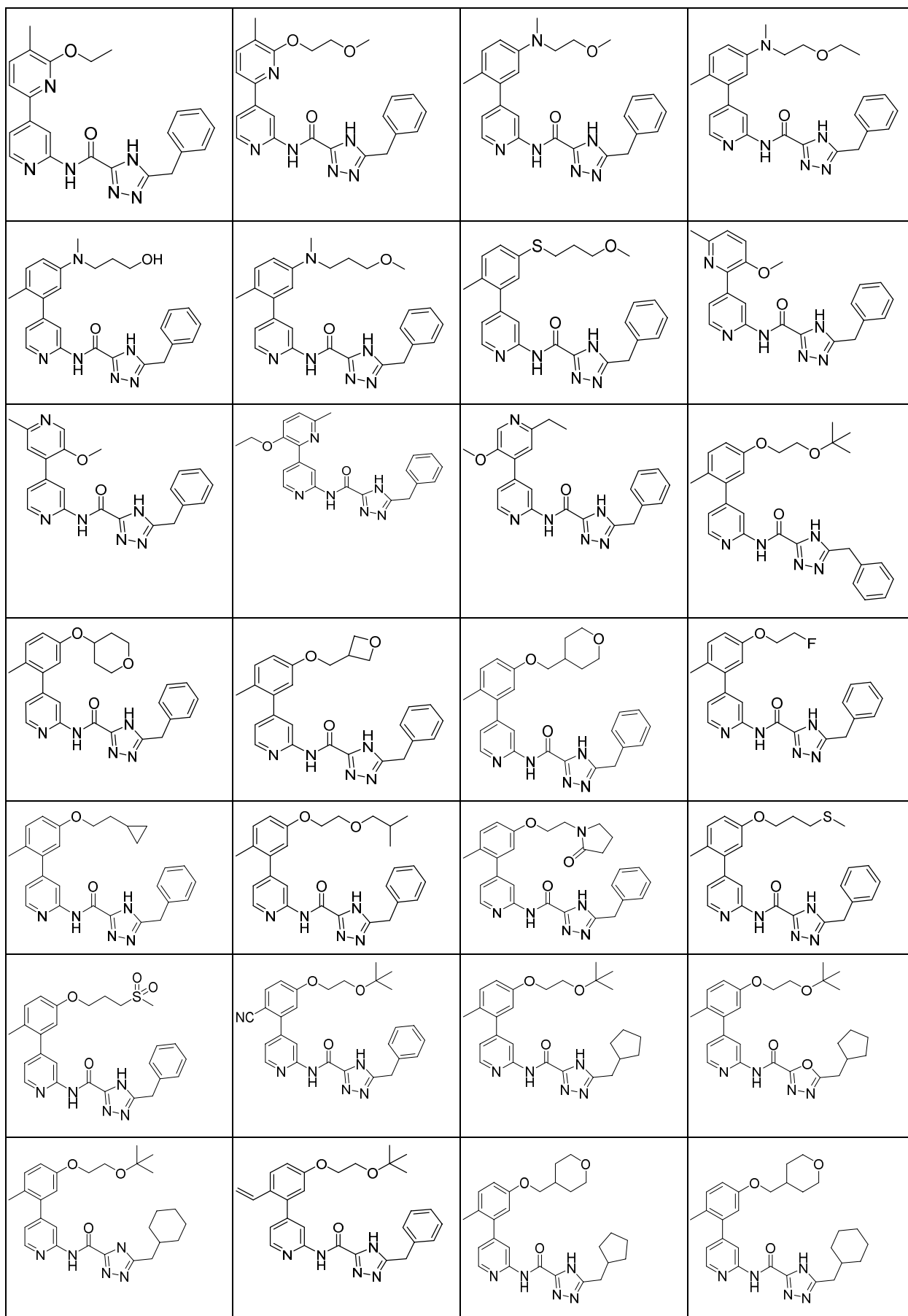
the aryl group mentioned above is a monocyclic or bicyclic group containing 6 to 12 carbon ring atoms and having at least one aromatic ring;

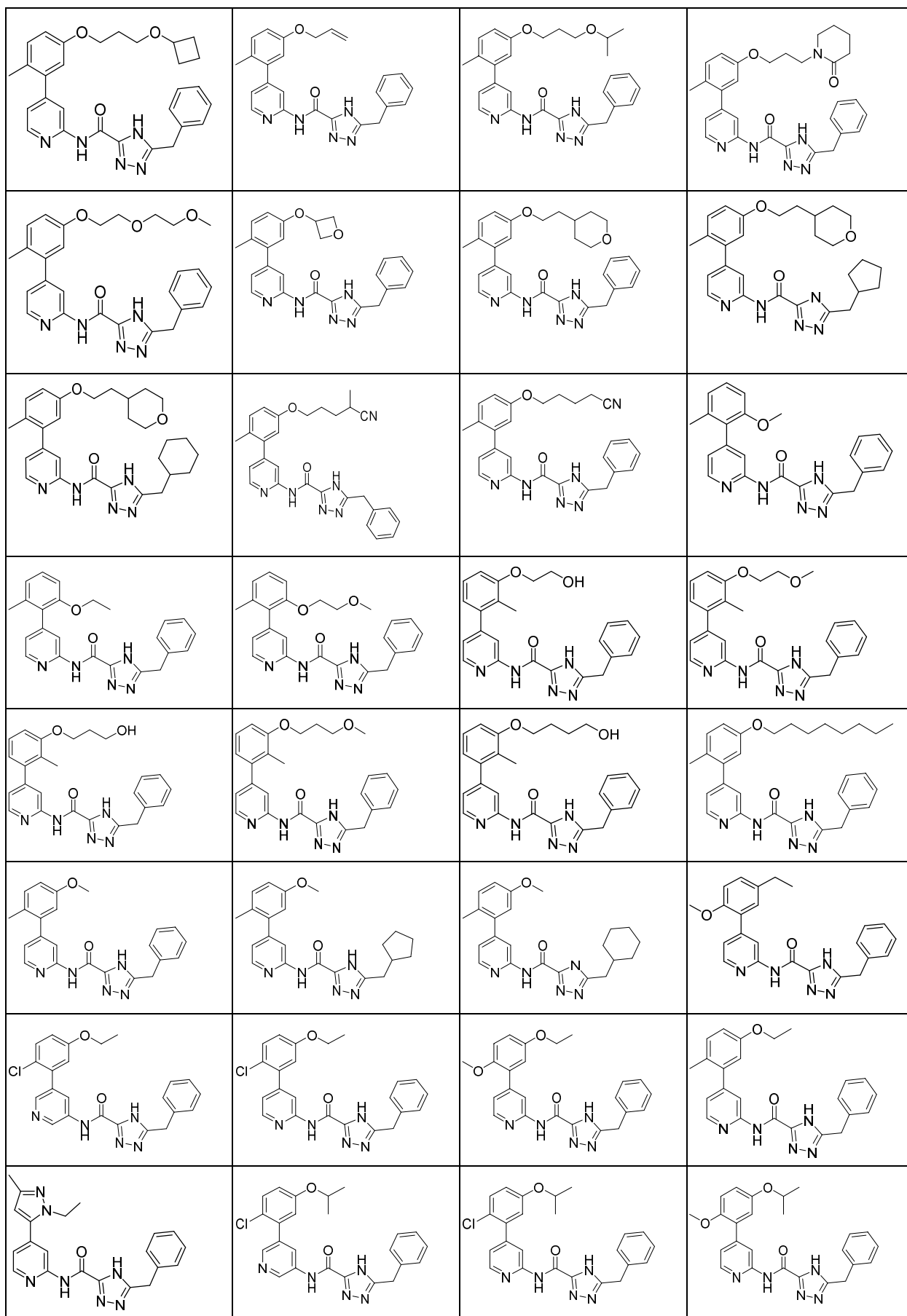
10 R₃ is hydrogen.

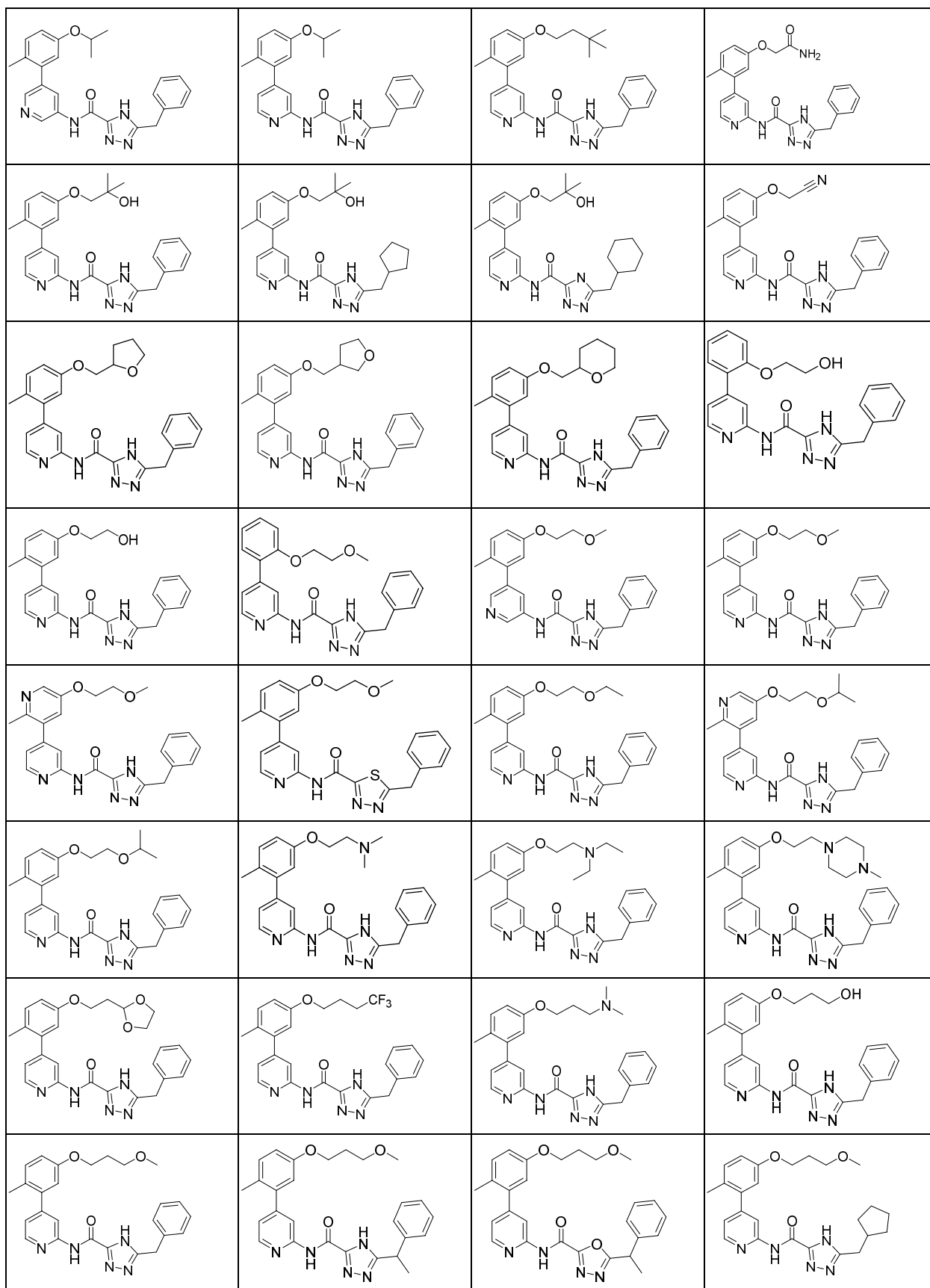
16. The compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to claim 1, wherein, the compound is selected from the following structures:

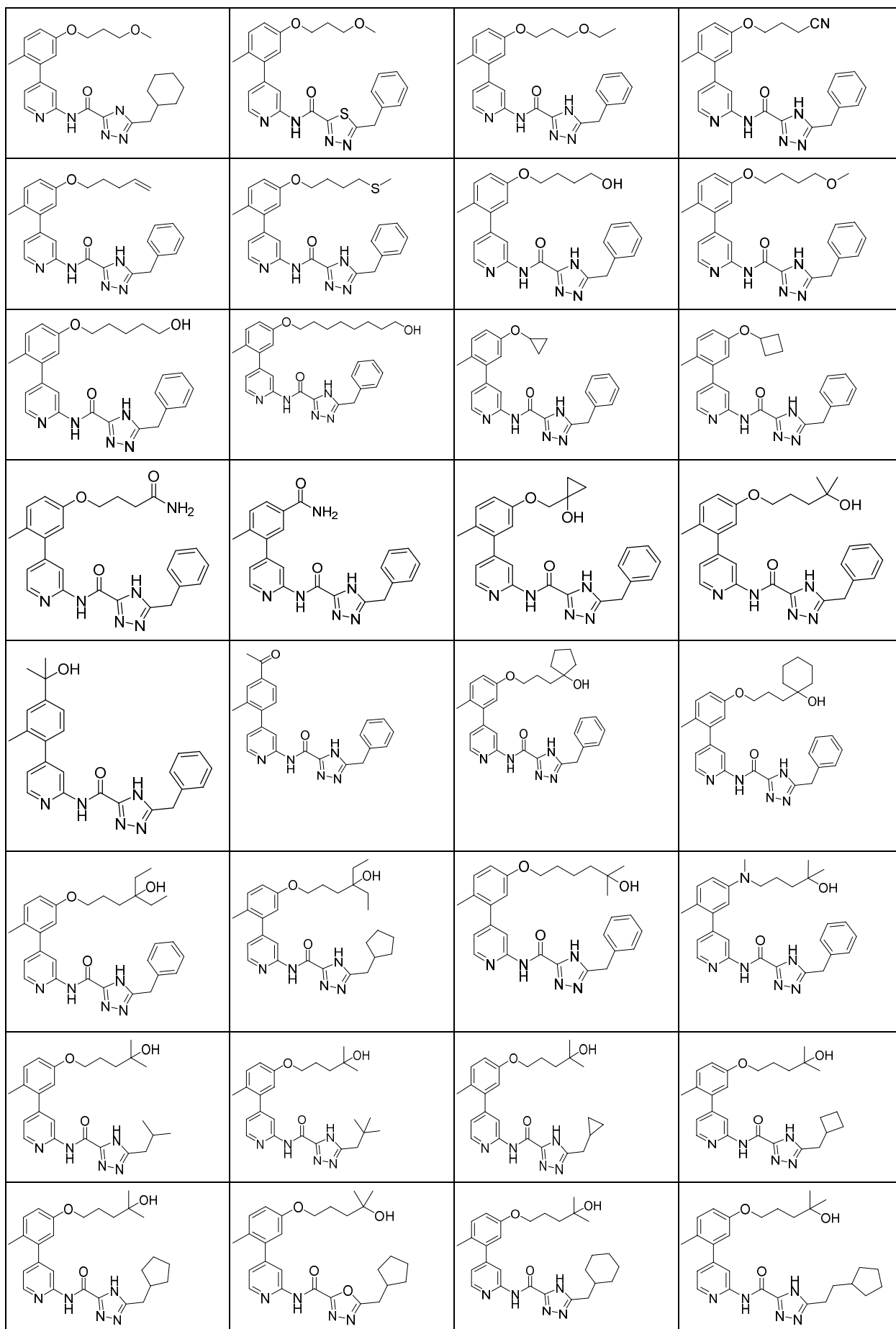


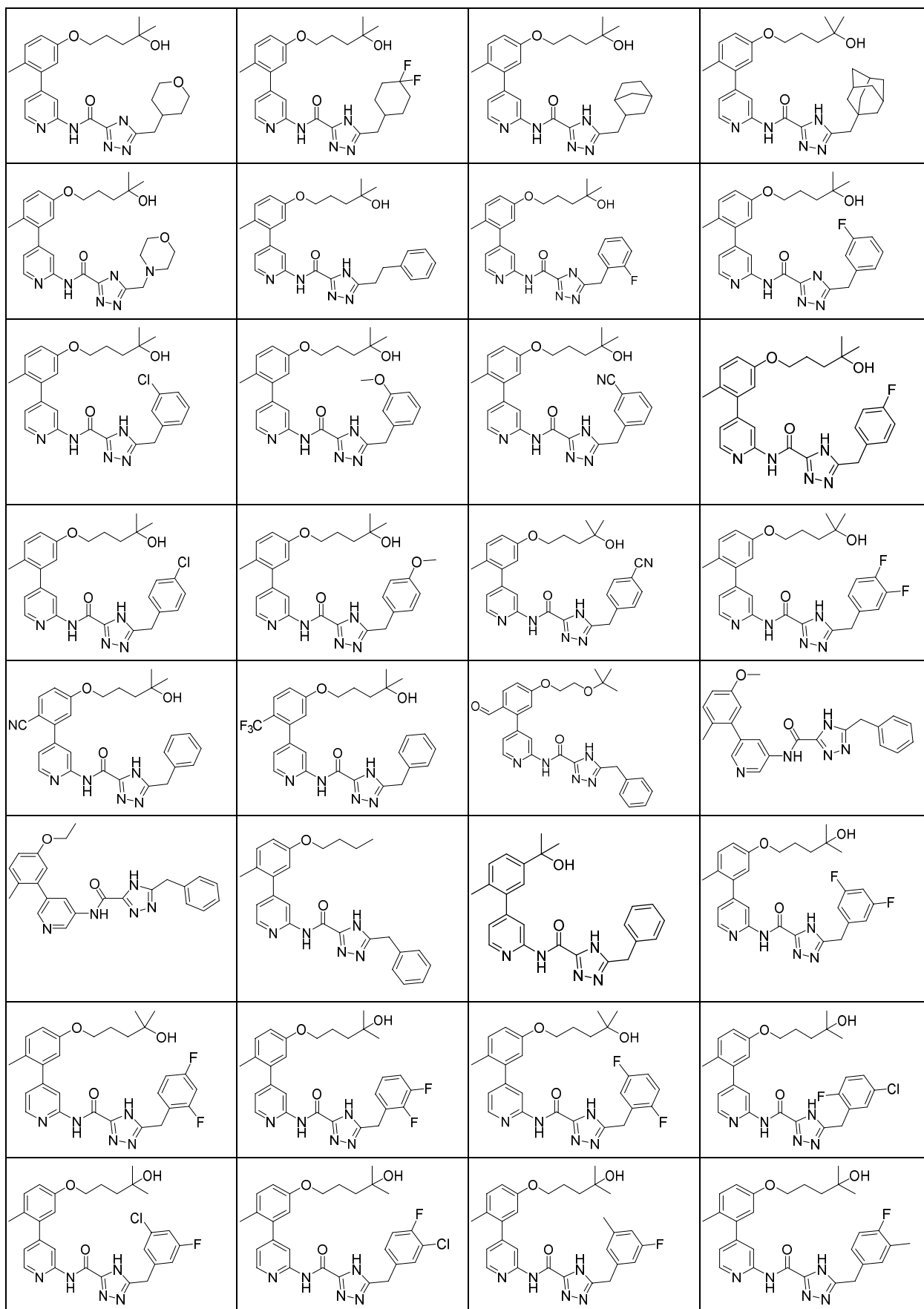


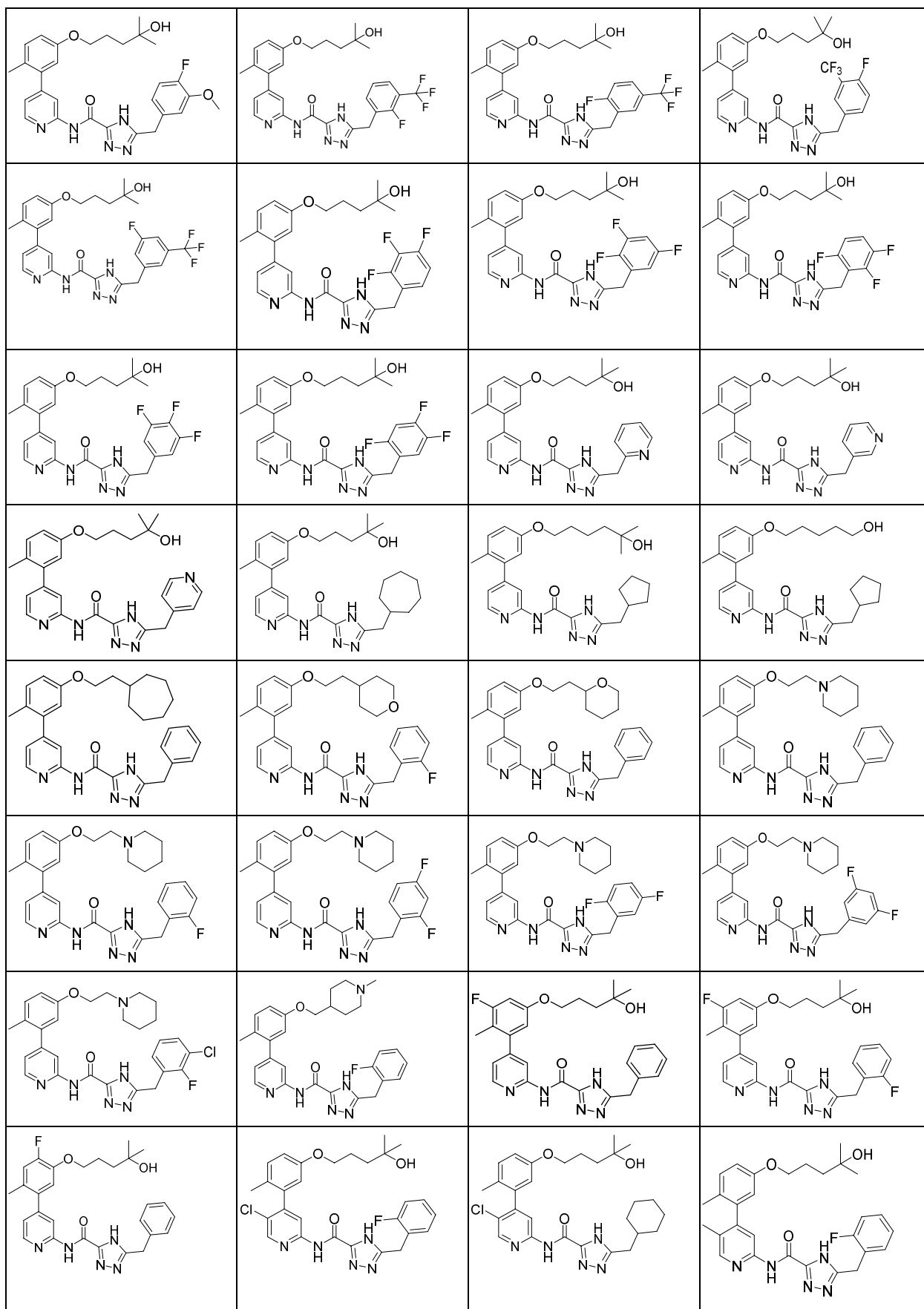


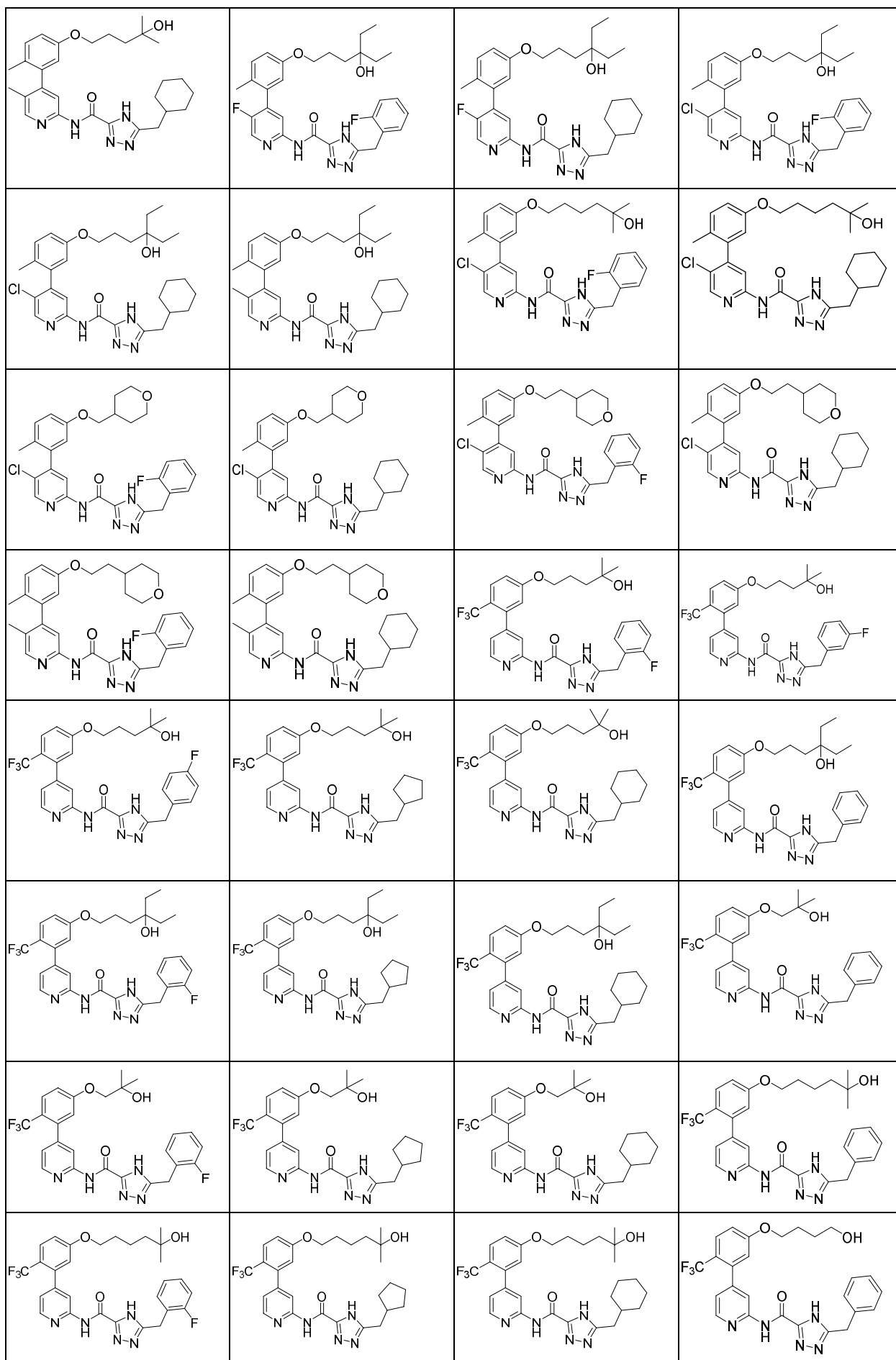


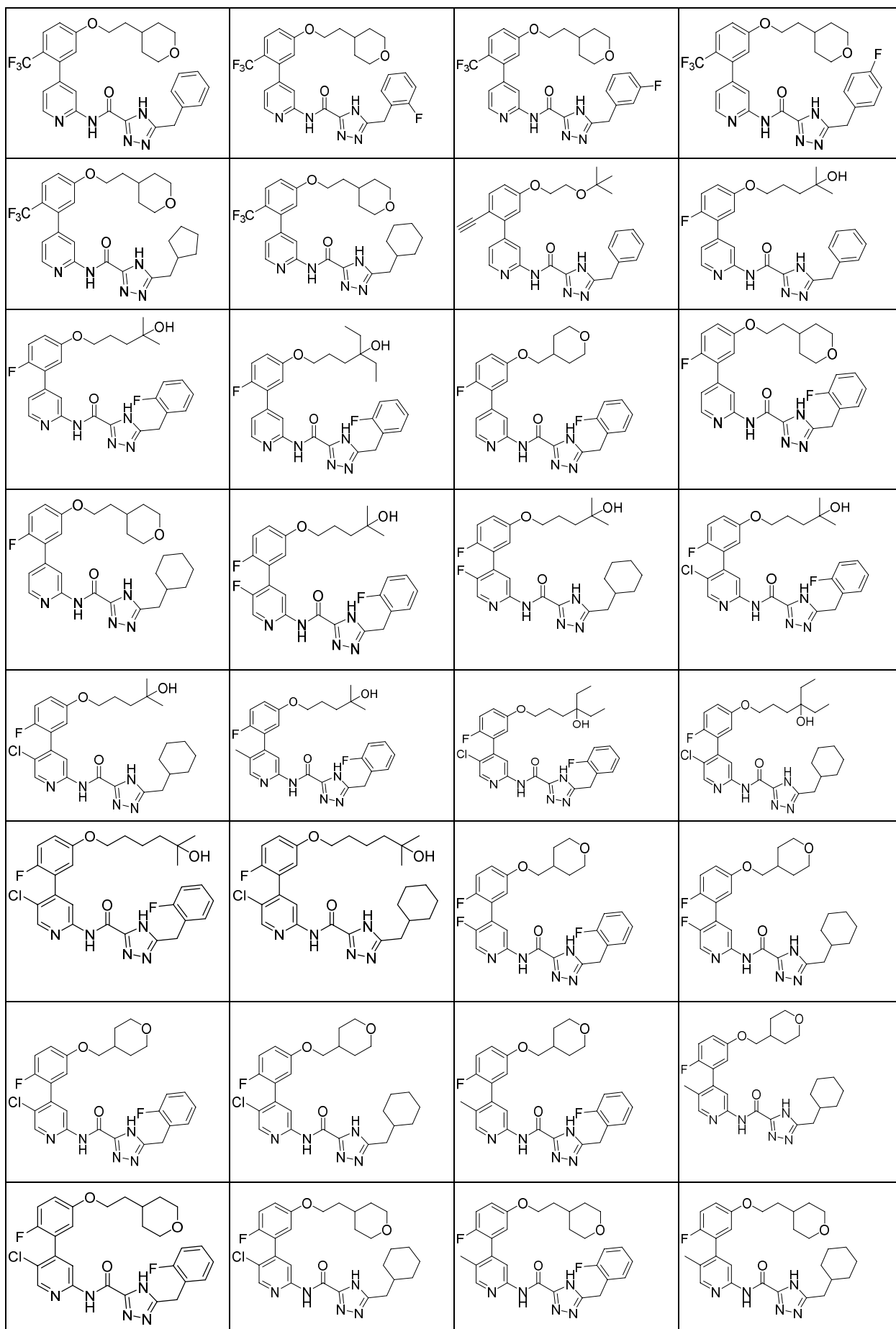


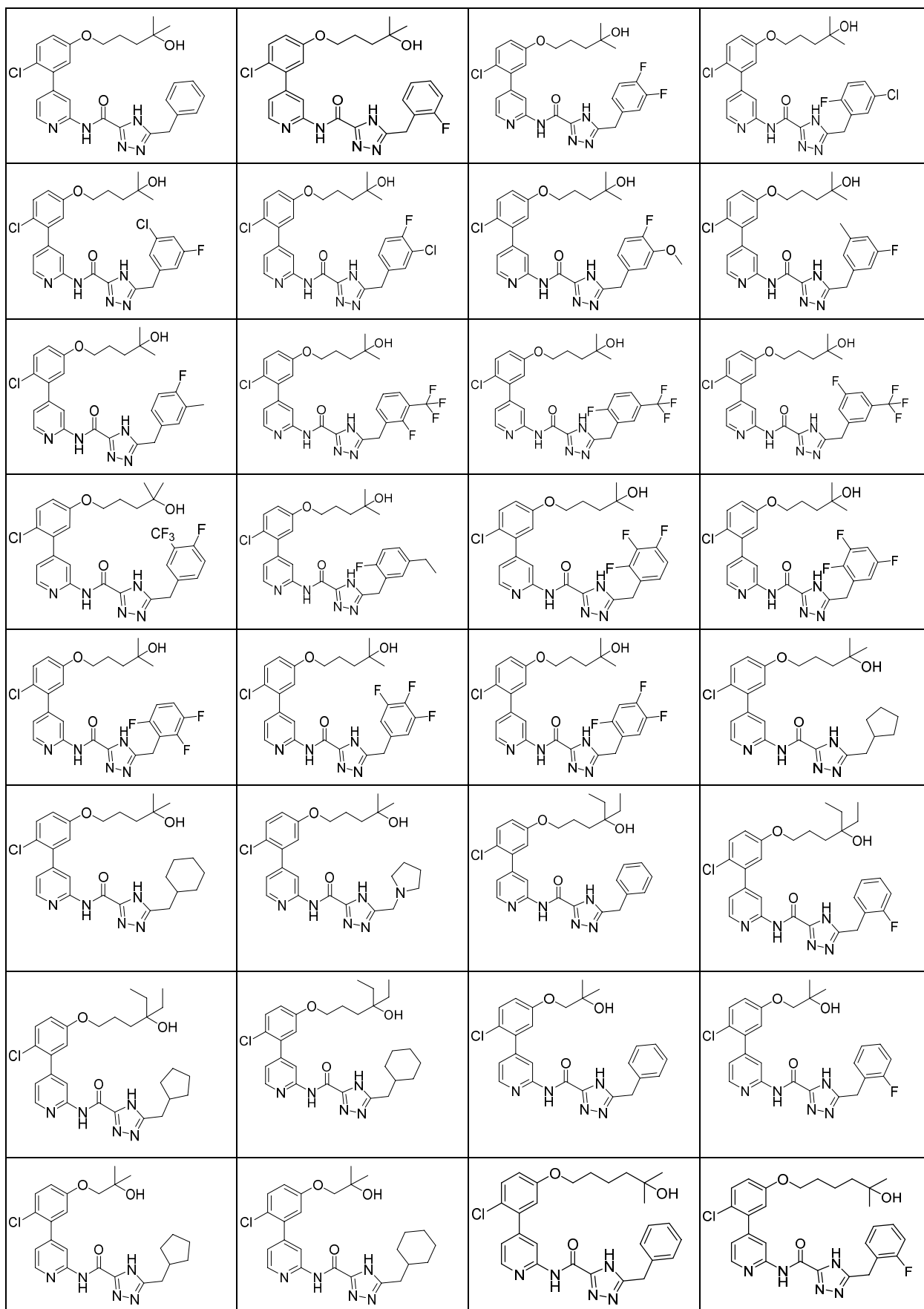


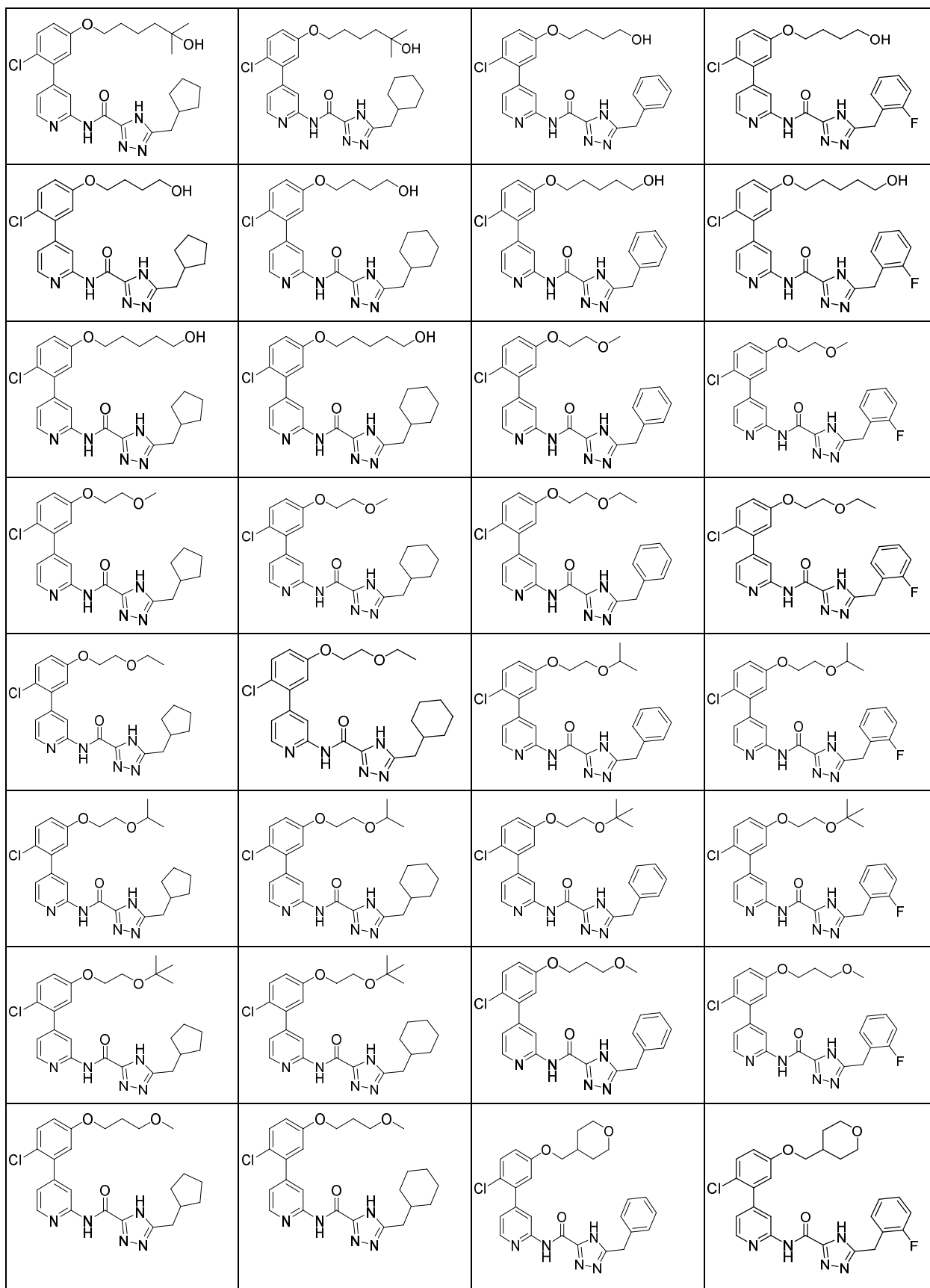


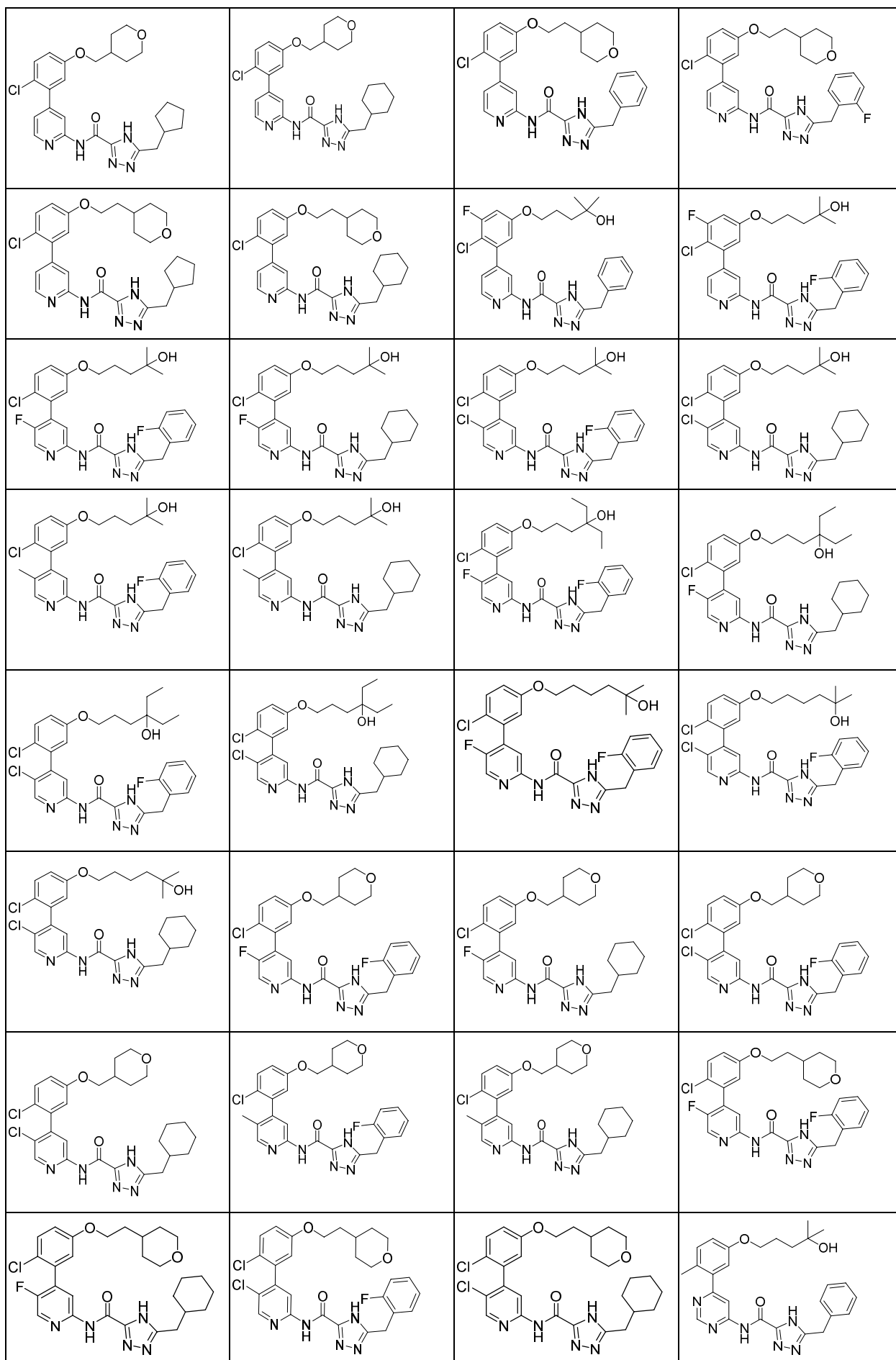


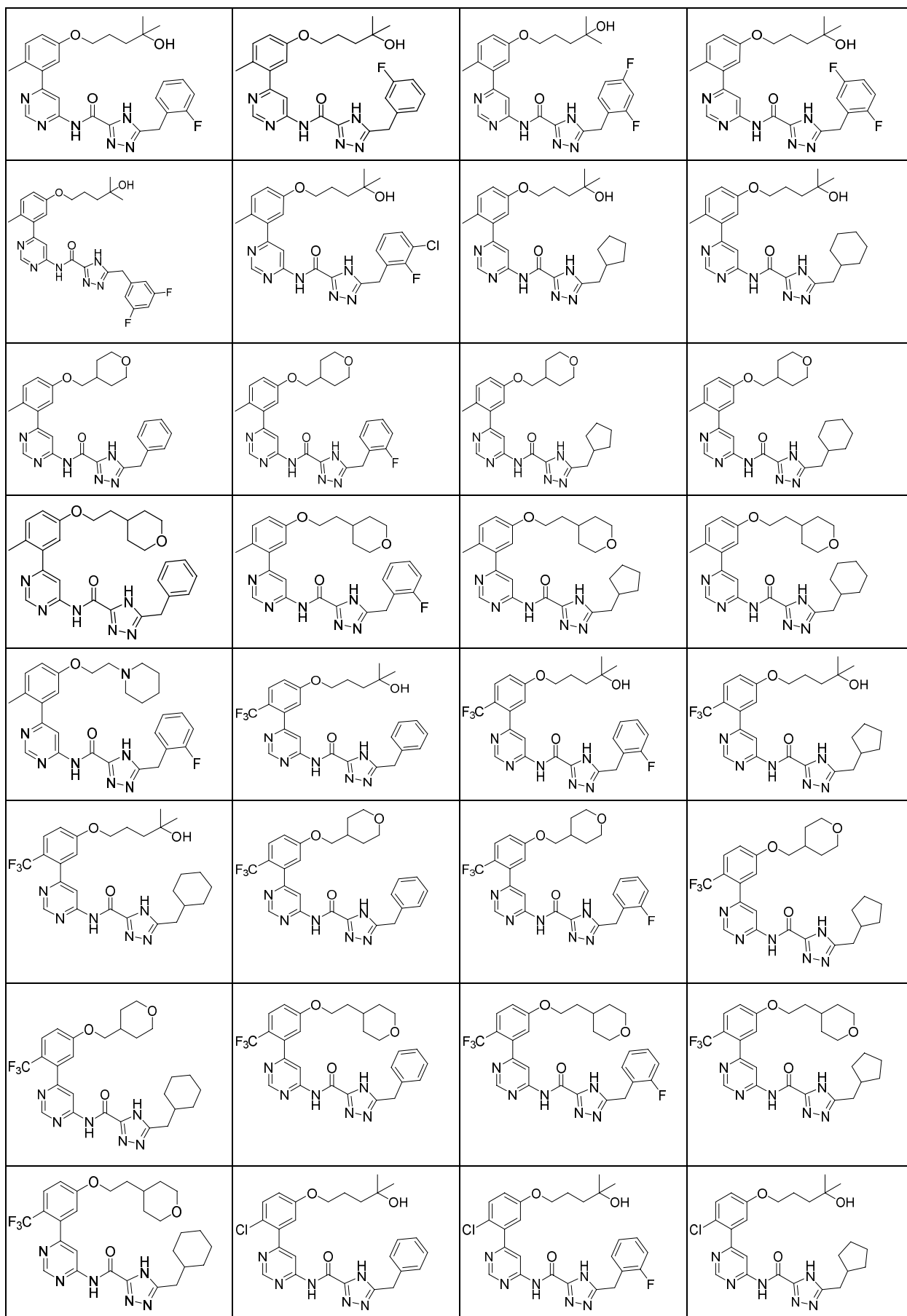


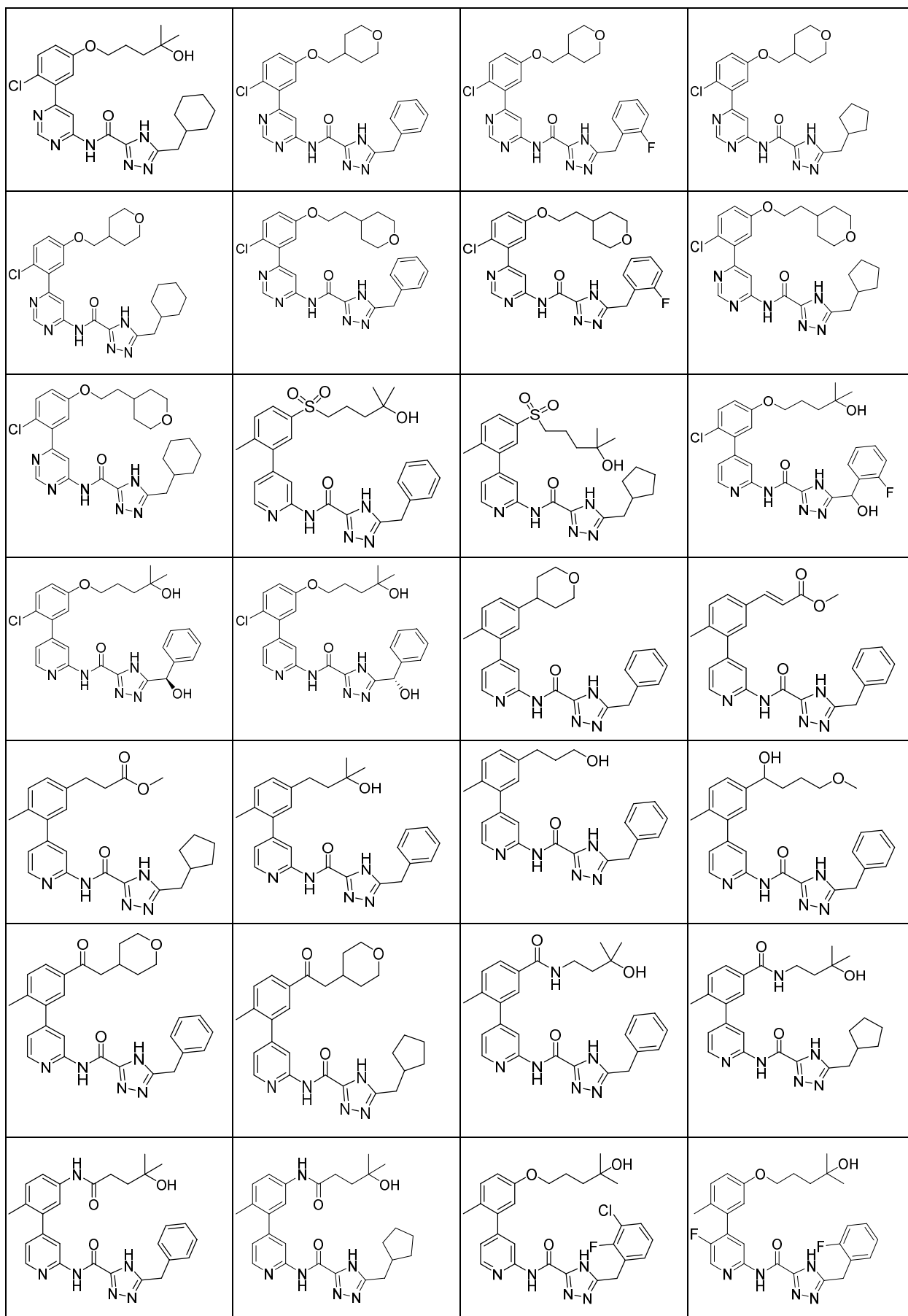


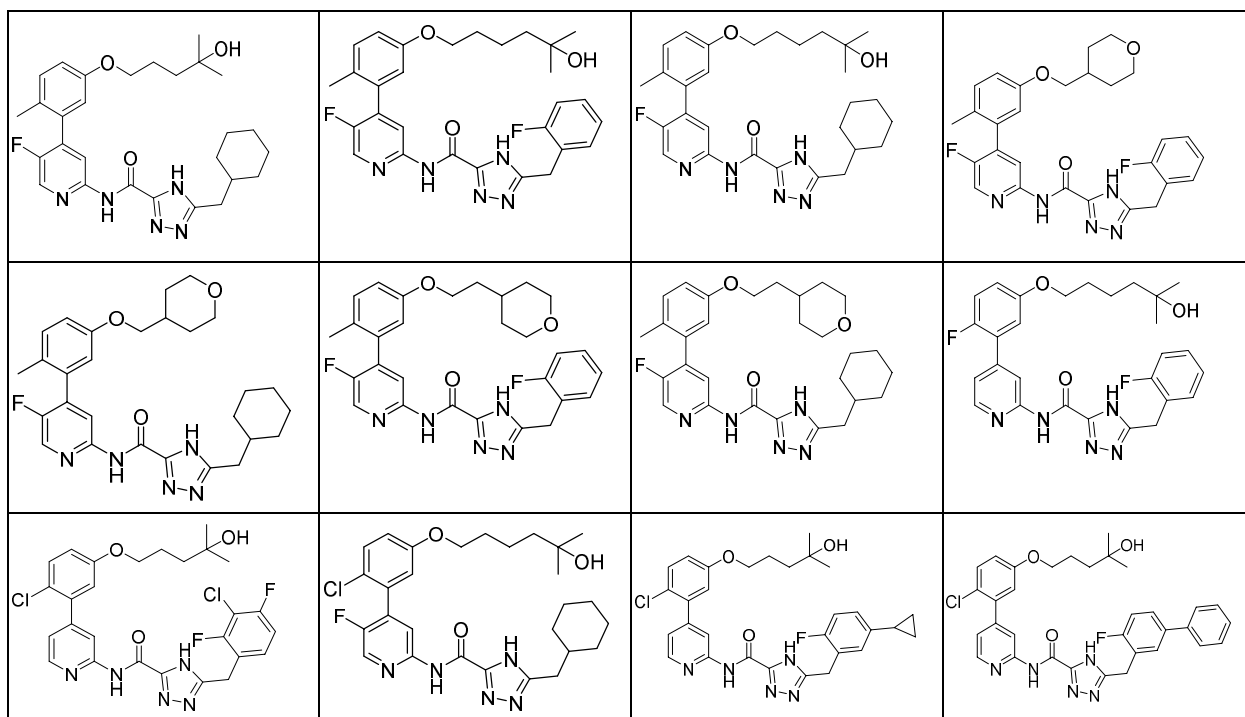












17. Use of the compound, the pharmaceutically acceptable salts, diastereomers, enantiomers or solvates thereof according to any one of claims 1-16, in the preparation of a medicament for treatment for RIP1-related diseases, wherein, the RIP1-related disease is selected from ocular fundus disease, xerophthalmia, psoriasis, leucoderma, dermatitis, alopecia areata, rheumatoid arthritis, colitis, multiple sclerosis, systemic lupus erythematosus, Crohn's disease, atherosclerosis, pulmonary fibrosis, liver fibrosis, myelofibrosis, non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, ovarian cancer, cervical cancer, colorectal cancer, melanoma, endometrial cancer, prostate cancer, bladder cancer, leukemia, gastric cancer, liver cancer, gastrointestinal stromal tumor, thyroid cancer, chronic myeloid leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma, nasopharyngeal cancer, esophageal cancer, brain tumor, B-cell and T-cell lymphoma, lymphoma, multiple myeloma, biliary cancer and sarcoma, cholangiocarcinoma, inflammatory bowel disease, ulcerative colitis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, spondyloarthritis, gout, SoJIA, Sjogren's syndrome, systemic scleroderma, antiphospholipid syndrome, vasculitis, osteoarthritis, non-alcoholic steatohepatitis, alcoholic steatohepatitis, autoimmune hepatitis, autoimmune hepatobiliary disease, primary sclerosing cholangitis, nephritis, celiac disease, autoimmune ITP, transplant rejection, ischemia-reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial infarction, Huntington's disease, Alzheimer's disease, Parkinson's disease, allergic diseases, asthma, atopic dermatitis, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converzyme-related fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor related periodic syndrome and periodontitis.

18. A pharmaceutical composition, comprising a compound, the pharmaceutically acceptable salts,

diastereomers, enantiomers or solvates thereof according to any one of claims 1-16, and one or more pharmaceutically acceptable carriers or excipients.