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Declarations under Rule 4.17:

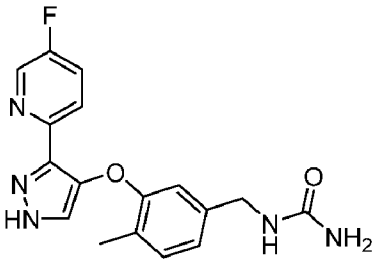
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

WO 2016/201662 A1

(54) Title: FLUOROPYRIDYL PYRAZOL COMPOUNDS



(I)

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

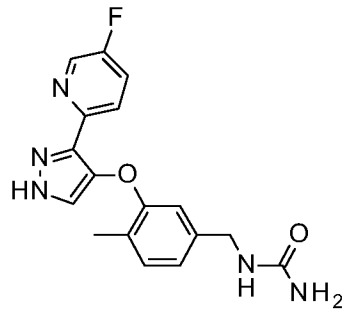
FLUOROPYRIDYL PYRAZOL COMPOUNDS

This invention relates to pyrazole compounds or pharmaceutically acceptable salts thereof. Compounds of this invention are inhibitors of methionine aminopeptidase 2 (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. These inhibitor compounds can be useful in the treatment of a MetAP2 mediated condition.

The present invention provides a compound of the Formula I



I

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 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, the invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof for use in therapy. Further, provided is a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament.

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

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

Individual isomers, enantiomers, and diastereomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the invention, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," *Stereochemistry of Organic Compounds*", Wiley-Interscience, 1994).

The 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

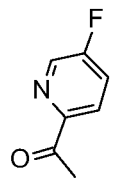
can be recovered by conventional methods well known in the art, including extraction, evaporation, precipitation, chromatography, filtration, trituration, and crystallization. In the schemes below, all substituents unless otherwise indicated, are as previously defined. The reagents and starting materials 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: "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 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

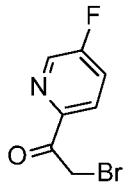


Add bis(triphenylphosphine) palladium(II) chloride (403 mg, 0.57 mmol), copper(I) iodide (328 mg, 1.7 mmol) and (1-ethoxyethenyl)trimethylstannane (5.1 g, 14 mmol) to a stirred solution of 2-bromo-5-fluoropyridine (2.0 g, 11 mmol) in acetonitrile (100 mL). Stir the resulting mixture at 100 °C under a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

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 $NaHCO_3$ aqueous solution (20 mL), dry over Na_2SO_4, 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

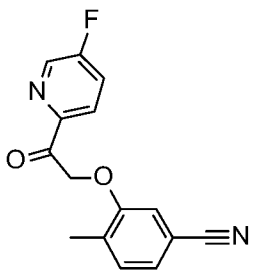
2-Bromo-1-(5-fluoro-2-pyridyl)ethanone



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* ($^{79}Br/^{81}Br$) 218.0/220.0 [M+H].

Preparation 3

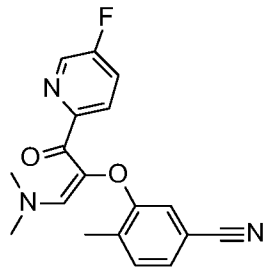
3-[2-(5-Fluoro-2-pyridyl)-2-oxo-ethoxy]-4-methyl-benzonitrile



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

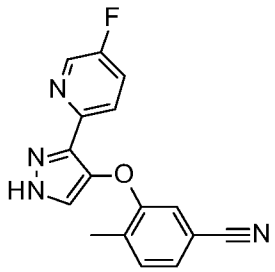
3-[(E)-2-(Dimethylamino)-1-(5-fluoropyridine-2-carbonyl)vinyloxy]-4-methylbenzonitrile



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

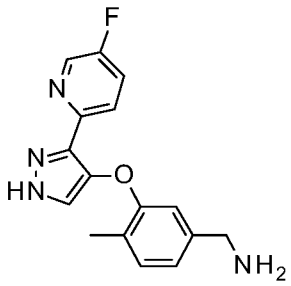
3-[[3-(5-Fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-benzonitrile



Add hydrazine hydrate (0.40 mL, 8.1 mmol) dropwise to a stirred solution of 3-[(E)-2-(dimethylamino)-1-(5-fluoropyridine-2-carbonyl)vinyloxy]-4-methylbenzonitrile (0.88 g, 2.7 mmol) in acetic acid (6.0 mL). Stir the mixture at room temperature for 14 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 $NaHCO_3$ aqueous solution (10 mL), dry over Na_2SO_4, 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 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

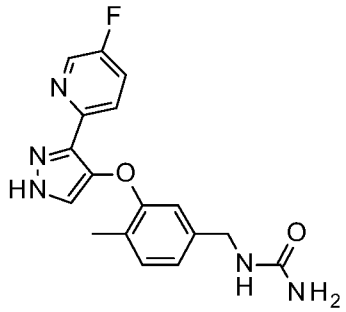


Add Raney nickel (300 mg, 3.5 mmol) to a stirred solution of 3-[[3-(5-fluoro-2-pyridyl)-1H-pyrazol-4-yl]oxy]-4-methyl-benzonitrile (0.67 g, 2.3 mmol) in 7.0 M ammonium solution in methanol (40 mL). Degas the reaction vessel three times with hydrogen and stir the mixture under hydrogen atmosphere for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

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

Example 1

[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 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

The compound exemplified herein are tested essentially as described below and exhibit an IC_{50} 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 2003, 42, 5035-5042. MetAP2 and MetAP1 are purified in the presence of 5 mM $MnCl_2$ and 2 mM $CoCl_2$ 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

(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 assay buffer (100 μl) (50 mM HEPES, 100 mM NaCl, 50 mg/mL BSA, 0.17 mM Triton™ X-100 at pH 7.5) for 40 minutes. After the reaction is stopped by the addition of CH_3CN (200 μl), the levels of product and remaining substrate are quantified with a mass spectrometer. The 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 assay buffer (100 μl) (50 mM HEPES, 100 mM NaCl, 0.1% BSA, 0.05% Tween®-20, 50 μM $CoCl_2$) for 60 minutes. The IC_{50} value is calculated typically from a 10-point dose titration curve using a 4-parameter equation.

The IC_{50} for the human and mouse MetAP2 assay for Example 1 is 4.0 ± 1.4 nM (n = 3) and 17.6 ± 4.7 (n = 4), respectively. The IC_{50} for human MetAP1 is 19.8 μM, 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

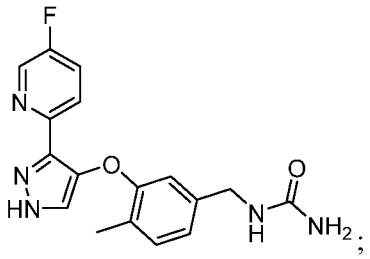
Co. Easton Pa. 1990 such as tablets, solid or gel filled capsules, powders, suspensions, or solutions. The composition can also include one or more pharmaceutically acceptable carriers, excipients, and diluents.

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.

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/CN2015/081746

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/10(2006.01)i; C07D 231/18(2006.01)i; A61K 31/435(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)

C07D403/-,C07D231/-,A61K 31/-, A 61P 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)

DWPI, SIPOABS, CNABS, CPRSABS, REGISTRY, CAPLUS (STN), lilly, Eili, +pyrazol+, +fluoropyridyl+, obesity, fat, weight w loss, ?MetAP??, methionine w aminopeptidase??, search according to 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.
A	WO 03051906 A2 (SMITHKLINE BEECHAM CORP) 26 June 2003 (2003-06-26) see the whole document, especially the abstract and the claims	1-6
A	WO 2010065879 A2 (ZAFGEN CORP) 10 June 2010 (2010-06-10) see the whole document, especially the abstract and the claims	1-6
A	WO 2012030922 A1 (DU PONT DE NEMOURS & CO E. I.) 08 March 2012 (2012-03-08) see the whole document, especially the abstract and the compounds in table 2	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	Date of mailing of the international search report
09 March 2016	**18 April 2016**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **XU,Chi** Telephone No. **(86-10)62086349**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/081746

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

[1] Claims 4 and 5 relate to a method of treatment of the human or animal body by therapy (see PCT Rule 39.1.(iv)). However, the search has been carried out and based on the use of the compound in manufacture of medicaments for treating corresponding diseases.

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/CN2015/081746

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 03051906 A2	26 June 2003	WO 03051906 A3	13 November 2003
		AU 2002359694 A1	30 June 2003
		AU 2002359694 A8	30 June 2003
WO 2010065879 A2	10 June 2010	WO 2010065879 A9	18 November 2010
		US 2012010290 A1	12 January 2012
WO 2012030922 A1	08 March 2012	CN 103079406 A	01 May 2013
		AU 2011295998 A1	21 February 2013
		US 2013143940 A1	06 June 2013
		EP 2611297 B1	17 June 2015
		UY 33582 A	30 March 2012
		US 2014221448 A1	07 August 2014
		JP 2013536856 A	26 September 2013
		US 9131693 B2	15 September 2015
		ES 2546671 T3	25 September 2015
		MX 2013002400 A	05 June 2013
		CN 105130900 A	09 December 2015
		AR 082869 A1	16 January 2013
		KR 20130139892 A	23 December 2013
		TW 201245155 A	16 November 2012
		EP 2611297 A1	10 July 2013
		US 8754115 B2	17 June 2014