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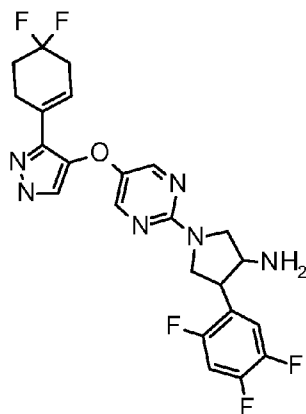
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(54) Title: PYRAZOLE COMPOUNDS



(I)

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

PYRAZOLE COMPOUNDS

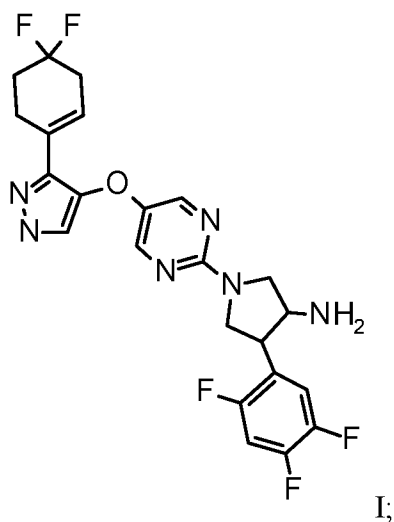
This invention relates to pyrazole compounds or pharmaceutically acceptable salts thereof. Compounds of this invention are inhibitors of methionine aminopeptidase 2 (MetAP2) and dipeptidyl peptidase-4 (DPP-4).

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 and DPP-4 mediated condition.

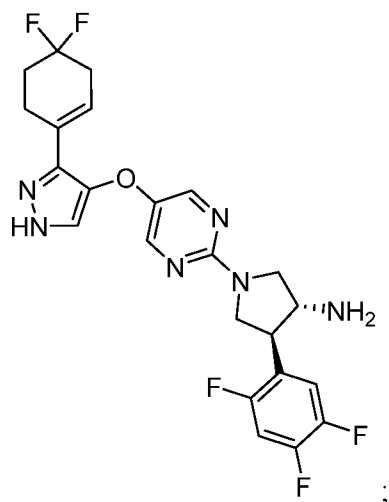
The present invention provides a compound of the Formula I



or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention, the compound is

-2-



or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention the compound is (3R,4S)-1-[5-[[3-(4,4-Difluorocyclohexen-1-yl)-1H-pyrazol-4-yl]oxy]pyrimidin-2-yl]-4-(2,4,5-trifluorophenyl)pyrrolidin-3-amine.

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, 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 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 Examples below. The specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different schemes, to prepare compounds of the invention, or salts thereof. The products of each step in the schemes below can be recovered by conventional methods well known in the art, including extraction, evaporation, precipitation, chromatography, filtration, trituration, and crystallization. In the schemes below, all substituents unless otherwise indicated, are as previously defined. 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: “AMC” refers to 7-amido-4-methylcoumarin hydrobromide; “BSA” refers to Bovine Serum Albumin; “DIO” refers to diet induced obese; “EDTA” refers to ethylenediaminetetraacetic acid; “HEC” refers to hydroxy ethyl cellulose; “HEPES” refers to 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; “HFD” refers to high fat diet; “HOAc” refers to acetic acid;

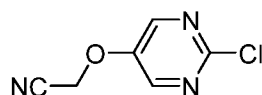
-4-

“IC₅₀” refers to the concentration of an agent that produces 50% of the maximal inhibitory response possible for that agent; “MeOH” refers to methyl alcohol or methanol; “THF” refers to tetrahydrofuran and “Tris” refers to tris(hydroxymethyl)aminomethane.

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Preparation 1

2-(2-Chloropyrimidin-5-yl)oxyacetonitrile

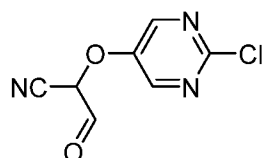


To a mixture of bromoacetonitrile (2.94 mL, 42.18 mmol), 2-chloropyrimidin-5-ol (5 g, 38.30 mmol) in CH₃CN (100 mL) is added potassium carbonate (7.94 g, 57.45 mmol). The reaction mixture is heated to 60 °C for 2 hours. After cooling to room temperature, the solid is filtered and the filtrate is concentrated under reduced pressure. The residue is purified by silica gel flash chromatography eluting with a gradient of 100% ether to 1/1 ether/ethyl acetate to give the title compound (6 g, 35.38 mmol, 92.37%) as a white solid. Mass spectrum (m/z): 170 (M+H).

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Preparation 2

2-(2-Chloropyrimidin-5-yl)oxy-3-oxo-propanenitrile



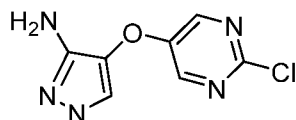
To a solution of 2-(2-chloropyrimidin-5-yl)oxyacetonitrile (6.00 g, 35.4 mmol) and ethyl formate (26.2 g, 354 mmol) in 1,2-dimethoxyethane (200 mL, 1930 mmol) is added potassium *tert*-butoxide (5.96 g, 53.1 mmol) portionwise at 0 °C. The mixture is stirred at 85 °C overnight. The mixture is concentrated, dissolved in water (200 mL) and the pH is adjusted to pH~4 with HOAc. The water phase is extracted with ethyl acetate (5 × 200 mL). The combined organic phases are washed with water (2 × 500 mL), dried, and concentrated to give the title compound (6.10 g, 30.9 mmol, 87.3%) as a brown solid which is used without further purification. Mass spectrum (m/z): 196 (M-H).

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-5-

Preparation 3

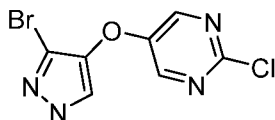
4-(2-Chloropyrimidin-5-yl)oxy-1H-pyrazol-3-amine



To a solution of 2-(2-chloropyrimidin-5-yl)oxy-3-oxo-propanenitrile (6.00 g, 30.4 mmol) in acetic acid (20 mL) and ethanol (40 mL) is added hydrazine (64 mass%) in water (5.00 mL). The solution is stirred for 2 hours at 85 °C, concentrated, and 7 N NH₃/MeOH (20 mL) is added. The mixture is stirred for 30 minutes and concentrated. The residue is purified by silica gel flash chromatography eluting with a gradient of 100% CH₂Cl₂ to 80% CH₂Cl₂ and 20% MeOH to give the title compound (3.15 g, 14.9 mmol, 49%) as an orange oil. Mass spectrum (m/z): 212 (M+H).

Preparation 4

5-[(3-Bromo-1H-pyrazol-4-yl)oxy]-2-chloro-pyrimidine

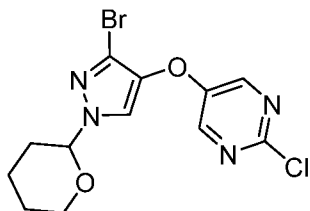


To a solution of *tert*-butyl nitrile (2.13 mL, 17.9 mmol) in CH₃CN (100 mL) is added copper (I) bromide (2.56 g, 17.9 mmol). The mixture is stirred at room temperature for 1 hour under N₂, followed by the addition of 4-(2-chloropyrimidin-5-yl)oxy-1H-pyrazol-3-amine (3.15 g, 14.9 mmol) in CH₃CN (10 mL). The mixture is stirred for 3 hours, concentrated and the residue is purified by silica gel flash chromatography eluting with a gradient of 100% CH₂Cl₂ to 80% CH₂Cl₂ and 20% MeOH to give the title compound (1.30 g, 4.72 mmol, 31.7%) as an orange oil. Mass spectrum (m/z): 275 (M+H).

-6-

Preparation 5

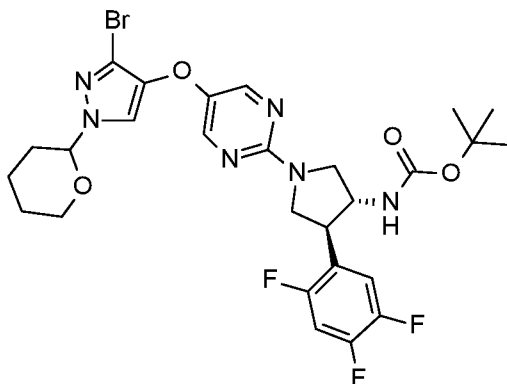
5-(3-Bromo-1-tetrahydropyran-2-yl-pyrazol-4-yl)oxy-2-chloro-pyrimidine



To a solution of 5-[(3-bromo-1H-pyrazol-4-yl)oxy]-2-chloro-pyrimidine (1.30 g, 4.72 mmol) in THF (50 mL) are added 3, 4-dihydro-2H-pran (2.15 mL, 23.6 mmol) and *p*-toluenesulfonic acid (0.246 g, 1.42 mmol). The mixture is stirred for 3 hours at 60 °C, concentrated, and the residue is purified by silica gel flash chromatography eluting with a gradient of 100% petroleum ether to 1:1 petroleum ether/ethyl acetate to give the title compound (1.5 g, 4.2 mmol, 88%) as white solid.

Mass spectrum (m/z): 259 (M+H).

Preparation 6

tert-Butyl N-[(3R,4S)-1-[5-(3-bromo-1-tetrahydropyran-2-yl-pyrazol-4-yl)oxypyrimidin-2-yl]-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamate

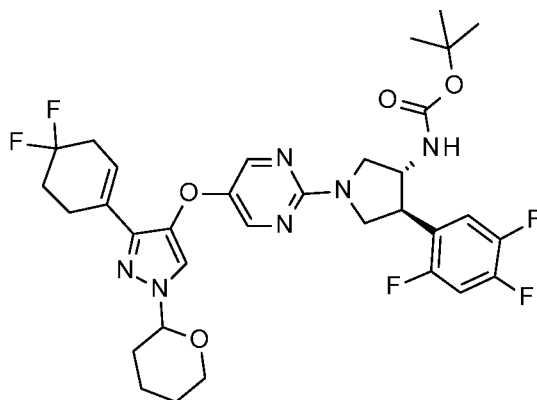
A mixture of 5-(3-bromo-1-tetrahydropyran-2-yl-pyrazol-4-yl)oxy-2-chloro-pyrimidine (1.50 g, 4.17 mmol), *tert*-butyl N-[(3R,4S)-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamate (1.45 g, 4.59 mmol) and potassium carbonate (1.73 g, 12.5 mmol) in DMSO (20 mL) is stirred at 100 °C overnight. The mixture is cooled to room temperature, poured into water (100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts are washed with water (2 × 50 mL), dried, and concentrated. The residue is purified by silica gel flash chromatography eluting with

-7-

a gradient of 100% CH₂Cl₂ to 80% CH₂Cl₂ and 20% MeOH to give the title compound (2.33 g, 3.64 mmol, 87.3%) as a yellow oil. Mass spectrum (m/z): 639 (M+H).

Preparation 7

- 5 *tert*-Butyl N-[(3R,4S)-1-[5-[3-(4,4-difluorocyclohexen-1-yl)-1-tetrahydropyran-2-yl-pyrazol-4-yl]oxypyrimidin-2-yl]-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamate

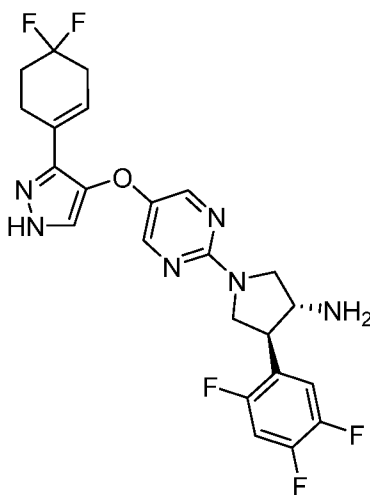


- To a mixture of *tert*-butyl N-[(3R,4S)-1-[5-(3-bromo-1-tetrahydropyran-2-yl-pyrazol-4-yl)oxypyrimidin-2-yl]-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamate (2.33 g, 3.64 mmol), 2-(4,4-difluorocyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.07 g, 4.37 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (0.136 g, 0.182 mmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (0.177 g, 0.364 mmol) and potassium phosphate tribasic (1.59 g, 7.29 mmol) is added water (8 mL) and 1,4-dioxane (40 mL). The mixture is stirred at 110 °C under N₂ overnight. The mixture is concentrated and the residue is purified by silica gel flash chromatography eluting with a gradient of 100% CH₂Cl₂ to 80% CH₂Cl₂ and 20% MeOH to give the title compound (1.61 g, 2.38 mmol, 65.3%) as a pale-yellow foam. Mass spectrum (m/z): 677 (M+H).

-8-

Example 1

(3R,4S)-1-[5-[[3-(4,4-Difluorocyclohexen-1-yl)-1H-pyrazol-4-yl]oxy]pyrimidin-2-yl]-4-(2,4,5-trifluorophenyl)pyrrolidin-3-amine



5 To a solution of *tert*-butyl N-[(3R,4S)-1-[5-[3-(4,4-difluorocyclohexen-1-yl)-1-tetrahydropyran-2-yl-pyrazol-4-yl]oxypyrimidin-2-yl]-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamate (1.5 g, 2.2 mmol) in dichloromethane (10 mL, 156.0 mmol) is added trifluoroacetic acid (10 mL) at room temperature. The mixture is stirred for 16 hours at room temperature and concentrated under reduced pressure. The residue is purified by silica gel flash chromatography eluting with a gradient of 100% CH₂Cl₂ (0.5% NH₄OH) to 90% CH₂Cl₂ (0.5% NH₄OH) 10% MeOH to give to give the title compound (1.02 g, 2.07 mmol, 93%) as a white foam. Mass spectrum (m/z): 493 (M+H), ¹H NMR (CD₃OD) δ 2.09-2.20 (m, 2H), 2.64-2.75 (m, 4H), 3.33-3.36 (m, 1H), 3.48-3.60 (m, 2H), 3.69-3.75 (m, 1H), 4.03-4.13 (m, 2H), 6.27 (s, 1H), 7.17-7.41 (m, 3H), 8.19 (s, 2H).

Assays

Enzymatic activity assay of MetAP2 and MetAP1

20 The compound exemplified herein is tested essentially as described below and exhibits an IC₅₀ for the human and mouse MetAP2 assay of lower than or equal to 1000 nM and is considered selective for MetAP2 with a MetAP1 value greater than 30 μM.

Full length MetAP2 (human and mouse) and MetAP1 (human) proteins are generated from Sf9 cells using procedure similar to that described in Biochemistry 2003,

42, 5035-5042. MetAP2 and MetAP1 are purified in the presence of 5 mM MnCl₂ and 2 mM CoCl₂ 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 200 μl CH₃CN, the levels of product and remaining substrate are quantified with a mass spectrometer. The activity of human MetAP1 is monitored by the formation of the fluorescent product rhodamine-methionine from the substrate methionine-rhodamine-methionine on a spectrophotometer with the excitation light at 460 nm and emission light at 535 nm. The reaction is typically conducted by incubating the enzyme, test compound and substrate (50 μM) in a 100 μl assay buffer (50 mM HEPES, 100 mM NaCl, 0.1% BSA, 0.05% Tween®-20, 50 μM CoCl₂) for 60 minutes. IC₅₀ value (concentration of test compound that provides 50% inhibition of MetAP2 activity) is calculated typically from a 10-point dose titration curve using a 4-parameter equation.

The IC₅₀ for the human and mouse MetAP2 assay Example 1 is lower than 1000 nM and IC₅₀ for hMetAP1 is >30 μM, demonstrating selective MetAP2 inhibition as compared with MetAP1.

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

-10-

minutes. After the reaction is stopped by the addition of 25 μ l ZnSO₄ (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 equation.

The IC₅₀ for Example 1 is lower than 1000 nM in the human and mouse DPP-4 assay and the results are shown in Table 1.

Table 1. Enzymatic activity of Example 1.

Example #	hMetAP2 IC ₅₀ (nM)	mMetAP2 IC ₅₀ (nM)	hMetAP1 IC ₅₀ (μ M)	hDPP-4 IC ₅₀ (nM)	mDPP-4 IC ₅₀ (nM)
1	9 $\pm$ 3 (n=7)	36 $\pm$ 34 (n=5)	>30	6 $\pm$ 2 (n=4)	26 $\pm$ 11 (n=4)

Mean $\pm$ SEM (n); SEM = standard error of the mean; n = number of determination.

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 in the high fat diet (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 the 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 20 mg/kg and 60 mg/kg once daily is about 4% and 17% weight loss compared to the vehicle group at day 14, respectively. 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.

5 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
10 samples are collected at 1 hour after the first 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.

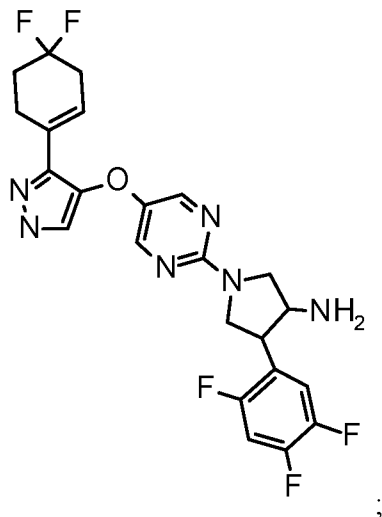
 Plasma DPP-4 enzyme activity in the present invention is monitored by the formation rate of fluorescence AMC from substrate Gly-Pro-AMC (Sigma, G2761) via
15 Envision plate reader. The reaction is typically conducted by incubating the plasma (20 µl) and substrate (10 µM) in a 40 µL assay buffer (0.01% 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
20 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 1 under the assay condition is 86% and 83% for 1 hour after the first dosing and upon termination, respectively. The data support
25 that the compound of Example 1 is associated with desired DPP-4 inhibition that could yield therapeutic glycemic control.

-12-

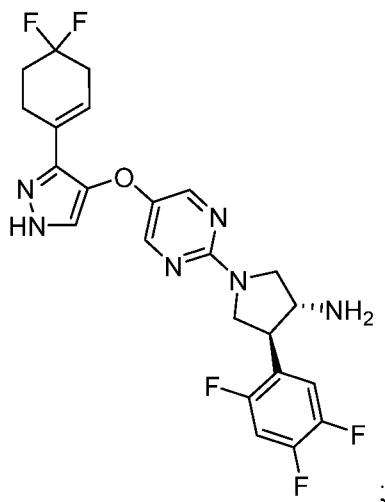
WE CLAIM:

1. A compound of the Formula



- 5 or a pharmaceutically acceptable salt thereof.

2. A compound as claimed by Claim 1 wherein the compound is



or a pharmaceutically acceptable salt thereof.

10

3. A compound or salt as claimed by Claim 1 wherein the compound is (3R,4S)-1-[5-[[3-(4,4-Difluorocyclohexen-1-yl)-1H-pyrazol-4-yl]oxy]pyrimidin-2-yl]-4-(2,4,5-trifluorophenyl)pyrrolidin-3-amine.

-13-

4. A pharmaceutical composition comprising a compound as claimed by any one of Claims 1 to 3, or a pharmaceutically acceptable salt thereof, and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

5 5. 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 3.

6. A method for treating obesity in a mammal in need thereof, comprising
10 administering to the mammal an effective amount of a compound, or pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 3.

7. A compound, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 3 for use in the manufacture of a medicament.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/073236

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/14(2006.01)i; A61K 31/506(2006.01)i; A61P 3/10(2006.01)i; A61P 3/04(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)

C07D 403,A61K 31,A61P 3

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,VEN,WPI,CPRS,CAPLUS,REGISGTRY(STN):dpp, +pyrazol+, metap2,+fluor+, +amin+,pyrimidin+,the structure of compound 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.
A	CN 103626775 A (NANJING HUAWEI MEDICAL TECHNOLOGY DEV CO) 12 March 2014 (2014-03-12) see the whole document	1-7
A	US 2010324054 A1 (BIFTU TESFAYEET AL.) 23 December 2010 (2010-12-23) see the whole document	1-7



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

17 November 2015

Date of mailing of the international search report

24 November 2015

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/073236

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.: **5-7**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 5-7 relate to the methods of diseases treatment, which do not comply with the requirement of PCT rule 39. This international search report is established on the basis of the technical subject-matters that are reasonably expected; claims 5-7 relate to the corresponding pharmaceutical use.
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/CN2015/073236

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	103626775	A	12 March 2014	CN	103626775	B	20 May 2015
US	2010324054	A1	23 December 2010	EP	2019677	B1	14 August 2013
				CA	2652367	A1	29 November 2007
				AU	2007254357	B2	21 July 2011
				WO	2007136603	A2	29 November 2007
				US	7928112	B2	19 April 2011
				WO	2007136603	A3	17 January 2008
				AU	2007254357	A1	29 November 2007
				EP	2019677	A2	04 February 2009
				EP	2019677	A4	21 September 2011
				JP	2009537528	A	29 October 2009
				JP	5167250	B2	21 March 2013
				US	2009209544	A1	20 August 2009
				US	7812027	B2	12 October 2010