

(21) Application No: 2415076.5
(22) Date of Filing: 22.11.2022
Date Lodged: 14.10.2024
(30) Priority Data:
(31) 202211018173 (32) 24.08.2022 (33) CN
(86) International Application Data:
PCT/CN2022/133423 Zh 22.11.2022
(87) International Publication Data:
WO2024/040768 Zh 29.02.2024

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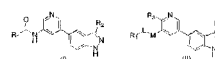
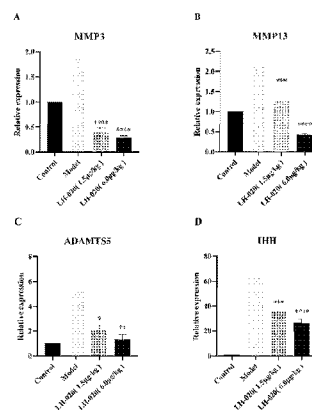
(51) INT CL:
C07D 401/14 (2006.01) A61K 31/416 (2006.01)
A61K 31/506 (2006.01) A61K 31/517 (2006.01)
A61K 31/519 (2006.01) A61P 19/02 (2006.01)
A61P 19/08 (2006.01) A61P 21/00 (2006.01)
A61P 29/00 (2006.01) C07D 213/16 (2006.01)
C07D 413/14 (2006.01) C07D 417/04 (2006.01)
C07D 491/048 (2006.01) C07D 495/04 (2006.01)
C07F 9/58 (2006.01) C07H 19/048 (2006.01)

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(58) Field of Search:
INT CL A61K, A61P, C07D, C07F, C07H
Other: CNTXT, VEN, CNABS, DWPI, WPABS, ENTXT,
USTXT, EPTXT, WOTXT, STN, CNKI,

(54) Title of the Invention: 5-pyridine-1H-indazole compound, pharmaceutical composition, and use
Abstract Title: 5-pyridine-1H-indazole compound, pharmaceutical composition, and use

(57) Disclosed in the present invention are a 5-pyridine-1H-indazole compound, a pharmaceutical composition, and a use. The structure of the compound is represented by formula I or II, and also comprised are an isomer or pharmaceutically acceptable salt thereof, or a mixture of said isomer and salt. The compound and the pharmaceutical composition thereof can effectively inhibit the activity of CLK2 and DYRK1A proteins, can be used for preparing drugs for treating osteoarthritis, can show the efficacy at a molecular level, has a more excellent therapeutic effect, and optimally, can reach a nano-molar concentration level. In addition, a preparation method for the compound is simple, convenient and easy to operate.



DRAWINGS OF THE SPECIFICATION

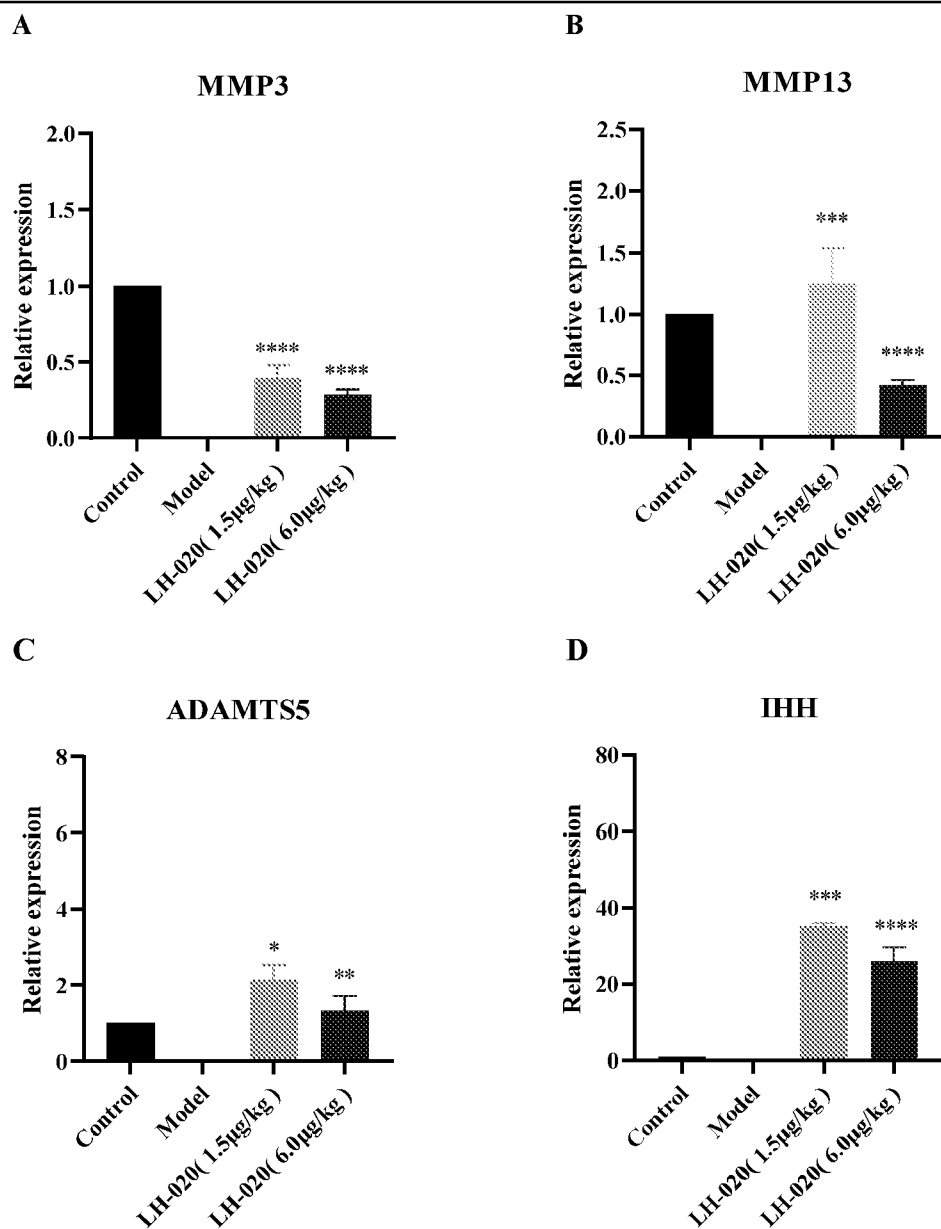


FIG. 1

SPECIFICATION

5-PYRIDINE-1H-INDAZOLE COMPOUND, PHARMACEUTICAL COMPOSITION, AND USE

TECHNICAL FIELD

The present invention relates to a 5-pyridine-1H-indazole compound, a pharmaceutical composition, and use, particularly to a 5-pyridine-1H-indazole compound which can be prepared to effectively inhibit activity of CLK2 or DYRK1A protein, a pharmaceutical composition, and use.

BACKGROUND

Osteoarthritis (OA) is characterized by synovial inflammation, cartilage loss, and subchondral bone remodeling. Despite the abundance of stem cells in the synovium of OA patients, the inability to regenerate joint cartilage is not due to a lack of stem cells. Instead, it is caused by improper differentiation of stem cells. The Wnt pathway plays a crucial role in organ development, cell differentiation, and tissue remodeling. Both abnormal activation and inhibition of the Wnt signaling pathway can lead to the disease. Therefore, the Wnt signaling pathway is a potential target for the treatment of osteoarthritis.

The Wnt signaling pathway is a group of multiple downstream channel signaling pathways triggered by the binding of the ligand protein Wnt to membrane protein receptors. Via this pathway, extracellular signals are transmitted into cells through an intracellular activation process of cell surface receptors. In the canonical Wnt pathway, when there is no Wnt protein on the surface of the cell membrane, the downstream β -catenin protein will be degraded by the glycogen synthase kinase 3 (GSK3) complex in the cytoplasm, preventing it from entering the nucleus to start the transcription of related Wnt genes; when there is Wnt protein on the surface of the cell membrane, it can inhibit the GSK3 complex, thereby allowing the β -catenin protein to accumulate in the nucleus and finally start the transcription of genes related to the Wnt pathway. There is a delicate balance between joint homeostasis and the Wnt pathway, and disruption of this balance may lead to OA.

The protein kinase family CLK (CDK-like kinase) is a dual specificity protein kinase that can regulate intracellular signaling through phosphorylation of tyrosine, serine, or threonine residue substrate proteins. It has four subtypes (CLK1, CLK2, CLK3, and

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CLK4), and the C segments of the proteins encoded by the four subtypes all have highly conserved gene sequences and have structurally similar amino acid sequences. The CLK2 subtype is present in most eukaryotes, and it participates in the phosphorylation of SR (serine/arginine) protein domains, thereby regulating the selective cleavage of RNA, plays an important role in gluconeogenesis and fatty acid oxidation in the liver, and is also a therapeutic target for liver cancer, breast cancer, and Alzheimer's disease and a potential therapeutic target for Wnt pathway and osteoarthritis.

Dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) belongs to the DYRK family and is highly conserved evolutionarily. In mammals, the DYRK family has five different subtypes, and only DYRK1A is located in the DSCR region of human chromosome 21. DYRK1A is expressed by the *dyrk1a* gene, and the encoded mature protein consists of 763 amino acids, including a protein kinase domain and other special structures. Many important proteins can serve as substrates for DYRK1A and are regulated by it, thus participating in various biological functions in cells. For example, neural development, cell proliferation and differentiation, tumorigenesis, and neurodegenerative diseases.

At present, no CLK2 inhibitor drug for treating osteoarthritis is successfully marketed, and only one small molecule drug SM-04690 enters clinical stage III, so that the clinical requirement cannot be met. SM04690 has significant CLK2 inhibitory activity but is not selective to the CLK family, which may have some side effects; in addition, it has insufficient inhibitory activity on the DYRK1A target and poor water solubility, so the druggability needs to be improved.

SUMMARY

Objective: Aiming at the problems of insufficient selectivity for the CLK family, insufficient inhibitory activity on the DYRK1A target, and the like, of the existing compounds, the present invention aims to provide a 5-pyridine-1H-indazole compound which can specifically inhibit activity of CLK2 and DYRK1A proteins, a pharmaceutical composition, and use.

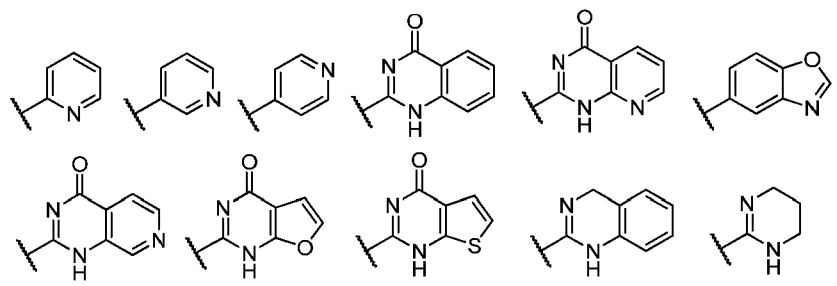
Technical scheme: As a first aspect to which the present invention relates, the 5-pyridine-1H-indazole compound of the present invention has a structure of formula I or II, and further comprises an isomer thereof, a pharmaceutically acceptable salt thereof, or a mixture thereof:

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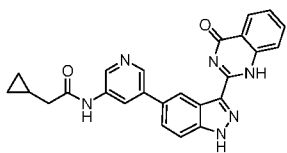
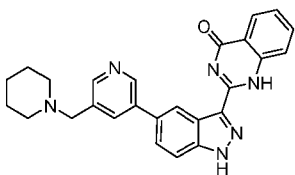
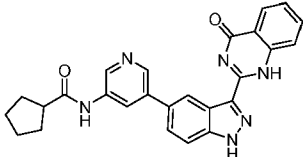
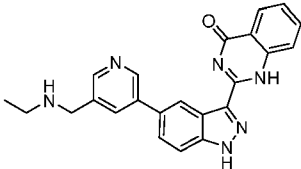
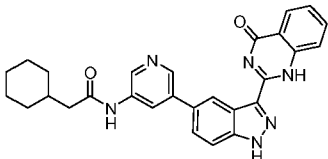
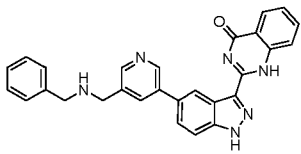
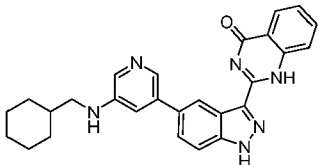
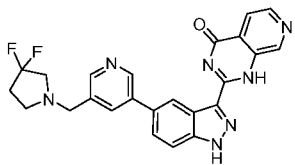
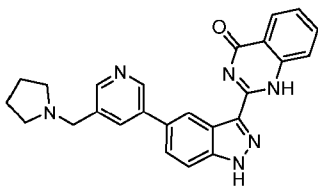
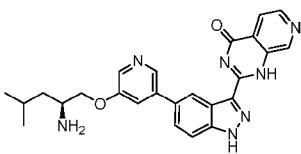
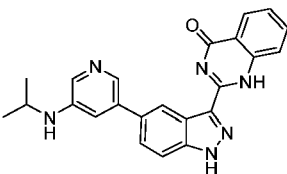
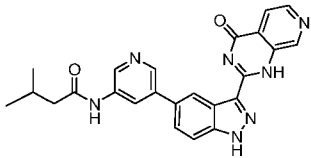
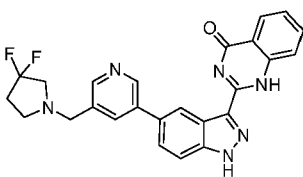
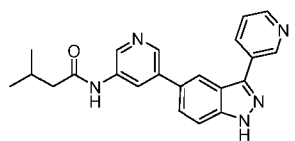
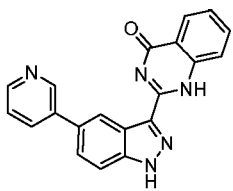
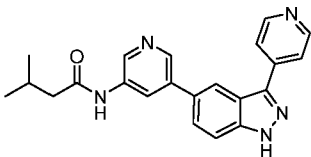
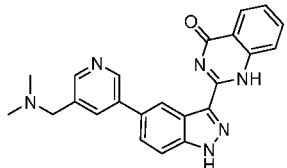
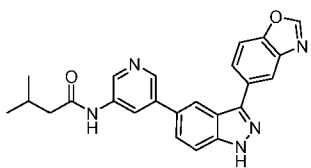
R₁ is selected from the following groups substituted with one or more of hydrogen, halogen, methoxy, trifluoromethyl, nitro, hydroxy, amino, azido, sulfonic acid group, or 3-6 membered ring: hydrogen, linear or branched C₁-C₁₀ alkyl, phenyl, a 4-6 membered heterocyclic ring, or a 4-6 membered ring;

L and M are selected from -CH₂-, -NH-, -O-, or a chemical bond;

R₂ is selected from the following groups:



SPECIFICATION

LH-003		LH-033	
LH-004		LH-034	
LH-005		LH-035	
LH-006		LH-036	
LH-007		LH-037	
LH-008		LH-038	
LH-009		LH-039	
LH-010		LH-040	
LH-011		LH-041	

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LH-012		LH-042	
LH-013		LH-043	
LH-014		LH-044	
LH-015		LH-045	
LH-016		LH-046	
LH-017		LH-047	
LH-018		LH-048	
LH-019		LH-049	
LH-020		LH-050	
LH-021		LH-051	

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LH-022		LH-052	
LH-023		LH-053	
LH-024		LH-054	
LH-025		LH-055	
LH-026		LH-056	
LH-027		LH-057	
LH-028		LH-058	
LH-029		LH-059	
LH-030		LH-060	

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The pharmaceutically acceptable salt of the compound described above is a salt formed by the compound described above and the following acids: hydrochloric acid, sulfuric acid, phosphoric acid, carbonic acid, nitric acid, hydrobromic acid, hydroiodic acid, maleic acid, fumaric acid, tartaric acid, citric acid, malic acid, methanesulfonic acid, *p*-toluenesulfonic acid, naphthalenesulfonic acid, succinic acid, acetic acid, mandelic acid, isobutyric acid, or malonic acid.

As a second aspect to which the present invention relates, the compound described above and a pharmaceutically acceptable carrier form a pharmaceutical composition to prepare common pharmaceutical formulations, such as tablets, capsules, syrups, suspending agents, or injections, and common pharmaceutical adjuvants, such as perfuming agents, sweeteners, liquid/solid fillers, diluents, etc., can be added to the formulations.

In a third aspect to which the present invention relates, the compound described above or a pharmaceutical composition thereof can be prepared into a CLK2 protein inhibitor drug, and also can be prepared into a DYRK1A protein inhibitor drug, which is specifically used for treating inflammation, including osteoarthritis, tendinopathy, or rheumatoid arthritis, having a chondroprotective effect.

Beneficial Effects: The present invention has the following remarkable advantages compared with the prior art:

- (1) such compounds and the pharmaceutical composition thereof can effectively inhibit activity of CLK2 protein and DYRK1A protein, and the IC_{50} values of enzyme level inhibition are less than 100 nM, preferably less than 10 nM, and significantly down-regulate the expression level of the protease related to cartilage decomposition in an inflammation model animal, exerting a chondroprotective effect;
- (2) such compounds and the pharmaceutical composition thereof are widely used and can be prepared into drugs for treating osteoarthritis; the drugs can exert drug effects at a molecular level and an animal level, and have more excellent treatment effect, which can optimally reach the nano-molar concentration level;
- (3) the preparation method for the compounds is simple, convenient, and easy to operate.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows RT-qPCR results for cartilage of ACLT model rats at week 5 (* $P < 0.05$,

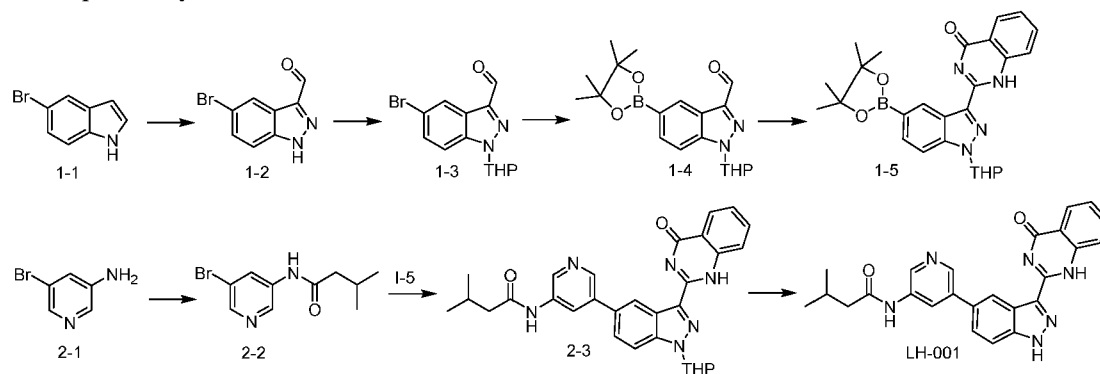
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**** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).**

DETAILED DESCRIPTION

The technical scheme of the present invention will be further described below with reference to the examples.

Example 1: Synthesis of LH-001



Synthesis of intermediate 1-2:

Starting material 1-1 (5-bromoindole, 0.1 mmol) and acetone were added into a three-necked flask. The mixture was cooled to 0 °C in an ice salt bath. An aqueous solution of sodium nitrite (0.8 mmol) was added dropwise, with the temperature maintained at no higher than 0 °C. After the addition was completed, dilute hydrochloric acid (2 N HCl) was added dropwise. The mixture was then warmed to room temperature and reacted for 4 h. The mixture was concentrated by rotary evaporation and filtered under vacuum to give a crude product. The crude product was slurried with dichloromethane to give brownish red solid 1-2. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.29 (s, 1H), 9.80 (s, 1H), 7.88 (d, $J = 1.2$ Hz, 1H), 7.44 - 7.31 (m, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_8\text{H}_6\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 224.9664, found 224.9657. The yield was 67%.

Synthesis of intermediate 1-3:

Intermediate 1-2 (0.1 mmol) was added to a three-necked flask. Tetrahydrofuran (80 mL) and *p*-toluenesulfonic acid (0.02 mmol) were added, and 3,4-dihydropyran (0.2 mmol) was added dropwise at room temperature. The mixture was then warmed to 65 °C and reacted for 8 h. After the reaction was completed as monitored by TLC, the reaction mixture was concentrated by rotary evaporation under reduced pressure to remove the solvent and purified by silica gel column chromatography to give a crude product of intermediate I-3. The crude product was slurried with petroleum ether to give white solid I-3. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.80 (s, 1H), 7.88 (s, 1H), 7.37 (d, $J = 1.0$ Hz, 2H), 6.27 (t, $J = 6.9$ Hz, 1H), 3.90 (dt, $J = 11.4, 7.0$ Hz, 1H), 3.77 (dt, J

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= 11.5, 7.0 Hz, 1H), 2.52 - 2.32 (m, 1H), 2.12 - 1.91 (m, 2H), 1.83 - 1.64 (m, 1H), 1.58 - 1.53 (m, 2H) ppm. HR-MS(ESI): Calculated for $C_{13}H_{14}BrN_2O_2$ $[M+H]^+$: 309.0239, found 309.0239. The yield was 74%.

Synthesis of intermediate I-4:

Intermediate 1-3 (0.1 mmol) was added to a single-necked flask, and bis(pinacolato)diboron (0.12 mmol), potassium acetate (0.3 mmol), Pd(dppf)Cl₂ (0.005 mmol), and dioxane (26 mL) were added. The mixture was warmed at reflux for 6 h. After the reaction was completed as monitored by TLC, the reaction mixture was cooled, filtered under vacuum, concentrated by rotary evaporation, and purified by silica gel column chromatography to give white solid 1-4. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.99 (s, 1H), 8.07 (d, *J* = 1.6 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.27 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.25 (t, *J* = 6.9 Hz, 1H), 3.90 (dt, *J* = 11.4, 7.0 Hz, 1H), 3.77 (dt, *J* = 11.4, 7.0 Hz, 1H), 2.52 - 2.32 (m, 1H), 2.12 - 1.91 (m, 2H), 1.86 - 1.48 (m, 3H), 1.41 (d, *J* = 15.1 Hz, 12H) ppm. HR-MS(ESI): Calculated for $C_{19}H_{26}BN_2O_4$ $[M+H]^+$: 357.1986, found 357.1983. The yield was 89%.

Synthesis of intermediate I-5:

Intermediate 1-4 (0.1 mmol) was added to a single-necked flask and dissolved with a mixed solvent of ethanol:dichloromethane (5:1). Anthranilamide (0.1 mmol) and iodine (0.1 mmol) were then added, and the mixture was refluxed at 80 °C for 30 min-60 min. After the TLC reaction was completed, 5% sodium thiosulfate was added to quench the reaction, and the mixture was extracted with dichloro and saturated brine. The organic phases were combined, dried, concentrated, and purified by column chromatography to give a crude product. The crude product was slurried with (petroleum ether:ethyl acetate = 1:1) to give pure product I-5. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.35 (s, 1H), 8.13 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.66 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.50 - 7.32 (m, 2H), 7.13 (td, *J* = 7.5, 2.0 Hz, 1H), 6.31 (t, *J* = 6.9 Hz, 1H), 3.90 (dt, *J* = 11.4, 7.0 Hz, 1H), 3.77 (dt, *J* = 11.4, 7.0 Hz, 1H), 2.52 - 2.32 (m, 1H), 2.12 - 1.91 (m, 2H), 1.86 - 1.48 (m, 3H), 1.42 (d, *J* = 15.1 Hz, 12H) ppm. HR-MS(ESI): Calculated for $C_{26}H_{30}BN_4O_4$ $[M+H]^+$: 473.2360, found 473.2357. The yield was 68%.

Synthesis of intermediate 2-2:

Isovaleric acid (0.1 mmol) and HATU (0.3 mmol) were dissolved in 40 mL of tetrahydrofuran. DIPEA (0.3 mmol) was then added, and the mixture was stirred at

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room temperature for about 15 min. Starting material 2-1 (0.1 mmol) was then added, and the mixture was stirred at room temperature for 1-3 h. After starting material 2-1 was completely reacted as detected by TLC, the reaction was stopped, and the reaction mixture was separated and purified by column chromatography to give intermediate 2-2.

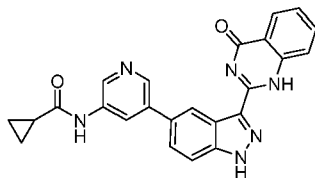
Synthesis of intermediate 2-3:

Intermediate 2-2 (0.1 mmol), intermediate 1-5 (0.1 mmol), sodium carbonate (0.3 mmol), Pd(dppf)Cl₂ (0.005 mmol), dioxane (9 mL), and water (1.5 mL) were added to a single-necked flask, and the system was purged of air with nitrogen 4 times. The mixture was warmed at reflux for 8 h. After the mixture was cooled, the mixture was filtered under vacuum, concentrated to dryness by rotary evaporation, and purified by silica gel column chromatography to give intermediate 2-3.

Synthesis of LH-001:

Intermediate 2-3 (0.1 mmol) was dissolved in 5 mL of dichloromethane. Trifluoroacetic acid (1 mmol) and triethylsilane (0.1 mmol) were added at room temperature, and the mixture was reacted at room temperature for 16-24 h. After the reaction was completed as detected by TLC, the reaction mixture was concentrated under reduced pressure and extracted with dichloromethane and saturated sodium bicarbonate. The organic phases were combined, dried, and concentrated to give the final product LH-001. ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.16 (s, 1H), 10.57 (s, 1H), 8.93 (t, *J* = 12.4 Hz, 3H), 8.67 (d, *J* = 2.1 Hz, 1H), 8.26 - 8.17 (m, 1H), 7.98 - 7.82 (m, 4H), 7.61 - 7.51 (m, 1H), 6.30 (s, 1H), 2.34 (d, *J* = 7.1 Hz, 2H), 2.17 (m, 1H), 1.03 (s, 3H), 1.01 (s, 3H) ppm. HR-MS(ESI): Calculated for C₂₅H₂₃N₆O₂ [M+H]⁺: 439.1882, found 439.1875.

The following compounds were prepared using a procedure similar to that in Example 1:

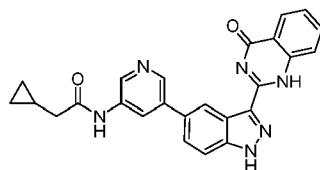


LH-002

¹H NMR (300 MHz, DMSO-*d*₆) δ 14.25 (s, 1H), 12.27 (s, 1H), 10.69 (s, 1H), 8.91 - 8.82 (m, 2H), 8.66 (s, 1H), 8.42 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 3H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 1.90 (q, *J* = 6.2 Hz, 1H), 0.91

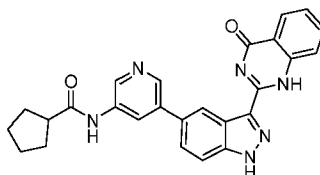
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(q, $J = 7.9, 5.5$ Hz, 4H) ppm. HR-MS(ESI): Calculated for $C_{24}H_{19}N_6O_2$ $[M+H]^+$: 423.1569, found 423.1562.



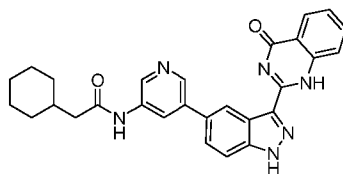
LH-003

^1H NMR (300 MHz, $DMSO-d_6$) δ 14.28 (s, 1H), 12.29 (s, 1H), 9.80 (s, 1H), 9.61 (d, $J = 1.3$ Hz, 1H), 8.83 (d, $J = 1.5$ Hz, 1H), 8.70 (d, $J = 1.3$ Hz, 1H), 8.13 (dd, $J = 7.4, 2.0$ Hz, 1H), 8.03 (t, $J = 1.3$ Hz, 1H), 7.71 - 7.55 (m, 3H), 7.45 (td, $J = 7.5, 2.0$ Hz, 1H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 2.10 (d, $J = 7.0$ Hz, 2H), 1.15 (m, 1H), 0.62 - 0.44 (m, 2H), 0.32 - 0.27 (m, 2H) ppm. HR-MS(ESI): Calculated for $C_{25}H_{21}N_6O_2$ $[M+H]^+$: 437.1726, found 437.1722.



LH-004

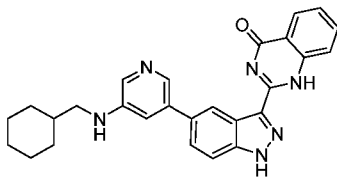
^1H NMR (300 MHz, $DMSO-d_6$) δ 14.16 (s, 1H), 10.56 (s, 1H), 8.93 (s, 2H), 8.67 (s, 1H), 8.20 (d, $J = 7.8$ Hz, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 7.88 (d, $J = 10.6$ Hz, 3H), 7.56 (t, $J = 7.4$ Hz, 1H), 5.78 (s, 2H), 2.91 (d, $J = 7.7$ Hz, 1H), 1.99 - 1.57 (m, 8H) ppm. HR-MS(ESI): Calculated for $C_{26}H_{23}N_6O_2$ $[M+H]^+$: 451.1882, found 451.1879.



LH-005

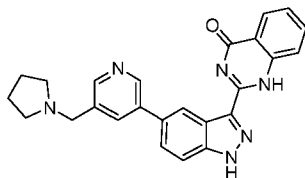
^1H NMR (300 MHz, $DMSO-d_6$) δ 14.43 (s, 1H), 11.66 (s, 1H), 10.31 (s, 1H), 8.90 (s, 1H), 8.81 (s, 1H), 8.70 (s, 1H), 8.53 (s, 1H), 8.21 (d, $J = 7.9$ Hz, 1H), 7.88 (dd, $J = 7.7, 8.3$ Hz, 4H), 7.55 (t, $J = 7.3$ Hz, 1H), 2.32 (d, $J = 6.9$ Hz, 2H), 1.86 - 1.66 (m, 6H), 1.25 (q, $J = 11.6, 10.8$ Hz, 3H), 1.05 (q, $J = 11.3$ Hz, 2H) ppm. HR-MS(ESI): Calculated for $C_{28}H_{27}N_6O_2$ $[M+H]^+$: 479.2195, found 479.2191.

SPECIFICATION



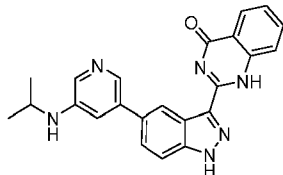
LH-006

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 14.08 (s, 1H), 12.21 (s, 1H), 8.83 (s, 1H), 8.22 (d, J = 8.2 Hz, 2H), 8.04 (d, J = 2.4 Hz, 1H), 7.89 (d, J = 4.0 Hz, 2H), 7.82 (s, 2H), 7.57 (dt, J = 8.2, 4.1 Hz, 1H), 7.38 (s, 1H), 3.05 (d, J = 6.7 Hz, 2H), 1.88 (d, J = 12.6 Hz, 2H), 1.77 - 1.60 (m, 5H), 1.26 (t, J = 10.7 Hz, 3H), 1.02 (dt, J = 12.0, 6.0 Hz, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_{27}\text{H}_{27}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 451.2246, found 451.2241.



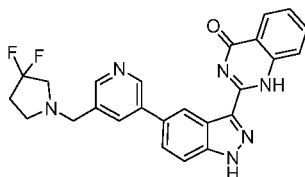
LH-007

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 14.11 (s, 1H), 12.22 (s, 1H), 8.90 (d, J = 10.1 Hz, 2H), 8.58 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 8.12 (s, 1H), 7.86 (dd, J = 14.2, 7.9 Hz, 4H), 7.57 (d, J = 7.2 Hz, 1H), 3.86 (s, 2H), 2.64 (s, 4H), 1.80 (d, J = 5.3 Hz, 4H) ppm. HR-MS(ESI): Calculated for $\text{C}_{25}\text{H}_{23}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 423.1933, found 423.1928.



LH-008

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 14.15 (s, 1H), 12.63 (s, 1H), 8.81 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 8.15 (s, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 3.6 Hz, 2H), 7.79 (d, J = 2.6 Hz, 2H), 7.55 (dq, J = 8.0, 3.8, 3.2 Hz, 1H), 7.23 (s, 1H), 5.88 (d, J = 7.9 Hz, 1H), 3.75 (d, J = 6.8 Hz, 1H), 1.25 (s, 3H), 1.23 (s, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{23}\text{H}_{21}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 397.1777, found 397.1769.



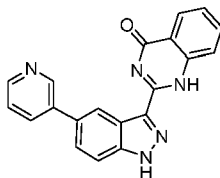
LH-009

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 14.14 (s, 1H), 12.21 (s, 1H), 8.96 (d, J = 2.2 Hz, 1H),

SPECIFICATION

8.89 (s, 1H), 8.60 (s, 1H), 8.24 - 8.13 (m, 2H), 7.88 - 7.69 (m, 4H), 7.59 - 7.52 (m, 1H), 3.92 (s, 2H), 3.11 (t, $J = 13.2$ Hz, 2H), 2.94 - 2.88 (m, 2H), 2.43 - 2.36 (m, 2H) ppm.

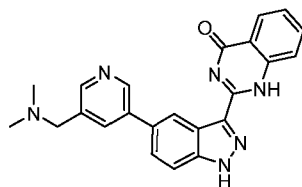
HR-MS(ESI): Calculated for $C_{25}H_{21}F_2N_6O$ $[M+H]^+$: 459.1745, found 459.1739.



LH-010

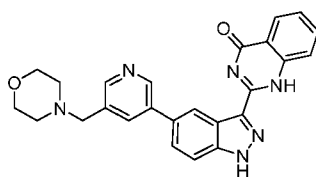
^1H NMR (300 MHz, $DMSO-d_6$) δ 14.27 (s, 1H), 12.28 (s, 1H), 9.00 (d, $J = 2.3$ Hz, 1H), 8.85 (s, 1H), 8.65 - 8.58 (m, 1H), 8.23 - 8.12 (m, 2H), 7.83 (dd, $J = 9.9, 6.4$ Hz, 3H), 7.73 (dd, $J = 8.7, 1.8$ Hz, 1H), 7.56 (dd, $J = 8.0, 4.8$ Hz, 1H), 7.49 - 7.42 (m, 1H) ppm.

HR-MS(ESI): Calculated for $C_{20}H_{14}N_5O$ $[M+H]^+$: 340.1198, found 340.1192.



LH-011

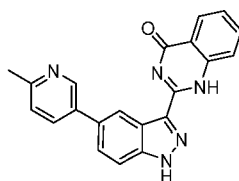
^1H NMR (300 MHz, $DMSO-d_6$) δ 14.28 (s, 1H), 12.14 (s, 1H), 8.89 (s, 2H), 8.52 (s, 1H), 8.17 (d, $J = 7.9$ Hz, 1H), 8.05 (s, 1H), 7.84 - 7.69 (m, 4H), 7.45 (d, $J = 3.5$ Hz, 1H), 3.58 (s, 2H), 2.25 (s, 6H) ppm. HR-MS(ESI): Calculated for $C_{23}H_{21}N_6O$ $[M+H]^+$: 397.1777, found 397.1771.



LH-012

^1H NMR (300 MHz, $DMSO-d_6$) δ 14.09 (s, 1H), 12.25 (s, 1H), 8.91 (d, $J = 2.2$ Hz, 1H), 8.87 (s, 1H), 8.57 (d, $J = 1.9$ Hz, 1H), 8.21 (d, $J = 7.9$ Hz, 1H), 8.12 (d, $J = 2.2$ Hz, 1H), 7.93 - 7.81 (m, 6H), 7.57 - 7.51 (m, 1H), 3.72 (s, 2H), 3.64 (d, $J = 4.7$ Hz, 6H) ppm.

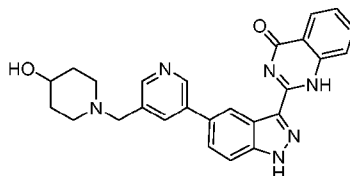
HR-MS(ESI): Calculated for $C_{25}H_{23}N_6O_2$ $[M+H]^+$: 439.1882, found 439.1879.



LH-013

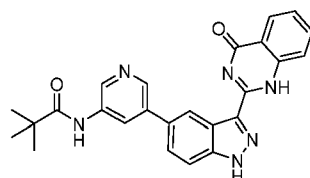
SPECIFICATION

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.11 (s, 1H), 12.22 (s, 1H), 8.61 - 8.47 (m, 3H), 8.19 (d, $J = 7.9$ Hz, 1H), 7.91 - 7.78 (m, 3H), 7.55 (dt, $J = 11.2, 5.3$ Hz, 2H), 7.44 (d, $J = 5.0$ Hz, 1H), 2.36 (s, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{21}\text{H}_{16}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$: 354.1355, found 354.1348.



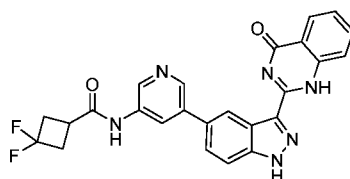
LH-014

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.11 (s, 1H), 12.29 (s, 1H), 8.92 (d, $J = 13.6$ Hz, 2H), 8.59 (s, 1H), 8.22 (d, $J = 7.9$ Hz, 2H), 7.91 (d, $J = 7.4$ Hz, 4H), 7.57 (ddd, $J = 8.2, 6.0, 2.2$ Hz, 1H), 3.77 (s, 1H), 3.65 (s, 2H), 1.81 (s, 2H), 1.53 (s, 3H), 1.25 (s, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{26}\text{H}_{25}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 453.2039, found 453.2041.



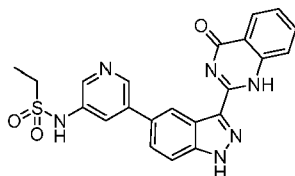
LH-015

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.14 (s, 1H), 12.20 (s, 1H), 9.68 (s, 1H), 8.98 (d, $J = 11.2$ Hz, 2H), 8.77 (s, 1H), 8.60 (s, 1H), 8.29 (t, $J = 7.7$ Hz, 1H), 8.04 - 7.89 (m, 4H), 7.63 (d, $J = 7.7$ Hz, 1H), 1.44 - 1.36 (m, 9H) ppm. HR-MS(ESI): Calculated for $\text{C}_{25}\text{H}_{23}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 439.1882, found 439.1878.



LH-016

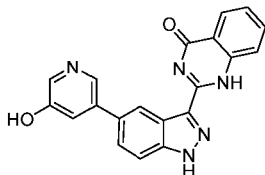
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.21 (s, 1H), 12.29 (s, 1H), 10.85 (s, 1H), 8.89 (d, $J = 8.1$ Hz, 2H), 8.73 (s, 1H), 8.56 (s, 1H), 8.21 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 7.2$ Hz, 4H), 7.63 - 7.50 (m, 1H), 2.93 - 2.85 (m, 3H), 1.23 (s, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_{25}\text{H}_{19}\text{F}_2\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 473.1538, found 473.1532.



SPECIFICATION

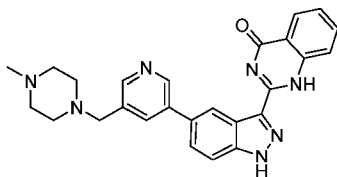
LH-017

^1H NMR (300 MHz, DMSO- d_6) δ 14.14 (s, 1H), 12.31 (s, 1H), 10.34 (s, 1H), 8.92 (s, 1H), 8.79 (s, 1H), 8.52 (s, 1H), 8.22 (d, $J = 7.6$ Hz, 1H), 8.05 (s, 1H), 7.90 (d, $J = 12.0$ Hz, 4H), 7.58 (s, 1H), 3.31 (s, 2H), 1.25 (s, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{22}\text{H}_{19}\text{N}_6\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 447.1239, found 447.1231.



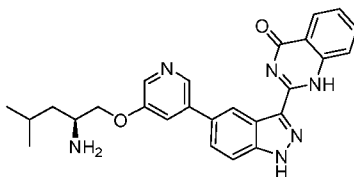
LH-018

^1H NMR (300 MHz, DMSO- d_6) δ 14.73 (s, 1H), 12.25 (s, 1H), 8.84 (s, 1H), 8.39 (s, 1H), 8.14 (d, $J = 8.9$ Hz, 2H), 7.74 (d, $J = 4.3$ Hz, 3H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.52 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 1H) ppm. HR-MS(ESI): Calculated for $\text{C}_{20}\text{H}_{14}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$: 356.1147, found 356.1141.



LH-019

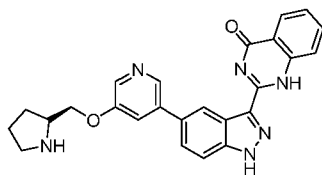
^1H NMR (300 MHz, DMSO- d_6) δ 14.22 (s, 1H), 12.32 (s, 1H), 9.03 - 8.92 (m, 2H), 8.65 (d, $J = 1.9$ Hz, 1H), 8.30 (d, $J = 7.9$ Hz, 1H), 8.18 (t, $J = 2.1$ Hz, 1H), 8.02 - 7.90 (m, 4H), 7.65 - 7.59 (m, 1H), 3.81 (s, 2H), 2.95 (s, 4H), 2.72 (s, 4H), 2.61 (s, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{26}\text{H}_{26}\text{N}_7\text{O}$ $[\text{M}+\text{H}]^+$: 452.2199, found 452.2203.



LH-020

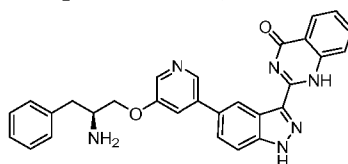
^1H NMR (300 MHz, DMSO- d_6) δ 14.16 (s, 1H), 12.30 (s, 1H), 8.88 (s, 1H), 8.67 (d, $J = 1.7$ Hz, 1H), 8.43 (d, $J = 2.6$ Hz, 1H), 8.23 - 8.18 (m, 2H), 7.93 - 7.84 (m, 4H), 7.61 - 7.53 (m, 1H), 4.46 (dd, $J = 10.7, 3.2$ Hz, 1H), 4.25 (dd, $J = 10.6, 6.7$ Hz, 1H), 3.66 (s, 1H), 2.91 (s, 1H), 2.75 (s, 1H), 1.83 - 1.60 (m, 3H), 0.98 (d, $J = 1.9$ Hz, 3H), 0.96 (d, $J = 2.0$ Hz, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{26}\text{H}_{27}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 455.2195, found 455.2191.

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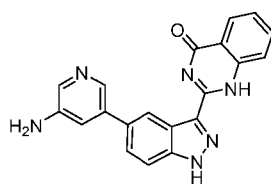
LH-021

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.36 (s, 1H), 12.18 (s, 1H), 8.57 (d, $J = 1.3$ Hz, 1H), 8.22 - 8.08 (m, 2H), 7.72 - 7.52 (m, 4H), 7.45 (td, $J = 7.5, 2.0$ Hz, 1H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 4.33 (dd, $J = 12.4, 7.0$ Hz, 1H), 4.16 (dd, $J = 12.4, 7.0$ Hz, 1H), 3.25 (d, $J = 7.0$ Hz, 1H), 2.97 (dt, $J = 9.4, 6.9$ Hz, 1H), 2.79 (dt, $J = 9.3, 6.9$ Hz, 1H), 1.77-1.65 (m, 3H), 1.41 (ddd, $J = 12.3, 7.6, 6.3$ Hz, 1H), 1.19 (s, 1H) ppm. HR-MS(ESI): Calculated for $\text{C}_{25}\text{H}_{23}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 439.1882, found 439.1878.



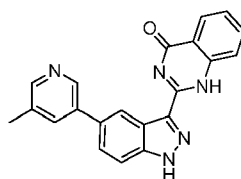
LH-022

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.05 (s, 1H), 12.53 (s, 1H), 8.78 - 8.71 (m, 1H), 8.59 (d, $J = 1.3$ Hz, 1H), 8.18 - 8.05 (m, 2H), 7.71 - 7.51 (m, 4H), 7.44 (td, $J = 7.5, 2.0$ Hz, 1H), 7.35 - 7.22 (m, 2H), 7.22 - 7.07 (m, 4H), 4.26 (dd, $J = 12.4, 7.0$ Hz, 1H), 4.07 (dd, $J = 12.4, 6.9$ Hz, 1H), 3.67 - 3.61 (m, 1H), 3.11 - 2.98 (m, 1H), 2.81 - 2.71 (m, 1H), 1.54 (s, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_{29}\text{H}_{25}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 489.2039, found 489.2029.



LH-023

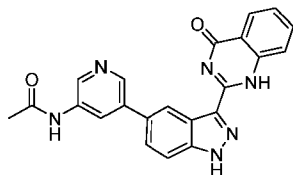
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.16 (s, 1H), 12.38 (s, 1H), 8.79 (d, $J = 1.1$ Hz, 1H), 8.52 (d, $J = 1.3$ Hz, 1H), 8.36 (d, $J = 1.3$ Hz, 1H), 8.13 (dd, $J = 7.4, 2.0$ Hz, 1H), 7.71 - 7.53 (m, 3H), 7.51 - 7.39 (m, 2H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 3.50 (s, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_{20}\text{H}_{15}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 355.1307, found 355.1301.



SPECIFICATION

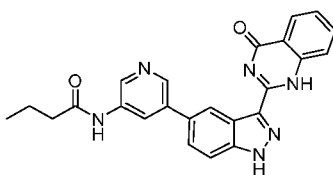
LH-024

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.42 (s, 1H), 12.27 (s, 1H), 8.83 - 8.73 (m, 2H), 8.48 (d, $J = 1.3$ Hz, 1H), 8.13 (dd, $J = 7.4, 2.0$ Hz, 1H), 7.89 (t, $J = 1.3$ Hz, 1H), 7.66 (dd, $J = 7.5, 2.0$ Hz, 1H), 7.63 - 7.50 (m, 2H), 7.45 (td, $J = 7.5, 2.0$ Hz, 1H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 2.48 (s, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{21}\text{H}_{16}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$: 354.1355, found 354.1350.



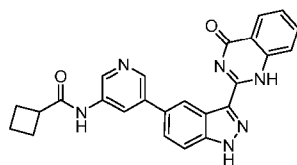
LH-025

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.52 (s, 1H), 12.22 (s, 1H), 9.80 (s, 1H), 9.58 (d, $J = 1.3$ Hz, 1H), 8.87 - 8.79 (m, 1H), 8.70 (d, $J = 1.3$ Hz, 1H), 8.13 (dd, $J = 7.5, 2.0$ Hz, 1H), 8.04 (t, $J = 1.3$ Hz, 1H), 7.71 - 7.55 (m, 3H), 7.45 (td, $J = 7.5, 2.0$ Hz, 1H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 2.20 (s, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{22}\text{H}_{17}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 397.1413, found 397.1410.



LH-026

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.62 (s, 1H), 12.12 (s, 1H), 9.80 (s, 1H), 9.60 (d, $J = 1.3$ Hz, 1H), 8.76 (d, $J = 1.6$ Hz, 1H), 8.68 (d, $J = 1.3$ Hz, 1H), 8.13 (dd, $J = 7.5, 2.1$ Hz, 1H), 7.91 (t, $J = 1.3$ Hz, 1H), 7.66 (dd, $J = 7.5, 2.0$ Hz, 1H), 7.65 - 7.49 (m, 2H), 7.45 (td, $J = 7.5, 2.0$ Hz, 1H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 2.37 (t, $J = 8.1$ Hz, 2H), 1.69 - 1.55 (m, 2H), 0.98 (t, $J = 8.0$ Hz, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{24}\text{H}_{21}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 425.1726, found 425.1720.

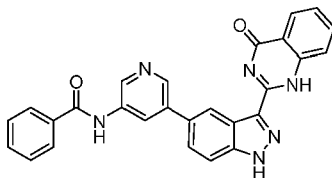


LH-027

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.55 (s, 1H), 12.14 (s, 1H), 9.80 (s, 1H), 9.62 (d, $J = 1.4$ Hz, 1H), 8.76 (d, $J = 1.5$ Hz, 1H), 8.68 (d, $J = 1.3$ Hz, 1H), 8.13 (dd, $J = 7.5, 2.0$ Hz, 1H), 7.91 (t, $J = 1.3$ Hz, 1H), 7.71 - 7.55 (m, 2H), 7.54 (dd, $J = 7.5, 1.5$ Hz, 1H),

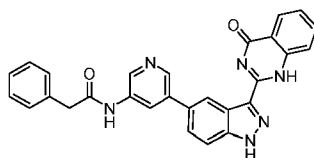
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7.45 (td, $J = 7.5, 2.0$ Hz, 1H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 3.22 (d, $J = 7.0$ Hz, 1H), 2.55 - 2.37 (m, 2H), 2.17 - 1.82 (m, 4H) ppm. HR-MS(ESI): Calculated for $C_{25}H_{21}N_6O_2$ $[M+H]^+$: 437.1726, found 437.1719.



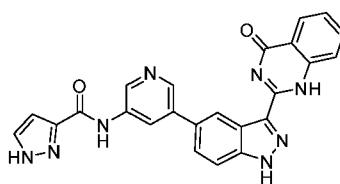
LH-028

^1H NMR (300 MHz, DMSO- d_6) δ 14.25 (s, 1H), 12.25 (s, 1H), 9.50 (d, $J = 1.3$ Hz, 1H), 8.86 (d, $J = 1.4$ Hz, 1H), 8.71 (d, $J = 1.3$ Hz, 1H), 8.14 (d, $J = 9.8$ Hz, 2H), 8.06 (d, $J = 1.2$ Hz, 1H), 8.02 - 7.90 (m, 2H), 7.71 - 7.40 (m, 6H), 7.31 (ddt, $J = 9.6, 7.2, 2.0$ Hz, 1H), 7.15 (td, $J = 7.5, 2.1$ Hz, 1H) ppm. HR-MS(ESI): Calculated for $C_{27}H_{19}N_6O_2$ $[M+H]^+$: 459.1569, found 459.1560.



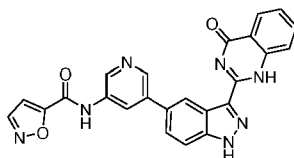
LH-029

^1H NMR (300 MHz, DMSO- d_6) δ 14.56 (s, 1H), 12.17 (s, 1H), 9.80 (s, 1H), 9.61 (d, $J = 1.2$ Hz, 1H), 8.71 (dd, $J = 14.1, 1.4$ Hz, 2H), 8.13 (dd, $J = 7.4, 2.0$ Hz, 1H), 7.81 (t, $J = 1.3$ Hz, 1H), 7.71 - 7.28 (m, 6H), 7.28 - 7.07 (m, 4H), 3.76 (s, 2H) ppm. HR-MS(ESI): Calculated for $C_{28}H_{21}N_6O_2$ $[M+H]^+$: 473.1726, found 473.1719.



LH-030

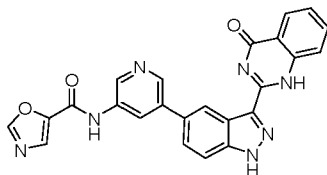
^1H NMR (300 MHz, DMSO- d_6) δ 14.16 (s, 1H), 12.12 (s, 1H), 12.35 (s, 1H), 9.53 - 9.42 (m, 2H), 8.83 (t, $J = 1.0$ Hz, 1H), 8.70 (d, $J = 1.3$ Hz, 1H), 8.19 - 8.02 (m, 2H), 7.71 - 7.55 (m, 3H), 7.45 (td, $J = 7.5, 2.0$ Hz, 1H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 6.86 (d, $J = 7.5$ Hz, 1H) ppm. HR-MS(ESI): Calculated for $C_{24}H_{17}N_8O_2$ $[M+H]^+$: 449.1474, found 449.1470.



SPECIFICATION

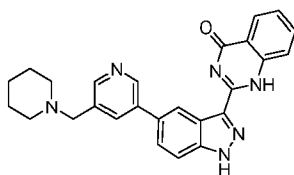
LH-031

^1H NMR (300 MHz, DMSO- d_6) δ 14.11 (s, 1H), 12.27 (s, 1H), 9.48 (d, J = 1.3 Hz, 2H), 8.90 (s, 1H), 8.80 (d, J = 1.5 Hz, 2H), 8.71 (d, J = 1.3 Hz, 2H), 8.13 (dd, J = 7.4, 2.0 Hz, 2H), 7.96 (t, J = 1.3 Hz, 2H), 7.67 (d, J = 2.0 Hz, 1H), 7.45 (s, 1H) ppm. HR-MS(ESI): Calculated for $\text{C}_{24}\text{H}_{16}\text{N}_7\text{O}_3$ $[\text{M}+\text{H}]^+$: 450.1315, found 450.1310.



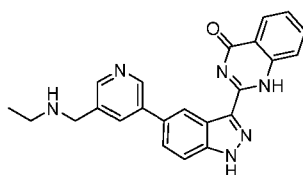
LH-032

^1H NMR (300 MHz, DMSO- d_6) δ 14.11 (s, 1H), 12.27 (s, 1H), 9.49 (d, J = 1.3 Hz, 1H), 8.90 (s, 1H), 8.79 (d, J = 1.5 Hz, 1H), 8.70 (d, J = 1.3 Hz, 1H), 8.13 (dd, J = 7.5, 2.0 Hz, 1H), 8.06 (s, 1H), 7.95 (t, J = 1.3 Hz, 1H), 7.71 - 7.50 (m, 3H), 7.45 (td, J = 7.5, 2.0 Hz, 1H), 7.39 (s, 1H), 7.14 (td, J = 7.5, 2.0 Hz, 1H) ppm. HR-MS(ESI): Calculated for $\text{C}_{24}\text{H}_{16}\text{N}_7\text{O}_3$ $[\text{M}+\text{H}]^+$: 450.1315, found 450.1309.



LH-033

^1H NMR (300 MHz, DMSO- d_6) δ 14.14 (s, 1H), 12.25 (s, 1H), 8.88 - 8.74 (m, 2H), 8.71 (d, J = 1.3 Hz, 1H), 8.23 - 8.13 (m, 2H), 7.71 - 7.51 (m, 3H), 7.45 (td, J = 7.5, 2.0 Hz, 1H), 7.14 (td, J = 7.5, 2.0 Hz, 1H), 3.69 (s, 2H), 2.43 (t, J = 5.3 Hz, 4H), 1.62 - 1.36 (m, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{26}\text{H}_{25}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 437.2090, found 437.2088.

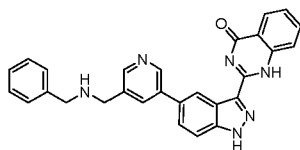


LH-034

^1H NMR (300 MHz, DMSO- d_6) δ 14.63 (s, 1H), 12.32 (s, 1H), 8.86 - 8.70 (m, 3H), 8.18 - 8.04 (m, 2H), 7.71 - 7.51 (m, 3H), 7.45 (td, J = 7.5, 2.0 Hz, 1H), 7.14 (td, J = 7.5, 2.0 Hz, 1H), 3.65 (s, 2H), 2.59 (q, J = 8.0 Hz, 2H), 1.37 (s, 1H), 1.11 (t, J = 8.0 Hz, 3H) ppm. HR-MS(ESI): Calculated for $\text{C}_{23}\text{H}_{21}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 397.1777, found

SPECIFICATION

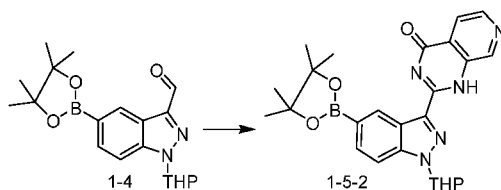
397.1770.



LH-035

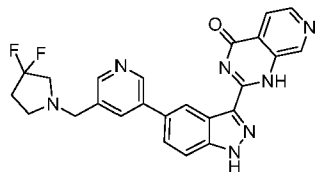
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.51 (s, 1H), 12.31 (s, 1H), 8.84 - 8.74 (m, 2H), 8.65 (d, $J = 1.3$ Hz, 1H), 8.20 - 8.09 (m, 2H), 7.71 - 7.56 (m, 3H), 7.51 - 7.20 (m, 6H), 7.14 (td, $J = 7.5, 2.0$ Hz, 1H), 3.65 (s, 4H), 1.69 (s, 1H) ppm. HR-MS(ESI): Calculated for $\text{C}_{28}\text{H}_{23}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 459.1933, found 459.1926.

Example 2: Synthesis of LH-036



Intermediate 1-4 (0.1 mmol) was added to a single-necked flask and dissolved with 5 mL of dimethylacetamide. 3-Aminopyridine-4-carboxamide (0.15 mmol), *p*-toluenesulfonic acid hydrate (0.15 mmol), and sodium bisulfite (0.15 mmol) were then added, and the mixture was reacted at 120 °C for 6-8 h. After the TLC reaction was completed, the reaction mixture was extracted with ethyl acetate and saturated brine three times. The organic phases were combined, dried, concentrated, and purified by column chromatography to give intermediate 1-5-2. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.31 (s, 1H), 9.47 (s, 1H), 8.41 - 8.27 (m, 2H), 8.13 (d, $J = 1.6$ Hz, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.37 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.31 (t, $J = 6.9$ Hz, 1H), 3.90 (dt, $J = 11.4, 7.0$ Hz, 1H), 3.77 (dt, $J = 11.4, 7.0$ Hz, 1H), 2.52 - 2.32 (m, 1H), 2.12 - 1.91 (m, 2H), 1.86 - 1.48 (m, 3H), 1.42 (d, $J = 14.9$ Hz, 12H) ppm. HR-MS(ESI): Calculated for $\text{C}_{25}\text{H}_{29}\text{BN}_5\text{O}_4$ $[\text{M}+\text{H}]^+$: 474.2313, found 474.2310. The yield was 75%.

The other steps were the same as those in Example 1 to give compound LH-036.



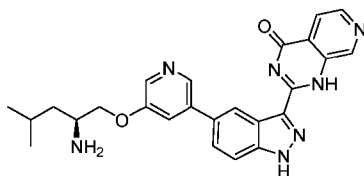
LH-036

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.19 (s, 1H), 12.66 (s, 1H), 9.29 (s, 1H), 8.97 (s, 1H), 8.90 (s, 1H), 8.69 (d, $J = 5.1$ Hz, 1H), 8.61 (s, 1H), 8.18 (s, 1H), 8.02 (d, $J = 5.1$

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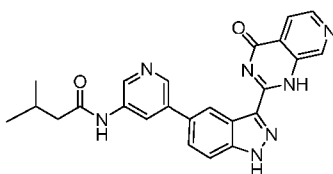
Hz, 1H), 7.88 (q, $J = 8.7$ Hz, 2H), 3.95 (s, 2H), 3.17 - 3.08 (m, 2H), 2.93 (t, $J = 6.9$ Hz, 2H), 2.38 (dq, $J = 15.3, 7.9, 7.4$ Hz, 2H) ppm. HR-MS(ESI): Calculated for $C_{24}H_{20}F_2N_7O$ $[M+H]^+$: 460.1697, found 460.1690.

The following compounds were prepared using a procedure similar to that in Example 2:



LH-037

^1H NMR (300 MHz, DMSO- d_6) δ 14.55 (s, 1H), 12.33 (s, 1H), 9.47 (s, 1H), 8.76 (t, $J = 1.0$ Hz, 1H), 8.65 (d, $J = 1.3$ Hz, 1H), 8.40 (d, $J = 5.0$ Hz, 1H), 8.31 (d, $J = 5.0$ Hz, 1H), 8.22 (d, $J = 1.4$ Hz, 1H), 7.61 (dd, $J = 16.8, 1.2$ Hz, 3H), 4.33 (dd, $J = 12.4, 7.0$ Hz, 1H), 4.08 (dd, $J = 12.4, 7.0$ Hz, 1H), 3.23 - 3.13 (m, 1H), 1.73 - 1.58 (m, 2H), 1.58 - 1.40 (m, 1H), 1.34 (s, 2H), 0.99 - 0.82 (m, 6H) ppm. HR-MS(ESI): Calculated for $C_{25}H_{26}N_7O_2$ $[M+H]^+$: 456.2148, found 456.2140.

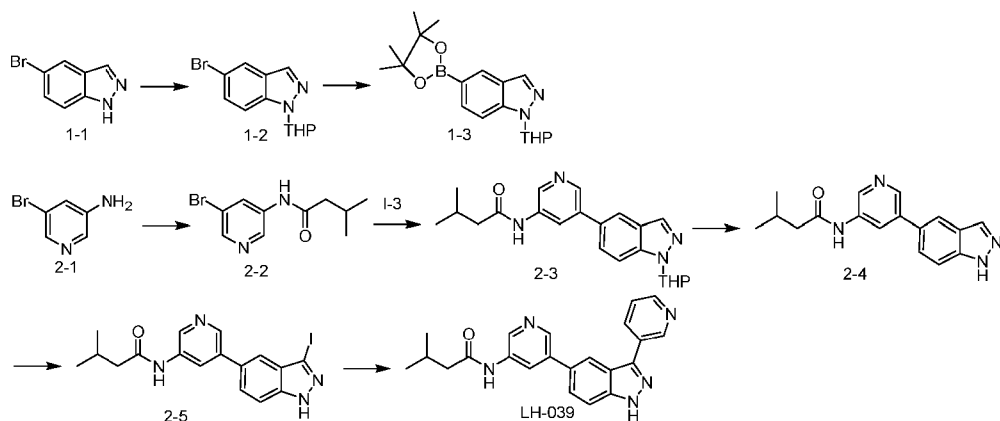


LH-038

^1H NMR (300 MHz, DMSO- d_6) δ 14.34 (s, 1H), 12.21 (s, 1H), 9.80 (s, 1H), 9.64 (d, $J = 1.4$ Hz, 1H), 9.47 (s, 1H), 8.82 - 8.70 (m, 2H), 8.40 (d, $J = 5.0$ Hz, 1H), 8.31 (d, $J = 5.0$ Hz, 1H), 8.00 (s, 1H), 7.61 (d, $J = 1.0$ Hz, 2H), 2.22 - 2.05 (m, 3H), 1.08 - 0.93 (m, 6H) ppm. HR-MS(ESI): Calculated for $C_{24}H_{22}N_7O_2$ $[M+H]^+$: 440.1835, found 440.1835.

Example 3: Synthesis of LH-039

SPECIFICATION



Synthesis of intermediate 1-2:

Intermediate 1-1 (0.1 mmol) was added to a three-necked flask. Tetrahydrofuran (50 mL) and *p*-toluenesulfonic acid (0.02 mmol) were added, and 3,4-dihydropyran (0.2 mmol) was added dropwise at room temperature. The mixture was reacted at 65 °C for 8 h. After the TLC reaction was completed, the reaction mixture was concentrated by rotary evaporation under reduced pressure to remove the solvent, and purified by silica gel column chromatography to give white solid I-2. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 7.97 (d, $J = 1.5$ Hz, 1H), 7.89 (s, 1H), 7.40 - 7.27 (m, 2H), 6.27 - 6.16 (m, 1H), 3.90 (dt, $J = 11.4, 7.0$ Hz, 1H), 3.77 (dt, $J = 11.5, 7.0$ Hz, 1H), 2.38 - 2.16 (m, 1H), 2.04 - 2.01 (m, 2H), 1.84 - 1.65 (m, 1H), 1.58 - 1.32 (m, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_{12}\text{H}_{14}\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 281.0290, found 281.0292. The yield was 85%.

Synthesis of intermediate 1-3:

Intermediate 1-2 (0.1 mmol) was added to a single-necked flask, and bis(pinacolato)diboron (0.12 mmol), potassium acetate (0.3 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.005 mmol), and dioxane (26 mL) were added. The mixture was warmed at reflux for 6 h. After the TLC reaction was completed, the reaction mixture was cooled, filtered under vacuum, concentrated by rotary evaporation, and purified by silica gel column chromatography to give white solid 1-3. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 7.97 (d, $J = 1.5$ Hz, 1H), 7.82 - 7.74 (m, 1H), 7.39 (d, $J = 7.5$ Hz, 1H), 7.25 (dd, $J = 7.5, 1.5$ Hz, 1H), 6.21 (t, $J = 6.9$ Hz, 1H), 3.90 (dt, $J = 11.4, 7.0$ Hz, 1H), 3.77 (dt, $J = 11.4, 7.0$ Hz, 1H), 2.40 - 2.21 (m, 1H), 2.16 - 1.91 (m, 2H), 1.85 - 1.48 (m, 3H), 1.40 (d, $J = 15.1$ Hz, 12H) ppm. HR-MS(ESI): Calculated for $\text{C}_{18}\text{H}_{26}\text{BN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 329.2036, found 329.2033. The yield was 89%.

Synthesis of intermediate 2-2:

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Starting material 2-1 (0.1 mmol) was dissolved in tetrahydrofuran. Triethylamine (0.15 mmol) and isovaleric anhydride (0.15 mmol) were added, and the mixture was warmed at reflux for 6-8 h. After the reaction was completed as detected by TLC, the reaction mixture was concentrated under reduced pressure to remove the solvent, the reaction solution was poured into an ice saturated sodium hydroxide solution to remove excess anhydride, and the mixture was extracted with ethyl acetate and saturated brine three times. The organic phases were combined, dried, and concentrated to give yellow powdery solid 2-2. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.80 (s, 1H), 9.58 (d, $J = 1.3$ Hz, 1H), 8.49 (d, $J = 1.3$ Hz, 1H), 7.87 (t, $J = 1.3$ Hz, 1H), 2.24 (m, 1H), 2.10 (d, $J = 6.9$ Hz, 2H), 0.95 (d, $J = 6.7$ Hz, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{10}\text{H}_{14}\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 257.0290, found 257.0286. The yield was 85%.

Synthesis of intermediate 2-3:

Intermediate 2-2 (0.1 mmol), intermediate 1-3 (0.1 mmol), sodium carbonate (0.3 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.005 mmol), dioxane (9 mL), and water (1.5 mL) were added to a single-necked flask, and the system was purged of air with nitrogen 4 times. The mixture was warmed at reflux for 8 h. After the mixture was cooled, the mixture was filtered under vacuum, concentrated to dryness by rotary evaporation, and purified by silica gel column chromatography to give intermediate 2-3. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.80 (s, 1H), 9.63 (d, $J = 1.3$ Hz, 1H), 8.69 (d, $J = 1.3$ Hz, 1H), 8.19 (t, $J = 1.6$ Hz, 1H), 8.03 (d, $J = 1.5$ Hz, 1H), 7.90 (t, $J = 1.3$ Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.51 (dd, $J = 7.5, 1.5$ Hz, 1H), 6.25 (t, $J = 6.9$ Hz, 1H), 3.90 (dt, $J = 11.5, 7.0$ Hz, 1H), 3.77 (dt, $J = 11.5, 7.0$ Hz, 1H), 2.64 - 2.57 (qd, $J = 12.4, 7.0$ Hz, 2H), 2.39 - 2.13 (m, 2H), 2.13 - 1.91 (m, 2H), 1.85 - 1.48 (m, 3H), 0.95 (dd, $J = 15.0, 6.8$ Hz, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{22}\text{H}_{27}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 379.2134, found 379.2132. The yield was 78%.

Synthesis of intermediate 2-4:

Intermediate 2-3 (0.1 mmol) was dissolved in 10 mL of tetrahydrofuran. *p*-Toluenesulfonic acid hydrate (1 mmol) was added at room temperature, and the mixture was warmed at reflux for 16-24 h. After the reaction was completed as detected by TLC, the reaction mixture was concentrated under reduced pressure and extracted with dichloromethane and saturated sodium bicarbonate. The organic phases were combined, dried, and concentrated to give intermediate 2-4. ^1H NMR (300 MHz,

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DMSO- d_6) δ 12.75 (s, 1H), 9.80 (s, 1H), 9.63 (d, $J = 1.3$ Hz, 1H), 8.50 (d, $J = 1.3$ Hz, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.96 (t, $J = 1.5$ Hz, 1H), 7.61 (t, $J = 1.3$ Hz, 1H), 7.43 - 7.24 (m, 2H), 2.24 - 2.05 (m, 3H), 0.95 (d, $J = 6.3$ Hz, 6H) ppm. HR-MS(ESI): Calculated for $C_{17}H_{19}N_4O$ $[M+H]^+$: 295.1559, found 295.1554. The yield was 74%.

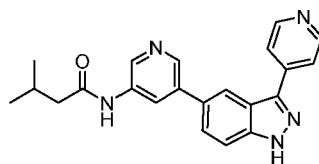
Synthesis of intermediate 2-5:

Intermediate 2-3 (0.1 mmol) was dissolved in 5 mL of dimethylformamide. Potassium hydroxide (0.15 mmol) and iodine (0.15 mmol) were added, and the mixture was stirred at room temperature for 16-24 h. After the reaction was completed as detected by TLC, the reaction mixture was extracted with ethyl acetate and saturated brine three times. The organic phases were combined, dried, and concentrated to give the intermediate 2-5. ^1H NMR (300 MHz, DMSO- d_6) δ 12.35 (s, 1H), 9.64 (s, 1H), 9.25 (d, $J = 1.3$ Hz, 1H), 8.57 (d, $J = 1.3$ Hz, 1H), 7.23 (t, $J = 1.5$ Hz, 1H), 7.4 (t, $J = 1.3$ Hz, 1H), 7.40 - 7.22 (m, 2H), 2.24 - 2.05 (m, 3H), 0.82 (d, $J = 6.3$ Hz, 6H) ppm. HR-MS(ESI): Calculated for $C_{17}H_{18}IN_4O$ $[M+H]^+$: 421.0525, found 421.0525. The yield was 65%.

Synthesis of LH-039:

Intermediate 2-5 (0.1 mmol), 3-pyridineboronic acid (0.1 mmol), sodium carbonate (0.3 mmol), Pd(dppf)Cl₂ (0.005 mmol), dioxane (9 mL), and water (1.5 mL) were added to a single-necked flask, and the system was purged of air with nitrogen 4 times. The mixture was warmed at reflux for 8 h. After the mixture was cooled, the mixture was filtered under vacuum, concentrated to dryness by rotary evaporation, and purified by silica gel column chromatography to give LH-039. ^1H NMR (300 MHz, DMSO- d_6) δ 13.62 (s, 1H), 10.23 (s, 1H), 9.30 (d, $J = 2.2$ Hz, 1H), 8.82 (d, $J = 2.3$ Hz, 1H), 8.74 (d, $J = 2.1$ Hz, 1H), 8.67 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.49 (dt, $J = 7.9, 2.0$ Hz, 1H), 8.40 - 8.32 (m, 2H), 7.83 - 7.73 (m, 2H), 7.60 (dd, $J = 8.0, 4.8$ Hz, 1H), 2.29 (d, $J = 7.1$ Hz, 2H), 2.14 (dq, $J = 13.5, 6.6$ Hz, 1H), 1.00 (s, 3H), 0.98 (s, 3H) ppm. HR-MS(ESI): Calculated for $C_{22}H_{22}N_5O$ $[M+H]^+$: 372.1824, found 372.1818.

The following compounds were prepared using a procedure similar to that in Example 3:



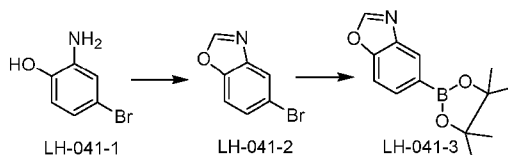
LH-040

^1H NMR (300 MHz, DMSO- d_6) δ 13.74 (s, 1H), 10.22 (s, 1H), 8.79 (t, $J = 3.3$ Hz, 1H),

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8.70 (dd, $J = 4.9, 1.8$ Hz, 3H), 8.40 - 8.30 (m, 2H), 8.11 - 8.01 (m, 2H), 7.81 - 7.66 (m, 2H), 2.25 (d, $J = 7.1$ Hz, 2H), 2.11 (dt, $J = 13.7, 6.8$ Hz, 1H), 0.96 (s, 3H), 0.93 (d, $J = 4.7$ Hz, 3H) ppm. HR-MS(ESI): Calculated for $C_{22}H_{22}N_5O$ $[M+H]^+$: 372.1824, found 372.1819.

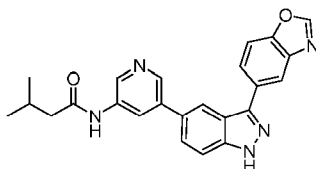
Example 4: Synthesis of LH-041



Starting material LH-041-1 (2-amino-4-bromophenol, 0.1 mmol) was dissolved in triethyl orthoformate. The mixture was refluxed overnight, concentrated under reduced pressure, and purified by column chromatography to give intermediate LH-041-2. ^1H NMR (300 MHz, $DMSO-d_6$) δ 8.25 (s, 1H), 7.58 (d, $J = 1.5$ Hz, 1H), 7.49 (dd, $J = 7.5, 1.6$ Hz, 1H), 7.25 (d, $J = 7.5$ Hz, 1H) ppm. HR-MS(ESI): Calculated for C_7H_5BrNO $[M+H]^+$: 197.9555, found 197.9523. The yield was 57%.

Intermediate LH-041-2 (0.1 mmol) was added to a single-necked flask, and bis(pinacolato)diboron (0.12 mmol), potassium acetate (0.3 mmol), $Pd(dppf)Cl_2$ (0.005 mmol), and dioxane (25 mL) were added. The mixture was warmed at reflux for 6 h. After the TLC reaction was completed, the reaction mixture was cooled, filtered under vacuum, concentrated by rotary evaporation, and purified by silica gel column chromatography to give intermediate LH-041-3. ^1H NMR (300 MHz, $DMSO-d_6$) δ 8.25 (s, 1H), 7.75 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.58 (d, $J = 7.4$ Hz, 1H), 7.48 (d, $J = 1.5$ Hz, 1H), 1.40 (s, 12H) ppm. HR-MS(ESI): Calculated for $C_{13}H_{17}BNO_3$ $[M+H]^+$: 246.1301, found 246.1281. The yield was 88%.

The other steps were the same as those in Example 3 to give compound LH-041.



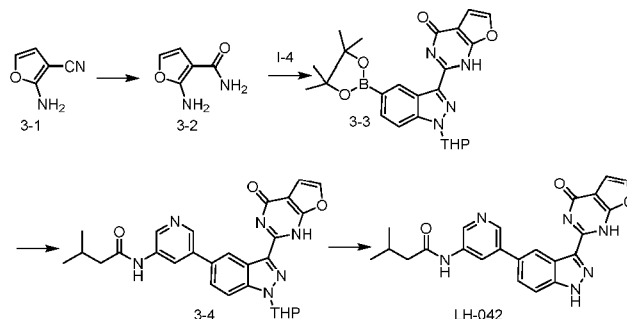
LH-041

^1H NMR (300 MHz, $DMSO-d_6$) δ 13.44 (s, 1H), 10.19 (s, 1H), 8.83 (s, 1H), 8.78 (d, $J = 2.3$ Hz, 1H), 8.70 (d, $J = 2.1$ Hz, 1H), 8.41 (d, $J = 1.6$ Hz, 1H), 8.34 (t, $J = 2.2$ Hz, 1H), 8.30 (d, $J = 1.4$ Hz, 1H), 8.14 (dd, $J = 8.5, 1.7$ Hz, 1H), 7.92 (dd, $J = 8.5, 0.6$ Hz, 1H), 7.78 - 7.67 (m, 1H), 6.54 (s, 1H), 2.25 (d, $J = 7.1$ Hz, 2H), 2.18 - 2.04 (m, 1H),

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0.96 (s, 3H), 0.94 (s, 3H) ppm. HR-MS(ESI): Calculated for $C_{24}H_{22}N_5O_2$ $[M+H]^+$: 412.1773, found 412.1769.

Example 5: Synthesis of LH-042



Synthesis of intermediate 3-2:

3-1 (0.1 mmol) was added into a single-necked flask, excess concentrated sulfuric acid was then added, and the mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction system was cooled to 0 °C, and the mixture was alkalinified with a 10% sodium hydroxide solution and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate, and the solvent was removed under vacuum. Recrystallization in ethanol was then performed to give 3-2.

Synthesis of intermediate 3-3:

Intermediate 3-2 (0.1 mmol) was added to a single-necked flask and dissolved with ethanol. Intermediate 1-4 in Example 1 (0.1 mmol) and iodine (0.1 mmol) were then added, and the mixture was refluxed at 80 °C for 8 h. After the TLC reaction was completed, 5% sodium thiosulfate was added to quench the reaction, and the mixture was extracted with dichloro and saturated brine. The organic phases were combined, dried, concentrated, and purified by column chromatography to give intermediate 3-3.

Synthesis of intermediate 3-4:

Intermediate 2-2 in Example 1 (0.1 mmol), intermediate 3-3 (0.1 mmol), sodium carbonate (0.3 mmol), Pd(dppf)Cl₂ (0.005 mmol), dioxane (9 mL), and water (1.5 mL) were added to a single-necked flask, and the system was purged of air with nitrogen 4 times. The mixture was warmed at reflux for 8 h. After the mixture was cooled, the mixture was filtered under vacuum, concentrated to dryness by rotary evaporation, and purified by silica gel column chromatography to give intermediate 3-4.

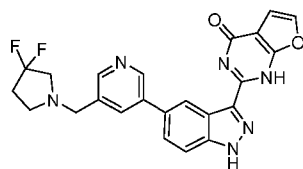
Synthesis of LH-042:

Intermediate 3-4 (0.1 mmol) was added into a 50 mL single-necked flask and dissolved

SPECIFICATION

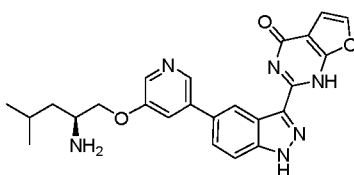
with 10 mL of dichloromethane. Excess trifluoroacetic acid (1 mmol) was added, and the mixture was stirred at room temperature overnight. After the reaction was completed as monitored by TLC, the reaction mixture was concentrated under vacuum to remove the solvent and excess trifluoroacetic acid, mixed with silica gel, and purified by column chromatography to give LH-042. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 14.26 (s, 1H), 12.20 (s, 1H), 10.12 (s, 1H), 9.80 (s, 1H), 9.59 (d, $J = 1.3$ Hz, 1H), 8.75 (d, $J = 1.5$ Hz, 1H), 8.68 (d, $J = 1.3$ Hz, 1H), 8.36 (s, 1H), 7.91 (t, $J = 1.2$ Hz, 1H), 7.64 - 7.49 (m, 2H), 6.88 (q, $J = 7.5$ Hz, 2H), 2.53 - 2.32 (m, 1H), 2.10 (d, $J = 7.0$ Hz, 2H), 0.96 (d, $J = 6.7$ Hz, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{23}\text{H}_{21}\text{N}_6\text{O}_3$ $[\text{M}+\text{H}]^+$: 429.1675, found 429.1670.

The following compounds were prepared using a procedure similar to that in Example 5:



LH-043

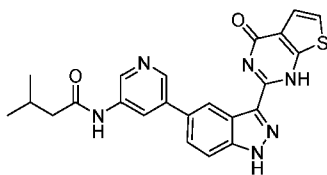
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.64(s, 1H), 10.34 (s, 1H), 8.83 (d, $J = 1.3$ Hz, 1H), 8.74 (dd, $J = 6.1, 1.5$ Hz, 2H), 8.08 (t, $J = 1.3$ Hz, 1H), 7.63 - 7.50 (m, 2H), 7.31 (d, $J = 7.5$ Hz, 1H), 6.98 (d, $J = 7.5$ Hz, 1H), 3.69 (s, 2H), 2.70 - 2.55 (m, 4H), 1.91 - 1.87 (m, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_{23}\text{H}_{19}\text{F}_2\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$: 449.1538, found 449.1528.



LH-044

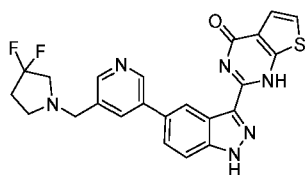
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.12(s, 1H), 10.15 (s, 1H), 8.79 - 8.71 (m, 1H), 8.60 (d, $J = 1.3$ Hz, 1H), 8.18 (d, $J = 1.4$ Hz, 1H), 7.60 (dt, $J = 16.7, 1.4$ Hz, 3H), 7.31 (d, $J = 7.5$ Hz, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 4.32 (dd, $J = 12.4, 7.0$ Hz, 1H), 4.09 (dd, $J = 12.4, 7.0$ Hz, 1H), 3.22 - 3.05 (m, 1H), 1.73 - 1.41 (m, 3H), 1.54 (s, 2H), 0.99 - 0.81 (m, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{24}\text{H}_{25}\text{N}_6\text{O}_3$ $[\text{M}+\text{H}]^+$: 445.1988, found 445.1976.

SPECIFICATION



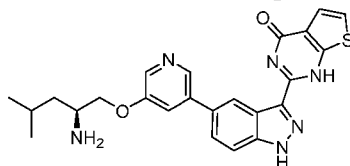
LH-045

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.24 (s, 1H), 10.31 (s, 1H), 9.80 (s, 1H), 9.60 (d, J = 1.3 Hz, 1H), 8.76 (d, J = 1.5 Hz, 1H), 8.68 (d, J = 1.3 Hz, 1H), 7.91 (t, J = 1.2 Hz, 1H), 7.65 - 7.49 (m, 2H), 7.36 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 2.32 (dt, J = 13.6, 6.8 Hz, 1H), 2.10 (d, J = 7.0 Hz, 2H), 0.96 (d, J = 6.8 Hz, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{23}\text{H}_{21}\text{N}_6\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 445.1447, found 445.1438.



LH-046

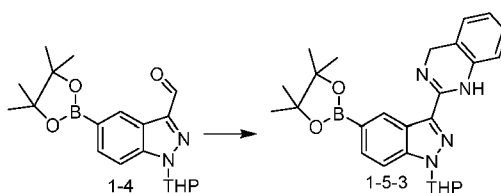
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.26 (s, 1H), 10.18 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.81 - 8.68 (m, 2H), 8.10 (t, J = 1.3 Hz, 1H), 7.64 - 7.50 (m, 2H), 7.36 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 3.69 (s, 2H), 2.70 - 2.55 (m, 4H), 1.91 - 1.75 (m, 2H) ppm. HR-MS(ESI): Calculated for $\text{C}_{23}\text{H}_{19}\text{F}_2\text{N}_6\text{OS}$ $[\text{M}+\text{H}]^+$: 465.1309, found 465.1298.



LH-047

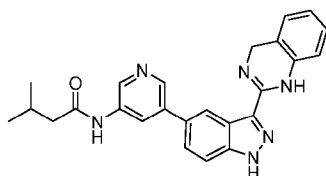
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.24 (s, 1H), 10.12 (s, 1H), 8.77 (t, J = 1.0 Hz, 1H), 8.60 (d, J = 1.3 Hz, 1H), 8.18 (d, J = 1.3 Hz, 1H), 7.60 (dt, J = 15.1, 1.4 Hz, 3H), 7.36 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 4.31 (dd, J = 12.4, 7.0 Hz, 1H), 4.09 (dd, J = 12.4, 7.0 Hz, 1H), 3.13 - 2.92 (m, 1H), 1.75 - 1.41 (m, 3H), 1.52 (s, 2H), 0.90 (dd, J = 15.0, 6.5 Hz, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{24}\text{H}_{25}\text{N}_6\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 461.1760, found 461.1756.

Example 6: Synthesis of LH-048



SPECIFICATION

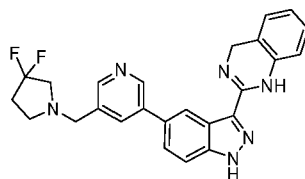
Intermediate 1-4 in route 1 (0.1 mmol) was added to a single-necked flask and dissolved with 10 mL of dimethylacetamide. *o*-Aminobenzylamine (0.15 mmol), *p*-toluenesulfonic acid hydrate (0.15 mmol), and sodium bisulfite (0.15 mmol) were then added, and the mixture was reacted at 120 °C for 6-8 h. After the TLC reaction was completed, the reaction mixture was extracted with ethyl acetate and saturated brine three times. The organic phases were combined, dried, concentrated, and purified by column chromatography to give intermediate 1-5-3. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.24 (s, 1H), 7.99 (d, *J* = 1.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.15 - 7.10 (m, 1H), 7.04 (td, *J* = 7.4, 2.0 Hz, 1H), 6.89 (td, *J* = 7.5, 2.1 Hz, 1H), 6.41 (dd, *J* = 7.4, 2.1 Hz, 1H), 6.26 (t, *J* = 6.9 Hz, 1H), 4.94 (d, *J* = 1.1 Hz, 2H), 3.90 (dt, *J* = 11.4, 7.0 Hz, 1H), 3.77 (dt, *J* = 11.5, 7.0 Hz, 1H), 2.52 - 2.32 (m, 1H), 2.12 - 1.91 (m, 2H), 1.86 - 1.48 (m, 3H), 1.41 (d, *J* = 14.9 Hz, 12H) ppm. HR-MS(ESI): Calculated for C₂₆H₃₂BN₄O₃ [M+H]⁺: 459.2567, found 459.2558. The yield was 78%. The other steps were the same as those in Example 1 to give compound LH-048.



LH-048

¹H NMR (300 MHz, DMSO-*d*₆) δ 12.36 (s, 1H), 10.28 (s, 1H), 9.80 (s, 1H), 9.51 (d, *J* = 1.3 Hz, 1H), 8.67 (d, *J* = 1.3 Hz, 1H), 8.47 (d, *J* = 1.5 Hz, 1H), 7.99 (t, *J* = 1.3 Hz, 1H), 7.62 - 7.47 (m, 2H), 7.15 - 7.11 (m, 1H), 7.04 (td, *J* = 7.5, 2.1 Hz, 1H), 6.90 (td, *J* = 7.5, 2.1 Hz, 1H), 6.41 (dd, *J* = 7.5, 2.1 Hz, 1H), 2.60 (d, *J* = 1.0 Hz, 2H), 2.29 (dd, *J* = 13.5, 6.8 Hz, 1H), 2.10 (d, *J* = 6.9 Hz, 2H), 0.96 (d, *J* = 6.7 Hz, 6H) ppm. HR-MS(ESI): Calculated for C₂₅H₂₅N₆O [M+H]⁺: 425.2090, found 425.2088.

The following compounds were prepared using a procedure similar to that in Example 6:

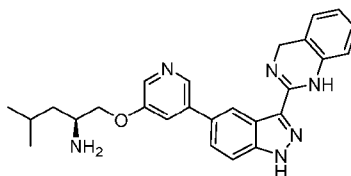


LH-049

¹H NMR (300 MHz, DMSO-*d*₆) δ 12.11 (s, 1H), 10.22 (s, 1H), 8.82 (d, *J* = 1.3 Hz, 1H), 8.71 (d, *J* = 1.3 Hz, 1H), 8.48 (d, *J* = 1.4 Hz, 1H), 8.08 (t, *J* = 1.3 Hz, 1H), 7.60 - 7.48

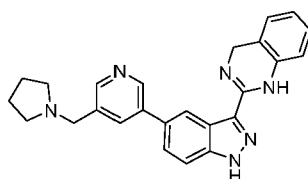
SPECIFICATION

(m, 2H), 7.15 - 7.05 (m, 1H), 7.04 (td, $J = 7.5$, 2.0 Hz, 1H), 6.90 (td, $J = 7.4$, 2.0 Hz, 1H), 6.41 (dd, $J = 7.5$, 2.1 Hz, 1H), 3.69 (s, 2H), 2.70 - 2.55 (m, 2H), 2.60 (s, 3H), 1.91 - 1.75 (m, 2H) ppm. HR-MS(ESI): Calculated for $C_{25}H_{23}F_2N_6$ $[M+H]^+$: 445.1952, found 445.1949.



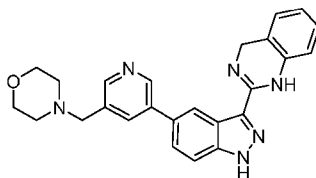
LH-050

^1H NMR (300 MHz, $DMSO-d_6$) δ 14.21 (s, 1H), 12.31 (s, 1H), 8.56 - 8.42 (m, 2H), 8.15 (d, $J = 1.3$ Hz, 1H), 7.57 (dd, $J = 13.9$, 1.2 Hz, 3H), 7.15 (ddt, $J = 7.4$, 2.1, 1.1 Hz, 1H), 7.04 (td, $J = 7.5$, 2.1 Hz, 1H), 6.90 (td, $J = 7.4$, 2.0 Hz, 1H), 6.41 (dd, $J = 7.5$, 2.1 Hz, 1H), 4.95 (d, $J = 1.2$ Hz, 2H), 4.33 (dd, $J = 12.4$, 7.0 Hz, 1H), 4.08 (dd, $J = 12.4$, 7.0 Hz, 1H), 3.13 - 3.07 (m, 1H), 1.74 - 1.39 (m, 3H), 1.56 (s, 2H), 0.90 (dd, $J = 15.0$, 6.4 Hz, 6H) ppm. HR-MS(ESI): Calculated for $C_{26}H_{29}N_6O$ $[M+H]^+$: 441.2403, found 441.2395.



LH-051

^1H NMR (300 MHz, $DMSO-d_6$) δ 12.32 (s, 1H), 10.21 (s, 1H), 8.82 (d, $J = 1.2$ Hz, 1H), 8.69 (d, $J = 1.3$ Hz, 1H), 8.49 (t, $J = 1.0$ Hz, 1H), 8.10 (t, $J = 1.3$ Hz, 1H), 7.55 (s, 1H), 7.15 (ddt, $J = 7.4$, 2.1, 1.0 Hz, 1H), 7.04 (td, $J = 7.5$, 2.1 Hz, 1H), 6.90 (td, $J = 7.4$, 2.0 Hz, 1H), 6.41 (dd, $J = 7.4$, 2.1 Hz, 1H), 3.69 (s, 2H), 2.68 - 2.51 (m, 3H), 2.60 (s, 4H), 1.91 - 1.74 (m, 4H) ppm. HR-MS(ESI): Calculated for $C_{25}H_{25}N_6$ $[M+H]^+$: 409.2141, found 409.2098.

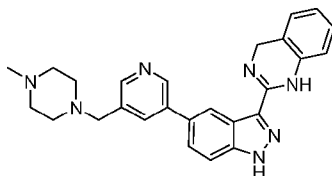


LH-052

^1H NMR (300 MHz, $DMSO-d_6$) δ 12.30 (s, 1H), 10.29 (s, 1H), 8.82 (d, $J = 1.3$ Hz, 1H), 8.70 (d, $J = 1.3$ Hz, 1H), 8.49 (d, $J = 1.9$ Hz, 1H), 8.09 (t, $J = 1.3$ Hz, 1H), 7.60 - 7.48

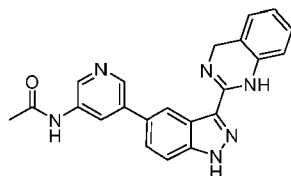
SPECIFICATION

(m, 2H), 7.15 (ddt, $J = 7.5, 2.1, 1.0$ Hz, 1H), 7.04 (td, $J = 7.5, 2.1$ Hz, 1H), 6.90 (td, $J = 7.4, 2.0$ Hz, 1H), 6.41 (dd, $J = 7.5, 2.1$ Hz, 1H), 3.69 (s, 2H), 3.58 (t, $J = 4.7$ Hz, 4H), 2.60 (d, $J = 1.0$ Hz, 2H), 2.39 (t, $J = 4.7$ Hz, 4H) ppm. HR-MS(ESI): Calculated for $C_{25}H_{25}N_6O$ $[M+H]^+$: 425.2090, found 425.2081.



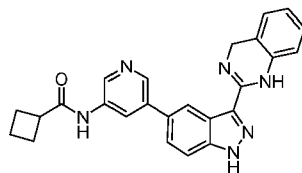
LH-053

^1H NMR (300 MHz, DMSO- d_6) δ 12.33 (s, 1H), 10.21 (s, 1H), 8.82 (d, $J = 1.3$ Hz, 1H), 8.69 (d, $J = 1.3$ Hz, 1H), 8.49 (t, $J = 1.0$ Hz, 1H), 8.10 (t, $J = 1.3$ Hz, 1H), 7.55 (s, 2H), 7.15 (ddt, $J = 7.5, 2.2, 1.0$ Hz, 1H), 7.04 (td, $J = 7.5, 2.0$ Hz, 1H), 6.90 (td, $J = 7.5, 2.1$ Hz, 1H), 6.41 (dd, $J = 7.5, 2.1$ Hz, 1H), 3.69 (s, 2H), 2.60 (d, $J = 1.0$ Hz, 2H), 2.48 (t, $J = 5.1$ Hz, 4H), 2.34 (t, $J = 5.2$ Hz, 4H), 2.24 (s, 3H) ppm. HR-MS(ESI): Calculated for $C_{26}H_{28}N_7$ $[M+H]^+$: 438.2406, found 438.2395.



LH-054

^1H NMR (300 MHz, DMSO- d_6) δ 13.26 (s, 1H), 12.22 (s, 1H), 9.80 (s, 1H), 9.58 (d, $J = 1.3$ Hz, 1H), 8.67 (d, $J = 1.3$ Hz, 1H), 8.47 (d, $J = 1.5$ Hz, 1H), 7.91 (t, $J = 1.2$ Hz, 1H), 7.61 - 7.47 (m, 2H), 7.15 (ddt, $J = 7.4, 2.1, 1.0$ Hz, 1H), 7.04 (td, $J = 7.5, 2.1$ Hz, 1H), 6.90 (td, $J = 7.4, 2.0$ Hz, 1H), 6.41 (dd, $J = 7.5, 2.1$ Hz, 1H), 2.60 (d, $J = 1.0$ Hz, 2H), 2.20 (s, 3H) ppm. HR-MS(ESI): Calculated for $C_{22}H_{19}N_6O$ $[M+H]^+$: 383.1620, found 383.1598.

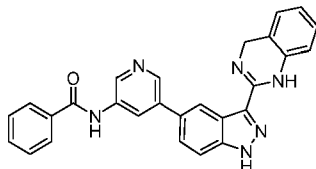


LH-055

^1H NMR (300 MHz, DMSO- d_6) δ 13.26 (s, 1H), 12.22 (s, 1H), 9.80 (s, 1H), 9.61 (d, $J = 1.3$ Hz, 1H), 8.67 (d, $J = 1.3$ Hz, 1H), 8.47 (d, $J = 1.4$ Hz, 1H), 7.90 (t, $J = 1.3$ Hz, 1H), 7.61 - 7.47 (m, 2H), 7.15 (ddt, $J = 7.4, 2.1, 1.0$ Hz, 1H), 7.04 (td, $J = 7.5, 2.1$ Hz,

SPECIFICATION

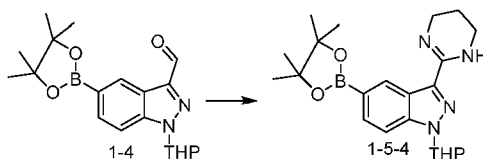
1H), 6.90 (td, $J = 7.4, 2.0$ Hz, 1H), 6.41 (dd, $J = 7.5, 2.1$ Hz, 1H), 3.21 (d, $J = 6.9$ Hz, 1H), 2.60 (d, $J = 1.0$ Hz, 2H), 2.48 (dt, $J = 12.4, 6.8$ Hz, 2H), 2.17 - 1.82 (m, 4H) ppm. HR-MS(ESI): Calculated for $C_{25}H_{23}N_6O$ $[M+H]^+$: 423.1933, found 423.1912.



LH-056

^1H NMR (300 MHz, $DMSO-d_6$) δ 14.26 (s, 1H), 12.22 (s, 1H), 9.50 (d, $J = 1.2$ Hz, 1H), 8.68 (d, $J = 1.2$ Hz, 1H), 8.49 (d, $J = 1.4$ Hz, 1H), 8.04 (s, 1H), 8.00 - 7.88 (m, 3H), 7.62 - 7.47 (m, 4H), 7.31 (ddt, $J = 9.6, 7.2, 2.0$ Hz, 1H), 7.15 (ddt, $J = 7.4, 2.2, 1.0$ Hz, 1H), 7.04 (td, $J = 7.5, 2.1$ Hz, 1H), 6.90 (td, $J = 7.5, 2.1$ Hz, 1H), 6.41 (dd, $J = 7.4, 2.1$ Hz, 1H), 2.60 (d, $J = 1.0$ Hz, 2H) ppm. HR-MS(ESI): Calculated for $C_{27}H_{21}N_6O$ $[M+H]^+$: 445.1777, found 445.1765.

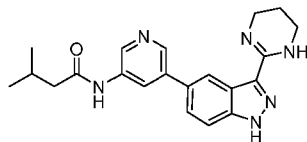
Example 7: Synthesis of LH-057



Intermediate 1-4 in route 1 (0.1 mmol) was added to a single-necked flask and dissolved with 5 mL of dimethylacetamide. Propanediamine (0.15 mmol), *p*-toluenesulfonic acid hydrate (0.15 mmol), and sodium bisulfite (0.15 mmol) were then added, and the mixture was reacted at 120 °C for 6-8 h. After the TLC reaction was completed, the reaction mixture was extracted with ethyl acetate and saturated brine for three times. The organic phases were combined, dried, concentrated, and purified by column chromatography to give intermediate 1-5-4. ^1H NMR (300 MHz, $DMSO-d_6$) δ 12.22 (s, 1H), 7.86 (d, $J = 1.5$ Hz, 1H), 7.47 - 7.33 (m, 2H), 7.25 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.22 (t, $J = 6.8$ Hz, 1H), 3.98 - 3.83 (m, 3H), 3.77 (dt, $J = 11.4, 7.0$ Hz, 1H), 3.62 (ddd, $J = 11.9, 4.4, 1.7$ Hz, 2H), 2.52 - 2.32 (m, 1H), 2.12 - 1.91 (m, 2H), 1.86 - 1.52 (m, 3H), 1.40 (d, $J = 15.1$ Hz, 13H), 1.23 - 1.08 (m, 1H) ppm. HR-MS(ESI): Calculated for $C_{22}H_{32}BN_4O_3$ $[M+H]^+$: 411.2567, found 411.2566. The yield was 78%.

The other steps were the same as those in Example 1 to give compound LH-057.

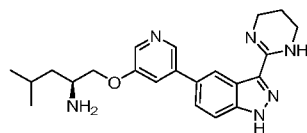
SPECIFICATION



LH-057

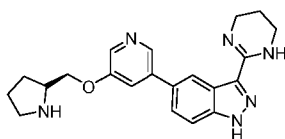
^1H NMR (300 MHz, DMSO- d_6) δ 14.32 (s, 1H), 9.80 (s, 1H), 9.58 (d, J = 1.3 Hz, 1H), 8.65 (d, J = 1.3 Hz, 1H), 8.38 (d, J = 1.3 Hz, 1H), 7.92 (t, J = 1.3 Hz, 1H), 7.60 - 7.43 (m, 3H), 3.52 (dt, J = 9.2, 5.5 Hz, 4H), 2.30 - 2.10 (m, 2H), 2.09 (d, J = 1.1 Hz, 1H), 1.60 (d, J = 5.6 Hz, 2H), 0.97 (d, J = 6.6 Hz, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{21}\text{H}_{25}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 377.2090, found 377.1998.

The following compounds were prepared using a procedure similar to that in Example 7:



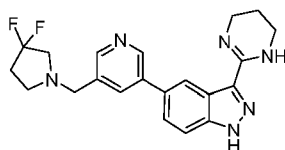
LH-058

^1H NMR (300 MHz, DMSO- d_6) δ 14.35 (s, 1H), 8.56 (d, J = 1.3 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 7.61 (t, J = 1.3 Hz, 1H), 7.53 (d, J = 1.1 Hz, 2H), 7.44 (s, 1H), 4.32 (dd, J = 12.4, 7.0 Hz, 1H), 4.08 (dd, J = 12.4, 7.0 Hz, 1H), 3.92 (td, J = 12.2, 3.1 Hz, 2H), 3.66 (ddd, J = 11.9, 4.4, 1.7 Hz, 2H), 3.20 - 3.04 (m, 1H), 1.74 - 1.33 (m, 6H), 1.25 - 1.12 (m, 1H), 0.90 (dd, J = 15.0, 6.4 Hz, 6H) ppm. HR-MS(ESI): Calculated for $\text{C}_{22}\text{H}_{29}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$: 393.2403, found 393.2403.



LH-059

^1H NMR (300 MHz, DMSO- d_6) 14.35 (s, 1H), 8.56 (d, J = 1.2 Hz, 1H), 8.38 (t, J = 1.0 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 7.57 (dd, J = 15.2, 1.2 Hz, 3H), 7.45 (s, 1H), 3.93 (td, J = 12.2, 3.1 Hz, 2H), 3.63 (ddd, J = 11.9, 4.4, 1.7 Hz, 2H), 3.21 (d, J = 6.9 Hz, 1H), 3.03 - 2.87 (m, 1H), 2.78 (dt, J = 9.6, 7.0 Hz, 1H), 1.89 - 1.18 (m, 7H) ppm. HR-MS(ESI): Calculated for $\text{C}_{21}\text{H}_{23}\text{N}_7\text{O}$ $[\text{M}+\text{H}]^+$: 389.1964, found 389.1971.



LH-060

SPECIFICATION

¹H NMR (300 MHz, DMSO-*d*₆) δ 14.36 (s, 1H), 8.79 (d, *J* = 1.3 Hz, 1H), 8.71 (d, *J* = 1.4 Hz, 1H), 8.37 (d, *J* = 1.3 Hz, 1H), 8.07 (t, *J* = 1.3 Hz, 1H), 7.59 - 7.42 (m, 3H), 3.69 (s, 2H), 3.52 (dt, *J* = 9.2, 5.5 Hz, 4H), 2.70 - 2.55 (m, 4H), 1.91 (tt, *J* = 15.9, 6.3 Hz, 2H), 1.60 - 1.55 (m, 2H) ppm. HR-MS(ESI): Calculated for C₂₁H₂₃F₂N₆ [M+H]⁺: 397.1952, found 397.1946.

Example 8: *In Vitro* Inhibitory Activity of Some Compounds of the Present Invention against the CLK Family and DYK1A Proteins

I. Experimental procedures

1. Preparation of 1× kinase reaction buffer

Name	Stock solution concentration	Volume	Final concentration
Tris	1 M (25X)	240 μL	40 mM
MgCl ₂	1 M (50X)	120 μL	20 mM
BSA	7.5% (75X)	80 μL	0.1%
DTT	1 M (500X)	3 μL	0.5 mM
ddH ₂ O		5557 μL	

2. Enzyme activity assay

(1) preparation of 2× kinase:

Name	Stock solution concentration	Final concentration
DYRK1A	200 ng/μL	0.2 ng/μL
CLK1	100 ng/μL	0.5 ng/μL
CLK2	100 ng/μL	0.5 ng/μL
CLK3	100 ng/μL	1 ng/μL
CLK4	100 ng/μL	0.5 ng/μL

(2) preparation of 4× substrate mixture:

	ATP	Substrate	
Name	Final concentration	Stock solution concentration	Final concentration
DYRK1A	30 μM	5 mg/mL	0.1 mg/mL
CLK1	50 μM	10 mg/mL	0.1 mg/mL
CLK2	50 μM	10 mg/mL	0.1 mg/mL
CLK3	30 μM	5 mg/mL	0.1 mg/mL
CLK4	50 μM	10 mg/mL	0.1 mg/mL

- ① The positive drug was diluted in a 4-fold gradient with DMSO in a dilution plate, with the final initial concentrations of the compound being 1 & 0.02 & 0.1 μM.
- ② The compound was diluted 50-fold into the 1× kinase reaction buffer and oscillated on an oscillator for 20 min.
- ③ The 2× kinase was prepared using the 1× enzyme reaction buffer.

SPECIFICATION

- ④ 2 μ L of the kinase was added per well to the reaction plate.
- ⑤ 1 μ L of the compound diluted in the buffer was added to each well. The plate was sealed with a plate-sealing film, centrifuged at 1000 rpm for 60 s, and incubated at 25 °C for 10 min.
- ⑥ 4 $\times$ ATP & sub mixture was prepared using the 1 $\times$ enzyme reaction buffer, and 1 μ L of the 4 $\times$ ATP & sub mixture was added to the reaction plate.
- ⑦ The plate was sealed with a plate-sealing film, centrifuged at 1000 rpm for 60 s, and incubated at 25 °C for 60 min.
- ⑧ 4 μ L of ADP-Glo was transferred to the 384 reaction plate, and the plate was centrifuged at 1000 rpm for 1 min and incubated at 25 °C for 40 min.
- ⑨ 8 μ L of Detection solution was transferred to the 384 reaction plate, and the plate was centrifuged at 1000 rpm for 1 min and incubated at 25 °C for 40 min.
- ⑩ The RLU (relative luminescence unit) signal was read using a BMG multifunctional microplate reader, and the signal intensity was used to characterize the degree of the kinase activity.

3. Data analysis

(1) the ratio of each well was calculated;

(2) the inhibition rate was calculated as follows:

compound inhibition rate (%inh) = 100% - (compound - positive control)/(negative control - positive control) $\times$ 100%

(3) the IC₅₀ was calculated, and the inhibition curves of the compounds were plotted: the following nonlinear fitting formula was used to obtain the IC₅₀ (half maximal inhibitory concentration) of the compounds: Graphpad 7.0 software was used for data analysis.

$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{Log IC}_{50} - X) \times \text{Hill Slope}))}$;

X: log value of the concentration of the compound, Y: inhibition rate (%inhibition).

II. Experimental results

Table 1. Enzymatic activity (IC₅₀) of some of compounds in the present invention

ID	CLK1	CLK3	CLK4	CLK2	DYRK1A
LH-001	A	A	C	A	B
LH-003	A	A	D	A	C
LH-004	A	B	C	B	B
LH-005	C	C	B	B	B
LH-006	B	C	B	B	B

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LH-009	A	A	B	A	A
LH-010	B	B	D	A	B
LH-011	C	C	D	A	C
LH-015	B	B	A	A	A
LH-016	A	B	B	A	B
LH-017	A	D	C	A	A
LH-018	C	B	A	A	A
LH-019	A	D	C	A	B
LH-020	A	C	B	A	A
LH-037	A	A	B	B	A
LH-039	C	A	C	B	B
LH-040	C	B	A	A	A
LH-041	B	A	B	A	B
LH-048	A	A	B	A	A
LH-049	C	B	D	A	A

Note: A: <10 nM, B: 10-50 nM, C: 50-100 nM, D: >100 nM.

As can be seen from Table 1, the compounds described in the present invention show effective inhibitory activity against CLK2 and DYRK1A. Meanwhile, the compounds described in the present invention, such as LH-020, show excellent CLK2 inhibitory activity and CLK3 selectivity (IC₅₀ for CLK2, CLK3 and DYRK1A was 2 nM, 81 nM and 3 nM, respectively, and the selectivity index for CLK3 was 41.5), which provides a basis for LH-020 to exert its pharmacological activity and avoid possible side effects.

Example 9: Pharmacodynamic (PD) Results of *In Vivo* of Representative Compound LH-020 of the Present Invention in Osteoarthritis Rats

I. Experimental procedures

1. 40 rats were evenly divided into 4 groups, namely, Control (normal rats injected with physiological saline into the joint cavity), Model (ACLT Model rats injected with physiological saline into the joint cavity), low-dose administration group (ACLT Model rats injected with LH020 (1.5 µg/kg) into the joint cavity), and high-dose administration group (ACLT Model rats injected with LH020 (6 µg/kg) into the joint cavity).
2. Knee osteoarthritis was induced by resection of anterior cruciate ligament of the rats (ACLT model).
3. The first week after surgery, physiological saline or LH-020 (1.5 µg/kg, 6 µg/kg) was injected into the joint cavity.
4. Week 5 after administration, cartilage was collected, and the expression of cartilage-associated proteases (MMP3, MMP13, ADAMTS5, IHH, etc.) was detected by RT-

SPECIFICATION

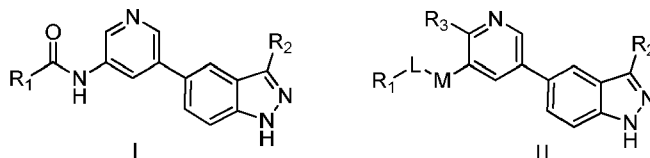
qPCR.

II. Experimental results

As can be seen in FIG. 1, as compared with the Control group (physiological saline was injected into the joint cavity), the expression of cartilage-degrading proteases MMP3, MMP13, ADAMTS5 and IHH was significantly increased in the arthritis model. In addition, as compared with the model group, the low-dose group and the high-dose group of LH-020 can significantly down-regulate the expression of MMP3, MMP13, ADAMTS5 and IHH, and the effect of the high-dose group was superior to that of the low-dose group, which shows that LH-020 has a significant chondroprotective effect and provides a basis for it to exert a pharmacological effect of treating osteoarthritis.

CLAIMS

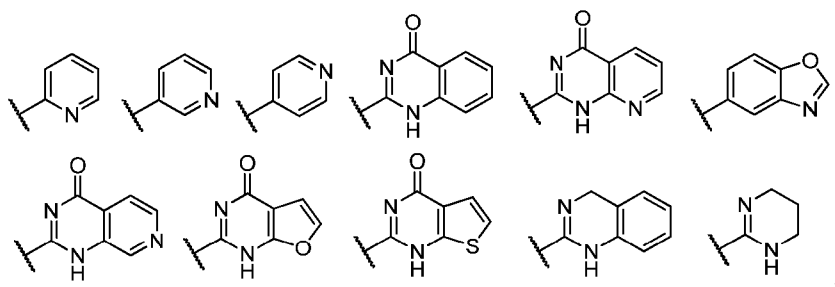
1. A 5-pyridine-1H-indazole compound, having a structure of formula I or II, wherein the compound further comprises an isomer thereof, a pharmaceutically acceptable salt thereof, or a mixture thereof:



R₁ is selected from the following groups substituted with one or more of hydrogen, halogen, methoxy, trifluoromethyl, nitro, hydroxy, amino, azido, sulfonic acid group, or 3-6 membered ring: hydrogen, linear or branched C₁-C₁₀ alkyl, phenyl, a 4-6 membered heterocyclic ring, or a 4-6 membered ring;

L and M are selected from -CH₂-, -NH-, -O-, or a chemical bond;

R₂ is selected from the following groups:

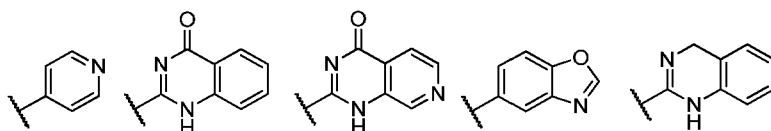


R₃ is selected from hydrogen or C₁-C₄ alkyl.

2. The compound according to claim 1, wherein in the structure:

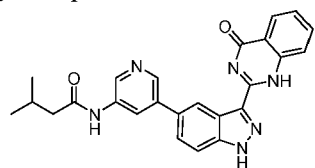
R₁ is selected from isobutyl, cyclopropylmethyl, cyclopentyl, α-aminoisopentyl, 3,3-difluorotetrahydropyrrolyl, hydrogen, morpholinyl, methyl, *tert*-butyl, ethanesulfonyl, or hydroxy;

R₂ is selected from the following groups:

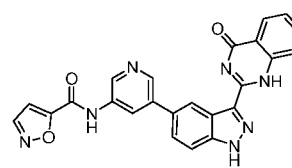


3. The compound according to claim 1, wherein the compound is selected from any one of the following compounds:

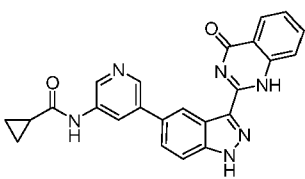
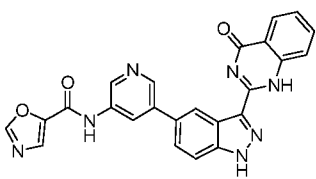
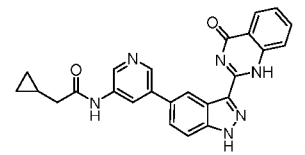
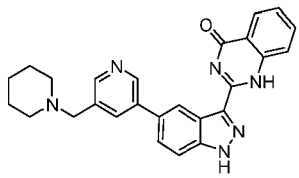
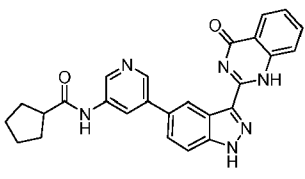
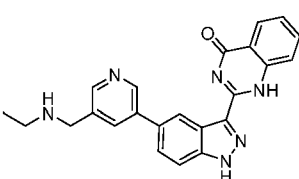
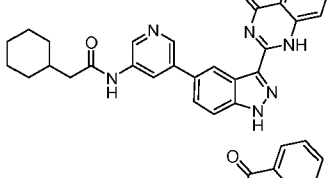
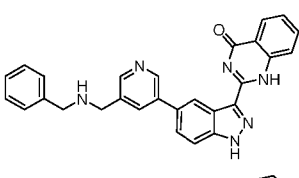
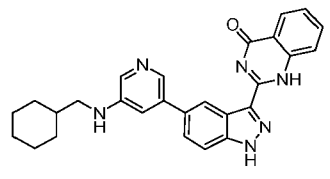
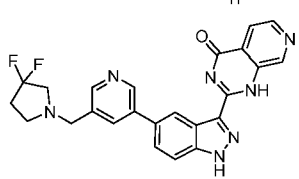
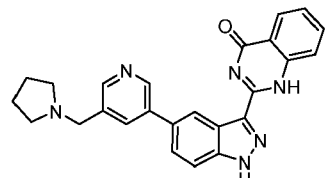
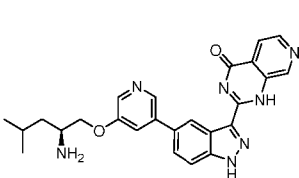
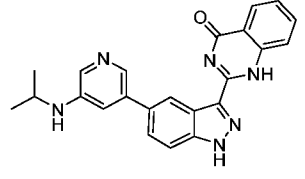
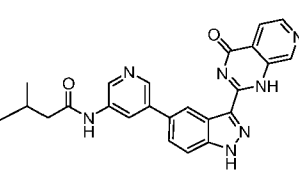
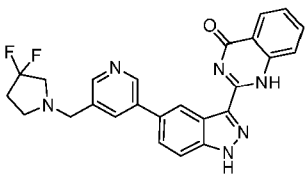
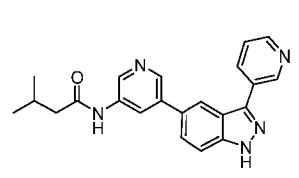
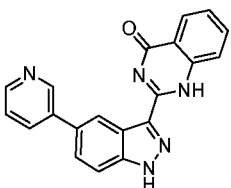
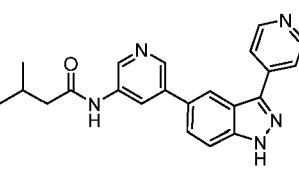
LH-001



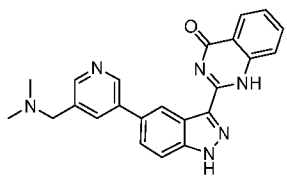
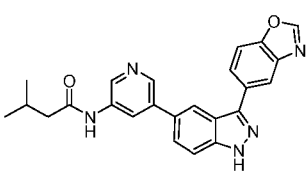
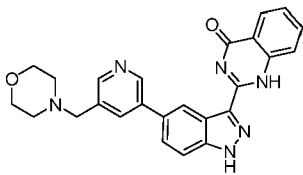
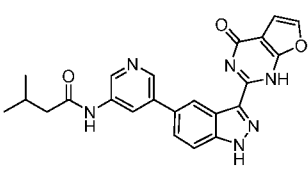
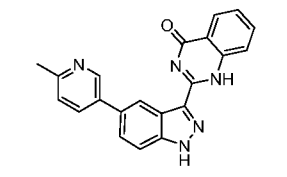
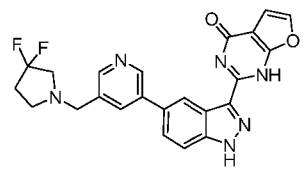
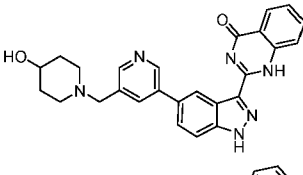
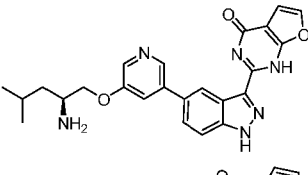
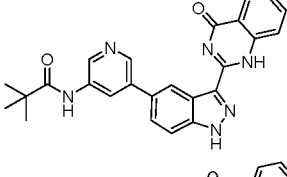
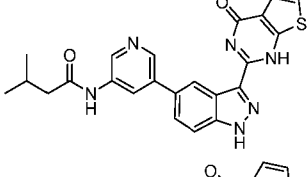
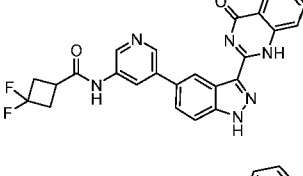
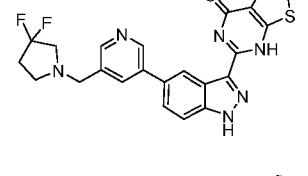
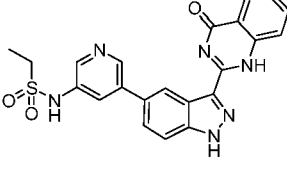
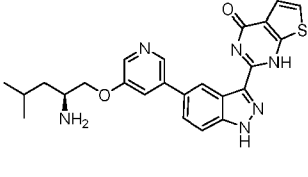
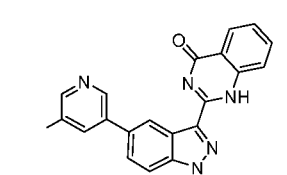
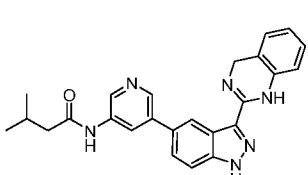
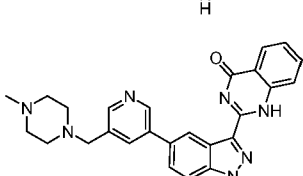
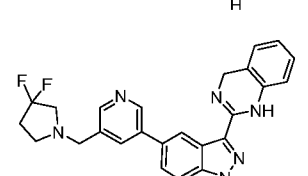
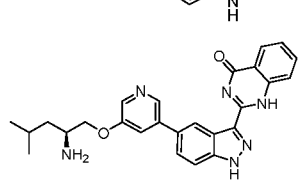
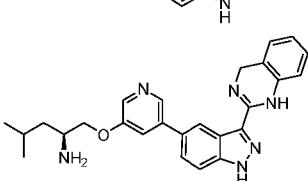
LH-031



CLAIMS

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LH-003		LH-033	
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LH-008		LH-038	
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CLAIMS

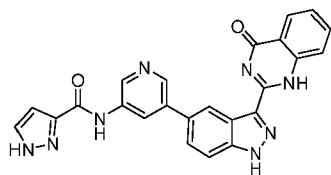
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CLAIMS

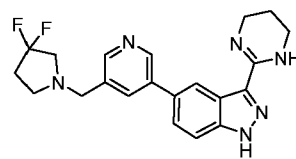
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LH-025		LH-055	
LH-026		LH-056	
LH-027		LH-057	
LH-028		LH-058	
LH-029		LH-059	

CLAIMS

LH-030



LH-060



4. The compound according to claim 1, wherein the pharmaceutically acceptable salt is a salt formed by the compound and the following acids: hydrochloric acid, sulfuric acid, phosphoric acid, carbonic acid, nitric acid, hydrobromic acid, hydroiodic acid, maleic acid, fumaric acid, tartaric acid, citric acid, malic acid, methanesulfonic acid, *p*-toluenesulfonic acid, naphthalenesulfonic acid, succinic acid, acetic acid, mandelic acid, isobutyric acid, or malonic acid.
5. A pharmaceutical composition, comprising the compound according to any one of claims 1-4 and a pharmaceutically acceptable carrier.
6. Use of the compound according to any one of claims 1-4 or the pharmaceutical composition according to claim 5 in the preparation of an inhibitor drug for CLK2 protein.
7. Use of the compound according to any one of claims 1-4 or the pharmaceutical composition according to claim 5 in the preparation of an inhibitor drug for DYRK1A protein.
8. The use according to claim 6 or 7, wherein the drug is a drug for treating inflammation.
9. The use according to claim 8, wherein the inflammation is osteoarthritis, tendinopathy, or rheumatoid arthritis.
10. The use according to claim 9, wherein the compound has a chondroprotective effect.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2022/133423

A. CLASSIFICATION OF SUBJECT MATTER

C07D401/14(2006.01)i;C07D413/14(2006.01)i;C07D471/04(2006.01)i;C07D491/048(2006.01)i;C07D495/04(2006.01)i
:A61K31/506(2006.01)i;A61K31/517(2006.01)i;A61K31/519(2006.01)i;A61P29/00(2006.01)i;A61P19/02(2006.01)i;A
61P19/08(2006.01)i;A61P21/00(2006.01)i;A61K31/416(2006.01)i;C07D213/16(2006.01)i;C07F9/58(2006.01)i;C07H19/
048(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D A61K A61P C07F C07H

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

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

CNXTX; VEN; CNABS; DWPI; WPABS; ENTXT; USTXT; EPTXT; WOTXT; STN; CNKI; Elsevier Science; 超星读秀,
DUXIU; 万方, WANFANG: 吡啶, 吡唑, 蛋白激酶, 抑制剂, 骨关节炎, 滑膜炎, 软骨, 双特异性酪氨酸磷酸化调节激酶,
WNT, osteoarthritis, os, likekinase, pyridine, Indazole, Protein kinase, Inhibitor, Synovitis, Cartilage, CLK2, DYRK1A, 通式I,
general formula I, 通式II, general formula II

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 115353508 A (CHINA PHARMACEUTICAL UNIVERSITY) 18 November 2022 (2022-11-18) claims 1-10	1-10
A	CN 102595899 A (EPITHERIX, LLC.) 18 July 2012 (2012-07-18) description, pp. 1-48, and compounds 1-133	1-10
A	CN 106032359 A (FUDAN UNIVERSITY et al.) 19 October 2016 (2016-10-19) entire document	1-10
A	CN 113164476 A (ARIZONA BOARD OF REGENTS ON BEHALF OF THE UNIVERSITY OF ARIZONA) 23 July 2021 (2021-07-23) entire document	1-10
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Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

05 May 2023

Date of mailing of the international search report

29 May 2023

Name and mailing address of the ISA/CN

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Authorized officer

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2022/133423**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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