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(71) Applicant: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(71) Applicant *(for MG only)*: **LILLY CHINA RESEARCH AND DEVELOPMENT CO., LTD.** [CN/CN]; 780 Cailun Road, Rm. 819, Zhangjiang High Technology Park, Pudong New Area, Shanghai 201203 (CN).

(72) Inventors: **HO, Koc Kan**; c/o Eli Lilly and Company P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **QUAN, Weiguo**; c/o Eli Lilly and Company P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **ZHOU, Jingye**; c/o Eli Lilly and Company P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(74) Agent: **CHINA PATENT AGENT (H.K.) LTD.**; 22/F., Great Eagle Center, 23 Harbour Road, Wanchai, Hong Kong (CN).

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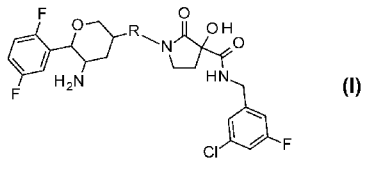
(54) Title: PYRROLIDINONE COMPOUNDS



(I)

(57) Abstract: The present invention provides compounds of the Formula (I) or a pharmaceutically acceptable salt thereof.

Pyrrolidinone Compounds

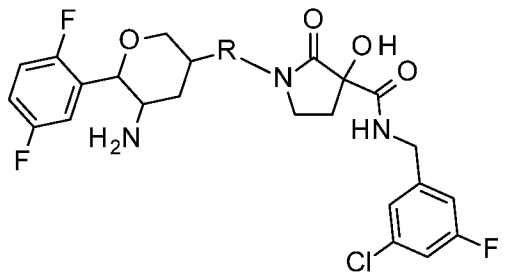
This invention relates to pyrrolidinone compounds, or a pharmaceutically acceptable salt thereof, and therapeutic use thereof. Compounds of this invention are inhibitors of methionine aminopeptidase 2 (MetAP2) and dipeptidyl peptidase-4 (DPP-4).

MetAP2 is a metalloproteinase that cleaves initiator methionine from nascent peptide emerging from the ribosomes. WO 2010/065879 reports small molecule MetAP2 inhibitors for obesity treatment.

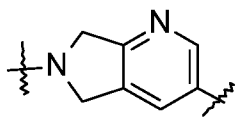
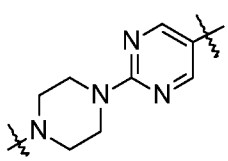
DPP-4 inhibitors are an established drug class to improve glycemic control in patients with type 2 diabetes mellitus. Compounds with dual inhibitory activity in both MetAP2 and DPP-4 are desired.

The present invention provides novel compounds with dual MetAP2 and DPP-4 inhibition. These dual inhibitor compounds can be useful in the treatment of a MetAP2 mediated condition.

The present invention provides a compound of the Formula I

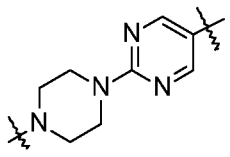


I;

Wherein R is selected from the group consisting of  and  ;

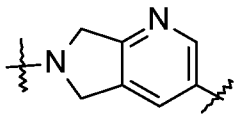
or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention is a compound of Formula I wherein R is



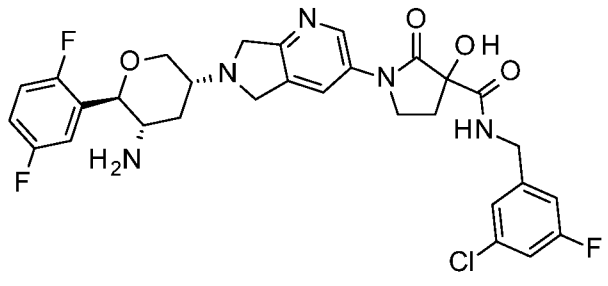
; or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention is a compound of Formula I wherein R is



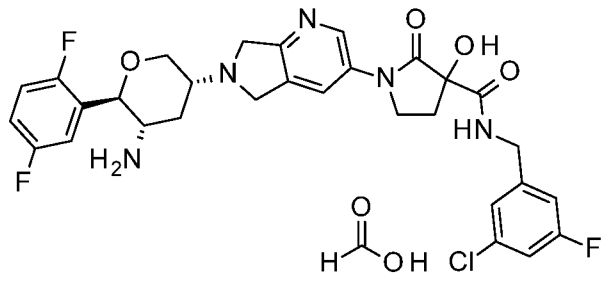
; or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention the compound is



; or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention the compound is



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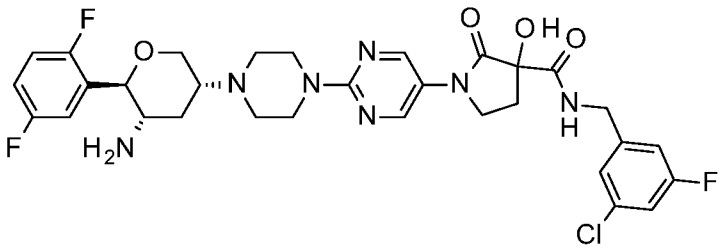
In an embodiment of the invention, the compound is



or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention the compound is selected from the group consisting of 1-[2-[4-[(3R,5S,6R)-5-Amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]piperazin-1-yl]pyrimidin-5-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1 and 1-[6-[(3R,5S,6R)-5-amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]-5,7-dihydropyrrolo[3,4-b]pyridin-3-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1, or a pharmaceutically acceptable salt thereof. In an embodiment of the invention, the compound is a hydrochloride salt.

The invention provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and at least one selected from the group consisting of a pharmaceutically acceptable carrier, diluent, and excipient.

The invention provides a method for treating type II diabetes in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. The invention provides a method for treating obesity in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of Formula I. In another embodiment of the invention, there is a method for treating a condition associated with MetAP2 modulation in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In another embodiment, the invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy. Further, provided is a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament.

Compounds of the present invention can be provided as a pharmaceutically acceptable salt. "Pharmaceutically acceptable salt" refers to salts of the compound of the invention considered to be acceptable for clinical and/or veterinary use. Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. *See, e.g.*, P. Stahl, *et al.*, Handbook of Pharmaceutical Salts: Properties, Selection and Use, (VCHA/Wiley-VCH, 2002); S.M. Berge, *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

Additionally, certain intermediates described in the following preparations may contain one or more nitrogen protecting groups. The variable protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The protection and deprotection conditions are well known to the skilled artisan and are described in the literature (See for example "*Greene's Protective Groups in Organic Synthesis*", Fourth Edition, by Peter G.M. Wuts and Theodora W. Greene, John Wiley and Sons, Inc. 2007).

Individual isomers, enantiomers, and diastereomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the invention, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," *Stereochemistry of Organic Compounds*", Wiley-Interscience, 1994). The designations "isomer 1" and "isomer 2" refer to the compounds that elute from chiral chromatography first and second, respectively, and if chiral chromatography is initiated early in the synthesis, the same designation is applied to subsequent intermediates and examples.

The compounds of the present invention, or salts thereof, may be prepared by a variety of procedures known in the art, some of which are illustrated in the Preparations and Example below. The specific synthetic steps for each of the routes described may be combined in different ways, to prepare compounds of the invention, or salts thereof. The products of each step can be recovered by conventional methods well known in the art, including extraction, evaporation, precipitation, chromatography, filtration, trituration, and crystallization. The reagents and starting materials are readily available to one of

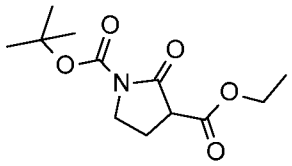
ordinary skill in the art. Others may be made by standard techniques of organic and heterocyclic chemistry which are analogous to the syntheses of known structurally-similar compounds and the procedures described in the Preparations and Examples which follow including any novel procedures.

The abbreviations used herein are defined according to *Aldrichimica Acta*, Vol. 17, No. 1, 1984. Other abbreviations are defined as follows: "BSA" refers to Bovine Serum Albumin; "DCM" refers to dichloromethane; "DIPEA" refers to diisopropylethylamine; "DMAc" refers to dimethylacetamide; "DMF refers to dimethylformamide; "DIO" refers to diet induced obese; "EDTA" refers to ethylenediaminetetraacetic acid; "EtOAc" refers to ethyl acetate; "FA" refers to formic acid; "HEC" refers to hydroxy ethyl cellulose; "HEPES" refers to 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; "HFD" refers to high fat diet; IC_{50}" refers to the concentration of an agent that produces 50% of the maximal inhibitory response possible for that agent; "HPLC" refers to high performance liquid chromatography; "i-PrOH" refers to isopropanol or isopropyl alcohol; "LiHMDS" refers to lithium hexamethyldisilazide; "MTBE" refers to methyl *t*-butyl ether; "RT" refers to retention time; "SFC" refers to supercritical fluid chromatography; "TFA" refers to trifluoroacetic acid; "THF" refers to tetrahydrofuran; and "Tris" refers to tris(hydroxymethyl)aminomethane.

The following preparations and examples further illustrate the invention.

Preparation 1

1-(*tert*-Butyl) 3-ethyl 2-oxopyrrolidine-1,3-dicarboxylate

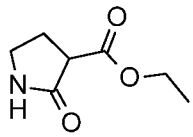


To THF (300 mL) is added LiHMDS (1.0 M, 6.80 L) at -70°C under N_2. Ethyl carbonochloridate (597.62 g, 5.51 mol) is added into the mixture at the same temperature. *tert*-Butyl 2-oxopyrrolidine-1-carboxylate (600.00 g, 3.24 mol) is added to the mixture,

and the mixture is stirred at -70°C for 30 minutes. The reaction mixture is poured into an ice cold saturated solution of NH_4Cl (1500 mL) and is separated. The aqueous layer is extracted with EtOAc (2×300 mL) and the combined organic extracts are washed with water (2×400 mL), brine (2×400 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue is slurried with MTBE (500 mL) at 15 °C for 20 minutes and filtered. The filter cake is washed with MTBE (2×100 mL) and dried in vacuum to give the title compound (270.00 g, 944.50 mmol, 29.15%) as a white solid.

Preparation 2

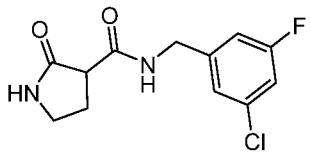
Ethyl 2-oxopyrrolidine-3-carboxylate



To a solution of 1-(*tert*-butyl) 3-ethyl 2-oxopyrrolidine-1,3-dicarboxylate (563.00 g, 2.19 mol) in DCM (200 mL) is added HCl/dioxane (4 M, 3.29 L) at 15 °C. The reaction mixture is stirred for 1 hour. The reaction mixture is concentrated under reduced pressure at 45 °C to give the title compound (381.00 g, 1.67 mol, 76.37%) as a brown oil. The crude material is used without further purification.

Preparation 3

N-[(3-Chloro-5-fluoro-phenyl)methyl]-2-oxo-pyrrolidine-3-carboxamide

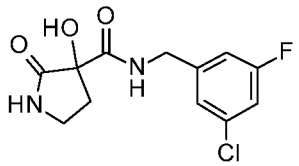


A solution of compound ethyl 2-oxopyrrolidine-3-carboxylate (180.00 g, 929.61 mmol) and (3-chloro-5-fluoro-phenyl)methanamine (148.36 g, 929.61 mmol) in xylene (4.00 L) is heated to 130 °C for 16 hours. The reaction mixture is cooled to 10 °C and a solid precipitates after 30 minutes. The suspension is filtered and the filter cake is washed with xylene (3×500 mL), petroleum ether (2×500 mL) and dried in vacuum to

give the title product (81 g). The filtrates are concentrated under reduced pressure and the residue in xylene (3 L) is heated to 130 °C for 40 hours. The reaction mixture is cooled to 10°C and solid precipitates after 30 minutes. The suspension is filtered and the filter cake is washed with xylene (2×500 mL), petroleum ether (2×500 mL), and dried in vacuum to give the title product (81.38 g). The combined product (164.38 g, 607.26 mmol, 65.32%) is obtained as a white solid. ES/MS m/z 270.9 (M+H).

Preparation 4

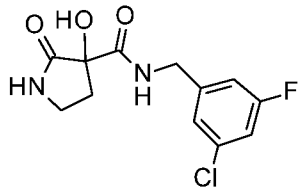
N-[(3-Chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide



N-[(3-Chloro-5-fluoro-phenyl)methyl]-2-oxo-pyrrolidine-3-carboxamide (164.38 g, 607.26 mmol) is dissolved in *tert*-butanol (6.00 L) at 80 °C over a period of 30 minutes. The reaction mixture is cooled to 15 °C. Sodium ethoxide (206.62 g, 3.04 mol) is added and the color of solution turns to yellow from colorless. *tert*-Butyl hydroperoxide (626.98 mL, 4.25 mol, 65% purity) is added to the mixture at 25 °C. The color of solution turns to white from yellow, and a solid is precipitated. The suspension is heated to 40 °C for 1 hour. The white suspension is quenched with saturated aqueous Na_2SO_3 (1500 mL) and the pH is adjusted to 7 with 4 N HCl (100 mL) and separated. The aqueous layer is extracted with DCM/iPrOH (3/1, 400 mL×2). The combined organic extracts are concentrated under reduced pressure. The residue is dissolved in DCM/iPrOH (3/1, 3 L) and washed with water (500 mL), brine (500 mL) and concentrated under reduced pressure. The yellow solid is slurried with DCM (400 mL) at 15 °C for 15 minutes and filtered. The filter cake is washed with DCM (150 mL×3) and dried in vacuum to give the title compound (169.00 g, 583.59 mmol, 96.10%) as a white solid. ES/MS m/z 286.9 (M+H).

Preparation 5

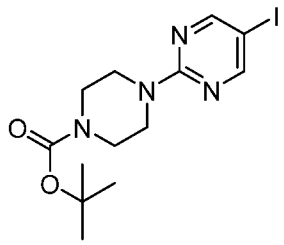
N-[(3-Chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1



N-[(3-Chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide (164.00 g, 572.05 mmol) is separated by chiral SFC (instrument: SFC-7; column: AD (250 mm*50 mm,10 μm); mobile phase: A CO_2 and B methanol; gradient: B 45%; column temp: 38 °C; flow rate: 200 mL/min; back pressure: 100 bar; wavelength: 220 nm) to give the title product compound, isomer 1, (58.86 g, 205.31 mmol, 35.89%), RT= 4.45 minutes as a white solid and another isomer (59.74 g, 208.38 mmol, 36.43%, RT= 5.96 min) as a white solid. ES/MS m/z 286.9 (M+H).

Preparation 6

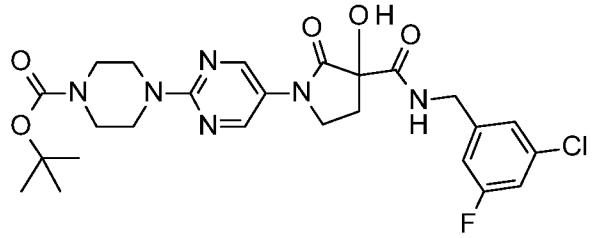
tert-Butyl 4-(5-iodopyrimidin-2-yl)piperazine-1-carboxylate



A solution of 2-chloro-5-iodo-pyrimidine (1.50 g, 6.24 mmol), *tert*-butyl piperazine-1-carboxylate (1.39 g, 7.49 mmol) and DIPEA (1.62 g, 12.5 mmol) in i-PrOH (10 mL) is stirred at 120 °C for 1 hour in a microwave reactor. The mixture is diluted with EtOAc (100 mL), washed with 1 N HCl acid, brine, dried over Na_2SO_4 and concentrated to give the title compound (2.36 g, 6.05 mmol, 96.9%) as a white solid, which is used without further purification. ES/MS m/z 335.0 (M-56).

Preparation 7

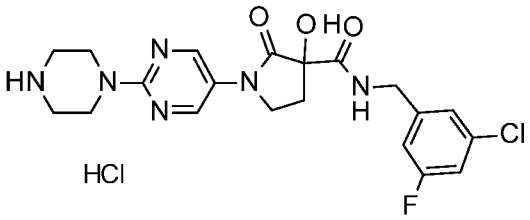
tert-Butyl 4-[5-[3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]pyrimidin-2-yl]piperazine-1-carboxylate, isomer 1



A solution of *tert*-butyl 4-(5-iodopyrimidin-2-yl)piperazine-1-carboxylate (2.36 g, 6.05 mmol), N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1 (1.91 g, 6.65 mmol) and Cs_2CO_3 (3.94 g, 12.1 mmol) in DMF (40 mL) and CH_3CN (20 mL) is degassed with a stream of N_2 for 15 minutes. CuI (1.27 g,7.86 mmol) and N,N'-dimethylethane-1,2-diamine (0.160 g, 1.81 mmol) and is added sequentially and the resulting mixture is stirred at 85 °C for 2 hours. Water (100 mL) is added and the pH is adjusted to pH= 5-6 by 1 N HCl, and extracted with EtOAc (100 mL×3), washed with brine, dried over Na_2SO_4, and concentrated to give the title compound (3.32 g, 6.05 mmol, 100%) as a brown solid, which is used without further purification. ES/MS m/z 549.2 (M+H).

Preparation 8

N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-1-(2-piperazin-1-ylpyrimidin-5-yl)pyrrolidine-3-carboxamide, isomer 1; hydrochloride

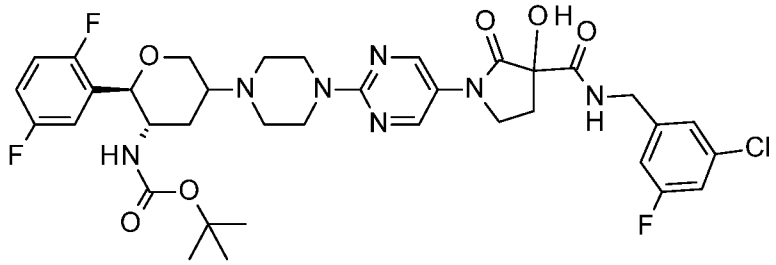


A solution of *tert*-butyl 4-[5-[3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]pyrimidin-2-yl]piperazine-1-carboxylate, isomer 1 (3.32

g, 6.05 mmol) in TFA (20 mL) and DCM (20 mL) is stirred at room temperature overnight. The solvent is removed under reduced pressure. 1 M HCl/methanol (40 mL) is added to this solution and stirred at room temperature for 20 minutes. The suspension is collected and dried by oil pump to give the title compound as a yellow solid (2 g, 4.121 mmol, 68.1%). ES/MS m/z 449.1 (M+H).

Preparation 9

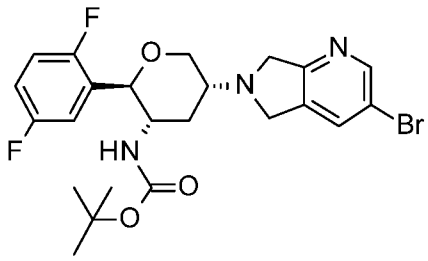
tert-Butyl N-[(2R,3S)-5-[4-[5-[3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]pyrimidin-2-yl]piperazin-1-yl]-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate, isomer 1



To a solution of N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-1-(2-piperazin-1-ylpyrimidin-5-yl)pyrrolidine-3-carboxamide, isomer 1; hydrochloride (1.50 g, 3.09 mmol) and *tert*-butyl N-[(2R,3S)-2-(2,5-difluorophenyl)-5-oxo-tetrahydropyran-3-yl]carbamate (1.21 g, 3.71 mmol) in DMAc (20 mL) is added DIPEA (0.799 g, 6.18 mmol) at room temperature and the mixture is stirred for 15 minutes. Acetic acid (0.557 g, 9.27 mmol) is added and the mixture is stirred at room temperature for another 15 minutes. Sodium triacetoxyborohydride (2.76 g, 12.4 mmol) is added to the mixture, and the mixture is stirred at room temperature overnight. Water (120 mL) is added to quench the reaction. 1 N HCl acid is added to adjust the pH to 6. This solution is extracted with EtOAc (60 mL×3) and the combined organic phase is concentrated to give the crude title product (2.35 g, 3.09 mmol, 100%), which is used without further purification. ES/MS m/z 760.2 (M+H).

Preparation 10

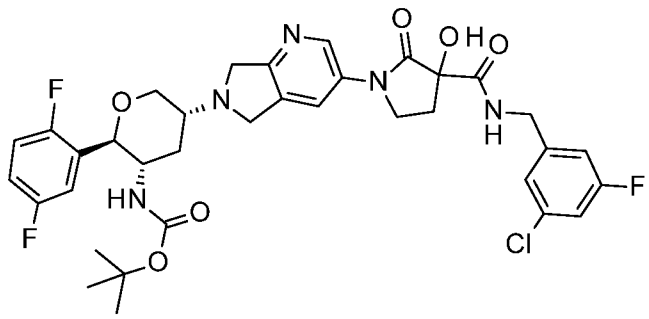
tert-Butyl N-[(2R,3S,5R)-5-(3-bromo-5,7-dihydropyrrolo[3,4-b]pyridin-6-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate



To a solution of 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine; hydrochloride (300 mg, 1.27mmol) and *tert*-butyl N-[(2R,3S)-2-(2,5-difluorophenyl)-5-oxo-tetrahydropyran-3-yl]carbamate (498 mg, 1.52 mmol) in N,N-dimethylacetamide (3 mL) is added N,N-diethylethanamine (0.33 g, 2.54 mmol) at room temperature and the mixture is stirred at room temperature for 15 minutes. Acetic acid (0.23 g, 3.82 mmol) is added and the mixture is stirred for another 15 minutes. Sodium triacetoxyborohydride (0.81 g, 3.82 mmol) is added to the mixture at - 10 °C and the mixture is stirred at room temperature overnight. 1 N HCl is added to adjust the pH to 6. The resulting solution is extracted with EtOAc (30 mL×3), dried over Na_2SO_4, and concentrated to dryness. The crude product is purified by silica gel chromatography to give the title compound (610 mg, 1.195 mmol, 93.82%) as a white solid that is used without further purification. ES/MS m/z 510.40 (M+H).

Preparation 11

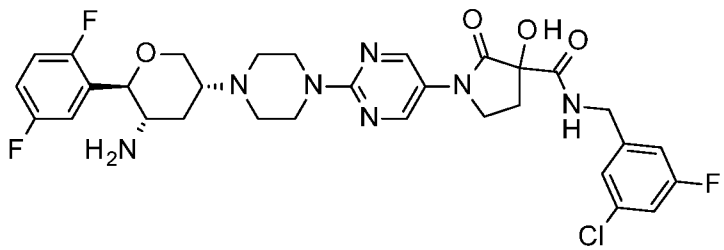
tert-Butyl N-[(2R,3S,5R)-5-[3-[3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]-5,7-dihydropyrrolo[3,4-b]pyridin-6-yl]-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate, isomer 1



A solution of *tert*-butyl N-[(2R,3S,5R)-5-(3-bromo-5,7-dihydropyrrolo[3,4-b]pyridin-6-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate (710 mg, 1.39 mmol), N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1 (439 mg, 1.53 mmol) and Cs_2CO_3 (0.906 g, 2.78 mmol) in DMF (7 mL) and CH_3CN (3 mL) is degassed with a stream of N_2 for 5 minutes, N,N'-dimethylethane-1,2-diamine (0.036 g, 0.41 mmol) and CuI (0.345 g, 1.81 mmol) are added sequentially and the resulting mixture is stirred at 90 °C for 7 hours. Water (50 mL) is added and the pH is adjusted to 6 by 1 N HCl and extracted with EtOAc (60 mL×3), washed by brine, dried over Na_2SO_4, and concentrated to give the title compound as a brown oil (0.43 g crude), which is used directly without further purification. ES/MS m/z 716.20 (M+H).

Example 1

1-[2-[4-[(3R,5S,6R)-5-Amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]piperazin-1-yl]pyrimidin-5-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1

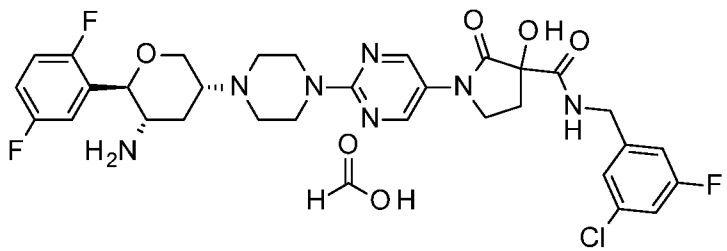


A solution of *tert*-butyl N-[(2R,3S)-5-[4-[5-[3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]pyrimidin-2-yl]piperazin-1-

yl]-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate, isomer 1 (2.35 g, 3.09 mmol) in TFA (20 mL) and DCM (20 mL) is stirred at room temperature for 2 hours. The solvent is removed to give an oil, which is separated by reversed-phase flash column chromatography (ACN in H_2O from 0 to 30%) to give a TFA mixture (3.21 g) of two isomers, which is then separated by basic Chiral SFC (instrument: MG II preparative SFC; column: ChiralPak IC, 250*30 mm; mobile phase: A CO_2 and B ethanol (0.1% NH_3H_2O); gradient: B 40%; column temp: 38 °C; flow rate: 55 mL/min; back pressure: 100 bar; wavelength: 220 nm) to give the title compound of Example 1 1-[2-[4-[(3R,5S,6R)-5-amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]piperazin-1-yl]pyrimidin-5-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1 (1.50 g, 2.27 mmol, 73.5% RT=4.62 min) as a white solid. ES/MS m/z 660.2 (M+H), ^{1}H NMR (CD_3OD, formic acid salt) δ 1.54 (q, 1H), 2.18 (m, 1H), 2.36 (m, 1H), 2.63 (m, 5H), 2.76 (m, 1H), 3.13 (m, 1H), 3.43 (t, 1H), 3.74 (m, 5H), 3.83 (m, 1H), 4.15 (m, 1H), 4.30 (dd, 2H), 4.34 (d, 1H), 6.96 (m, 2H), 7.07 (m, 3H), 7.16 (m, 1H), 8.51 (s, 2H).

Example 2

1-[2-[4-[(3R,5S,6R)-5-Amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]piperazin-1-yl]pyrimidin-5-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1; formic acid

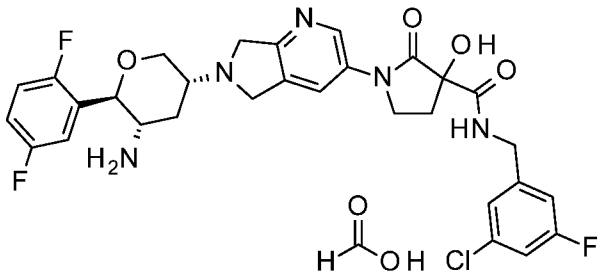


A solution of *tert*-butyl N-[(2R,3S)-5-[4-[5-[3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]pyrimidin-2-yl]piperazin-1-yl]-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate, isomer 1 (0.501 g, 0.659 mmol) in TFA (10 mL) and DCM (10 mL) is stirred at room temperature for 2 hours.

The solvent is removed to give an oil, which is separated by FA-HPLC (column: sunfire C18 su, 30*100 mm; mobile phase: water (0.1% FA) and ACN (0.1% FA); gradients: 0-22% in 10 minutes, stop at 18 min; flow: 30 mL/min; retention time: 7.5 min) to give the title compound, (184mg, 0.26 mmol, 39.54%) as a white solid. ES/MS m/z 660.2 (M+H), ^{1}H NMR (CD_3OD) δ 1.54 (q, 1H), 2.18 (m, 1H), 2.36 (m, 1H), 2.63 (m, 5H), 2.76 (m, 1H), 3.13 (m, 1H), 3.43 (t, 1H), 3.74 (m, 5H), 3.83 (m, 1H), 4.15 (m, 1H), 4.30 (dd, 2H), 4.34 (d, 1H), 6.96 (m, 2H), 7.07 (m, 3H), 7.16 (m, 1H), 8.51 (s, 2H).

Example 3

1-[6-[(3R,5S,6R)-5-amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]-5,7-dihydropyrrolo[3,4-b]pyridin-3-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1; formic acid



A solution of *tert*-butyl N-[(2R,3S,5R)-5-[3-[3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]-5,7-dihydropyrrolo[3,4-b]pyridin-6-yl]-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate, isomer 1 (0.43 g, 0.60 mmol) in TFA (5 mL) and DCM (5 mL) is stirred at room temperature for 2 hours. The solvents are removed under reduced pressure and the pH is adjusted to pH=7 by DIPEA. The resulting solution is separated by FA-Prep-HPLC (column: sunfire C18 su, 30*100 mm; mobile phase: water (0.1% FA) and ACN (0.1% FA); gradients: 9-29% in 10 minutes, stop at 18 min; flow: 30 mL/min; retention time: 10 min) to give the title compound (231 mg, 0.35 mmol, 57.88%) as a pale yellow solid. ES/MS m/z 616.20 (M+H), ^{1}H NMR (CD_3OD) δ 1.74 (q, 1H), 2.33 (m, 1H), 2.63 (m, 1H), 2.77 (m, 1H), 3.10 (m, 1H), 3.50 (m, 2H), 4.08 (m, 6H), 4.38 (d, 2H), 4.50 (d, 1H), 4.58 (d, 1H), 7.08 (m, 2H), 7.22 (m, 3H), 7.33 (m, 1H), 8.17 (d, 1H), 8.74 (d, 1H).

Assays

Enzymatic activity assay of MetAP2

The compounds exemplified herein are tested essentially as described below and exhibits an IC_{50} for the human and mouse MetAP2 assay of lower than or equal to 1000 nM.

Full length MetAP2 (human and mouse) proteins are generated from Sf9 cells using procedure similar to that described in Biochemistry 2003, 42, 5035-5042. MetAP2 is purified in the presence of 5 mM $MnCl_2$ and 2 mM $CoCl_2$ respectively, and stored at -78 °C before use.

Inhibition of the catalytic activity of human and mouse MetAP2 by compounds in the present invention is measured by monitoring the formation of the product peptide (Gly-Lys-Val-Lys-Val-Gly-Val-Asn-Gly) from the substrate peptide (Met-Gly-Lys-Val-Lys-Val-Gly-Val-Asn-Gly) via LC/MS. The reaction is typically conducted by incubating the enzyme, test compound and substrate (150 μM) in a 100 μl assay buffer (50 mM HEPES, 100 mM NaCl, 50 mg/mL BSA, 0.17 mM Triton™ X-100 at pH 7.5) for 40 minutes. After the reaction is stopped by the addition of CH_3CN (200 μl), the levels of product and remaining substrate are quantified with a mass spectrometer. The IC_{50} value is calculated typically from a 10-point dose titration curve using a 4-parameter equation.

The IC_{50} for the human and mouse MetAP2 assay for Examples 1, 2 and 3 is lower than 1000 nM. An IC_{50} for the human and mouse MetAP2 assay lower than 1000 nM support that the compound inhibits MetAP2.

Table 1

Example #	hMetAP2 IC_{50} (nM)	mMetAP2 IC_{50} (nM)
1	127 ± 52, n=3	84.1 ± 15.7, n=3
2	80.5 ± 17.7, n=2	72.2 ± 7.3, n=2
3	147 ± 10, n=3	90.2 + 7.4, n=3

Enzymatic activity assay of DPP-4

Human DPP-4 ((39-766)-His) and mouse DPP-4 ((29-760)-His) are purified for use in the assay. The final concentration of hDPP-4 and mDPP-4 in the assay is 0.04 nM and 0.22 nM respectively.

Inhibition of the catalytic activity of human and mouse DPP-4 by the compound in the present invention is monitored by the formation of product fluorescence AMC (7-amido-4-methylcoumarin hydrobromide) from substrate Gly-Pro-AMC (Sigma, G2761) on an Envision plate reader. The reaction is typically conducted by incubating the enzyme, test compound, and substrate (10 μM) in a 75 μl assay buffer (0.01% BSA, 0.1 mM EDTA, 50 μM Tris-HCl, 0.01% Triton™-X100, 0.1 M NaCl at pH 7.5) for 30 minutes. After the reaction is stopped by the addition of $ZnSO_4$ (25 μl, 10 mM), the formation of fluorescent product AMC is measured on an Envision plate reader with the excitation wavelength at 355 nm and emission wavelength at 460 nm. The IC_{50} value is calculated typically from a 10-point dose titration curve using the 4-parameter logistic equation.

The IC_{50} for Example 1 and 2 is lower than 1000 nM in the human and mouse DPP-4 assay and the results are shown in Table 1. The data support that the compounds inhibit DPP-4.

Table 2

Example #	hDPP-4 IC_{50} (nM)	mDPP-4 IC_{50} (nM)
1	15.6 ± 4.7, n=3	28.9 ± 3.0, n=3
2	21.1 ± 7.3, n=2	34.4 + 5.5, n=3
3	1.87 ± 0.24, n=3	1.22

Therapeutic Weight Loss Effect Measurement of Compounds

To determine the therapeutic weight loss effects and improvement of metabolic parameters, the compound from the invention is tested HFD feeding induced obese mouse model (DIO mice). In this model, C57/Bl6J male mouse is fed with the 60% HFD (D12492i, Research Diets) for 16 ~ 28 weeks to establish obesity with body weight reaching around 50 g. The mice will gradually increase their body weight to about 50 g

and maintain that weight in this obese state. Test compound (via the vehicle of 0.5% HEC plus 0.25% Tween®-80 at 5 mL/kg) is administered orally to the obese DIO mice once or twice daily throughout the study duration. The dose-dependent weight loss of obese DIO mice for Example 1 of the oral treatment at 60 mg/kg once daily is about 4.0% weight loss compared to the vehicle group at day 14. The data support that the compound of Example 1 is associated with desired weight loss and could offer a therapeutic weight loss effect.

DPP-4 pharmacodynamics Assay in Mouse

To determine the in vivo DPP-4 inhibition by MetAP2 plus DPP-4 dual inhibitor compounds, C57B/L6 lean mice are administrated with the compound in fed states and then DPP-4 target engagement in plasma is measured.

Animals are weighed and randomized by body weight. Each mouse is dosed via oral gavage with vehicle or testing compound formulated with vehicle for up to 3 times. The first dose is administrated at 9~10 am on day 1. The second dose is administrated at 16:30~17:30 on day 1. The third dose is administrated at 9~10 am on day 2. The mice are fasted for 6 hours after the last dose before termination at ~3 pm on day 2. Blood samples are collected at 1 hour after the first dosing and upon termination. EDTA-K_2 at final concentration of 5 mM is used as an anticoagulant. Plasma, isolated from the blood samples, is used to determine the plasma DPP-4 enzyme activity.

Plasma DPP-4 enzyme activity in the present invention is monitored by the formation rate of fluorescence AMC from substrate Gly-Pro-AMC (Sigma, G2761) via Envision plate reader. The reaction is typically conducted by incubating the plasma (20 µl) and substrate (10 µM) in a 40 µL assay buffer (0.01% BSA, 0.1 mM EDTA, 50 µM Tris-HCl, 0.01% Triton™-X100, 0.1 M NaCl at pH 7.5). Fluorescence signal is read immediately after the start of the reaction in kinetic model in Envision plate reader. The excitation wavelength is set at 355 nm and emission wavelength is set at 460 nm. The plasma DPP-4 activity is calculated from reaction velocity. The percentage plasma DPP-

4 inhibition is normalized against plasma DPP-4 activity in the vehicle group, which is set as 0% inhibition.

The plasma DPP-4 inhibition for Example 2 and under the assay condition is 92% for 1 hour after the first dosing and 92% at 6 hours upon termination. The plasma DPP-4 inhibition for Example 3 under the assay condition is 91% for 1 hour after the first dosing and 92% at 6 hours upon termination. The data support that the compounds of Example 2 and Example 3 are associated with desired DPP-4 inhibition that could yield therapeutic glycemic control.

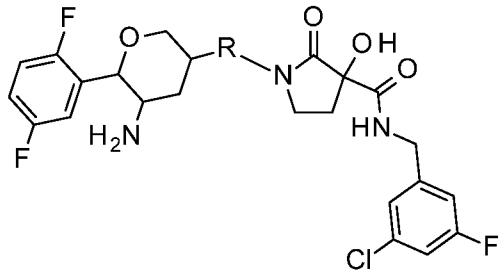
The exemplified compounds of the present invention can be readily formulated into pharmaceutical compositions in accordance with accepted practices known in the art such as found in Remington's "Pharmaceutical Sciences", Gennaro, Ed., Mack Publishing Co. Easton Pa. 1990 such as tablets, solid or gel filled capsules, powders, suspensions, or solutions. The composition can also include one or more pharmaceutically acceptable carriers, excipients, and diluents.

Preferred pharmaceutical compositions are formulated as a tablet or capsule for oral administration. The tablet or capsule can include a compound of the present invention in an amount effective to treat obesity.

The pharmaceutical composition is administered to a patient in amounts effective to treat obesity. The pharmaceutical composition is administered to a patient in need thereof in amounts effective to provide desired weight loss. An appropriate amount or dose effective to treat a patient can be determined by a health care provider.

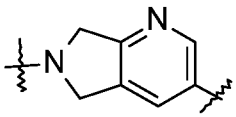
WE CLAIM:

1. A compound of the formula

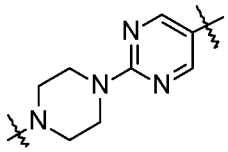


;

wherein R is selected from the group consisting of

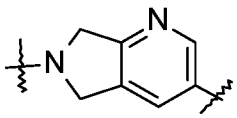


and

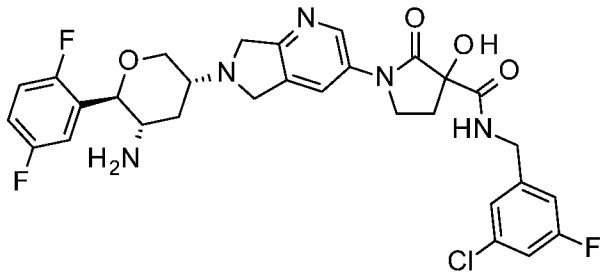


;

or a pharmaceutically acceptable salt thereof.

2. A compound or salt as claimed by Claim 1 wherein R is  .

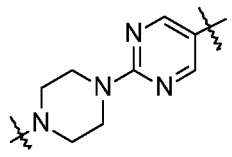
3. A compound or salt as claimed by Claim 2 wherein the compound is



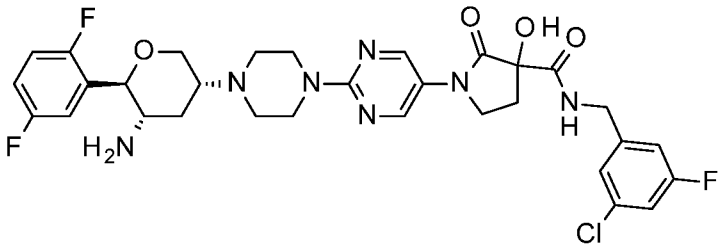
.

4. A compound as claimed by Claim 3 wherein the salt is formic acid.

5. A compound or salt as claimed by Claim 1 wherein R is



6. A compound or salt as claimed by Claim 5 wherein the compound is



7. A compound or salt as claimed by Claim 1 wherein the compound is selected from the group consisting of 1-[6-[(3R,5S,6R)-5-amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]-5,7-dihydropyrrolo[3,4-b]pyridin-3-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1 and 1-[2-[4-[(3R,5S,6R)-5-Amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]piperazin-1-yl]pyrimidin-5-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide, isomer 1.

8. A compound or salt as claimed by any one of Claims 1 to 7 wherein the salt is the hydrochloride salt.

9. A pharmaceutical composition comprising a compound as claimed by any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

10. A method for treating type II diabetes in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 8.

11. A method for treating obesity in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound, or pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 8.

12. A compound, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 8 for use in the manufacture of a medicament.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/083514

A. CLASSIFICATION OF SUBJECT MATTER

C07D 207/277(2006.01)i; C07D 413/12(2006.01)i; C07D 401/04(2006.01)i; C07D 401/06(2006.01)i; C07D 401/12(2006.01)i; C07D 403/04(2006.01)i; C07D 403/12(2006.01)i; C07D 405/12(2006.01)i; A61P 35/00(2006.01)i; A61K 31/402(2006.01)i; A61K 31/4025(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)

C07D207, C07D413, C07D401, C07D403, C07D705, A61P35, A61K31

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

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

CNKI,CPRSABS,VEN,STN(REG,CAPLUS):PYRROLIDINONE, DPP, metAP2, methionine aminopeptidase, dipeptidyl peptidase, obesity,diabet+, ELI LILLY,metalloproteinase,aminopeptidase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 103153951 A (MERCK PATENT GMBH) 12 June 2013 (2013-06-12) the whole document, expecially claims 8, 11-14 and the abstract	1-9, 12
A	US 7238724 B2 (ABBOTT LAB) 03 July 2007 (2007-07-03) the whole document	1-9, 12
A	WO 2014056938 A1 (SANOFI SA) 17 April 2014 (2014-04-17) the whole document	1-9, 12
A	US 2007238753 A1 (MADAR DAVID J ET AL.) 11 October 2007 (2007-10-11) the whole document	1-9, 12
A	WO 2007015767 A1 (LILLY CO ELI ET AL.) 08 February 2007 (2007-02-08) the whole document	1-9, 12
A	US 2006019831 A1 (BASF AG) 26 January 2006 (2006-01-26) the whole document	1-9, 12

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2016	**14 April 2016**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**XING,Weiwei**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62086316**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/083514

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

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

1. ☑ Claims Nos.: **10-11**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 10-11 are directed to a method of treatment of the human/animal body (Rule 39.1(iv) PCT)

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

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2015/083514

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	103153951	A	12 June 2013	IL	225626	D0	27 June 2013
				EP	2627631	A1	21 August 2013
				US	2013296274	A1	07 November 2013
				AU	2011316199	B2	23 July 2015
				US	8895535	B2	25 November 2014
				CA	2814369	A1	19 April 2012
				WO	2012048775	A1	19 April 2012
				JP	2013544781	A	19 December 2013
				DK	2627631	T3	01 February 2016
				MX	2013004004	A	24 April 2013
				KR	20130143053	A	30 December 2013
				EA	201300442	A1	29 November 2013
				EP	2627631	B1	16 December 2015
				AU	2011316199	A1	02 May 2013
				SG	189853	A1	28 June 2013
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