

NOVEL OXO-PYRIDINE COMPOUND, PREPARATION METHOD THEREFOR, AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

- [1] The present application claims priority to Invention Patent No. CN 202211647390.2, filed on December 21, 2022, and entitled “NOVEL OXO-PYRIDINE COMPOUND, PREPARATION METHOD THEREFOR, AND USE THEREOF”, which is explicitly incorporated herein by reference.

TECHNICAL FIELD

- [2] The present disclosure relates to the field of pharmaceutical chemistry, and in particular to an oxo-pyridine compound or a salt or isomer thereof, a preparation method therefor and the use thereof in the preparation of drugs for treating and/or preventing FXIa receptor-associated diseases, especially for use in the preparation of drugs for treating and/or preventing cerebrovascular arterial diseases and/or peripheral arterial diseases or the like.

BACKGROUND ART

- [3] Thromboembolism is a disease caused by abnormal blood clots formed in blood vessels of living humans and animals. Thrombosis is caused by three factors: vessel injury, changes in blood composition, and blood stasis. It is a group of complications resulting from various diseases and reasons. Due to variations in underlying diseases and differences in thromboembolic locations, thrombotic disorders may be clinically manifested as myocardial infarction, stroke, deep vein thrombosis (DVT), pulmonary embolism, atrial fibrillation, cerebral infarction or the like. Notably, myocardial infarction, cerebral infarction and pulmonary infarction triggered mainly by embolism and infarction are leading causes of death, claiming nearly 12 million lives worldwide each year, almost a quarter of the world's total deaths.
- [4] Coagulation factor XI (FXI) is a plasma serine proteinase zymogen essential for maintaining endogenous pathways. Upon activation, it converts into activated coagulation factor XIa (FXIa), which plays a key role during the amplification of the coagulation cascade. In the coagulation cascade, thrombin can feedback activate FXI, and the activated FXI subsequently promotes the production of a significant amount of thrombin, thereby amplifying the coagulation cascade. Therefore, drugs targeting FXI can block the intrinsic pathway and

suppress the amplification of the coagulation cascade, thus having an antithrombotic effect. In recent years, the clinical data regarding the correlation between human coagulation factor XI (FXI) deficiency or elevation in FXI level and the occurrence of thrombotic diseases, coupled with antithrombotic experimental studies in animals with FXI deficiency, knockout or inhibition show that, compared with a direct FXa inhibitor, the inhibition of FXI may offer a reduced bleeding risk. Therefore, FXI is a new target for antithrombotic prevention and treatment.

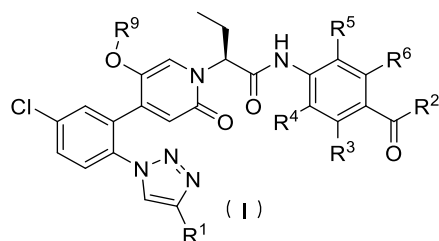
- [5] Reported FXI inhibitors mainly include monoclonal antibodies, antisense oligonucleotides, small chemical molecules, polypeptides or proteins, and peptidomimetics. Currently, milvexian, developed jointly by BMS and Johnson & Johnson, has completed Phase II clinical trials, showing a significantly lower risk of bleeding. The Phase I clinical trial of BMS's small-molecule FXIa inhibitor BMS-962122 for intravenous injection has been completed, but the research and development have been halted. The small-molecule oral FXIa inhibitor ONO-7684, developed by Ono Pharmaceutical Co., Ltd. (Japan), has entered Phase I clinical trials. Monoclonal antibodies and antisense oligonucleotides need to be administered by injection, and have limitations such as high cost, delayed onset of therapeutic effect, and possible challenges in control.
- [6] The efficacy, pharmacokinetics and toxicity of drugs in organisms are influenced by a variety of factors and also exhibit corresponding complexity. Minor changes in chemical structure at any position, such as deuteration, may cause changes in the efficacy, pharmacokinetics and toxicity in vivo. Compared with corresponding non-deuterated drugs, the variation of the pharmacokinetics and other properties of deuterated drugs exhibits great contingency and unpredictability. Deuteration at some sites has the effect of extending the half-life, e.g., marketed donafenib tosylate and deuterated tetrabenazine, while deuteration at some sites can not extend but shorten the half-life (Scott L. Harbeson, Roger D. Tung. Deuterium in Drug Discovery and Development, P405-406). In addition, the hydrogen at some sites on drug molecules cannot be deuterated easily due to steric hindrance, making the deuteration sites of a drug unpredictable.
- [7] Asundexian, an FXI inhibitor from Bayer, has entered Phase III clinical trial, with an average terminal half-life of up to 17.8 h, which is a long half-life, and a risk of bleeding, which is superior to apixaban to some degree but still relatively high. Therefore, the research and development of a novel small-molecule FXIa inhibitor drug with stronger activity, better absorption, relatively rapid metabolism, lower risk of bleeding and better safety can

compensate for the shortcomings of current clinical anticoagulant and antithrombotic drugs that are prone to bleeding complications and meet the unmet clinical needs.

SUMMARY OF THE INVENTION

[8] The compound of the present disclosure is a novel oxo-pyridine compound, and the compounds in most examples demonstrate a good anticoagulant effect and have a strong inhibitory effect on FXIa.

[9] In one aspect, the present disclosure provides a compound represented by formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof:



wherein

R¹ is selected from halogen or trifluoromethyl;

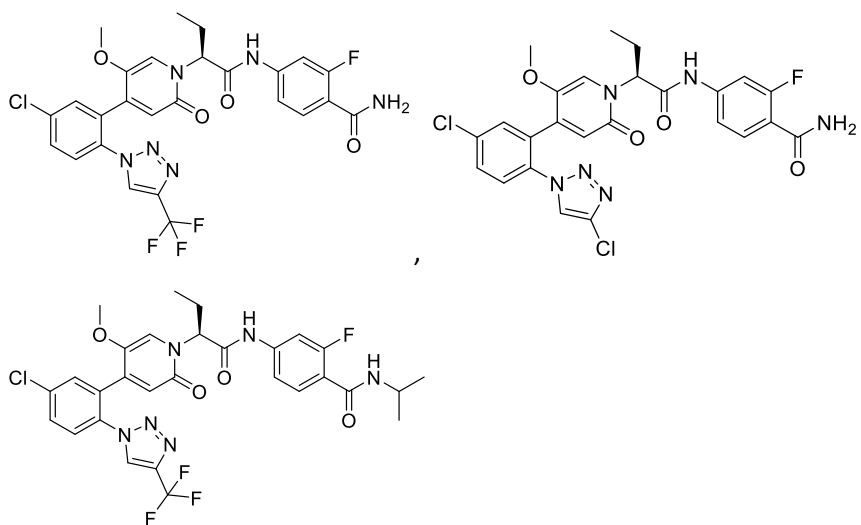
R² is independently selected from NH₂, NHR⁷, OH or OR⁸, wherein R⁷ and R⁸ are selected from alkyl or cycloalkyl, and hydrogen of R⁷ and R⁸ may be substituted with one or more deuterium;

R³ and R⁶ are independently selected from hydrogen, halogen, alkoxy, haloalkyl or CONH₂;

R⁴ and R⁵ are independently selected from hydrogen, halogen, alkoxy or haloalkyl; and

R⁹ is independently selected from CH₃ or CD₃; and

wherein the following compounds are excluded:



[10] Further, in the above compound, or the stereoisomer or pharmaceutically acceptable salt thereof, the R¹ is selected from chloro or trifluoromethyl;

or/and R^2 is independently selected from NH_2 , NHR^7 , OH or OR^8 , wherein R^7 and R^8 are selected from methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl or tert-butyl, and hydrogen of R^7 and R^8 may be substituted with one or more deuterium;

or/and R^3 and R^6 are independently selected from hydrogen, fluoro, chloro, methoxy, trifluoromethyl or $CONH_2$;

or/and R^4 and R^5 are independently selected from hydrogen, fluoro, chloro, methoxy or trifluoromethyl;

or/and R^9 is independently selected from CH_3 or CD_3 .

[11]Further, in the above compound, or the stereoisomer or pharmaceutically acceptable salt thereof, the R^1 is selected from trifluoromethyl;

or/and R^2 is independently selected from NH_2 , NHR^7 , OH or OR^8 , wherein R^7 and R^8 are selected from methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl or tert-butyl, and hydrogen of R^7 and R^8 may be substituted with one or more deuterium;

or/and R^3 and R^6 are independently selected from hydrogen, fluoro, chloro, methoxy, trifluoromethyl or $CONH_2$;

or/and R^4 and R^5 are independently selected from hydrogen, fluoro or chloro;

or/and R^9 is independently selected from CH_3 or CD_3 .

[12]Further, in the above compound, or the stereoisomer or pharmaceutically acceptable salt thereof, the R^1 is selected from trifluoromethyl;

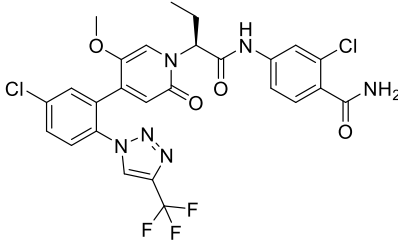
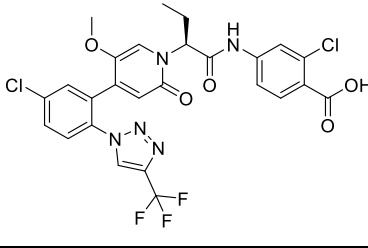
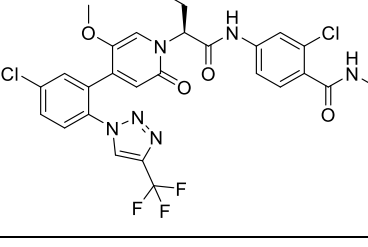
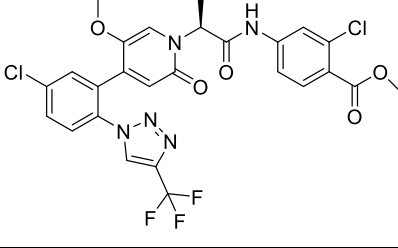
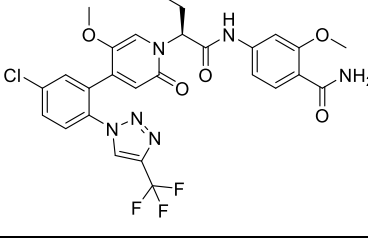
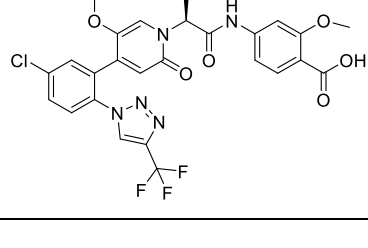
or/and R^2 is independently selected from NH_2 , $NHCH_3$, $NHCD_3$, OH , OCH_3 , OCD_3 or $OC(CH_3)_3$;

or/and R^3 and R^6 are independently selected from fluoro, chloro, methoxy or trifluoromethyl;

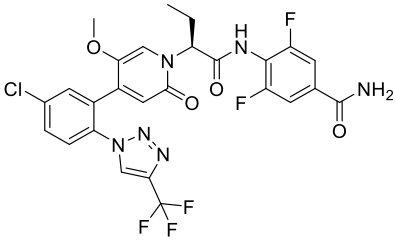
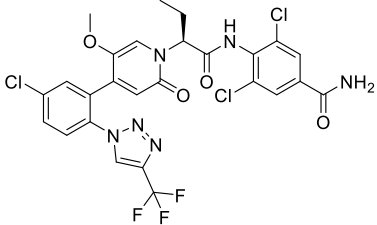
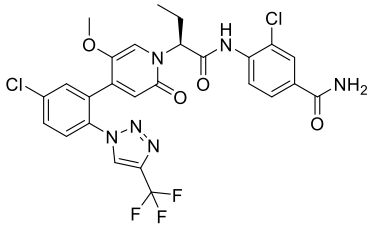
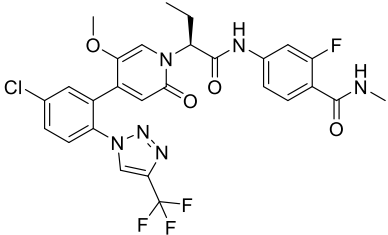
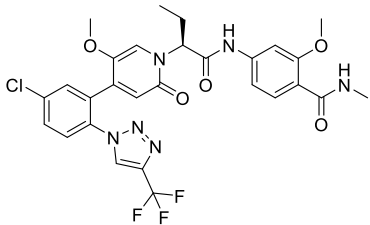
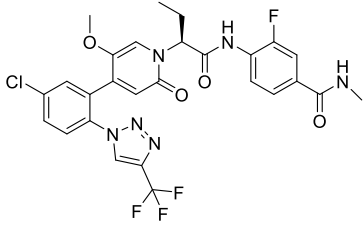
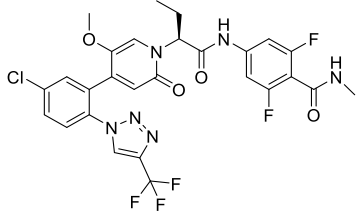
or/and R^4 and R^5 are independently selected from hydrogen, fluoro or chloro;

or/and R^9 is independently selected from CH_3 or CD_3 .

[13]Further, the above compound, or the stereoisomer or pharmaceutically acceptable salt thereof includes the following structures:

No.	Structure	Name
Compound 1		(S)-2-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)benzamide
Compound 2		(S)-2-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)benzoic acid
Compound 3		(S)-2-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)-N-methylbenzamide
Compound 4		Methyl (S)-2-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)benzoate
Compound 5		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)-2-methoxybenzamide
Compound 6		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)-2-methoxybenzoic acid

Compound 7		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)-2-(trifluoromethyl)benzamide
Compound 8		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)phthalamide
Compound 9		(S)-2-chloro-4-(2-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)benzoic acid
Compound 10		(S)-2-chloro-4-(2-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)benzamide
Compound 11		(S)-4-(2-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)-2-(trifluoromethyl)benzamide
Compound 12		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)-2,3-difluorobenzamide
Compound 13		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxypyridin-1(2H)-yl)butanamido)-3-fluorobenzamide

Compound 14		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-3,6-difluorobenzamide
Compound 15		(S)-3,5-dichloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)benzamide
Compound 16		(S)-3-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-benzamide
Compound 17		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-2-fluoro-N-methylbenzamide
Compound 18		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-2-methoxy-N-methylbenzamide
Compound 19		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-3-fluoro-N-methylbenzamide
Compound 20		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-2,6-difluoro-N-methylbenzamide

Compound 21		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- <i>d</i> ₃)-2-oxypyridin-1(2H)-yl)butanamido)-2-fluorobenzamide
Compound 22		(S)-2-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- <i>d</i> ₃)-2-oxypyridin-1(2H)-yl)butanamido)benzamide
Compound 23		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- <i>d</i> ₃)-2-oxypyridin-1(2H)-yl)butanamido)-3-fluorobenzamide
Compound 24		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- <i>d</i> ₃)-2-oxypyridin-1(2H)-yl)butanamido)-3-fluoro-N-methylbenzamide
Compound 25		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- <i>d</i> ₃)-2-oxypyridin-1(2H)-yl)butanamido)-2-fluoro-N-methylbenzamide
Compound 26		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy)-2-oxypyridin-1(2H)-yl)butanamido)-2-fluoro-N-(methyl- <i>d</i> ₃)benzamide

Compound 27		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- <i>d</i> ₃)-2-oxopyridin-1(2H)-yl)butanamido)-2-fluoro-N-(methyl- <i>d</i> ₃)benzamide
Compound 28		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy)-2-oxopyridin-1(2H)-yl)butanamido-3,3,4,4,4- <i>d</i> ₅)-2-fluorobenzamide
Compound 29		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-3,4,6- <i>d</i> ₃)-5-(methoxy)-2-oxopyridin-1(2H)-yl)butanamido)-2-fluorobenzamide
Compound 30		(S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- <i>d</i> ₃)-2-oxopyridin-1(2H)-yl)butanamido-3,3,4,4,4- <i>d</i> ₅)-2-fluoro-N-(methyl- <i>d</i> ₃)benzamide

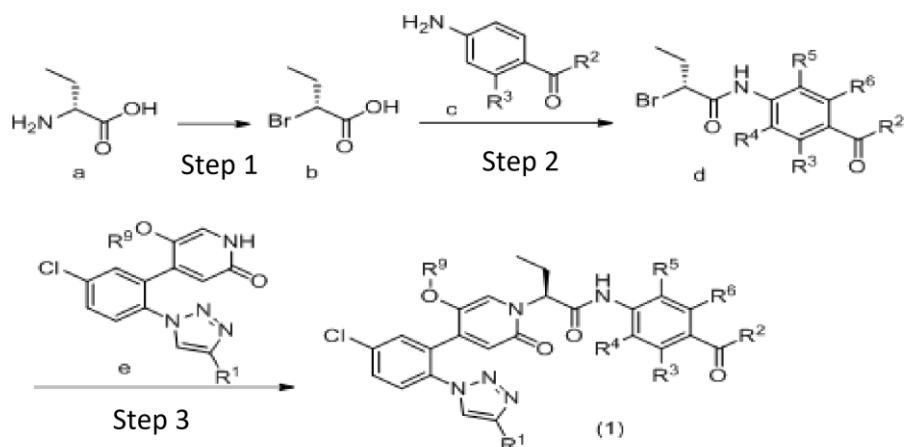
[14]In the present disclosure, if the chemical nomenclature conflicts with the structural formula, the compound structure represented by the numbering will control.

[15]Further, hydrogen in the structure of the above compound, or the stereoisomer or pharmaceutically acceptable salt thereof may be substituted with one or more deuterium.

[16]Further, the deuterated compound obtained by substituting the hydrogen in the structure of the compound above, or the stereoisomer or pharmaceutically acceptable salt thereof with one or more deuterium includes, but is not limited to, compound 28, compound 29 and compound 30.

[17]In another aspect, the present disclosure provides a method for preparing the compound above, or the stereoisomer or pharmaceutically acceptable salt thereof, which includes the following steps:

when R² is NH₂, NHR⁷ or OR⁸, the synthesis route is as follows:



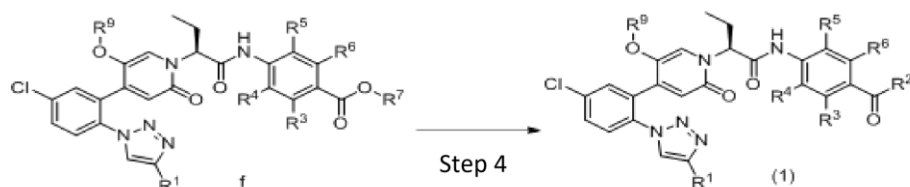
wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 are defined correspondingly the same as in any one of claims 1-6;

step 1: bromination of starting material **a** to produce intermediate **b**;

step 2: condensation of intermediate **b** with starting material **c** to produce intermediate **c**;
and

step 3: a substitution reaction of intermediate **d** with compound **e** to produce a compound of formula (1); and

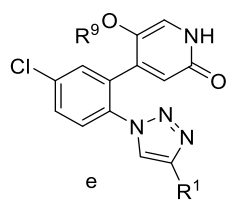
when R^2 is OH, the synthesis route is as follows:



wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 and R^9 are defined correspondingly the same as in any one of claims 1-6;

step 4: hydrolysis of compound **f** under a basic condition to produce the compound of formula (1).

[18]Further, the present disclosure further provides a key intermediate having a structure as represented by formula **e** below:



, where R^1 is selected from halogen or trifluoromethyl, and R^9 is selected from CH_3 or CD_3 ; preferably, the R^1 is selected from halogen or trifluoromethyl, and R^9 is selected from CD_3 .

[19]Further, the intermediate described above is selected from the following compounds:

5-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d3)pyridine-2(1H)-one; and

4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d3)pyridine-2(1H)-one.

[20]The aforementioned term “halogen” includes fluorine, chlorine, bromine or iodine; preferably fluorine, chlorine or bromine.

[21]In a third aspect, the present disclosure provides a pharmaceutical composition comprising any one of the compounds described above, or the stereoisomer or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

[22]In a fourth aspect, the present disclosure further provides the use of the compound above, or the stereoisomer or pharmaceutically acceptable salt thereof in the preparation of drugs for treating and/or preventing an FXIa receptor-associated disease.

[23]Further, the aforementioned FXIa receptor-associated disease is selected from a cerebrovascular arterial disease and/or a peripheral arterial disease.

[24]Further, the aforementioned FXIa receptor-associated disease is selected from transient ischemic attack (TIA), ischemic stroke, including cardioembolic stroke such as stroke caused by atrial fibrillation, non-cardioembolic stroke such as lacunar stroke, stroke caused by an aortic or arteriolar disease or stroke of undetermined etiology, cryptogenic stroke, embolic stroke, embolic stroke of undetermined source, or an event leading to stroke or TIA and originating from thrombosis and/or thromboembolism, and/or a peripheral arterial condition leading to the peripheral arterial disease, including peripheral arterial occlusion, acute limb ischemia, amputation, reocclusion and restenosis after intervention (for example, angioplasty, stent implantation or surgery and bypass grafting), and/or stent thrombosis.

[25]In the present disclosure, the term “alkyl” denotes a linear or branched saturated C1-C16 alkyl group. Other alkyl moieties that contain an “alkyl” substituent are explained in the same manner.

[26]Beneficial effects: compared with the prior art, the compound of the present disclosure has a better in-vitro anticoagulant effect while exhibiting a highly consistent correlation with the in-vitro FXIa inhibitory effect. Additionally, the compounds in some examples of the present disclosure have superior pharmacokinetic characteristics in rats following injection administration. For example, compound 21, compound 25, compound 26, and compound 27 have better AUC and Cmax, thus having better efficacy. Furthermore, the compounds also have rapid elimination characteristics and higher safety.

DETAILED DESCRIPTION OF THE INVENTION

[27]The present disclosure will be further described below in details with reference to examples and test examples, which are intended to illustrate the technical solutions of the present disclosure only and should not be construed as limiting the present disclosure, and any equivalent substitution in the art that are made in accordance with the description of the present disclosure shall fall within the protection scope of the present disclosure.

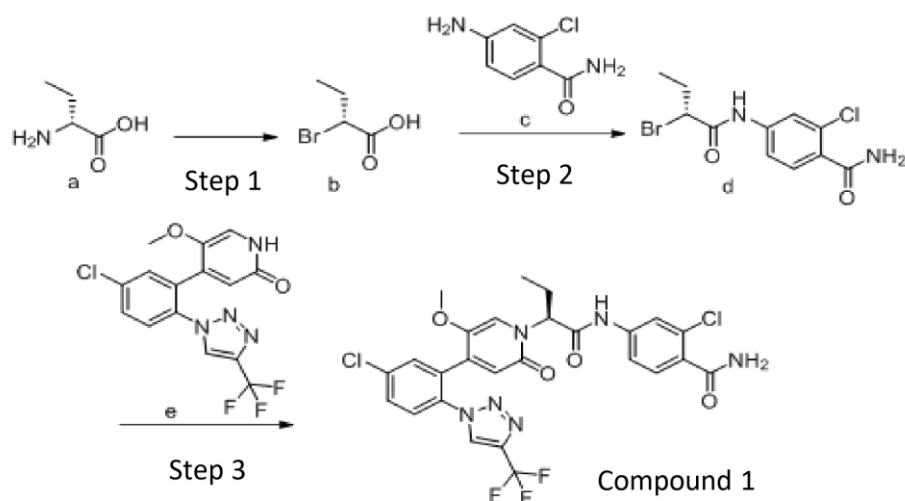
[28]All of the compounds, and the stereoisomer or pharmaceutically acceptable salt thereof in the present disclosure can be prepared by selecting the synthesis routes in the examples, and the conventional conditions of the reaction raw materials and reaction solvents can be adjusted according to the requirements for substituents or salt formation, which can be achieved by those skilled in the art based on the description of the present disclosure. Furthermore, unless otherwise stated, the column chromatography of the present disclosure refers to silica gel column chromatography, and unless otherwise stated, the elution solvent, whether it is a single or mixed elution solvent, can be determined based on the reaction solvent and the common general knowledge of those skilled in the art or using commonly used means.

[29]The structure of the compound is determined by nuclear magnetic resonance (^1H NMR) or liquid chromatography-mass spectrometry (LC-MS).

[30]The liquid chromatography-mass spectrometry (LC-MS) instrument is Agilent G6120B (used with liquid-phase Agilent 1260). The nuclear magnetic resonator (^1H NMR) is Bruker AVANCE-400 or Bruker AVANCE-800, the shift (δ) of nuclear magnetic resonance (^1H NMR) is given in parts per million (ppm), the solvent for determination is DMSO, the internal standard is tetramethylsilane (TMS), and the chemical shift is given in 10^{-6} (ppm).

[31]The term "room temperature" in the present disclosure means a temperature in a range of 10-30°C.

Example 1: preparation of compound 1



Step 1: (R)-2-bromo-3-propionic acid

[32] 5 g (48.49 mmol) of concentrated sulfuric acid was added to 60 ml of water and cooled to 5°C or lower, 23 g (193.3 mmol) of potassium bromide and 5 g (48.49 mmol) of D-2-aminobutyric acid were added, and 5 g (72.46 mmol) of sodium nitrite dissolved in 30 ml of water was added dropwise over about 30 min, with the temperature controlled at 0-5°C or lower. After the completion of addition, the mixture was stirred for reaction at 0-5°C overnight. On the next day, the reaction solution was extracted twice with ethyl acetate, the organic phases were combined, successively washed with water and saturated brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated to dryness to obtain 7.5 g of an oil, which was directly used in the next step without purification.

Step 2: preparation of (R)-4-(2-bromobutanamido)-2-chlorobenzamide

[33] 441 mg (2.64 mmol) of (R)-2-bromo-3-propionic acid was dissolved in 4 ml of tetrahydrofuran, 300 mg (1.76 mmol) of 4-amino-2-chlorobenzamide was added, and the mixture was cooled to 0°C or lower; 654 mg (8.27 mmol) of pyridine was added, and then 2.24 g (3.52 mmol) of 1-propylphosphoric anhydride (50% ethyl acetate solution) diluted with 2 ml of tetrahydrofuran was added dropwise; and after the completion of addition, the solution was stirred at 0-5°C for 10 min and stirred at room temperature to allow a reaction for 30 min. After the reaction was completed, water was added to quench the reaction, and EA was added for extraction; the organic phase was successively washed with 5% citric acid, saturated sodium bicarbonate, water, and saturated brine, and dried over anhydrous sodium sulfate; and the solvent was evaporated to dryness to obtain 540 mg of a crude product. 5 ml of ethyl acetate was added to the crude product, and the mixture was stirred at room temperature for 2 h and filtered; and the filter cake was washed with ethyl acetate

and dried under vacuum to obtain 430 mg of a white solid, with a yield of 76.4% and a purity of 96.55%.

[34]ESI-MS: $m/z = 319.0$ (M+H)⁺.

Step 3: preparation of title compound 1

[35]200 mg (0.539 mmol) of 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one, 5 ml of isopropanol and 2 ml of acetone were mixed, 187 mg (1.624 mmol) of tetramethylguanidine was added and stirred for 5 min, and 207 mg (0.648 mmol) of (R)-4-(2-bromobutanamido)-2-chlorobenzamide was added, and stirred for reaction at room temperature overnight. After the reaction was completed, saturated ammonium chloride was added to quench the reaction, and ethyl acetate was added for extraction; the organic phase was successively washed with water and saturated brine, and dried over anhydrous sodium sulfate; and the solvent was evaporated to dryness to obtain 400 mg of a crude product. The crude product was purified on a column with an eluent (ethyl acetate : petroleum ether = 1:2), and the product was collected to obtain 245 mg of a white solid. The yield was 74.6%, and the purity was 96.20%.

[36]ESI-MS: $m/z = 609.1$ (M+H)⁺.

[37]¹H NMR (400 MHz, DMSO-d₆) δ :10.67 (s, 1H), 9.14 (d, 1H), 7.98 - 7.72 (m, 5H), 7.60 - 7.30 (m, 3H), 7.13 (s, 1H), 6.53 (s, 1H), 5.51 (dd 1H), 3.25 (s, 3H), 2.14-2.04 (m, 2H), 0.78 (t, 3H).

Example 2: preparation of compound 2

Step 1: preparation of methyl (S)-2-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)benzoate

[38]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with methyl 4-amino-2-chlorobenzoate, to prepare the title compound, with a purity of 96.20%.

[39]ESI-MS: $m/z = 624.1$ (M+H)⁺.

Step 2: preparation of title compound 2

[40]To 250 mg (0.40 mmol) of methyl (S)-2-chloro-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)benzoate was added 5 ml of methanol, the mixture was heated to 50°C, 51 mg (1.215 mmol) of lithium hydroxide monohydrate dissolved in 2.5 ml of water was added, and the resulting solution was stirred for reaction at 50°C for 1 h. After the reaction was completed, 5% aqueous citric acid solution was added to quench the reaction, and ethyl acetate was added for extraction; the organic phase was successively washed with water and saturated brine, and dried over anhydrous sodium sulfate; and the solvent was evaporated to dryness to obtain 245 mg of a

crude product. 5 ml of ethyl acetate was added to the crude product, and the mixture was stirred at room temperature for 2 h and filtered; and the filter cake was washed with ethyl acetate and dried under vacuum to obtain 200 mg of a white solid, with a yield of 81.9% and a purity of 97.89%.

[41]ESI-MS: $m/z = 610.1$ (M+H)⁺.

[42]¹H NMR (400 MHz, DMSO-d₆) δ :12.88 (s, 1H), 10.89 (s, 1H), 9.19 (s, 1H), 8.05 - 7.88 (m, 3H), 7.69 - 7.36 (m, 3H), 7.28 (s, 1H), 6.55 (s, 1H), 5.58 (dd 1H), 3.28 (s, 3H), 2.15-2.03 (m, 2H), 0.76 (t, 3H).

Example 3: preparation of compound 3

[43]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-chloro-N-methylbenzamide, to prepare the title compound 3, with a purity of 96.80%.

[44]ESI-MS: $m/z = 623.1$ (M+H)⁺.

[45]¹H NMR (400 MHz, DMSO-d₆) δ :10.58 (s, 1H), 9.11 (s, 1H), 7.91 - 7.66 (m, 4H), 7.58 - 7.25 (m, 3H), 7.15 (s, 1H), 6.51 (s, 1H), 5.53 (dd 1H), 3.26 (s, 3H), 2.88 (d, 3H), 2.12-2.01 (m, 2H), 0.79 (t, 3H).

Example 4: preparation of compound 4

[46]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with methyl 4-amino-2-chlorobenzoate, to prepare the title compound 4, with a purity of 97.90%.

[47]ESI-MS: $m/z = 624.1$ (M+H)⁺.

[48]¹H NMR (400 MHz, DMSO-d₆) δ :10.53 (s, 1H), 9.18 (s, 1H), 7.91 - 7.75 (m, 3H), 7.56 - 7.25 (m, 3H), 7.16 (s, 1H), 6.50 (s, 1H), 5.56 (dd 1H), 4.10 (s, 3H), 3.28 (s, 3H), 2.18-2.07 (m, 2H), 0.79 (t, 3H).

Example 5: preparation of compound 5

[49]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-methoxy-benzamide, to prepare the title compound 5, with a purity of 97.95%.

[50]ESI-MS: $m/z = 605.2$ (M+H)⁺.

[51]¹H NMR (400 MHz, DMSO-d₆) δ :10.68 (s, 1H), 9.14 (d, 1H), 7.95 - 7.73 (m, 4H), 7.56 (m, 2H), 7.46 (d, 1H), 7.19 (dd, 1H), 7.14 (s, 1H), 6.53 (s, 1H), 5.54 (dd, 1H), 3.86 (s, 3H), 3.25 (s, 3H), 2.16-2.04 (m, 2H), 0.78 (t, 3H).

Example 6: preparation of compound 6

Step 1: preparation of methyl (S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-2-methoxybenzoate

[52]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with methyl 4-amino-2-methoxy-benzoate, to prepare the title compound, with a purity of 97.20%. ESI-MS: $m/z = 620.0$ ($M+H$)⁺.

Step 2: preparation of title compound 6

[53]To 250 mg (0.403 mmol) of methyl (S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-2-methoxybenzoate was added 6 ml of methanol, 68 mg (1.62 mmol) of lithium hydroxide monohydrate dissolved in 3 ml of water was added, and the mixture was stirred for reaction at 60°C for 1 h. After the reaction was completed, the system was cooled to room temperature, 5% aqueous citric acid solution was added to quench the reaction, and ethyl acetate was added for extraction; the organic phase was successively washed with water and saturated brine, and dried over anhydrous sodium sulfate; and the solvent was evaporated to dryness to obtain 250 mg of a crude product. The crude product was purified using a column with an eluent (dichloromethane : methanol = 50 : 1), and the target product was collected to obtain 198 mg of a white solid, with a yield of 81.1% and a purity of 97.66%.

[54]ESI-MS: $m/z = 606.1$ ($M+H$)⁺.

[55]¹H NMR (400 MHz, DMSO-d₆) δ :12.35 (s, 1H), 10.68 (s, 1H), 9.14 (d, 1H), 7.93 - 7.75 (m, 3H), 7.68 (d, 1H), 7.54 (d, 1H), 7.22 - 7.10 (m, 2H), 6.54 (s, 1H), 5.54 (dd, 1H), 3.78 (s, 3H), 3.25 (s, 3H), 2.14-2.04 (m, 2H), 0.79 (t, 3H).

Example 7: preparation of compound 7

[56]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-trifluoromethyl-benzamide, to prepare the title compound 7, with a purity of 95.21%.

[57]ESI-MS: $m/z = 643.1$ ($M+H$)⁺.

[58]¹H NMR (400 MHz, DMSO-d₆) δ :10.80 (s, 1H), 9.13 (s, 1H), 8.12 (d, 1H), 8.02 - 7.72 (m, 5H), 7.54-7.51 (m, 2H), 7.14 (s, 1H), 6.54 (s, 1H), 5.51 (dd, 1H), 3.25 (s, 3H), 2.23 - 2.03 (m, 2H), 0.79 (t, 3H).

Example 8: preparation of compound 8

[59]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-1,2-dibenzamide, to prepare the title compound 8, with a purity of 98.69%.

[60]ESI-MS: $m/z = 618.2$ ($M+H$)⁺.

[61]¹H NMR (400 MHz, DMSO-d₆) δ :11.09 (s, 1H), 9.20 (s, 1H), 8.28 - 7.96 (m, 5H), 7.85 - 7.59 (m, 5H), 7.28 (s, 1H), 6.96 (s, 1H), 5.98 (dd 1H), 3.29 (s, 3H), 2.23-2.15 (m, 2H), 0.80 (t, 3H).

Example 9: preparation of compound 9

[62]The preparation method was the same as that in Example 2, except that 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one was replaced with 4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one, to prepare the title compound 9, with a purity of 97.25%.

[63]ESI-MS: $m/z = 576.1$ ($M+H$)⁺.

[64]¹H NMR (400 MHz, DMSO-d₆) δ :12.88 (s, 1H), 10.89 (s, 1H), 9.19 (s, 1H), 8.01 - 7.85 (m, 3H), 7.68 - 7.32 (m, 3H), 7.25 (s, 1H), 6.53 (s, 1H), 5.59 (dd 1H), 3.27 (s, 3H), 2.16-2.02 (m, 2H), 0.77 (t, 3H).

Example 10: preparation of compound 10

[65]The preparation method was the same as that in Example 1, except that 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one, to prepare the title compound 10, with a purity of 98.14%.

[66]ESI-MS: $m/z = 575.1$ ($M+H$)⁺.

[67]¹H NMR (400 MHz, DMSO-d₆) δ :10.70 (s, 1H), 9.15 (d, 1H), 7.97 - 7.71 (m, 5H), 7.59 - 7.28 (m, 3H), 7.15 (s, 1H), 6.54 (s, 1H), 5.52 (dd 1H), 3.28 (s, 3H), 2.15-2.03 (m, 2H), 0.78 (t, 3H).

Example 11: preparation of compound 11

[68]The preparation method was the same as that in Example 7, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-trifluoromethyl-benzamide, and then 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one, to prepare the title compound 11, with a purity of 97.46%.

[69]ESI-MS: $m/z = 609.1$ ($M+H$)⁺.

[70]¹H NMR (400 MHz, DMSO-d₆) δ :10.79 (s, 1H), 9.11 (s, 1H), 8.10 (d, 1H), 8.00 - 7.69 (m, 5H), 7.56-7.53 (m, 2H), 7.18 (s, 1H), 6.56 (s, 1H), 5.53 (dd, 1H), 3.28 (s, 3H), 2.21 - 2.00 (m, 2H), 0.77 (t, 3H).

Example 12: preparation of compound 12

[71]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2,3-difluoro-benzamide, to prepare the title compound 12, with a purity of 98.27%.

[72]ESI-MS: $m/z = 611.1$ (M+H)⁺.

[73]¹H NMR (400 MHz, DMSO-d₆) δ : 10.57 (s, 1H), 9.15 (s, 1H), 7.88 - 7.81 (m, 2H), 7.79 (d, J = 2.1 Hz, 2H), 7.71 (d, J = 9.1 Hz, 2H), 7.53 - 7.37 (m, 1H), 7.10 (s, 1H), 6.55 (s, 1H), 5.68 (s, 1H), 3.24 (s, 3H), 2.11 (dt, J = 17.0, 8.6 Hz, 2H), 0.79 (t, J = 7.2 Hz, 3H).

Example 13: preparation of compound 13

[74]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-3-fluoro-benzamide, to prepare the title compound 13, with a purity of 98.64%.

[75]ESI-MS: $m/z = 593.1$ (M+H)⁺.

[76]¹H NMR (400 MHz, DMSO-d₆) δ : 10.41 (s, 1H), 9.15 (d, J = 1.0 Hz, 1H), 8.05 - 7.93 (m, 2H), 7.88 - 7.81 (m, 2H), 7.80 - 7.78 (m, 1H), 7.78 - 7.67 (m, 2H), 7.47 (s, 1H), 7.11 (s, 1H), 6.54 (s, 1H), 5.71 (s, 1H), 3.24 (s, 3H), 2.25 - 1.95 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 14: preparation of compound 14

[77]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-3,5-difluoro-benzamide, to prepare the title compound 14, with a purity of 98.76%.

[78]ESI-MS: $m/z = 611.1$ (M+H)⁺.

[79]¹H NMR (400 MHz, DMSO-d₆) δ : 10.37 (s, 1H), 9.13 (s, 1H), 8.13 (s, 1H), 7.87 - 7.80 (m, 2H), 7.78 (d, J = 2.0 Hz, 1H), 7.69 (s, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.07 (s, 1H), 6.56 (s, 1H), 5.65 (s, 1H), 3.22 (s, 3H), 2.15 - 1.95 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H).

Example 15: preparation of compound 15

[80]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-3,5-dichloro-benzamide, to prepare the title compound 15, with a purity of 98.12%.

[81]ESI-MS: $m/z = 643.1$ (M+H)⁺.

[82]¹H NMR (400 MHz, DMSO-d₆) δ : 10.37 (s, 1H), 9.13 (s, 1H), 8.13 (s, 1H), 7.92 - 7.88 (m, 2H), 7.82-7.78 (m, 1H), 7.69 (s, 1H), 7.66-7.62(m, 2H), 7.07 (s, 1H), 6.56 (s, 1H), 5.65 (s, 1H), 3.22 (s, 3H), 2.18 - 1.98 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H).

Example 16: preparation of compound 16

[83]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-3-chloro-benzamide, to prepare the title compound 16, with a purity of 98.48%.

[84]ESI-MS: $m/z = 609.1$ (M+H)⁺.

[85]¹H NMR (400 MHz, DMSO-d₆) δ: 10.08 (s, 1H), 9.16 (s, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.84 (m, 4H), 7.79 (d, J = 2.1 Hz, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 6.57 (s, 1H), 5.69 (s, 1H), 3.24 (s, 3H), 2.28 - 2.03 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H).

Example 17: preparation of compound 17

[86]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluoro-N-methylbenzamide, to prepare the title compound 17, with a purity of 97.95%.

[87]ESI-MS: m/z = 607.1 (M+H)⁺.

[88]¹H NMR (400 MHz, DMSO-d₆) δ: 10.83 (s, 1H), 9.14 (d, J = 1.1 Hz, 1H), 8.13 - 8.06 (m, 1H), 7.89 - 7.80 (m, 2H), 7.79 (d, J = 2.0 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.37 (dd, J = 8.5, 2.0 Hz, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.52 (t, J = 7.8 Hz, 1H), 3.25 (s, 3H), 2.76 (d, J = 4.6 Hz, 3H), 2.18 - 2.02 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 18: preparation of compound 18

[89]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-methoxy-N-methylbenzamide, to prepare the title compound 18, with a purity of 96.25%.

[90]ESI-MS: m/z = 619.2 (M+H)⁺.

[91]¹H NMR (400 MHz, DMSO-d₆) δ: 10.72 (s, 1H), 9.14 (d, J = 1.1 Hz, 1H), 8.13 - 8.06 (m, 1H), 7.89 - 7.80 (m, 2H), 7.79 (d, J = 2.0 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.37 (dd, J = 8.5, 2.0 Hz, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.52 (t, J = 7.8 Hz, 1H), 3.86 (s, 3H), 3.25 (s, 3H), 2.76 (d, J = 4.6 Hz, 3H), 2.18 - 2.02 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 19: preparation of compound 19

[92]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-3-fluoro-N-methylbenzamide, to prepare the title compound 19, with a purity of 98.20%.

[93]ESI-MS: m/z = 607.1 (M+H)⁺.

[94]¹H NMR (400 MHz, DMSO-d₆) δ: 10.40 (s, 1H), 9.15 (d, J = 1.0 Hz, 1H), 8.49 (d, J = 4.6 Hz, 1H), 7.98 (t, J = 8.1 Hz, 1H), 7.89 - 7.80 (m, 2H), 7.79 (dd, J = 2.1, 0.7 Hz, 1H), 7.71 (dd, J = 11.8, 1.9 Hz, 1H), 7.66 (dd, J = 8.4, 2.0 Hz, 1H), 7.11 (s, 1H), 6.54 (s, 1H), 5.70 (s, 1H), 3.24 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 2.12 (dt, J = 15.2, 7.5 Hz, 2H), 0.78 (t, J = 7.1 Hz, 3H).

Example 20: preparation of compound 20

[95]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2,5-difluoro-N-methylbenzamide, to prepare the title compound 20, with a purity of 98.20%.

[96]ESI-MS: $m/z = 625.1$ ($M+H$)⁺.

[97]¹H NMR (400 MHz, DMSO-d₆) δ : 10.85 (s, 1H), 9.14 (d, $J = 1.1$ Hz, 1H), 8.55 (q, $J = 4.6$ Hz, 1H), 7.88 - 7.81 (m, 2H), 7.80 - 7.76 (m, 1H), 7.36 (d, $J = 9.8$ Hz, 2H), 7.12 (s, 1H), 6.54 (s, 1H), 5.48 (s, 1H), 3.25 (s, 3H), 2.75 (d, $J = 4.6$ Hz, 3H), 2.08 (tt, $J = 16.0, 8.4$ Hz, 2H), 0.78 (t, $J = 7.2$ Hz, 3H).

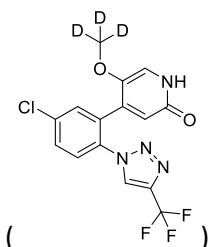
Example 21: preparation of compound 21

[98]The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluorobenzamide, and 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d₃)pyridine-2(1H)-one, to prepare the title compound 21, with a purity of 97.65%.

[99]ESI-MS: $m/z = 596.2$ ($M+H$)⁺.

[100] ¹H NMR (400 MHz, DMSO-d₆) δ : 10.79 (s, 1H), 9.14 (d, $J = 1.0$ Hz, 1H), 7.89 - 7.81 (m, 2H), 7.79 (dd, $J = 2.1, 0.7$ Hz, 1H), 7.74 - 7.60 (m, 2H), 7.55 (d, $J = 11.3$ Hz, 2H), 7.37 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.53 (s, 1H), 2.16 - 2.05 (m, 2H), 0.78 (t, $J = 7.2$ Hz, 3H).

[101] The structural confirmation data of the intermediate in step 3: 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d₃)pyridine-2(1H)-one was as follows:



[102] ESI-MS: $m/z = 374.1$ ($M+H$)⁺.

[103] ¹H NMR (400 MHz, DMSO-d₆) δ : 11.21 (s, 1H), 9.18 (s, 1H), 7.81 (s, 2H), 7.72 (s, 1H), 6.95 (s, 1H), 6.41 (s, 1H).

Example 22: preparation of compound 22

[104] The preparation method was the same as that in Example 1, except that 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d₃)pyridine-2(1H)-one, to prepare the title compound 22, with a purity of 97.65%.

[105] ESI-MS: $m/z = 612.1$ ($M+H$)⁺.

[106] ^1H NMR (400 MHz, DMSO- d_6) δ : 10.79 (s, 1H), 9.14 (d, J = 1.0 Hz, 1H), 7.97 - 7.79 (m, 2H), 7.79 (dd, J = 2.1, 0.7 Hz, 1H), 7.74 - 7.60 (m, 2H), 7.55 (d, J = 11.3 Hz, 2H), 7.37 (dd, J = 8.6, 2.0 Hz, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.53 (s, 1H), 2.16 - 2.05 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 23: preparation of compound 23

[107] The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-3-fluorobenzamide, and 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- d_3)pyridine-2(1H)-one, to prepare the title compound 23, with a purity of 97.65%.

[108] ESI-MS: m/z = 596.2 ($M+H$) $^+$.

[109] ^1H NMR (400 MHz, DMSO- d_6) δ : 10.41 (s, 1H), 9.15 (d, J = 1.0 Hz, 1H), 8.05 - 7.93 (m, 2H), 7.88 - 7.81 (m, 2H), 7.80 - 7.78 (m, 1H), 7.78 - 7.67 (m, 2H), 7.47 (s, 1H), 7.11 (s, 1H), 6.54 (s, 1H), 5.71 (s, 1H), 2.25 - 1.95 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 24: preparation of compound 24

[110] The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-3-fluoro-N-methylbenzamide, and 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- d_3)pyridine-2(1H)-one, to prepare the title compound 24, with a purity of 97.65%.

[111] ESI-MS: m/z = 610.2 ($M+H$) $^+$.

[112] ^1H NMR (400 MHz, DMSO- d_6) δ : 10.40 (s, 1H), 9.15 (d, J = 1.0 Hz, 1H), 8.49 (d, J = 4.6 Hz, 1H), 7.98 (t, J = 8.1 Hz, 1H), 7.89 - 7.80 (m, 2H), 7.79 (dd, J = 2.1, 0.7 Hz, 1H), 7.71 (dd, J = 11.8, 1.9 Hz, 1H), 7.66 (dd, J = 8.4, 2.0 Hz, 1H), 7.11 (s, 1H), 6.54 (s, 1H), 5.70 (s, 1H), 2.77 (d, J = 4.5 Hz, 3H), 2.12 (dt, J = 15.2, 7.5 Hz, 2H), 0.78 (t, J = 7.1 Hz, 3H).

Example 25: preparation of compound 25

[113] The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluoro-N-methylbenzamide, and 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy- d_3)pyridine-2(1H)-one, to prepare the title compound 25, with a purity of 98.85%.

[114] ESI-MS: m/z = 610.2 ($M+H$) $^+$.

[115] ^1H NMR (400 MHz, DMSO- d_6) δ : 10.80 (s, 1H), 9.20 - 9.08 (m, 1H), 8.10 (q, J = 4.2 Hz, 1H), 7.93 - 7.81 (m, 2H), 7.78 (d, J = 2.1 Hz, 1H), 7.70 - 7.58 (m, 2H), 7.37 (dd, J = 8.6, 2.0 Hz,

1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.52 (s, 1H), 2.76 (d, J = 4.6 Hz, 3H), 2.20 - 2.02 (m, J = 7.6 Hz, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 26: preparation of compound 26

[116] The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluoro-N-(methyl-d3)benzamide, to prepare the title compound 26, with a purity of 99.12%.

[117] ESI-MS: m/z = 610.2 (M+H)⁺.

[118] ¹H NMR (400 MHz, DMSO-d6) δ: 10.79 (s, 1H), 9.14 (d, J = 1.1 Hz, 1H), 8.06 (d, J = 3.4 Hz, 1H), 7.92 - 7.81 (m, 2H), 7.81 - 7.76 (m, 1H), 7.70 - 7.60 (m, 2H), 7.37 (dd, J = 8.6, 2.0 Hz, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.51 (d, J = 8.6 Hz, 1H), 3.25 (s, 3H), 2.19 - 1.99 (m, J = 7.1 Hz, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 27: preparation of compound 27

[119] The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluoro-N-(methyl-d3)benzamide, and 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d3)pyridine-2(1H)-one, to prepare the title compound 27, with a purity of 98.07%.

[120] ESI-MS: m/z = 613.2 (M+H)⁺.

[121] ¹H NMR (400 MHz, DMSO-d6) δ: 10.79 (s, 1H), 9.14 (d, J = 1.1 Hz, 1H), 8.06 (d, J = 3.4 Hz, 1H), 7.90 - 7.76 (m, 3H), 7.71 - 7.60 (m, 2H), 7.37 (dd, J = 8.6, 2.0 Hz, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.52 (s, 1H), 2.09 (h, J = 7.1 Hz, 2H), 0.78 (t, J = 7.2 Hz, 3H).

Example 28: preparation of compound 28

[122] The preparation method was the same as that in Example 1, except that D-2-aminobutyric acid in step 1 was replaced with (R)-2-aminobutyric acid-3,3,4,4-d5 acid, and 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluoro-benzamide, to prepare the title compound 28, with a purity of 97.36%.

[123] ESI-MS: m/z = 598.2 (M+H)⁺.

[124] ¹H NMR (400 MHz, DMSO-d6) δ: 10.72 (s, 1H), 9.10 (d, 1H), 7.98 - 7.74 (m, 5H), 7.62 - 7.36 (m, 3H), 7.11 (s, 1H), 6.56 (s, 1H), 5.50 (dd 1H), 3.26 (s, 3H).

Example 29: preparation of compound 29

[125] The preparation method was the same as that in Example 1, except that 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluoro-benzamide, and 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3

was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl-3,4,6-d3)-5-(methoxy)pyridine-2(1H)-one, to prepare the title compound 29, with a purity of 97.66%.

[126] ESI-MS: $m/z = 596.2$ ($M+H$)⁺.

[127] ¹H NMR (400 MHz, DMSO-d₆) δ : 10.80 (s, 1H), 9.15 (d, 1H), 7.92 - 7.82 (m, 2H), 7.77 (d, $J = 2.1$ Hz, 1H), 7.72 - 7.62 (m, 2H), 7.13 (s, 1H), 6.54 (s, 1H), 5.52 (s, 1H), 3.28 (s, 3H), 2.21 - 2.03 (m, $J = 7.6$ Hz, 2H), 0.79 (t, $J = 7.2$ Hz, 3H).

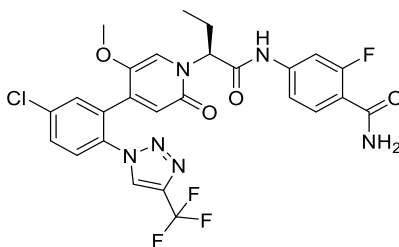
Example 30: preparation of compound 30

[128] The preparation method was the same as that in Example 1, except that D-2-aminobutyric acid in step 1 was replaced with (R)-2-aminobutyric acid-3,3,4,4,4-d₅ acid, 4-amino-2-chlorobenzamide in step 2 was replaced with 4-amino-2-fluoro-N-(methyl-d₃)benzamide, and 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxypyridine-2(1H)-one in step 3 was replaced with 4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d₃)pyridine-2(1H)-one, to prepare the title compound 30, with a purity of 98.62%.

[129] ESI-MS: $m/z = 618.2$ ($M+H$)⁺.

[130] ¹H NMR (400 MHz, DMSO-d₆) δ : 10.78 (s, 1H), 9.16 (d, $J = 1.1$ Hz, 1H), 8.06 (d, $J = 3.4$ Hz, 1H), 7.92 - 7.78 (m, 3H), 7.71 - 7.60 (m, 2H), 7.37 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.52 (s, 1H).

Comparative example 1: preparation of (S)-4-(2-(4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-methoxy-2-oxopyridin-1(2H)-yl)butanamido)-2-fluorobenzamide



[131] The compound was synthesized following the method described in patent CN 108026072 B, with a purity of 98.5%.

[132] ESI-MS: $m/z = 593.1$ ($M+H$)⁺.

[133] ¹H NMR (400 MHz, DMSO-d₆) δ : 10.78 (s, 1H), 9.14 (s, 1H), 7.88 - 7.77 (m, 3H), 7.72 - 7.61 (m, 2H), 7.55 (d, 2H), 7.37 (dd, 1H), 7.13 (s, 1H), 6.54 (s, 1H), 5.52 (dd, 1H), 3.25 (s, 3H), 2.18 - 2.00 (m, 2H), 0.78 (t, 3H).

Test example 1: determination of in-vitro anticoagulant effect in human plasma

1. Test sample

[134] Compounds 1-30 in examples and compound in comparative example 1.

2. Test method

[135] The blood of a healthy human was collected using a sodium citrate anticoagulant tube (1 : 9), immediately mixed with the anticoagulant until uniform, and centrifuged at 4,000 r/min at room temperature for 15 min. After centrifugation, the plasma sample was pipetted and frozen (-80°C) for later use.

[136] A proper amount of a compound was weighed and prepared into a 10-100 mM stock solution using 100% of DMSO (the specific concentration of the stock solution was determined based on the properties of the compound); and then working solutions with various concentrations (specifically: 1 μ M, 3 μ M and 10 μ M, respectively) were prepared from the stock solution using the healthy human plasma as a solution and thoroughly mixed. After incubation at 37°C for 3 min, the sample was placed on an instrument (model: CS-2000I) to determine APTT.

3. Data processing

[137] GraphPad Prism software was used for analysis to calculate the APTT prolongation rate at each concentration.

4. Test results

[138] The results are shown in the table below. As shown, the APTT prolongation rates for all tested compounds 1, 2, 5, 6, 13, 17, 21, 25, 26 and 27 at 1 μ M were superior to that of the compound in comparative example 1 and are greater than 50%. Based on the test results, it can be estimated that the EC150 of the aforementioned compounds of the present disclosure is less than 1 μ M.

Table 1 Test results of in-vitro anticoagulant effect in human plasma

Sample	APTT prolongation rate (%)		
	1 μ M	3 μ M	10 μ M
Compound 1	55.9	65.8	136.5
Compound 2	63.5	88.9	124.8
Compound 3	48.2	66.5	92.0
Compound 4	31.5	54.3	102.6
Compound 5	56.0	84.6	125.8
Compound 6	66.3	78.0	135.1
Compound 7	37.9	52.4	73.4
Compound 8	34.7	64.5	93.8
Compound 9	44.3	69.5	103.8
Compound 10	38.6	56.0	98.9

Compound 11	18.7	26.9	42.0
Compound 12	23.2	33.5	81.1
Compound 13	50.2	80.2	175.9
Compound 14	0.9	9.1	18.5
Compound 15	24.2	30.0	51.1
Compound 16	7.0	11.7	26.8
Compound 17	57.7	82.6	145.3
Compound 18	33.2	46.1	90.6
Compound 19	24.2	44.0	77.1
Compound 20	19.2	49.2	98.6
Compound 21	52.3	76.8	147.6
Compound 22	35.6	62.0	105.9
Compound 23	48.8	81.2	168.0
Compound 24	35.1	73.2	132.5
Compound 25	56.8	76.7	158.5
Compound 26	53.2	78.3	159.5
Compound 27	55.8	79.7	142.5
Compound 28	35.8	63.3	102.9
Compound 29	38.9	73.1	105.5
Compound 30	48.1	79.0	138.4
Comparative example 1	40.1	69.8	130.1

Test example 2: Activity assay of coagulation factor FXIa inhibitor

1. Test sample

[139] The compounds in examples and comparative example 1.

2. Test procedure

- 1) An assay buffer solution (50 mM HEPES, 5 mM KCl, 145 mM NaCl, 1 mg/ml PEG8000, with a pH of 7.4) was prepared and equilibrated to room temperature;
- 2) a 10X compound working solution was prepared;
- 3) a 0.8 nM human FXIa working solution (2X) was prepared and thoroughly mixed for later use;
- 4) 20 μ L of the FXIa working solution in step 3) was added to all the assay wells of a 384-well plate (Coring, 3702) and centrifuged (200 g, RT) for 10 s;

5) 4 μ L of the compound working solution in step 2) was added to the corresponding assay wells in the 384-well plate and centrifuged (200 g, RT) for 10 s, and then the working plate was incubated at 25°C for 20 min;

6) a 750 μ M S-2366 working solution (2.5X) was prepared and thoroughly mixed for later use;

7) 16 μ L of the S-2366 working solution in step 6) was added to all the assay wells in a 384-well plate and centrifuged (200 g, RT) for 10 s, and then the working plate was incubated at 37°C for 45 min; and

8) after incubation, the absorbance OD405nm was read using EnVision, and the data were collected.

3. Data analysis

1) $Z' \text{ factor} = 1 - 3 \cdot (SD_{\text{Max}} + SD_{\text{Min}}) / (\text{Mean}_{\text{Max}} - \text{Mean}_{\text{Min}})$;

2) $CV_{\text{Max}} = (SD_{\text{Max}} / \text{Mean}_{\text{Max}}) \cdot 100\%$;

3) $CV_{\text{Min}} = (SD_{\text{Min}} / \text{Mean}_{\text{Min}}) \cdot 100\%$;

4) $S/B = \text{Singal} / \text{Background}$;

5) blank control: 0.1% DMSO; positive control: comparative example 1;

6) calculation formula for IC_{50} : $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{Log}IC_{50} - X) \cdot \text{HillSlope}))}$

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

[140] Concentration setting: 5 concentrations: 200 nM, 40 nM, 8 nM, 1.6 nM and 0.32 nM, and IC_{50} value was detected.

4. Test results

[141] The test results are shown in the table below: All of the tested compounds of the present disclosure have a relatively significant in-vitro inhibitory effect on FXIa, among which compounds 2, 6, 17, 21, 25, 26 and 27 of the present disclosure have a stronger inhibitory effect on FXIa than the compound in comparative example 1, especially for compounds 2 and 6 which exhibit a more significant effect. Other tested compounds of the present disclosure have an inhibitory effect on FXIa comparable to that of the comparative example.

Table 2 Activity assay of coagulation factor FXIa inhibitor

Sample	IC ₅₀ (nM)	Sample	IC ₅₀ (nM)
Compound 1	7.53	Compound 2	0.91
Compound 5	5.60	Compound 6	0.96
Compound 9	6.32	Compound 13	25.5
Compound 17	1.65	Compound 18	9.06
Compound 21	2.09	Compound 22	4.23
Compound 25	1.87	Compound 26	1.15
Compound 27	2.98	Comparative example 1	7.80

Test example 3: Study of pharmacokinetics in rats

1. Test sample

[142] Compound in comparative example 1 and compounds 2, 6, 21, 25, 26, 27 and 28 in examples.

2. Test operation

[143] In the experiment, 48 male SD rats were divided into 8 groups (6 in each group): a group for comparative example 1, a group for compound 2, a group for compound 6, a group for compound 21, a group for compound 25, a group for compound 26, a group for compound 27, and a group for compound 28, respectively. The rats were fasted for 12 h before administration, with free access to water only. Each group was administered via intragastrical gavage at a dose of 30 mg/kg.

[144] Blank blood samples were collected before administration, and blood samples were collected at the following predetermined time points after administration: 5 min, 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 5 h, 7 h and 24h. About 0.5 mL of blood was collected, placed in an EDTA-K₂ tube, centrifuged to separate plasma, and stored at -80°C. The drug plasma concentration was measured using a liquid chromatography-tandem mass spectrometry analysis system (LC-MS/MS), and pharmacokinetic parameters, such as AUC_{0-t}, C_{max}, T_{max} and t_{1/2}, were calculated based on the drug plasma concentration data using DAS 2.0 software.

3. Test results

[145] The experimental results of the pharmacokinetic study of oral administration in rats are shown in the table below. Compared with comparative example 1, compounds 2, 6, 21, 25, 26 and 27 in the examples have better absorption characteristics, showing significantly improved **AUC_(0-t)**. Notably, compound 21, compound 25, compound 26, and compound 27

have significantly improved AUC and C_{max} relative to comparative example 1 at the same dose, indicating that the compounds in these examples can achieve the same efficacy at a lower dose.

[146] Additionally, compared with comparative example 1 and compound 28, compound 21, compound 25, compound 26, and compound 27 have a shorter half-life and a pharmacokinetic characteristic of rapid elimination, indicating that the compounds have a lower safety risk of potential bleeding. It also demonstrates that not all the deuteration sites have an effect of extending half-life. Notably, the present disclosure unexpectedly found that only deuterated compounds at R⁹ and/or R² sites in the structure of general formula (1) have more advantageous pharmacokinetic results.

Table 3 Pharmacokinetic results

Compound	AUC _(0-t) (ug/L*h)	t _{1/2} (h)	T _{max} (h)	C _{max} (ug/L)
Comparative example 1	73,998	6.14	2.83	6,300
Compound 2	85,885	7.75	3.94	6,737
Compound 6	89,785	7.08	4.10	6,437
Compound 21	273,612	2.96	5.00	26,867
Compound 25	159,025	1.9	2.30	26,467
Compound 26	128,935	3.33	2.70	21,034
Compound 27	290,874	4.01	4.43	27,189
Compound 28	70,918	5.88	5.13	6,222

Test example 4: Effect of continuous in-vivo administration on general condition and food intake of rats

1. Test drug

[147] Comparative example 1, and compound 2, compound 21, compound 25, compound 26 and compound 27 in examples.

2. Test scheme

[148] 70 healthy adult SD rats were randomly divided into 7 groups: a blank group, a group for comparative example 1, a group for compound 2, a group for compound 21, a group for compound 25, a group for compound 26, and a group for compound 27. Each group had 10 rats, equally distributed by gender. The rats received drug administrations via oral gavage once a day for 14 consecutive days, following the administration regimen outlined in the table below. The blank group was given an equal volume of a vehicle. After

administration, the effects of the drugs on the general condition and food intake of rats were observed and recorded.

Table 4 Continuous administration regimen

Experiment grouping	Test substance	Number of animals	Administration dose (mg/kg)	Dosing volume (ml/kg)	Route of administration
Blank group	Vehicle	10	/	10	PO
Group for comparative example 1	Comparative example 1	10	500	10	PO
Group for compound 2	Compound 2	10	500	10	PO
Group for compound 21	Compound 21	10	500	10	PO
Group for compound 25	Compound 25	10	500	10	PO
Group for compound 26	Compound 26	10	500	10	PO
Group for compound 27	Compound 27	10	500	10	PO

3. Test results

[149] In the study on the general condition of the rats in each group after 14 consecutive days of oral gavage administration, piloerection and hypoactivity were found in 1/3 or more of the rats in the comparative example 1 group; and no apparent abnormalities were observed in the remaining groups.

[150] After 14 days of continuous oral gavage administration, the food intake of the rats in each group was observed. The results are shown in the table below.

Table 5 Observation results of food intake of rats (within 24 hours after the last administration)

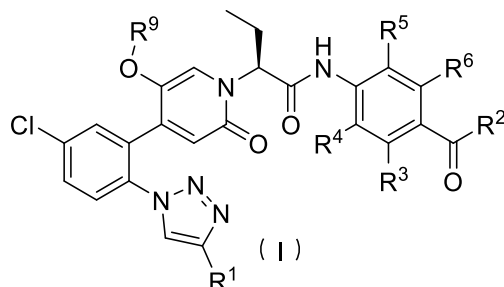
Group	Blank group	Group for comparative example 1	Group for compound 2	Group for compound 21
Food intake (g, mean±SD)	27.68±1.45	24.98±0.92**	27.22±1.33	27.08±1.23
Group	Compound 25	Compound 26	Compound 27	
Food intake (g, mean±SD)	27.00±1.42	26.49±1.21	27.08±1.19	
Note: **P < 0.01 vs blank group				

[151] As can be seen from the table above, compared with the blank group, the rats in the group for comparative example 1 showed a significantly reduced food intake ($P < 0.001$) within 24 hours after the last administration. By contrast, the rats in the groups for compound 2, compound 21, compound 25, compound 26 and compound 27 showed essentially the same food intake as the blank group within 24 hours after the last administration, with no statistically significant difference. The compounds of the present disclosure demonstrate higher safety profiles with reduced tissue toxicity risk.

[152] The examples described above are only one of the preferred embodiments of the present disclosure and should not be construed as limiting the scope of protection of the present disclosure. Any modification or refinement made without substantive departure from the core design concept and spirit of the present disclosure, which still solves technical problems consistent with the present disclosure, shall be included in the scope of protection of the present disclosure.

Claims

1. A compound represented by Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof:



wherein

R¹ is selected from halogen and trifluoromethyl;

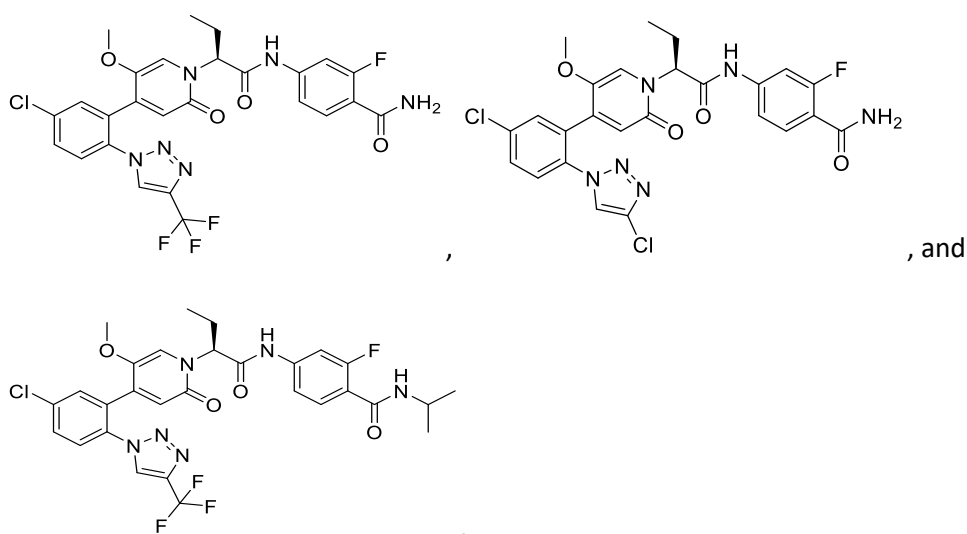
R² is independently selected from NH₂, NHR⁷, OH and OR⁸, wherein R⁷ and R⁸ are selected from alkyl and cycloalkyl, and the hydrogen of R⁷ and R⁸ may be substituted with one or more deuterium;

R³ and R⁶ are independently selected from hydrogen, halogen, alkoxy, haloalkyl and CONH₂;

R⁴ and R⁵ are independently selected from hydrogen, halogen, alkoxy and haloalkyl; and

R⁹ is independently selected from CH₃ and CD₃;

wherein the following compounds are excluded:



2. The compound of claim 1, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

R¹ is selected from chloro or trifluoromethyl; and/or

R² is independently selected from NH₂, NHR⁷, OH and OR⁸, wherein R⁷ and R⁸ are selected from methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl and tert-butyl, and the hydrogen of R⁷ and R⁸ may be substituted with one or more deuterium; and/or

R³ and R⁶ are independently selected from hydrogen, fluoro, chloro, methoxy, trifluoromethyl and CONH₂; and/or

R⁴ and R⁵ are independently selected from hydrogen, fluoro, chloro, methoxy and trifluoromethyl; and/or

R⁹ is independently selected from CH₃ and CD₃.

3. The compound of claim 1, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

R¹ is trifluoromethyl; and/or

R² is independently selected from NH₂, NHR⁷, OH and OR⁸, wherein R⁷ and R⁸ are selected from methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl and tert-butyl, and the hydrogen of R⁷ and R⁸ may be substituted with one or more deuterium; and/or

R³ and R⁶ are independently selected from hydrogen, fluoro, chloro, methoxy, trifluoromethyl and CONH₂; and/or

R⁴ and R⁵ are independently selected from hydrogen, fluoro and chloro; and/or

R⁹ is independently selected from CH₃ and CD₃.

4. The compound of any one of claims 1-3, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

R¹ is trifluoromethyl; and/or

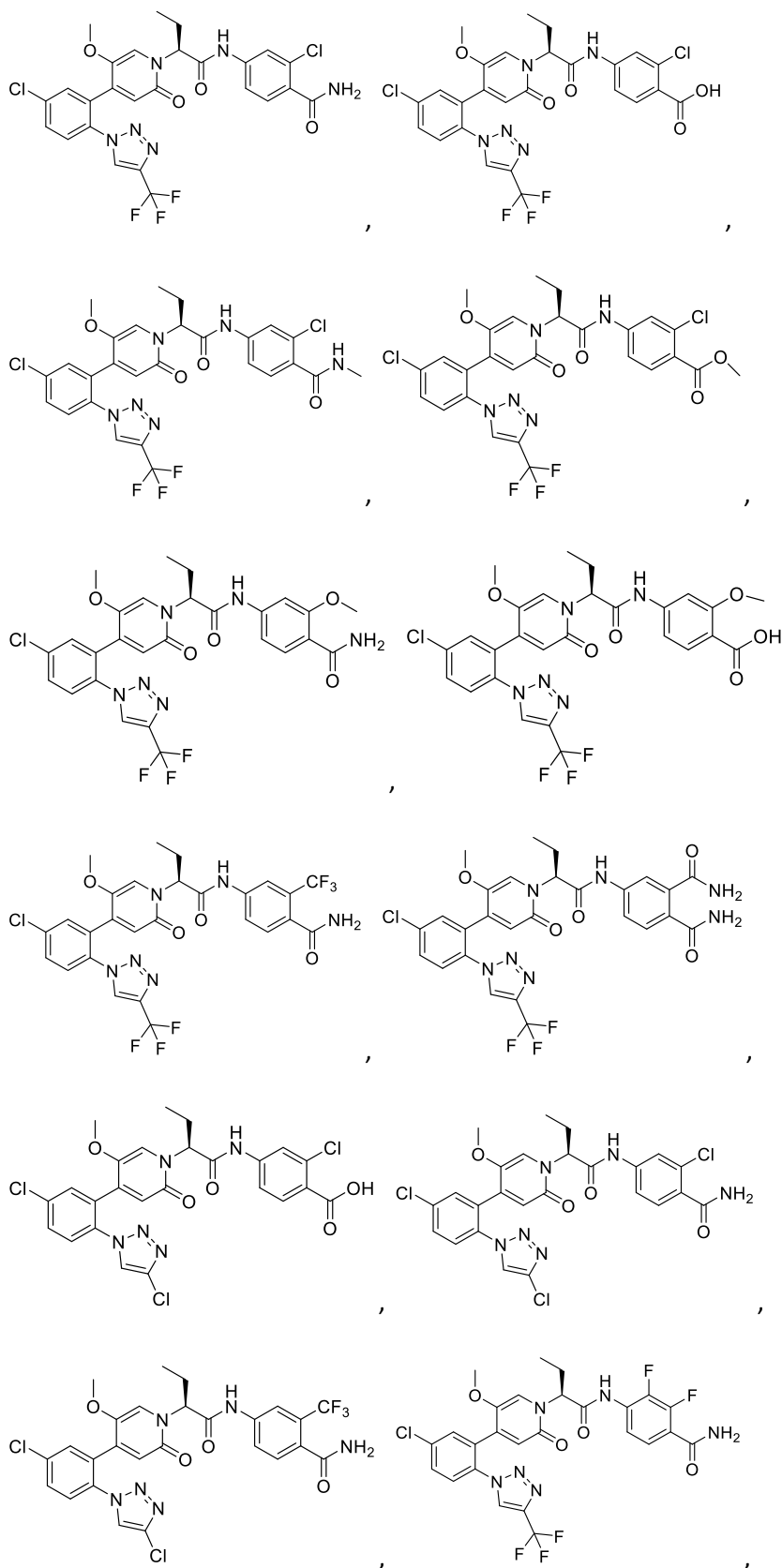
R² is independently selected from NH₂, NHCH₃, NHCD₃, OH, OCH₃, OCD₃ and OC(CH₃)₃; and/or

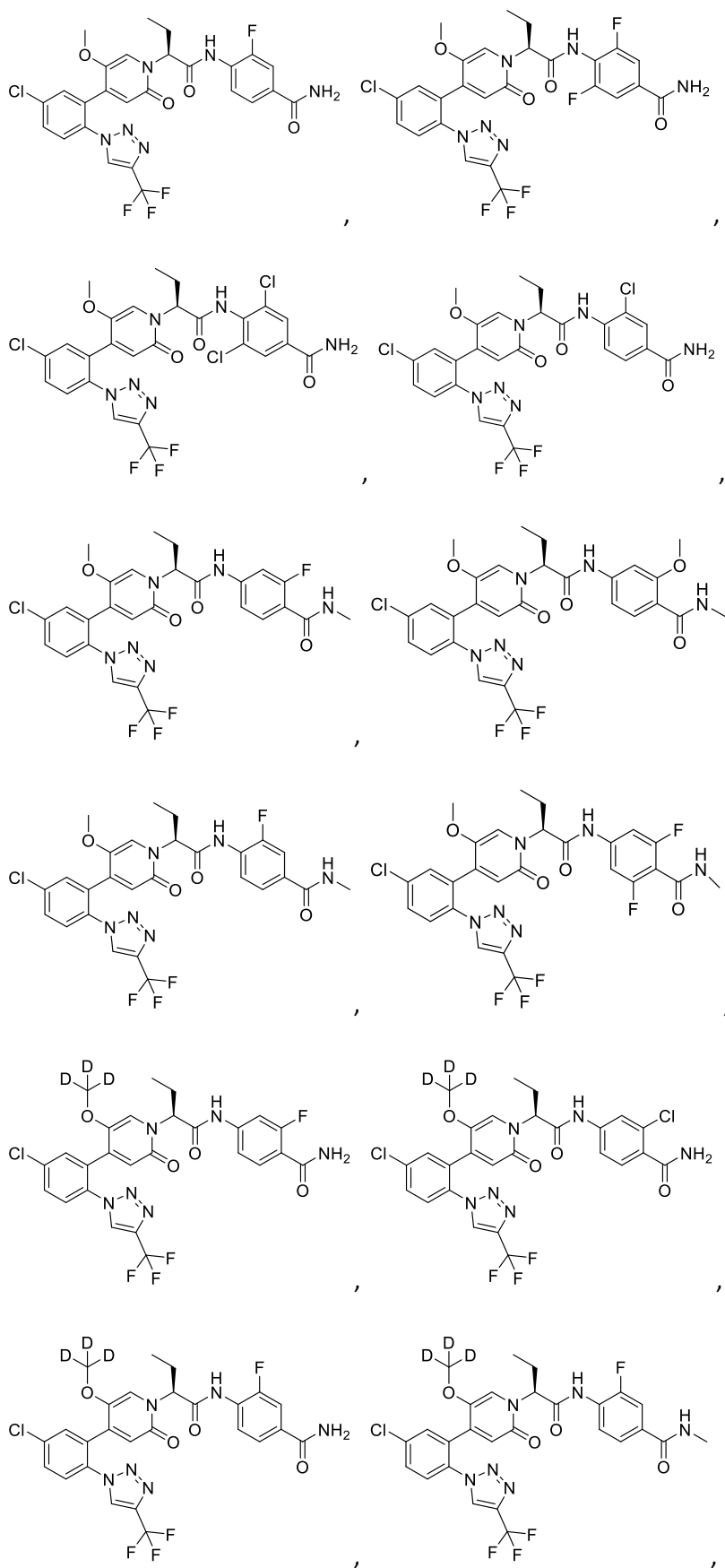
R³ and R⁶ are independently selected from fluoro, chloro, methoxy and trifluoromethyl; and/or

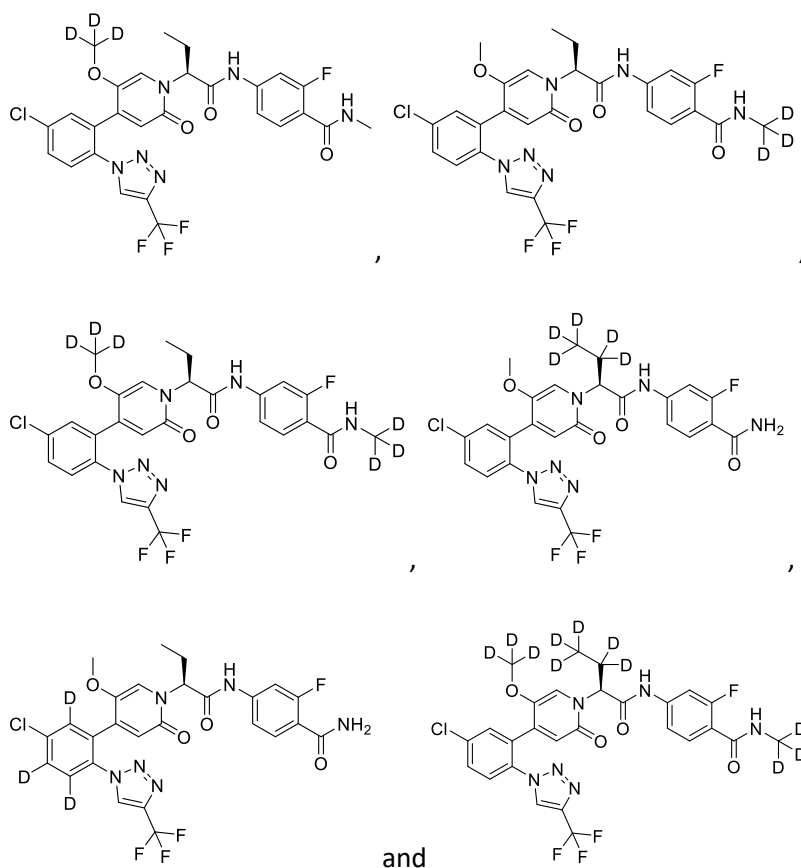
R⁴ and R⁵ are independently selected from hydrogen, fluoro and chloro; and/or

R⁹ is independently selected from CH₃ and CD₃.

5. The compound of any one of claims 1-4, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein the compound is selected from the following structures:

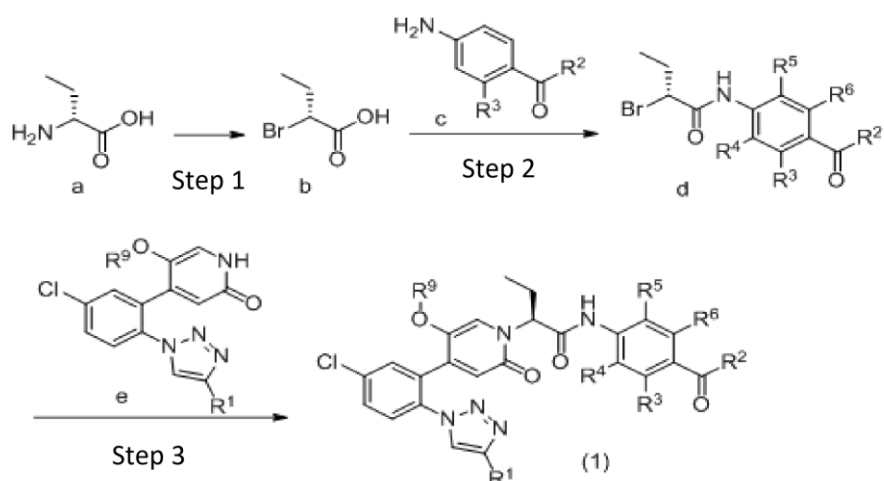






6. The compound of any one of claims 1-5, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein the hydrogen in the compound or the stereoisomer or pharmaceutically acceptable salt thereof may be substituted with one or more deuterium.
7. The compound of any one of claims 1-6, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein the compound is prepared by a method comprising the following steps:

when R^2 is NH_2 , NHR^7 or OR^8 , the synthesis route is as follows:



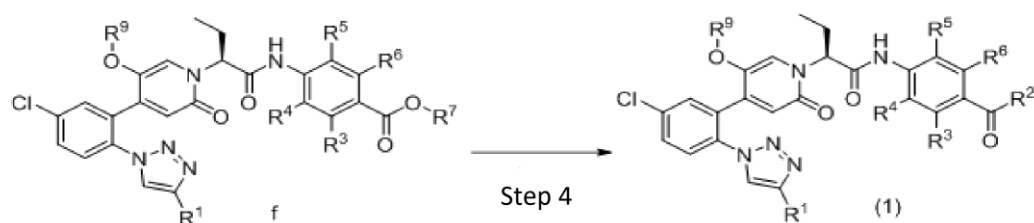
wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 are defined the same as those in any one of claims 1-6;

step 1: bromination of starting material a to produce intermediate b;

step 2: condensation of intermediate b with starting material c to produce intermediate c;
and

step 3: a substitution reaction of intermediate d with compound e to produce a compound of Formula (1); and

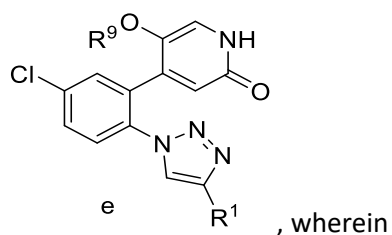
when R^2 is OH, the synthesis route is as follows:



wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 and R^9 are defined the same as those in any one of claims 1-6;

step 4: hydrolysis of compound f under a basic condition to produce a compound of Formula (1).

8. A key intermediate having a structure represented by Formula e below:



R^1 is selected from halogen and trifluoromethyl, and R^9 is selected from CH_3 and CD_3 ;

preferably, R^1 is selected from halogen and trifluoromethyl, and R^9 is CD_3 .

9. The intermediate of claim 8, wherein the intermediate is selected from the following compounds:

4-(5-chloro-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d3)pyridine-2(1H)-one; and

4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-5-(methoxy-d3)pyridine-2(1H)-one.

10. A pharmaceutical composition comprising

the compound of any one of claims 1-6, or a stereoisomer or pharmaceutically acceptable salt thereof, and

a pharmaceutically acceptable excipient.
11. Use of the compound of any one of claims 1-6 or a stereoisomer or pharmaceutically acceptable salt thereof in the preparation of a medicament for treating and/or preventing an FXIa receptor-associated disease.
12. The use of claim 9, wherein the FXIa receptor-associated disease is selected from a cerebrovascular arterial disease and/or a peripheral arterial disease; preferably, the FXIa receptor-associated disease is selected from transient ischemic attack (TIA), ischemic stroke, including cardioembolic stroke such as stroke caused by atrial fibrillation, non-cardioembolic stroke such as lacunar stroke, stroke caused by an aortic or arteriolar disease or stroke of undetermined etiology, cryptogenic stroke, embolic stroke, embolic stroke of undetermined source, or an event leading to stroke or TIA and originating from thrombosis and/or thromboembolism, and/or a peripheral arterial condition leading to the peripheral arterial disease, including peripheral arterial occlusion, acute limb ischemia, amputation, reocclusion and restenosis after intervention (for example, angioplasty, stent implantation or surgery, and bypass grafting), and/or stent thrombosis.