

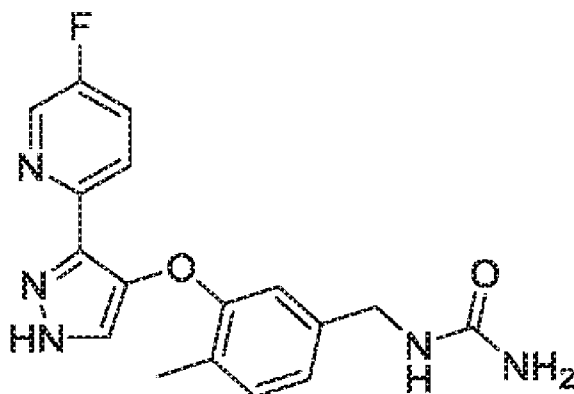


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[Continued on next page]

(54) **Title:** FLUOROPYRIDYL PYRAZOL COMPOUNDS

(57) **Abstract:** The present invention provides com-
pounds of the Formula (I); or a pharmaceutically ac-
ceptable salt thereof.



(I)

**Declarations under Rule 4.17:**

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*

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FLUOROPYRIDYL PYRAZOL COMPOUNDS

This invention relates to pyrazole compounds or pharmaceutically acceptable salts thereof. Compounds of this invention are inhibitors of methionine aminopeptidase 2

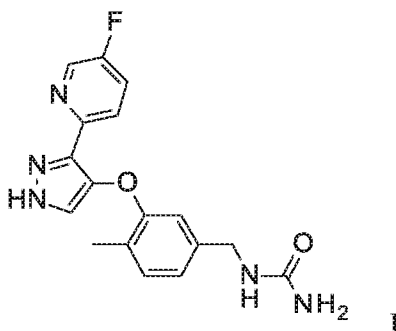
5 (MetAP2).

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.

The present invention provides novel compounds with MetAP2 inhibition activity.

10 These inhibitor compounds can be useful in the treatment of a MetAP2 mediated condition.

The present invention provides a compound of the Formula I



15 or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention the compound is 3-[[3-(5-Fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-phenyl]methylurea.

The invention provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and at least one selected from
20 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

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mammal an effective amount of a compound of Formula I. 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.

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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.

10 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).

20 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).

25 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 below

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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.

5 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.

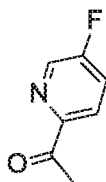
The abbreviations used herein are defined according to *Aldrichimica Acta*, Vol. 17, No. 1, 1984. Other abbreviations are defined as follows: "BSA" refers to Bovine Serum Albumin; "DIO" refers to diet induced obese; "HEC" refers to hydroxy ethyl cellulose; "HEPES" refers to 4-(2-hydroxyethyl)-1-piperazineethanesulfonic 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

10 performance liquid chromatography; and "THF" refers to tetrahydrofuran.

The following preparations and example further illustrate the invention.

Preparation 1

1-(5-Fluoro-2-pyridyl)ethanone



20 Add bis(triphenylphosphine) palladium(II) chloride (403 mg, 0.57 mmol), copper(I) iodide (328 mg, 1.7 mmol) and (1-ethoxyethenyl)trimethylstannane (5.1 g, 14 mmol) to a stirred solution of 2-bromo-5-fluoropyridine (2.0 g, 11 mmol) in acetonitrile (100 mL). Stir the resulting mixture at 100 °C under a N_2 atmosphere for 2 hours and

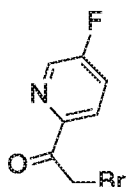
25 then cool to room temperature. Add water (50 mL) to quench the reaction and extract with ethyl acetate (3×100 mL). Dry the combined organic extracts over Na_2SO_4 , and concentrate under reduced pressure to give a residue. Dissolve the residue in THF (10

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mL) and add 5 M HCl (2 mL). Stir the mixture at room temperature for 1 hour and extract with ethyl acetate (3 × 20 mL). Wash the combined organic extracts with saturated NaHCO₃ aqueous solution (20 mL), dry over Na₂SO₄, and concentrate under reduced pressure to give the crude product. Purify the crude product by silica gel flash chromatography, eluting with a gradient solvent of 0~100% ethyl acetate in petroleum ether to give the title compound as a colorless oil (0.65 g, 41%). ES/MS *m/z* 140 (M+H).

Preparation 2

2-Bromo-1-(5-fluoro-2-pyridyl)ethanone



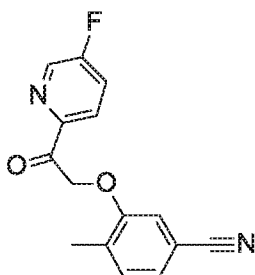
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Add a solution of 1-(5-fluoro-2-pyridyl)ethanone (0.65 g, 4.2 mmol) in THF (4 mL) to a stirred solution of phenyltrimethylammonium tribromide (1.7 g, 4.6 mmol) in THF (16 mL). Stir the resulting mixture at 35 °C for 5 hours. Filter off the solid and concentrate the filtrate under reduced pressure to give a residue. Purify the residue by silica gel flash chromatography, eluting with a gradient solvent of 0~100% ethyl acetate in petroleum ether to give the title compound as a colorless oil (0.78 g, 85%). ES/MS *m/e* (⁷⁹Br/⁸¹Br) 218.0/220.0 [M+H].

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Preparation 3

3-[2-(5-Fluoro-2-pyridyl)-2-oxo-ethoxy]-4-methyl-benzonitrile



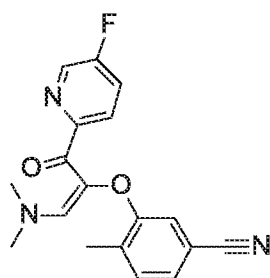
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Add potassium carbonate (0.99 g, 7.1 mmol) to a stirred solution of 2-bromo-1-(5-fluoro-2-pyridyl)ethanone (0.78 g, 3.6 mmol) and 3-hydroxy-4-methyl-benzonitrile (0.53 g, 3.7 mmol) in acetonitrile (15 mL). Stir the mixture at 60 °C for 1 hour. Filter off the solid and concentrate the filtrate under reduced pressure to give a residue. Purify the residue by silica gel flash chromatography, eluting with a gradient solvent of 0~100% ethyl acetate in petroleum ether to give the title compound as a white solid (0.96 g, 76%). ES/MS m/z 271 (M+H).

Preparation 4

3-[(E)-2-(Dimethylamino)-1-(5-fluoropyridine-2-carbonyl)vinyl]oxy]-4-methylbenzonitrile

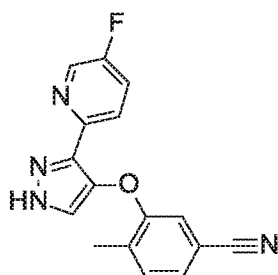


Add *N,N*-dimethylformamide dimethyl acetal (0.64 g, 5.4 mmol) to a stirred solution of 3-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]-4-methyl-benzonitrile (0.96 g, 2.7 mmol) in toluene (15 mL). Heat the mixture to 100 °C under microwave irradiation with stirring for 3 hours and cool to room temperature. Evaporate the solvent under reduced pressure to give the crude title compound as a brown oil (0.88 g, 100%), which is used directly without further purification. ES/MS m/z 326 (M+H).

Preparation 5

3-[[3-(5-Fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-benzonitrile

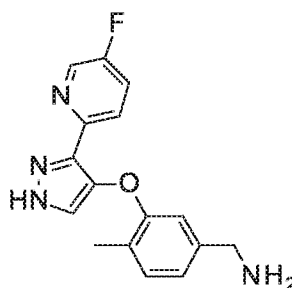
-6-



Add hydrazine hydrate (0.40 mL, 8.1 mmol) dropwise to a stirred solution of 3-
 [(E)-2-(dimethylamino)-1-(5-fluoropyridine-2-carbonyl)vinyl]oxy]-4-methylbenzonitrile
 (0.88 g, 2.7 mmol) in acetic acid (6.0 mL). Stir the mixture at room temperature for 14
 5 hours. Filter off the solid and pour the filtrate into icy water (10 mL). Extract with
 dichloromethane (3 × 20 mL). Wash the combined organic extracts with saturated
 NaHCO₃ aqueous solution (10 mL), dry over Na₂SO₄, and concentrate under reduced
 pressure to give a residue. Purify the residue by silica gel flash chromatography, eluting
 with a gradient solvent of 0~100% ethyl acetate in petroleum ether to give the title
 10 compound as a pale yellow solid (0.67 g, 85%). ES/MS m/z 295 (M+H).

Preparation 6

[3-[[3-(5-Fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-phenyl]methanamine



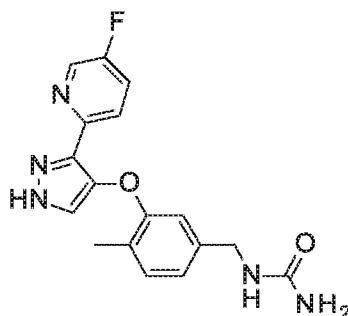
15 Add Raney nickel (300 mg, 3.5 mmol) to a stirred solution of 3-[[3-(5-fluoro-2-
 pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-benzonitrile (0.67 g, 2.3 mmol) in 7.0 M
 ammonium solution in methanol (40 mL). Degas the reaction vessel three times with
 hydrogen and stir the mixture under hydrogen atmosphere for 14 hours. Filter off the
 solid and concentrate the filtrate under reduced pressure to give the title compound as a

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yellow oil (0.68 g, 100%), which is used directly without further purification. ES/MS m/z 299 (M+H).

Example 1

5 [3-[[3-(5-Fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-phenyl]methylurea



Add potassium cyanate (0.37 g, 4.6 mmol) to a stirred solution of [3-[[3-(5-fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-phenyl]methanamine (0.68 g, 2.3 mmol) in a mixture of methanol (10 mL) and acetic acid (0.5 mL). Stir the resulting mixture at 50 °C
10 for 1 hour. Add triethylamine (0.5 mL) and evaporate the solvent under reduced pressure to give a residue. Purify the residue by preparative HPLC to give the title compound as a white solid (0.24 g, 29%). ES/MS m/z 342 (M+H).

Enzymatic activity assay of MetAP2 and MetAP1

15 The compound exemplified herein are tested essentially as described below and exhibit an IC₅₀ for the human and mouse MetAP2 assay of lower than 500 nM and are considered selective for MetAP2 with a MetAP1 value greater than 10 μM.

Full length MetAP2 (human and mouse) and MetAP1 (human) proteins are generated from Sf9 cells using a procedure similar to that described in Biochemistry
20 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.

Compound 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

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(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 μ M) in assay buffer (100 μ l) (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 μ l), 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 μ M) in assay buffer (100 μ l) (50 mM HEPES, 100 mM NaCl, 0.1% BSA, 0.05% Tween®-20, 50 μ M CoCl₂) for 60 minutes. The IC₅₀ value is calculated typically from a 10-point dose titration curve using a 4-parameter equation.

The IC₅₀ for the human and mouse MetAP2 assay for Example 1 is 4.0 ± 1.4 nM (n = 3) and 17.6 ± 4.7 (n = 4), respectively. The IC₅₀ for human MetAP1 is 19.8 μ M, demonstrating selective MetAP2 inhibition as compared with MetAP1.

Therapeutic Weight Loss Effect Measurement of Compounds.

To determine the therapeutic weight loss effects and improvement of metabolic parameters, compounds from the invention are tested in the 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 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 daily throughout the study duration. The weight loss of obese DIO mice by Example 1 by at 3 mg/kg and 10 mg/kg once a day is about 3% and 8% 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 offers an anti-obesity effect.

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

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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.

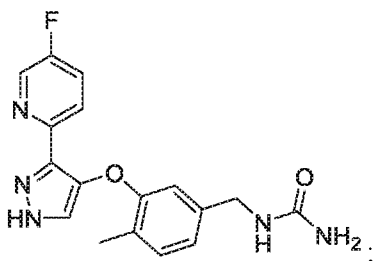
Preferred pharmaceutical compositions are formulated as a tablet or capsule for oral administration. The tablet or capsule can include a compound of the present invention in an amount effective to treat obesity.

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

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WE CLAIM:

1. A compound of the Formula



or a pharmaceutically acceptable salt thereof.

2. A compound or salt as claimed by Claim 1 wherein the compound [3-[[3-(5-Fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-phenyl]methylurea.

3. A pharmaceutical composition comprising a compound as claimed by any one of Claims 1 or 2, or a pharmaceutically acceptable salt thereof, and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

4. 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 or 2.

5. 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 or 2.

6. A compound, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 or 2 for use in the manufacture of a medicament.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/036360

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 A61K31/4439 A61P3/04 A61P3/10
ADD.

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

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)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/114578 A1 (BOEHRINGER INGELHEIM INT [DE]) 31 July 2014 (2014-07-31) page 94; compound XX.14 page 151 - page 153 -----	1-6
A	WO 2014/170197 A1 (BOEHRINGER INGELHEIM INT [DE]) 23 October 2014 (2014-10-23) the whole document -----	1-6
X,P	WO 2015/089800 A1 (LILLY CO ELI [US]; LILLY CHINA RES AND DEV CO LTD [CN]) 25 June 2015 (2015-06-25) the whole document -----	1-6



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

16 August 2016

Date of mailing of the international search report

13/09/2016

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/036360

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014114578 A1	31-07-2014	AU 2014210013 A1	04-06-2015
		EP 2948442 A1	02-12-2015
		JP 2016509598 A	31-03-2016
		US 2014213568 A1	31-07-2014
		WO 2014114578 A1	31-07-2014
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		US 2014315882 A1	23-10-2014
		WO 2014170197 A1	23-10-2014
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		CN 105814039 A	27-07-2016
		KR 20160075827 A	29-06-2016
		WO 2015089800 A1	25-06-2015
		WO 2015094913 A1	25-06-2015