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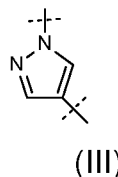
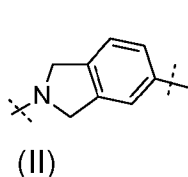
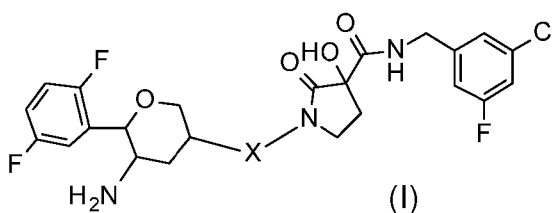
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(54) Title: PYRROLIDINONE COMPOUNDS



(57) Abstract: The present invention provides a compound which is formula (I), wherein X is selected from the group consisting of formula (II) and (III); or a pharmaceutically acceptable salt thereof, methods for treating obesity, providing therapeutic weight loss, and compositions.

PYRROLIDINONE COMPOUNDS

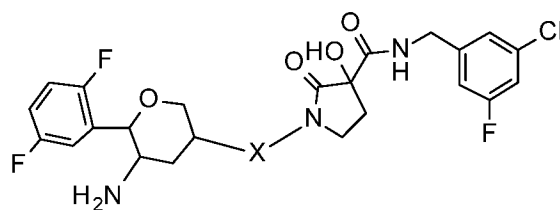
This invention relates to pyrrolidinone compounds, or a pharmaceutically acceptable salt thereof, and therapeutic use thereof. Compounds of this invention are inhibitors of methionine aminopeptidase 2 (MetAP2) and dipeptidyl peptidase-4 (DPP-4).

5 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
10 MetAP2 and DPP-4 are desired.

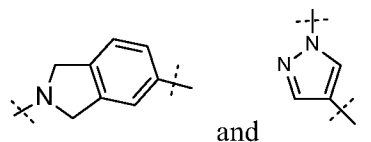
The present invention provides certain novel compounds with dual MetAP2 and DPP-4 inhibition. These dual inhibitor compounds can be useful in the treatment of a MetAP2 mediated condition.

The present invention provides a compound of the Formula I

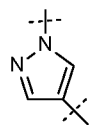


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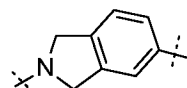
wherein X is selected from the group consisting of



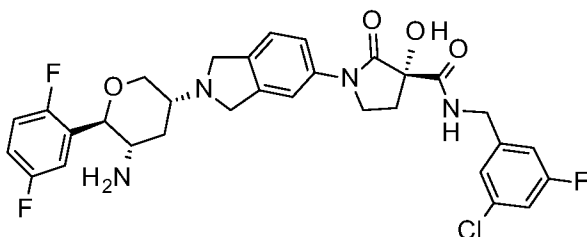
In an embodiment of the invention, X is



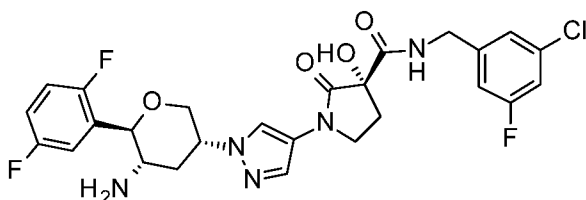
20 In an embodiment of the invention X is



In an embodiment of the invention the compound of Formula I is



In an embodiment of the invention the compound of Formula I is



- 5 In an embodiment of the invention the compound of Formula I is (3S)-1-[2-
 [(3R,5S,6R)-5-Amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]isoindolin-5-yl]-N-[(3-
 chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide
 or a pharmaceutically acceptable salt thereof.

- 10 In an embodiment of the invention the compound of the Formula I is (1R,3S)-1-
 [1-[(3S,5S,6R)-5-Amino-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]pyrazol-4-yl]-N-[(3-
 chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide or a
 pharmaceutically acceptable salt thereof.

In a preferred embodiment, the compound of Formula I is a pharmaceutically acceptable salt thereof.

- 15 In a preferred embodiment, the compound of Formula I is a hydrochloride salt.

The present invention also provides a pharmaceutical composition comprising a compound of Formula I as described above or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers, diluents or excipients.

The present invention also provides a method for treating obesity in a mammal.

- 20 The method comprises administering to the mammal in need of treatment a compound as described above for Formula I, or a pharmaceutically acceptable salt thereof. The invention provides a method for inducing desired weight loss in a mammal in need

thereof, comprising administering an effective amount of a compound of Formula I. The invention provides a method for therapeutic weight weight loss in a mammal in need thereof, comprising administering an effective amount of a compound of Formula I.

The present invention provides a compound according to Formula I or a
5 pharmaceutically acceptable salt thereof as described above for use in therapy.

In yet another form, the present invention provides a compound as described above according to Formula I, a pharmaceutically acceptable salt thereof, or pharmaceutical composition for use in the treatment of obesity in a mammal in need thereof. Preferably the mammal is a human.

10 The present invention also provides a pharmaceutical composition comprising a compound of Formula I as described above or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers, diluents or excipients, and optionally in combination with one or more pharmaceutically active agents. Additional pharmaceutically active agents include for example, metformin and/or
15 sitagliptin. In an embodiment of the invention the additional pharmaceutically active is metformin. In an embodiment of the invention the additional pharmaceutically active agent is sitagliptin. In an embodiment of the invention the additional pharmaceutically active is an SGLT-2 inhibitor. The skilled artisan will recognize that the second pharmaceutically active agent is suitable for administration sequentially or concomitantly
20 with a MetAP2 modulator.

The present invention provides a method for treating a condition modulated by MetAP2 activity. The present invention provides a method for treating obesity in a patient. The invention provides a method of treating type two diabetes in a patient in need of treatment comprising administering to the patient an effective amount of a
25 compound of Formula I or a pharmaceutically acceptable salt thereof. Preferably the patient is a human. The present invention provides a method for treating nonalcoholic steatohepatitis in a patient in need of such treatment, comprising administering to the patient an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention provides use of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of obesity. The present invention provides the use of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment to provide therapeutic weight loss.

The term “treating” (or “treat” or “treatment”) as used herein refers to restraining, slowing, or stopping the progression or alleviating the severity of an existing symptom, condition, or disorder. It is preferable that “treating” includes alleviating symptoms in a patient with a condition associated with modulation of DPP-IV and MetAP2. Preferably “treating” includes augmenting insulin levels in a patient with type II diabetes. Preferably, “treating” includes providing therapeutic weight loss in a patient in need thereof.

As used herein, the term “effective amount” refers to the amount or dose of compound of the invention or a pharmaceutically acceptable salt thereof which upon single or multiple dose administration to the patient, provides the desired effect in the patient. Preferably, the effective amount is 500mg or less per dose. It will be understood that the amount of active agent actually administered will be determined by a physician, in light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual active agent administered, the age, weight, and response of the individual patient, and the severity of the patient’s symptoms and other relevant circumstances.

A compound of the present invention is preferably formulated as pharmaceutical compositions administered by any route which makes the compound bioavailable. Most preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing same are well known in the art. *See, e.g., Remington: The Science and Practice of Pharmacy* (D.B. Troy, Editor, 21st Edition, Lippincott, Williams & Wilkins, 2006).

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.

5 The abbreviations used herein are defined according to *Aldrichimica Acta*, Vol. 17, No. 1, 1984. Other abbreviations are defined as follows: "ACN" refers to acetonitrile; "Boc" refers to *tert*-butoxycarbonyl; "BSA" refers to Bovine Serum Albumin; ; "DCM" refers to dichloromethane; "DIPEA" refers to diisopropylethylamine; "DMF" refers to N,N-dimethylformamide; "DIO" refers to diet induced obese; "EtOAc" refers to ethyl acetate; "HEC" refers to hydroxy ethyl cellulose; "HEPES" refers to 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; "HFD" refers to high fat diet; "HPLC" refers to high performance liquid chromatography; "IC₅₀" refers to the concentration of an agent that produces 50% of the maximal inhibitory response possible for that agent; "i-PrOH" refers to isopropanol or isopropyl alcohol; "LiHMDS" refers to lithium hexamethyldisilazide; "MeOH" refers to methanol or methyl alcohol; "MTBE" refers to methyl *t*-butyl ether; "SFC" refers to supercritical fluid chromatography; "t_(R)" refers to retention time; "TFA" refers to trifluoroacetic acid; and "THF" refers to tetrahydrofuran.

 The intermediates described in the following Schemes and preparations may contain a number of nitrogen, hydroxy, and acid protecting groups such as esters. 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, e.g., Greene and Wuts, *Protective Groups in Organic Synthesis*, (T. Greene and P. Wuts, eds., 2d ed. 1991).

25 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

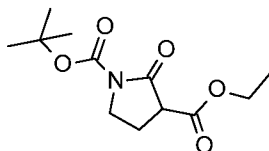
“isomer 1” and “isomer 2” refer to the compounds that elute from chiral chromatography first and second, respectively, and if chiral chromatography is initiated early in the synthesis, the same designation is applied to subsequent intermediates and examples.

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.

All substituents unless otherwise indicated, are as previously defined. The reagents and starting materials are generally 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.

Preparation 1

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

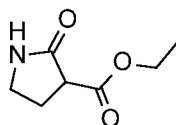


To THF (300 mL) is added LiHMDS (1.0 M, 6.80 L) at -70°C under N₂. Ethyl carbonochloridate (597.62 g, 5.51 mol) and *tert*-butyl 2-oxopyrrolidine-1-carboxylate (600.00 g, 3.24 mol) are added to the mixture at the same temperature and the mixture is stirred at -70 °C for 30 minutes. The reaction mixture is poured into an ice cold saturated solution of NH₄Cl (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 Na₂SO₄, 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. ¹H NMR (CDCl₃) δ 1.32 (t, 3H), 1.54 (s, 9H), 2.25 (m, 1H), 2.39 (m, 1H), 3.54 (m, 1H), 3.72 (m, 1H), 3.90 (m, 1H), 4.25 (q, 2H).

Preparation 2

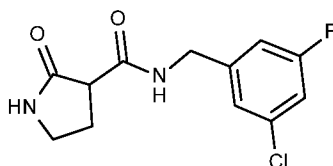
10 Ethyl 2-oxopyrrolidine-3-carboxylate



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



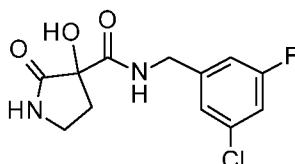
20 A solution of ethyl 2-oxopyrrolidine-3-carboxylate (180.00 g, 929.61 mmol) and (3-chloro-5-fluoro-phenyl)methanamine (148.36 g, 929.61 mmol) in xylene (4.00 L) is heated to 130 °C for 16 hours. The reaction mixture is cooled to 10 °C and a solid precipitates after 30 minutes. The suspension is filtered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

25

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



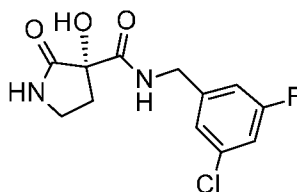
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N-[(3-Chloro-5-fluoro-phenyl)methyl]-2-oxo-pyrrolidine-3-carboxamide (164.38 g, 607.26 mmol) is dissolved in *tert*-butanol (6.00 L) at 80 °C over a period of 30 minutes. The reaction mixture is cooled to 15 °C. Sodium ethoxide (206.62 g, 3.04 mol) 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 the 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 Na₂SO₃ (1500 mL) and the pH is adjusted to 7 with 4 N HCl (100 mL) and separated. The aqueous layer is extracted with DCM/*i*PrOH (3/1, 2 × 400 mL). The combined organic extracts are concentrated under reduced pressure. The residue is dissolved in DCM/*i*PrOH (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 (3 × 150 mL) 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).

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Preparation 5

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

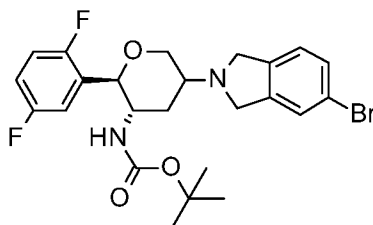


N-[(3-Chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide (164.00 g, 572.05 mmol) is separated by chiral SFC (instrument: SFC-7; column: AD (250 mm*50 mm, 10 μ m); mobile phase: A CO₂ and B methanol; gradient: B 45%; column temperature: 38 °C; flow rate: 200 mL/minute; back pressure: 100 bar; wavelength: 220 nm) to give the title product compound (58.86 g, 205.31 mmol, 35.89%), $t_{(R)}$ = 4.45 minutes as a white solid. ES/MS m/z 286.9 (M+H).

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Preparation 6

tert-Butyl N-[(2R,3S)-5-(5-bromoisindolin-2-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate



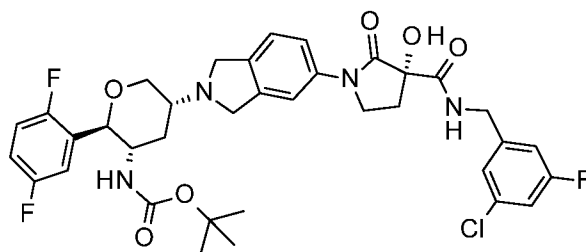
To a solution of 5-bromoisindoline hydrochloride (5.00 g, 20.7 mmol) and *tert*-butyl N-[(2R,3S)-2-(2,5-difluorophenyl)-5-oxo-tetrahydropyran-3-yl]carbamate (7.45 g, 22.7 mmol) in N,N-dimethylacetamide (50 mL) is added N-ethyl-N-isopropyl-propan-2-amine (6.28 g, 62.04 mmol) and the mixture is stirred at room temperature for 15 minutes. Acetic acid (6.21 g, 103.4 mmol) is added to this solution and the mixture is stirred for another 15 minutes. Sodium triacetoxyboranuide (9.23 g, 41.36 mmol) is added to this solution at -5 °C and this resulting solution is stirred at room temperature for 4 hours. The solution is diluted with water (400 mL) and stirred for 10 minutes. The solid is collected by filtration and washed with water. The solid is dissolved in EtOAc (200 mL), washed with water and brine, dried over Na₂SO₄ and concentrated to give the title

product (10.1 g, 19.8 mmol, 95.9%) as an off-white solid. Crude HNMR shows it to be a $\geq 9/1$ mixture of two diastereoisomers which is used without further purification. ES/MS m/z $^{79}\text{Br}/^{81}\text{Br}$ 509.1/511.10 (M+1)

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Preparation 7

tert-Butyl [(2R,3S,5R)-5-(5-((3S)-3-[(3-chloro-5-fluorobenzyl)carbamoyl]-3-hydroxy-2-oxopyrrolidin-1-yl)-1,3-dihydro-2H-isoindol-2-yl)-2-(2,5-difluorophenyl)tetrahydro-2H-pyran-3-yl]carbamate



10

A solution of *tert*-butyl N-[(2R,3S)-5-(5-bromoisindolin-2-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate (6.15 g, 12.1 mmol), (3R)-N-[(3-Chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide (3.46 g, 12.1 mmol) and Cs_2CO_3 (7.87 g, 24.1 mmol) in DMF (100 mL) and CH_3CN (50 mL) is degassed with a stream of N_2 for 15 minutes. N,N'-dimethylethylenediamine (0.323 g, 3.62 mmol) and CuI (3.02 g, 15.7 mmol) is 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 with 1 N HCl, extracted with EtOAc (3 × 60 mL), washed with brine, dried over Na_2SO_4 and concentrated to dryness. The crude product is purified with silica gel column chromatography to give the title compound *tert*-butyl N-[(2R,3S,5R)-5-[5-[(3S)-3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]isoindolin-2-yl]-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate (3.6 g, 4.9 mmol, 40%) as a brown solid.

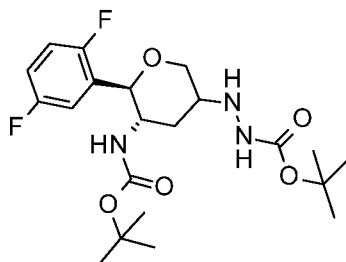
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Preparation 8

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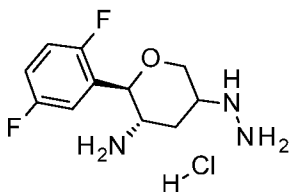
tert-Butyl N-[[[(5S,6R)-5-(*tert*-butoxycarbonylamino)-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]amino]carbamate



A solution of *tert*-butyl N-[(2R,3S)-2-(2,5-difluorophenyl)-5-oxo-tetrahydropyran-3-yl]carbamate (3.50 g, 10.7 mmol) and *tert*-butyl N-aminocarbamate (1.70 g, 12.8 mmol) in acetic acid (20.0 mL) is stirred at 25 °C for 10 minutes. Sodium cyanoborohydride (1.41 g, 21.4 mmol) is added slowly and the mixture is stirred at 25 °C for 16 hours. The reaction mixture is diluted with water and the pH is adjusted to 9 with the addition of 5 N solution of NaOH solution and the temperature is maintained below 20 °C. The mixture is extracted with DCM (3 × 120 mL), washed with brine, dried and concentrated to give the crude product, which is purified by combi-flash (silica gel, 20 g, biotage, UV 254, MeOH in DCM 0~5%) over 30 minutes to give the title product (4.50 g, 10.1 mmol, 94.9%) as an off white solid. ES/MS *m/z* 444.1 (M+H).

Preparation 9

(2R,3S)-2-(2,5-Difluorophenyl)-5-hydrazino-tetrahydropyran-3-amine hydrochloride



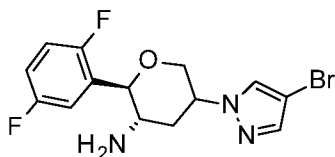
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To a solution of *tert*-butyl N-[(5S,6R)-5-(*tert*-butoxycarbonylamino)-6-(2,5-difluorophenyl)tetrahydropyran-3-yl]amino]carbamate (2.00 g, 4.51 mmol) in dichloromethane (30.0 mL) is added HCl in EtOAc (12.0 mL, 48.0 mmol, 4.00 mol/L) slowly. The resulting mixture is stirred at 20 °C for 2 hours. The solvent is evaporated under reduced pressure to give the title product (1.26 g, 4.50 mmol, 99.9%) as a white solid.

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Preparation 10

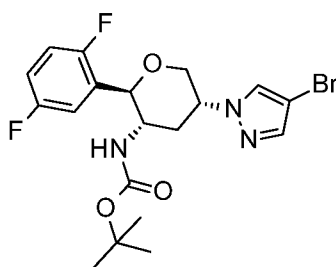
(2R,3S)-5-(4-bromopyrazol-1-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-amine



To a solution of (2R,3S)-2-(2,5-difluorophenyl)-5-hydrazino-tetrahydropyran-3-amine hydrochloride (1.26 g, 4.50 mmol) and 2-bromomalonaldehyde (0.84 g, 5.41 mmol) in acetic acid (15.0 mL, 262 mmol) is added toluenesulfonic acid hydrate (0.043 g, 0.225 mmol) and the mixture is stirred at 20 °C for 2 hours. The reaction mixture is diluted with water and the pH adjusted to 7 by the addition of 5 N NaOH solution. The temperature is maintained below 20 °C. The mixture is extracted with DCM (3 × 180 mL), washed with brine, dried, and concentrated to give the crude title compound (1.20 g, 3.35 mmol, 74.4%) as a yellow oil, which is used without further purification. ES/MS m/z 358.20 (M+H).

Preparation 11

tert-Butyl N-[(2R,3S,5R)-5-(4-bromopyrazol-1-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate



To a solution of (2R,3S)-5-(4-bromopyrazol-1-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-amine (1.20 g, 3.35 mmol) and triethylamine (0.68g, 6.70 mmol) in DCM (30.0 mL) is added di-*tert*-butyl dicarbonate (0.89g, 4.02 mmol) and the mixture is stirred at 20 °C for 16 hours. Water (40 mL) is added and the mixture is extracted with DCM (3 × 50 mL), washed with 0.05 N HCl solution (20 mL) and brine,

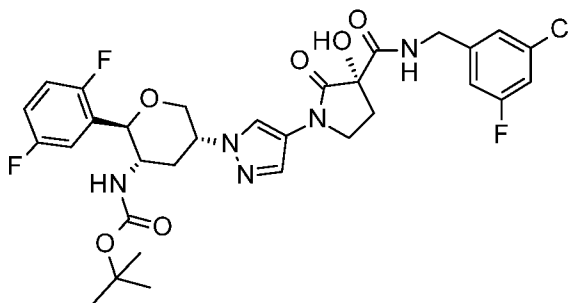
dried, and concentrated. The crude product is purified by combi-flash (silica gel, 20 g, biotage, UV 254, eluting with EA in PE 20~30%) over 30 minutes to obtain the title compound (800 mg, 1.61 mmol, 92.4 mass%, 48.1%) as a yellow solid. ES/MS m/z ($^{79}\text{Br}/^{81}\text{Br}$) 358.1/360.0, $M-100$).

5

Preparation 12

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

10

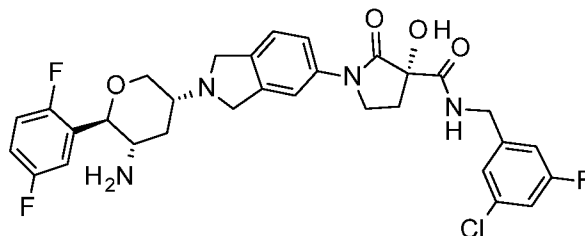


A solution of *tert*-butyl N-[(2R,3S,5R)-5-(4-bromopyrazol-1-yl)-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate (700 mg, 1.41 mmol), (3R)-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide (0.45 g, 1.55 mmol) and cesium carbonate (0.92 g, 2.82 mmol) in DMF (25.0 mL) and acetonitrile (20.0 mL) is degassed with a stream of N_2 for 15 minutes. $\text{N,N}'$ -Dimethylmethanediamine (0.037g, 0.423 mmol) and CuI (0.35 g, 1.83 mmol) are added sequentially and the resulting mixture is stirred at 85 °C for 2 hours. Concentrated ammonium hydroxide (6 mL) and water (100 mL) are added, and this mixture is extracted with EtOAc ($3 \times 150\text{mL}$). The combined organic phase is washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue is purified by silica gel flash chromatography eluting with MeOH/DCM (0% to 10%) to give the title product (480 mg, 0.690 mmol, 48.9%) as an off white solid. ES/MS m/z 686.20 ($M+23$).

25

Example 1

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



5

A solution of *tert*-butyl [(2R,3S,5R)-5-(5-{(3S)-3-[(3-chloro-5-fluorobenzyl)carbamoyl]-3-hydroxy-2-oxopyrrolidin-1-yl}-1,3-dihydro-2H-isoindol-2-yl)-2-(2,5-difluorophenyl)tetrahydro-2H-pyran-3-yl]carbamate (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 7 with DIPEA. The resulting solution is separated by Prep HPLC column: xbridge C18 5 μ , 30*150 mm, mobile phase: water (10 mM NH_4HCO_3) and ACN eluting with a gradient of 33-43% in 11 minutes, stop at 17 minutes, flow: 35 mL/minutes, retention time: 8.7 minutes to give the title product (0.051 g, 0.083 mmol, 13.74%) as a pale yellow solid. ES/MS m/z 615.20 (M+H).

15

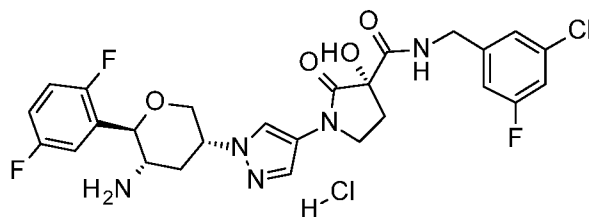
^1H NMR (CD_3OD) δ 1.42 (q, 1H), 2.16 (m, 1H), 2.41 (m, 1H), 2.62 (m, 1H), 2.85 (m, 2H), 3.31 (t, 1H), 3.82 (m, 1H), 3.93 (m, 5H), 4.19 (m, 2H), 4.30 (d, 1H), 4.39 (d, 1H), 6.93 (m, 4H), 7.12 (m, 2H), 7.22 (d, 1H), 7.40 (m, 1H), 7.54 (s, 1H).

20

Example 2

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

25



To *tert*-butyl N-[(2R,3S,5S)-5-[4-[(3S)-3-[(3-chloro-5-fluoro-phenyl)methylcarbamoyl]-3-hydroxy-2-oxo-pyrrolidin-1-yl]pyrazol-1-yl]-2-(2,5-difluorophenyl)tetrahydropyran-3-yl]carbamate (480 mg, 0.690 mmol) in DCM (15.0 mL) is slowly added HCl in EtOAc (5.00 mL). The resulting mixture is stirred at 20 °C for 2 hours. The solvent is evaporated under reduced pressure to give the crude material. The product is purified by Prep-HPLC (0.05% HCl-ACN) to give the title product (220 mg, 0.387 mmol, 56.1%) as an off-white solid. MS (ESI) m/z ($^{35}\text{Cl}/^{37}\text{Cl}$) 564.3/566.3 [M+H]. ^1H NMR (CD_3OD) δ 2.31 (m, 1H), 2.46 (q, 1H), 2.65 (m, 2H), 3.65 (m, 1H), 3.83 (m, 3H), 4.26 (m, 2H), 4.46 (m, 1H), 4.75 (m, 2H), 7.04 (m, 2H), 7.20 (m, 3H), 7.36 (m, 1H), 7.84 (s, 1H), 8.22 (s, 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 CH₃CN (200 µl), the levels of product and remaining substrate are quantified with a mass spectrometer. The IC₅₀ value is calculated typically from a 10-point dose titration curve using a 4-parameter equation.

5 The IC₅₀ for the human and mouse MetAP2 assay for Example 1 and 2 is lower than 1000 nM. An IC₅₀ 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	52	31
2	533 ± 56, n=5	201 ± 19, n=5

10

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.

15 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
20 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 ZnSO₄ (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 IC₅₀ value is calculated typically from a 10-point dose titration curve using the 4-parameter logistic
25 equation.

The IC₅₀ 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.

5 **Table 2**

Example #	hDPP-4 IC ₅₀ (nM)	mDPP-4 IC ₅₀ (nM)
1	3	4 ± 0.8, n=2
2	2 ± 0.6, n=4	<1

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/B16J 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 2 of the oral treatment at 60 mg/kg once daily is about 4.2 % weight loss compared to the vehicle group at day 14. The data support that the compound of Example 2 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 once via oral gavage with vehicle or testing compound formulated with vehicle at 9~10 am. The mice are fasted for 6 hours after dosing before termination at 3~4 pm. Blood samples

are collected at 1 hour after dosing and upon termination. EDTA-K₂ 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 under the assay conditions is 87% for 1 hour after an oral dose of 6 mg/kg. The data supports that the compound is associated with desired DPP-4 inhibition that could yield therapeutic glycemic control.

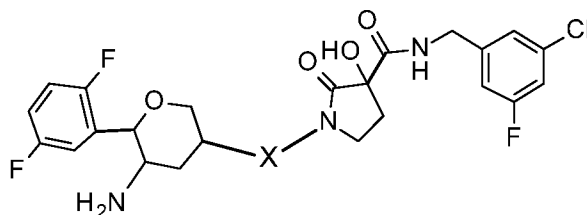
The exemplified compounds of the present invention can be readily formulated into pharmaceutical compositions in accordance with accepted practices known in the art such as found in Remington's "Pharmaceutical Sciences", Gennaro, Ed., Mack Publishing Co. Easton Pa. 1990 such as tablets, solid or gel 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.

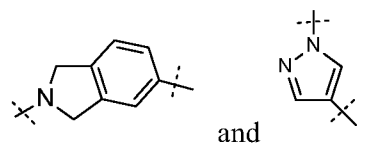
The pharmaceutical composition is administered to a patient in amounts effective to treat obesity. An appropriate amount or dose effective to treat a patient can be determined by a health care provider.

What is claimed is:

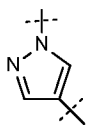
1. A compound of the Formula



- 5 wherein X is selected from the group consisting of
or a pharmaceutically acceptable salt thereof.

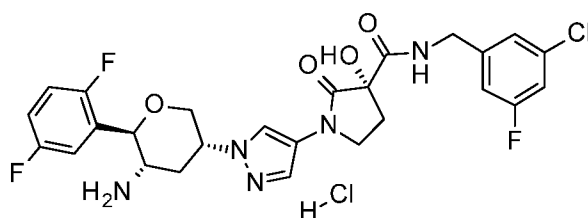


2. The compound or pharmaceutically acceptable salt thereof, as claimed by Claim 1



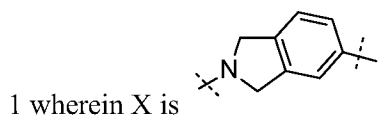
wherein X is

- 10 3. The compound or pharmaceutically acceptable salt thereof as claimed by either of
Claims 1 or 2 wherein the compound is

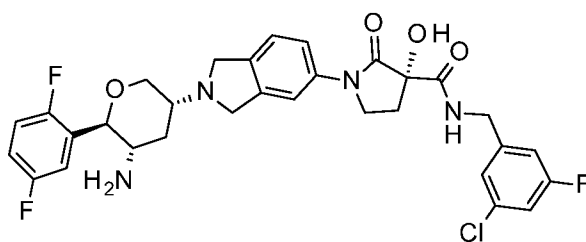


4. The compound or pharmaceutically acceptable salt thereof as claimed by any one
of Claims 1 to 3 wherein the compound is (1R,3S)-1-[1-[(3S,5S,6R)-5-Amino-6-
15 (2,5-difluorophenyl)tetrahydropyran-3-yl]pyrazol-4-yl]-N-[(3-chloro-5-fluoro-
phenyl)methyl]-3-hydroxy-2-oxo-pyrrolidine-3-carboxamide.

5. The compound or pharmaceutically acceptable salt thereof, as claimed by Claim



6. The compound or pharmaceutically acceptable salt thereof as claimed by either of
5 Claims 1 or 5 wherein the compound is



7. The compound as claimed by any one of Claims 1, 5 or 6 wherein the compound
is (3S)-1-[2-[(3R,5S,6R)-5-Amino-6-(2,5-difluorophenyl)tetrahydropyran-3-
10 yl]isoindolin-5-yl]-N-[(3-chloro-5-fluoro-phenyl)methyl]-3-hydroxy-2-oxo-
pyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof.
8. A method for providing therapeutic weight loss in a mammal in need thereof,
comprising administering an effective amount of a compound as claimed by any
one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof.
- 15 9. 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 7.
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
20 pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 7.
11. A compound or pharmaceutically acceptable salt thereof, as claimed by any one of
claims 1-7 for use in therapy.
12. A compound or pharmaceutically acceptable salt thereof, as claimed by any one of
Claims 1 to 7 for use in the treatment of type II diabetes.

13. A compound or pharmaceutically acceptable salt thereof, as claimed by any one of claims 1-7 for use in the treatment of obesity.
14. Use of a compound, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 7 in the manufacture of a medicament.
- 5 15. A pharmaceutical composition comprising a compound as claimed by any one of Claims 1 to 7 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.
16. A pharmaceutical composition comprising a compound as claimed by any one of Claims 1 to 7 or a pharmaceutically acceptable salt thereof and at least one of a
10 pharmaceutically acceptable carrier, diluent and excipient; in combination with at least one additional pharmaceutically active agent

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/095187

A. CLASSIFICATION OF SUBJECT MATTER

C07D 207/277(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 405/04(2006.01)i; C07D 409/12(2006.01)i; C07D 413/10(2006.01)i; A61K 31/4025(2006.01)i; A61P 35/00(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; C07D401; C07D403; C07D405; C07D409; C07D413; A61K31; A61P35

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)

VEN, CPRS, CNKI, REG, CAPLUS(STN), obesity, diabetes, MetAP, methionine aminopeptidase, DTTP, dipeptidyl peptidase, search the structure in claim 1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 103153951 A (MERCK PATENT GMBH) 12 June 2013 (2013-06-12) see the claims and examples	1-16
X	CN 104245675 A (MERCK PATENT GMBH) 24 December 2014 (2014-12-24) see the claims and examples	1-16



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

20 April 2016

Date of mailing of the international search report

08 August 2016

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/095187

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.: **8-13**
because they relate to subject matter not required to be searched by this Authority, namely:
 - [1] Claims 8-13 relate to a method for treating diseases mediated by MetAP-2 or DPP-4, such as obesity and diabetes which belong to a method for the treatment of the human/animal body (Rule 39.1(iv) PCT). Nevertheless, the search has been carried out based on the use of the compounds in the manufacture of medicaments for treating diseases mediated by MetAP-2 or DPP-4.
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/CN2015/095187

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	EP	2627631	A1	21 August 2013
				IL	225626	D0	27 June 2013
				US	2013296274	A1	07 November 2013
				CA	2814369	A1	19 April 2012
				US	8895535	B2	25 November 2014
				AU	2011316199	B2	23 July 2015
				WO	2012048775	A1	19 April 2012
				JP	2013544781	A	19 December 2013
				DK	2627631	T3	01 February 2016
				EA	201300442	A1	29 November 2013
				KR	20130143053	A	30 December 2013
				MX	2013004004	A	24 April 2013
				ES	2563317	T3	14 March 2016
				AU	2011316199	A1	02 May 2013
				EP	2627631	B1	16 December 2015
				AR	083402	A1	21 February 2013
				SG	189853	A1	28 June 2013
				DE	102010048374	A1	19 April 2012
				EA	022299	B1	30 December 2015
CN	104245675	A	24 December 2014	WO	2013149704	A1	10 October 2013
				DE	102012006884	A1	10 October 2013
				US	2015031670	A1	29 January 2015
				EP	2834221	A1	11 February 2015
				PH	12014501964	A1	17 November 2014
				CA	2869337	A1	10 October 2013
				SG	11201406059P	A	27 November 2014
				CL	2014002640	A1	16 January 2015
				JP	2015512426	A	27 April 2015
				KR	20150004820	A	13 January 2015
				EA	201401081	A1	27 February 2015
				AR	090602	A1	26 November 2014
				MX	2014011906	A	12 November 2014
				AU	2013243020	A1	20 November 2014
				PE	24522014	A1	28 January 2015