



(51) International Patent Classification:

C07D 403/12 (2006.01) *A61P 29/00* (2006.01)
A61K 31/501 (2006.01)

(21) International Application Number:

PCT/US2018/025100

(22) International Filing Date:

29 March 2018 (29.03.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/478,789 30 March 2017 (30.03.2017) US

(71) Applicant: **BRISTOL-MYERS SQUIBB COMPANY**
[US/US]; Route 206 and Province Line Road, Princeton,
New Jersey 08543 (US).

(72) Inventors: **CHEN, Ke**; 42 South Drive, East Brunswick,
New Jersey 08816 (US). **DEERBERG, Joerg**; 11 Irongate
Ct., Columbus, New Jersey 08022 (US). **LIN, Dong**; c/o
Bristol-Myers Squibb Company, Route 206 and Province
Line Road, Princeton, New Jersey 08543 (US). **DUM-
MELDINGER, Michael**; c/o Bristol-Myers Squibb Com-
pany, Route 206 and Province Line Road, Princeton, New
Jersey 08543 (US). **INANKUR, Bahar**; c/o Bristol-My-
ers Squibb Company, Route 206 and Province Line Road,
Princeton, New Jersey 08543 (US). **KOLOUCHIN,
Sergei V.**; c/o Bristol-Myers Squibb Company, Route 206
and Province Line Road, Princeton, New Jersey 08543
(US). **LI, Jun**; c/o Bristol-Myers Squibb Company, Route
206 and Province Line Road, Princeton, New Jersey 08543
(US). **ROGERS, Amanda J.**; c/o Bristol-Myers Squibb
Company, Route 206 and Province Line Road, Princeton,
New Jersey 08543 (US). **ROSSO, Victor W.**; c/o Bris-
tol-Myers Squibb Company, Route 206 and Province Line
Road, Princeton, New Jersey 08543 (US). **SIMMONS,
Eric M.**; c/o Bristol-Myers Squibb Company, Route 206
and Province Line Road, Princeton, New Jersey 08543
(US). **SOUMEILLANT, Maxime C. D.**; c/o Bristol-My-

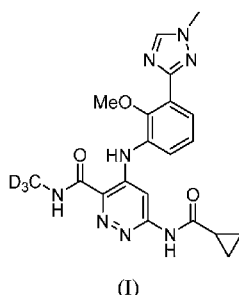
ers Squibb Company, Route 206 and Province Line Road,
Princeton, New Jersey 08543 (US). **TREITLER, Daniel
S.**; c/o Bristol-Myers Squibb Company, Route 206 and
Province Line Road, Princeton, New Jersey 08543 (US).
WANG, Jianji; 9 Aster Way, Dayton, New Jersey 08810
(US). **ZHENG, Bin**; c/o Bristol-Myers Squibb Company,
Route 206 and Province Line Road, Princeton, New Jersey
08543 (US). **SMITH, Michael J.**; c/o Bristol-Myers Squibb
Company, Route 206 and Province Line Road, Princeton,
New Jersey 08543 (US). **STROTMAN, Neil A.**; c/o Bris-
tol-Myers Squibb Company, Route 206 and Province Line
Road, Princeton, New Jersey 08543 (US). **TYMONKO,
Steven**; 577 Oxford Ln, Lindenhurst, Illinois 60046 (US).
BENKOVICS, Tamas; 7 Vincent Court, East Brunswick,
New Jersey 08816 (US).

(74) Agent: **KORSEN, Elliott** et al.; Bristol-Myers Squibb
Company, Route 206 and Province Line Road, Princeton,
New Jersey 08543 (US).

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,
KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: PROCESS FOR THE PREPARATION OF 6-(CYCLOPROPANEAMIDO)-4-((2-METHOXY-3-(1-METHYL-1H-1,2,4-
TRIAZOL-3-YL)PHENYL)AMINO)-N-(METHYL-D3)PYRIDAZINE-3-CARBOXAMIDE



(57) Abstract: The invention relates to an improved process for synthesiz-
ing 6-(cyclopropaneamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-N-(m-
ethyl-d3)pyridazine-3-carboxamide of the formula: [INSERT CHEMICAL STRUCTURE HERE]
Compound I is currently in clinical trials for the treatment of auto-immune and auto-inflammatory dis-
eases such as psoriasis.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *of inventorship (Rule 4.17(iv))*

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))*

PROCESS FOR THE PREPARATION OF 6-(CYCLOPROPANEAMIDO)-4-((2-METHOXY-3-(1-METHYL-1H-1,2,4-TRIAZOL-3-YL)PHENYL)AMINO)-N-(METHYL-D3)PYRIDAZINE-3-CARBOXAMIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

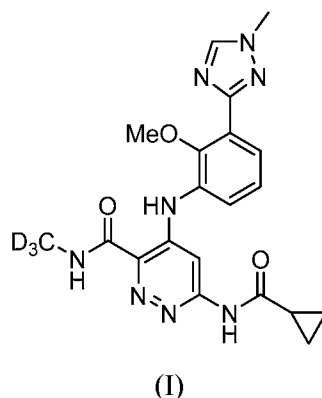
This application claims the benefit of U.S. Provisional Application No. 62/478,789, filed March 30, 2017, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention generally relates to a process for the preparation of 6-(cyclopropaneamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-N-(methyl-d3)pyridazine-3-carboxamide, a Tyk2 inhibitor currently in clinical trials for the treatment of auto-immune and auto-inflammatory diseases such as psoriasis, as well as novel intermediates used in the process.

BACKGROUND OF THE INVENTION

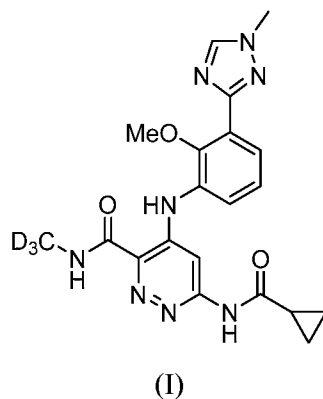
There is disclosed a process for the preparation of 6-(cyclopropaneamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-N-(methyl-d3)pyridazine-3-carboxamide, of formula I:



Compound I, compositions comprising Compound I, and methods of using Compound I are disclosed in U.S Patent No. 9,505,748 B2, which is assigned to the present assignee and is incorporated herein by reference in its entirety.

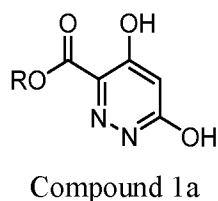
SUMMARY OF THE INVENTION

In a first aspect, the invention provides a process for preparing Compound I of the formula:



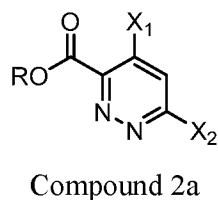
5 comprising the steps of

a) reacting compound 1a of the formula,



10 where R is C₁-C₆ alkyl or aryl;

with activating reagents to afford Compound 2a of the formula,

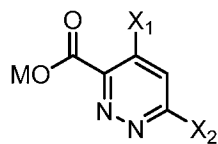


15

where X₁ and X₂ are independently halide or sulfonate; and R is defined as above,

b) subsequently reacting Compound 2a with an aqueous base to afford Compound 3a of the formula,

20

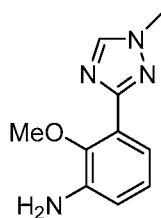


Compound 3a

where M is H, Li, Na, K, Cs, Ca, Mg, or Zn, and X₁ and X₂ are as defined above,

5

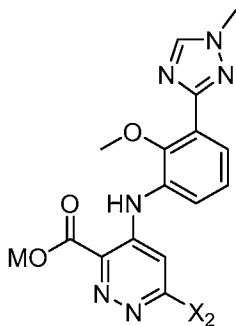
c) reacting Compound 3a, with Compound 7 of the formula



Compound 7

10

in a suitable solvent, and optionally in the presence of an acid, a base, or metal salts to afford Compound 8a of the formula,



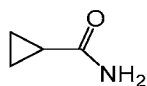
Compound 8a

15

where M and X₂ are defined as above,

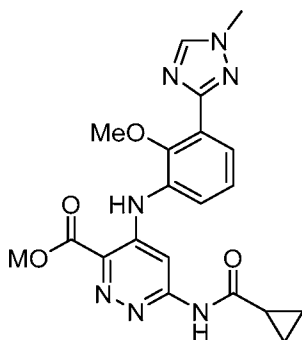
d) reacting Compound 8a with Compound 10 of the formula

20



Compound 10

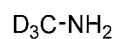
in the presence of a suitable transition metal catalyst, a ligand, one or more bases, and one
 5 or more suitable solvents to afford Compound 9a of the formula,



Compound 9a

10 where M is defined as above,

e) reacting Compound 9a with Compound 13 (free base or salts thereof) of the
 formula

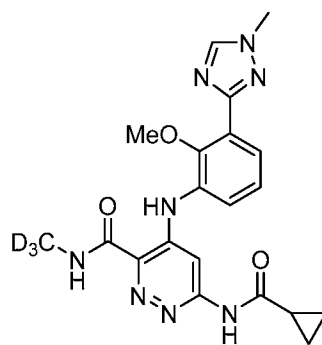


15

Compound 13

in the presence of one or more suitable activators, one or more suitable solvents, and
 optionally a base, to afford final product Compound I.

20 In a second aspect, the invention provides a process for preparing Compound I of
 the formula:

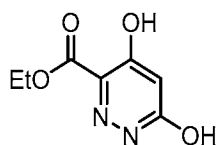


(I)

comprising the steps of

a) reacting a compound 1 of the formula

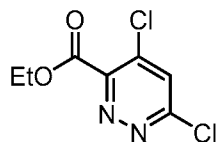
5



Compound 1

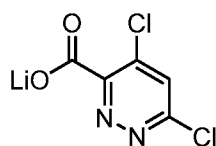
with POCl₃ and optionally an amine base, followed optionally by a buffered aqueous

10 workup to afford Compound 2 of the formula



Compound 2

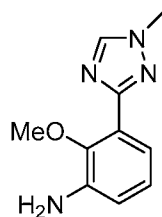
15 b) subsequently reacting Compound 2 with LiBr and DiPEA in water and acetonitrile to afford Compound 3 of the formula



Compound 3

20

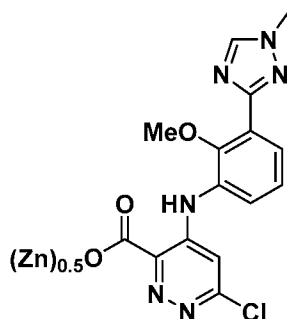
- c) reacting Compound 3, with Compound 7 of the formula



Compound 7

5

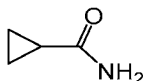
in the presence of zinc acetate in water and 2-propanol, to afford Compound 8 of the formula,



Compound 8

10 or a hydrate or solvate thereof;

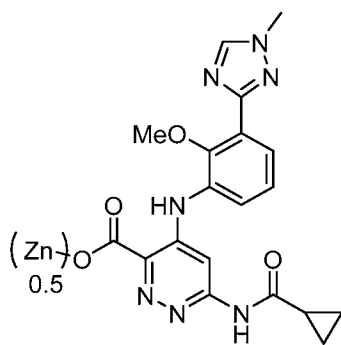
- d) reacting Compound 8 with Compound 10 of the formula



Compound 10

15

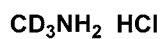
in a palladium catalyzed C-N coupling reaction in the presence of a phosphine ligand, and base, using a dual-base system comprised of potassium carbonate and DBU, followed optionally by isolation from aqueous acetic acid, to afford Compound 9 of the formula



Compound 9

or a hydrate or solvate thereof;

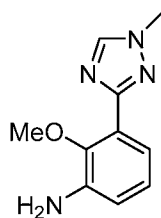
- e) reacting Compound 9 with EDC or other coupling agents and Compound 13 of the
5 formula



Compound 13

- 10 to afford final product Compound I, which may be further purified by crystallization from NMP/IPA.

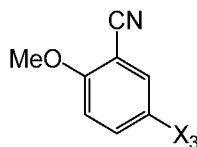
In a third aspect of the invention, there is provided a process of preparing Compound 7 of the formula



Compound 7

comprising

- a) reacting compound 4a of the formula

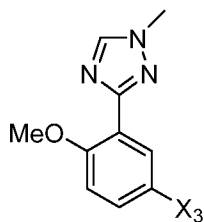


Compound 4a

where X₃ is Cl, Br, I or F;

with *N*-methyl-*N*-formylhydrazine and a suitable base to afford Compound 5a of the formula

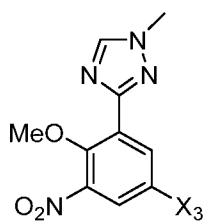
5



Compound 5a

where X₃ is defined as above

10 b) which is then nitrated to afford Compound 6a of the formula

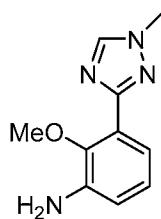


Compound 6a

where X₃ is defined as above

15 c) which is subsequently reduced to afford Compound 7.

In a fourth aspect of the invention, there is provided a process of preparing Compound 7 of the formula

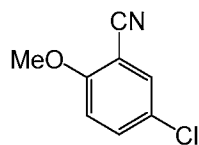


Compound 7

20

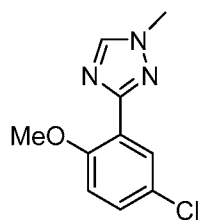
comprising

a) reacting compound 4 of the formula



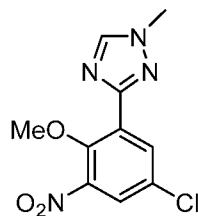
Compound 4

- 5 with *N*-methyl-*N*-formylhydrazine in the presence of potassium *tert*-butoxide to afford Compound 5 of the formula



Compound 5

- 10 b) which is then reacted with nitric acid in the presence of concentrated sulfuric acid to afford Compound 6 of the formula



Compound 6

- 15 c) which is subsequently reacted with hydrogen gas in the presence of Pd/C, sodium bicarbonate or sodium carbonate and methanol to afford Compound 7.

- In a 5th aspect of the invention, there is provided a general process of preparing
20 Compound 13 of the formula



Compound 13

comprising

- a) reacting d4-methanol of the formula



- 5 with activating reagents to afford compound 11a of the formula:

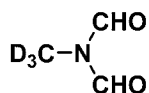


Compound 11a

where X₄ is independently halide or sulfonate,

10

- b) which is then reacted with sodium diformylamide to afford Compound 12 of the formula



15

Compound 12

- c) which is then hydrolyzed to afford Compound 13 of the formula



20

Compound 13

Compound 13 can be isolated as the free base, or as an HCl or HBr salt.

In a 6th aspect of the invention, there is provided a process of preparing

- 25 Compound 13 of the formula



Compound 13

comprising

- 30 a) reacting d4-methanol of the formula



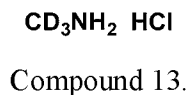
with tosyl chloride in the presence of aqueous sodium hydroxide to afford compound 11 of the formula:



b) which is then reacted with sodium diformylamide to afford Compound 12 of the formula



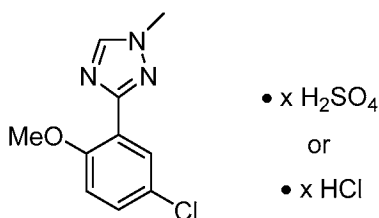
c) which is then hydrolyzed in the presence of hydrochloride in methanol to afford
15 Compound 13 (as hydrochloride salt) of the formula



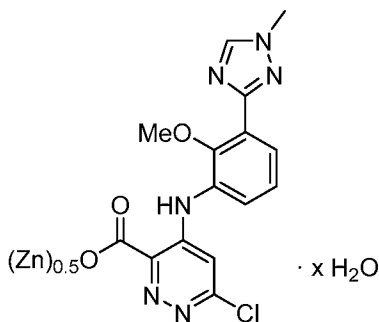
20 In a 7th aspect of the invention, there are provided novel intermediates identified above as Compounds 5, 6, 8, 9 and 12.

In an 8th aspect of the invention, there are provided compound 3, 5, 8 and 9 of the formula as its salt or hydrate form. In particular,

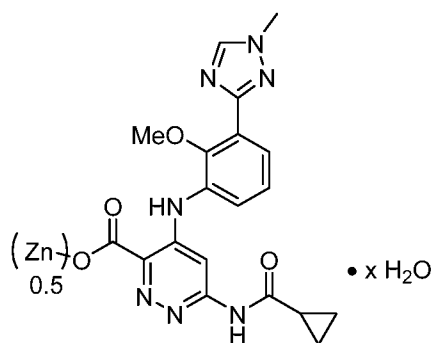




Compound 5b or 5c



Compound 8b



Compound 9b

10 Another aspect of the invention provides Compound I prepared by the process of Claim 1.

 A final aspect of the invention provides a method for treating auto-immune and auto-inflammatory diseases such as psoriasis comprising administering to a mammalian species, preferably a human, in need thereof, a therapeutically effective amount of
15 Compound I, wherein Compound I is prepared utilizing the novel process steps of the invention.

 The processes of the invention have several important advantages over prior syntheses of Compound I. In particular, due to the short sequence of chemical steps, high

yields and process improvement, the throughput, cycle-time, and overall yield have been dramatically improved. Additionally, the process consistently provides Compound I in high quality for use as a pharmaceutical API.

For the conversion of Compound 8(a) to Compound 9(a), the processes of the first and second aspects are conducted in the presence of a palladium catalyst. Preferred palladium catalysts include, but are not limited to Pd(OAc)₂, PdCl₂(MeCN)₂, Pd₂(dba)₃, Pd(dba)₂, [(Allyl)PdCl]₂, [(Crotyl)PdCl]₂.

The processes of the first and second aspects are also conducted in the presence of a ligand. Preferred ligands include, but are not limited to phosphine ligands such as SL-J009-1, SL-J009-2, SL-J002-1, SL-J002-2, DPEphos, Xantphos, DPPF, DCyPF, BINAP, or derivatives thereof.

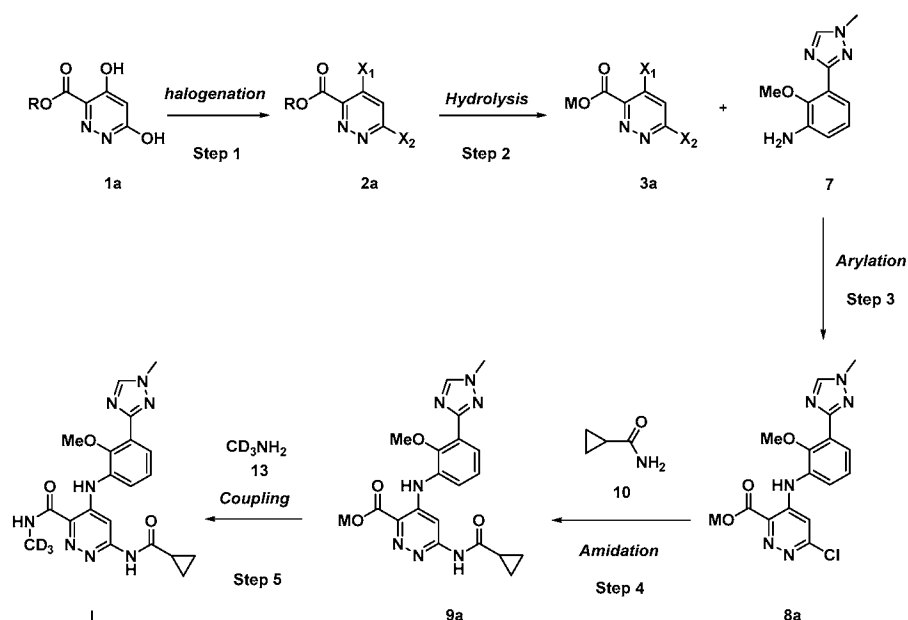
The processes of the first and second aspects are also conducted in the presence of a base. Preferred bases include, but are not limited to, K₂CO₃, K₃PO₄, Cs₂CO₃, DBU, DBN, TMG, or combinations thereof, particularly DBU/K₂CO₃.

DETAILED DESCRIPTION OF THE INVENTION

The following schemes illustrate the improved synthetic steps of the invention. These Schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to manufacture compounds disclosed herein.

As shown below in Scheme 1, the general preparation of compound I is described. Compound 1a is reacted with an activating reagent to give 4,6-diactivatedpyridazine Compound 2a. Ester hydrolysis occurs in the presence of a base to generate compound 3a as carboxylic acid or its salt form. Compound 3a can be selectively substituted at C4 position with compound 7 through contact with an appropriate acid, base or metal salt, or under neutral conditions in the absence of any additives, yielding Compound 8a. Compound 8a can be isolated as its free form, or optionally as a salt with an appropriate base. Compound 8a, in the presence of a metal, an appropriate ligand, and a base, will undergo a coupling process with compound 10 to form Compound 9a. Lastly, the coupling of compound 9a with compound 13 occurs in the presence of an activating reagent and an optional base generates compound I.

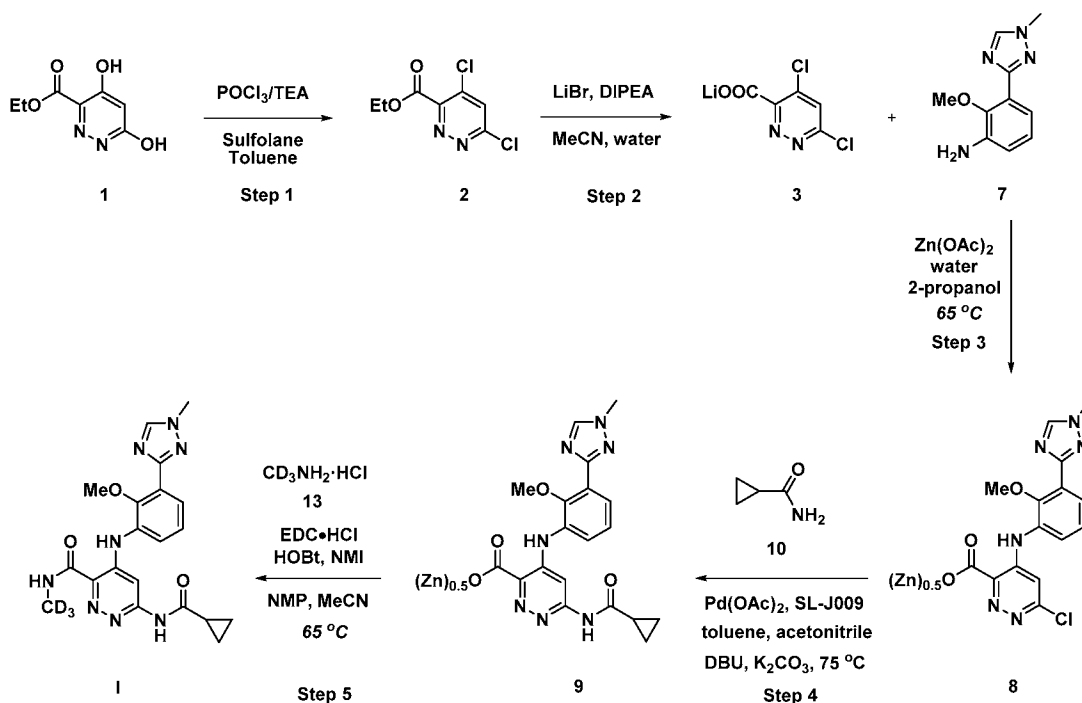
Scheme 1



As shown below in Scheme 2, the preparation of Compound I is described.

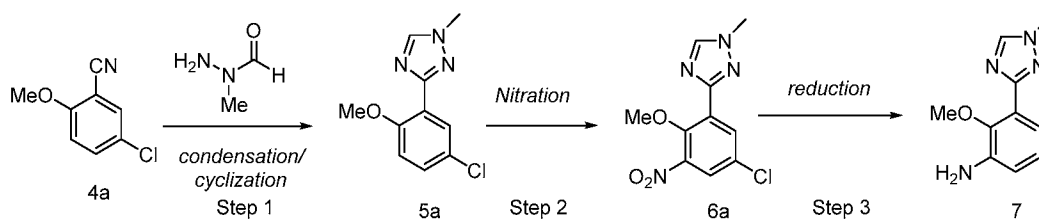
Diethyl 1,3-acetonedicarboxylate is sequentially treated with 4-acetamidobenzenesulfonyl
 5 azide and Hunig's base, tributylphosphine and water, and acetic acid, to generate Ethyl
 4,6-dihydroxypyridazine-3-carboxylate (Compound 1). Chlorodehydration with
 phosphorus oxychloride affords the corresponding dichloride (Compound 2), which
 undergoes hydrolysis in the presence of lithium bromide and Hunig's base in aqueous
 acetonitrile to yield the lithium carboxylate (Compound 3). Nucleophilic aromatic
 10 substitution with compound 7 takes place at C4 position of compound 3, in the presence
 of zinc acetate, leading to the formation of compound 8 as a zinc salt. Subsequent
 coupling with compound 10 is catalyzed by palladium acetate and a Josiphos ligand to
 generate compound 9. Finally, compound 9 undergoes an amidation with compound 13
 in the presence of EDC, HOBt and NMI, affording compound I.

Scheme 2



Scheme 3

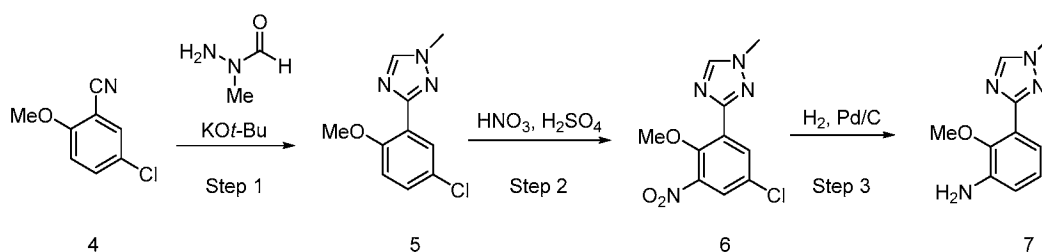
Another process of the invention is disclosed in Scheme 3 shown below. The
 5 general preparation of compound 7 is described. A cyclocondensation of compound 4a
 with *N*-methyl-*N*-formylhydrazine affords compound 5a, which undergoes nitration to
 give compound 6a. Reduction then delivers the corresponding compound 7.



10 As shown below in Scheme 4, the preparation of Compound 7 is described.
 Compound 4 reacts with *N*-methyl-*N*-formylhydrazine in the presence of potassium tert-
 butoxide to give compound 5. Treatment of compound 5 with nitric acid and concentrated
 sulfuric acid delivers compound 6, which reacts with hydrogen gas in the presence of
 Pd/C and sodium carbonate or sodium bicarbonate to give compound 7.

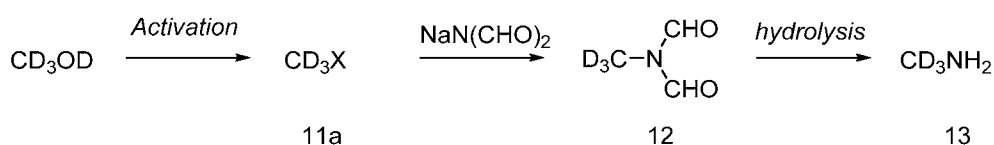
15

Scheme 4



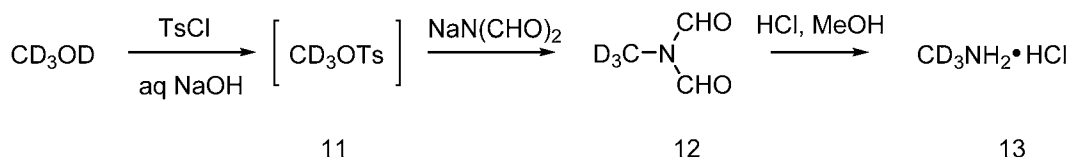
Another process of the invention is disclosed in Scheme 5 shown below. The general preparation of compound 13 is described. D4-methanol reacts with a suitable activating reagent to generate compound 11a, which undergoes displacement upon treatment of sodium diformylamide to form compound 12. The subsequent hydrolysis generates compound 13.

Scheme 5



As shown below in Scheme 6, the preparation of Compound 13 is described. D4-methanol reacts with tosyl chloride in the presence of aq sodium hydroxide to give compound 11. Reaction of this compound with sodium diformylamide affords compound 12, which hydrolyzes in the presence of acidic methanol to give compound 13 as its hydrochloride salt.

Scheme 6



Examples

The invention will now be further described by the following working example(s), which are preferred embodiments of the invention. All temperatures are in degrees Celsius (°C) unless otherwise indicated. These examples are illustrative rather than

limiting and it is to be understood that there may be other embodiments that fall within the spirit and scope of the invention as defined by the claims appended hereto.

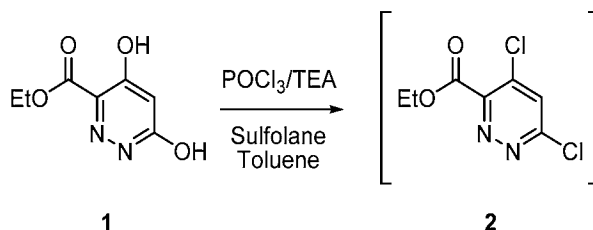
For ease of reference, the following abbreviations may be used herein.

5

Abbreviations

Abbreviation	Name
ACN	acetonitrile
AcOH	acetic acid
AP	area percent
aq.	aqueous
conc.	concentrated
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPEA	N,N-diisopropylethylamine (Hunig's base)
EDC HCl	1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
equiv.	Molar Equivalents
h	hour(s)
HOBt	1-hydroxy benzotriazole
HPLC	high pressure liquid chromatography
IPA	Isopropyl alcohol
min	minute(s)
Me	methyl
NaOH	Sodium Hydroxide
NMP	<i>n</i> -methylpyrrolidinone
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon
rt/RT	room temperature
sat.	saturated
<i>t</i> -BuOK	Potassium <i>tert</i> -butoxide
THF	Tetrahydrofuran
TsCl	p-toluenesulfonyl chloride

Example 1



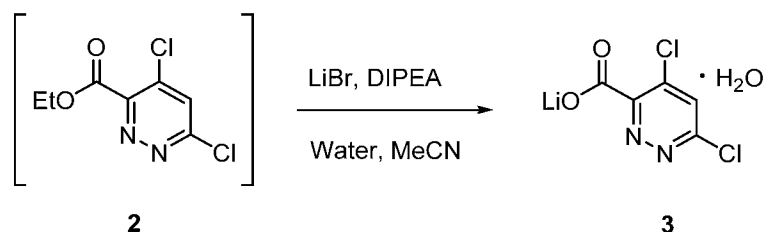
5

To a glass lined reactor were charged toluene (0.26 Kg), sulfolane (3.4 Kg), compound 1 (1.0 Kg) and POCl₃ (2.7 Kg). The crude was cooled to 0 °C. Triethylamine (0.89 Kg) was charged, and the resulting crude mixture was heated to 65 °C and aged till reaction reached completion. The reaction mass was cooled to 5 °C.

10 In a separate reactor, water (7.5 Kg) was charged and cooled to 5 °C. The reaction mass was added slowly to the water solution, maintaining the internal temperature below 5 °C. Additional water (0.5 Kg) was used to rinse the reactor and aid the transfer. The resulting mixture was agitated at 5 °C for 3 hours, then extracted with MTBE three times (3 x 4.5 Kg). The combined organic layers were washed sequentially with aq pH 7 buffer solution (5.0 L/Kg, 15 wt% KH₂PO₄/K₂HPO₄) and water (2.5 Kg). The crude was
 15 distilled under vacuum until total volume became approximately 3 L/Kg. ACN (2 x 6.3 Kg) was added followed by additional distillations back to ~3 L/Kg. The crude was cooled to 20 °C to afford **Compound 2** as a 30-36 wt% solution in 90-95% yield.

20

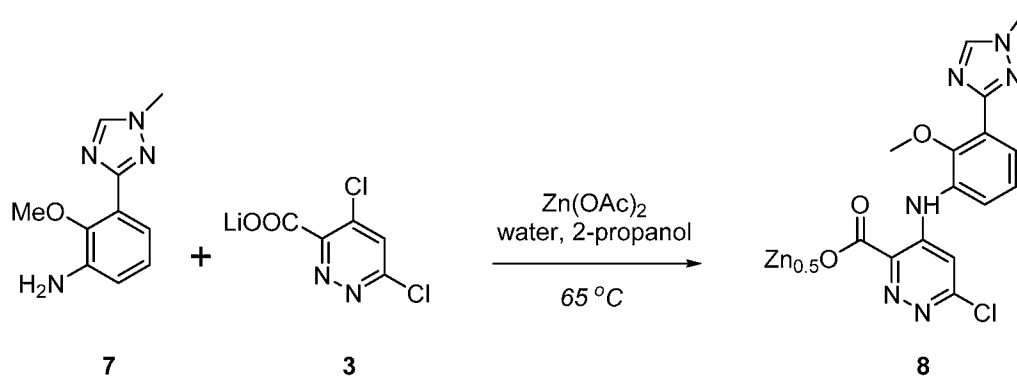
Example 2



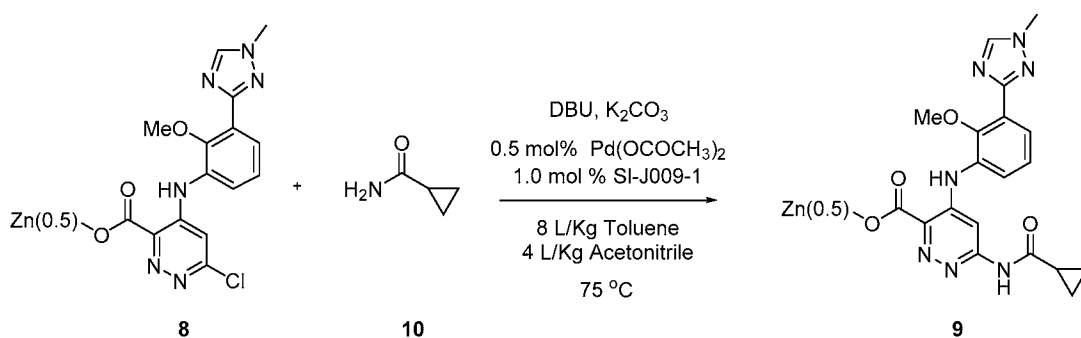
ACN (2.7 Kg), lithium bromide (1.18 Kg) and water (0.65 Kg) were charged to a glass-lined reactor at 25 °C. **Compound 2** crude solution prepared above (limiting reagent) was added, followed by DIPEA (1.82 Kg). The resulting slurry was agitated at

25 °C until reaction reached completion. The product was isolated by filtration. The crude solid was washed with ACN (1.6 Kg). The cake was dried under vacuum at 45 °C. **Compound 3** was isolated in 98 AP and 83% yield.

5

Example 3

Water (6.0 Kg, 6.0 L/Kg) and **compound 7** (1.0 Kg) were charged to a glass-lined reactor at 25 °C. Zinc acetate dehydrate (1.08 Kg, 1.0 equiv) was added, followed by **compound 3** (1.28 Kg, 1.20 equiv). The reactor line was rinsed with 2-propanol (0.79 Kg, 1.0 L/Kg) and water (1.50 Kg, 1.50 L/Kg). The resulting homogeneous solution was heated to 65 °C and aged until reaction reached completion. Water (7.0 Kg, 7.0 L/Kg) was added, and the crude mixture was cooled to 20 °C and aged for 30 min. The product was isolated by filtration. The crude solid was washed sequentially with water (6.0 Kg, 6.0 L/Kg), water (6.0 Kg, 6.0 L/Kg), THF (5.3 Kg, 6.0 L/Kg) and THF (5.3 Kg, 6.0 L/Kg). The cake was dried under vacuum at 70 °C. **Compound 8** was isolated in 98 AP and 94% yield.

Example 4

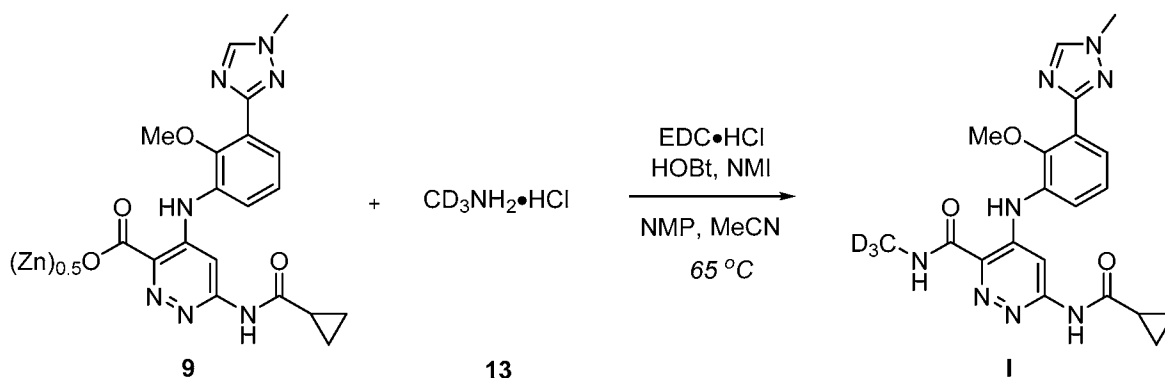
20

A separate glass-lined reactor was flushed with nitrogen. Toluene (0.87 Kg, 1.0 L/Kg) and MeCN (0.79 Kg, 1.0 L/Kg) were charged, followed by (2*R*)-1-[(1*R*)-1-[bis(1,1-dimethylethyl) phosphino] ethyl]-2-(dicyclohexylphosphino)ferrocene (Josiphos SL-009-01) (14.1 g, 1.0 mol%) and palladium acetate (2.9 g, 0.5 mol%). The reactor line
5 was rinsed with toluene (0.43 Kg, 0.5 L/Kg). The resulting pre-formed catalyst solution was kept under nitrogen until further usage.

At 20 °C, toluene (3.46 Kg, 4.0 L/Kg) and ACN (1.57 Kg, 2.0 L/Kg) were charged to a glass-lined reactor flushed with nitrogen. **Compound 8** (1.00 Kg) was
10 added, followed by DBU (0.39 kg, 1.00 equiv). The reactor line was rinsed with toluene (0.43 Kg, 0.5 L/Kg). **Compound 10** (0.54 Kg, 2.5 equiv) and K₂CO₃ (325 mesh grade, 0.70 Kg, 2.0 equiv) were added to the reaction mixture, followed by toluene (1.30 Kg, 1.5 L/Kg) and ACN (0.79 Kg, 1.0 L/Kg). The pre-formed catalyst solution was transferred into the reaction mixture, which was then heated to 75 °C and agitated until the reaction
15 reached completion.

The reaction crude was cooled to 20 °C. Aq. acetic acid (50 Volume %, 4.0 Kg, 4.0 L/Kg) was charged slowly over the course of 1 h. Glacial acetic acid (10.5 Kg, 10.0 L/Kg) was then added. The resulting homogeneous solution was washed twice with heptane (2 × 3.42 kg, 2 × 5.0 L/Kg). The bottom aq. layer was collected and transferred
20 to a clean reactor. Water (5.0 Kg, 5.0 L/Kg) was added, followed by **compound 9** seeds (0.01 Kg, 1.0 wt%). The slurry was aged for 2 h at 20 °C. Additional water (2.0 Kg, 2.0 L/Kg) was added, and the slurry was further aged for 6 h. The product was isolated by filtration. The crude cake was washed with aq. ACN (50 Volume %, 4.5 Kg, 5.0 L/Kg) followed by ACN (3.9 Kg, 5.0 L/Kg). The cake was dried under vacuum at 65 °C.
25 **Compound 9** was isolated in 98.5AP and 84% yield.

Example 5



NMP (2.06 Kg, 2.0 L/Kg) and ACN (0.78 Kg, 1.0 L/Kg) were charged to a glass-lined reactor and agitated at 20 °C. N-Methylimidazole (0.13 Kg, 0.7 eq), **Compound 13** (0.17 Kg, 1.2 eq) and **Compound 9** (1.00 Kg) were charged to the reaction mixture. The mixture was heated to 65 °C and aged until homogeneous. HOBt 20% wet (0.17 Kg, 0.5 eq), followed by EDC HCl (0.54 Kg, 1.4 eq) were then charged to the reaction mixture. The reactor was rinsed with ACN (0.78 Kg, 1.0 L/Kg), then the resulting mixture was aged at 65 °C until reaction reaches completion. The reaction was quenched by charging water (1.0 Kg, 1 L/Kg), then diluted with ACN (3.0 Kg, 3 L/Kg). The reaction mixture was aged at 65 °C for 1 h, before cooling to 0 °C, and aged for an additional 12 h at 0 °C. The product was isolated by filtration. The wet cake was washed with 2:1 Water:ACN (2.8 Kg, 3 L/Kg) then ACN (2.4 Kg, 3 L/Kg), before drying under full vacuum at 65 °C. **Compound I** was isolated in >99.5% purity and 91% yield

If needed, the product can be subjected to optional recrystallization as follows.

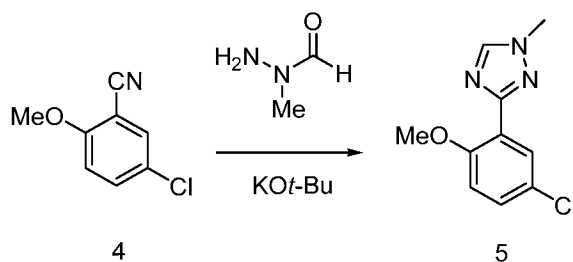
NMP (6.2 kg, 6.0 L/Kg) and **Compound I** (1.0 Kg) were charged to a glass-lined reactor. The batch was heated to 70°C to form a pale yellow solution, which was then transferred through a polish filter to a clean vessel at 70 °C. 2-Propanol (2.4 kg, 3 L/Kg) was added, followed by **Compound I** seeds (0.005 Kg, 0.005 Kg/Kg). After aging for 1 h, additional 2-propanol (4.8 kg, 6 L/Kg) was charged over the course of 2 h (3 L/Kg/hr). The slurry was aged for 1 h at 70 °C, cooled slowly to 0 °C and aged for additional 12 h at 0 °C. Product was isolated by filtration. The wet cake was washed with 2-propanol (2 x 3.1 kg, 2 x 4 L/Kg) before drying under full vacuum at 65 °C. **Compound I** was isolated in >99.9% purity and 83% yield.

Example 6



To a glass lined reactor were charged methanol (1.6 Kg/Kg, 2.0 L/Kg) and methylhydrazine (1 Kg) at 0 °C. Methyl formate (0.57 Kg/Kg, 1.1equiv) was added drop-wise. The crude was warmed up to 20 °C and aged for additional 6 h. The crude was distilled under vacuum until total volume became approximately 0.5 L/Kg. Five put/take distillations with 2-MeTHF (5 x 3.6 Kg/Kg) were undertaken for the purpose of azeotropic drying. The crude was cooled to 20 °C. N-Methyl-N-formylhydrazine was isolated as 89-90 wt% solution in 89-91% yield.

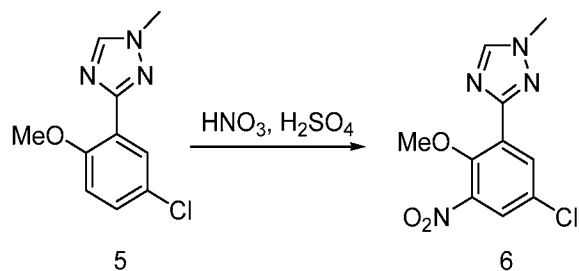
Example 7



5

To a glass lined reactor were charged potassium tert-butoxide (1.5 Kg/Kg, 2.4 equiv) and THF (12.2 Kg/Kg) at 0 °C. A mixture of **compound 4** (1.0 Kg), N-Methyl-N-formylhydrazine (1.0 Kg/Kg, 2.30 equiv) and THF (5.3 Kg/Kg, 6.0 L/Kg) was added slowly. The reactor line was rinsed with THF (0.5 Kg/Kg). The reaction crude was aged at 0 °C until reaction reached completion. Water (5.0 Kg/Kg) was added, and the resulting mixture was aged at 0 °C for 30 min, heated to 40 °C and aged for additional 30 min. The layers were separated and the aq layer discarded. The organic layer was washed with brine (15 wt%, 5.7 Kg/Kg) before distilling under vacuum until total volume became approximately 5 L/Kg. Four put/take distillations with ethyl acetate (4 x 10 L/Kg) were undertaken for the purpose of azeotropic drying. The crude was cooled to 20 °C. Sulfuric acid (0.66 Kg/Kg, 1.10 equiv) was added, and the slurry was agitated for 2-3 h. Product was isolated by filtration. The cake was consecutively washed with ethyl acetate (2 x 6.5 L/Kg) and heptane (8 L/Kg), and dried under vacuum at 45 °C. **Compound 5** was isolated in 99 AP and 83% yield.

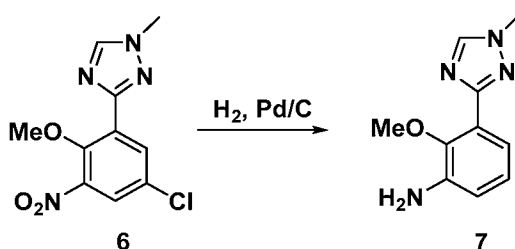
Example 8



To a glass lined reactor were charged concentrated sulfuric acid (4.5 Kg/Kg) and compound 5 (1.0 Kg) at 0-5 °C. Nitric acid (68 wt%, 0.35 Kg/Kg, 1.2 equiv) was added drop-wise. The mixture was agitated at 0-5 °C until reaction reached completion.

In a separate reactor, water (12 Kg/Kg) and methanol (6.5 Kg/Kg, 8.3 L/Kg) were mixed well at 20 °C. The nitration crude was transferred slowly into the methanol water mixture. The reactor line was rinsed with methanol (0.5 Kg/Kg). The crude was heated to 40-45 °C. Aq. ammonium hydroxide (25 wt%, 7.4 Kg/Kg) was added slowly. The resulting slurry was cooled to 20 °C and agitated for 3 h. Product was isolated by filtration. The cake was washed with water (2 x 6 L/Kg), and dried under vacuum at 45 °C. **Compound 6** was isolated in 99 AP and 95% yield.

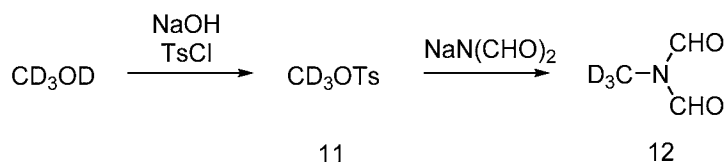
Example 9



To a high pressure reactor flushed with nitrogen were charged methanol (8.0 Kg/Kg) and **compound 6** (1.0 Kg). With careful exclusion of oxygen, sodium bicarbonate (0.6 Kg/Kg, 2.0 equiv) and Pd/C (10% loading, 50 % wet, 0.02 Kg/Kg) were added. The reactor was pressurized with hydrogen (41-46 psi), and the reaction mixture was aged at 20 °C for 6 h then heated to 45 °C and aged till reaction reached completion.

The reactor was flushed with nitrogen, and the reaction crude was filtered to remove Pd/C. Methanol (5 Kg/Kg) was used to aid the transfer. The combined filtrates were distilled under vacuum until total volume became approximately 2.5 L/Kg. Water (10 Kg/Kg) was added, and the crude was distilled under vacuum until total volume became approximately 2.5 L/Kg. The crude was heated to 70 °C. Brine (25 wt%, 9.0 Kg/Kg) was added, and the resulting crude was agitated for 6 h at 70 °C. After cooling down to 0 °C, the crude was further aged for 6 h. Product was isolated by filtration. The cake was washed with brine (pre-cooled to 0 °C, 25 wt%, 2.0 Kg/Kg), and dried under vacuum at 45 °C. **Compound 7** was isolated in 99 AP and 88% yield.

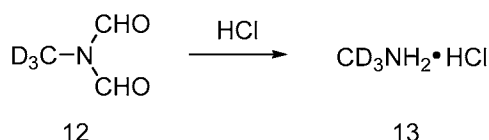
10

Example 10

To a glass lined reactor flushed with nitrogen were charged water (16.3 L/Kg) and sodium hydroxide (3.3 Kg, 3.0 equiv). The mixture was aged till sodium hydroxide reached full dissolution. The crude was cooled to 0 °C. D4-Methanol (1.0 Kg) and THF (, 4.5 L/Kg) were charged. A solution of TsCl (6.3 Kg, 1.2 equiv) in THF (6.3 Kg, 7.1 L/Kg) was added over the course of 2 h. The crude was agitated at 0 °C until reaction reached completion. The batch was warmed to 20 °C. The layers were separated. The collected organic layer was diluted with MTBE (4.0 Kg, 5.4 L/Kg), washed with brine twice (25 wt%, 4.0 Kg followed by 12 Kg). The organic layer was distilled under vacuum until total volume became approximately 10 L/Kg. Two put/take distillations with ACN (2 × 10 L/Kg) were undertaken for the purpose of azeotropic drying. The crude was cooled to 20 °C. ACN (10.0 Kg, 12.8 L/Kg) and NaN(CHO)₂ (3.3 Kg, 1.2 equiv) were added. The crude was heated to 65 °C and agitated until reaction reached completion. After cooling down to 5 °C, the mixture was filtered, and the crude cake was washed with ACN twice (2 × 2.5 Kg, 2 × 3.2 L/Kg). The combined filtrates were distilled under vacuum until total volume became approximately 3 L/Kg. The crude was cooled to 20 °C. **Compound 12** was isolated as an oil with 80-85 wt% in 60-70% yield.

30

Example 11



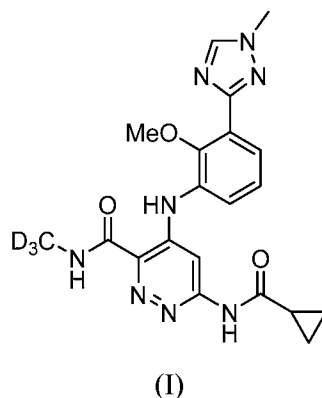
5 To a glass lined reactor were charged **compound 12** (1.0 Kg) and methanol (3.9 Kg, 5.0 L/Kg) at 20 °C. A solution of HCl in IPA (5-6 N, 4.5 Kg, 1.5 equiv) was added. The resulting mixture was heated to 50 °C and agitated until reaction reached completion. THF (10 Kg, 11.2 L/Kg) was added slowly and the crude was cooled to 0 °C over 2 h to afford a slurry. The product was isolated by filtration. The cake was washed with THF
 10 (3.7 Kg, 4.1 L/Kg), and dried under vacuum at 45 °C. **Compound 13** was isolated in 80% yield.

If needed, the product can be subjected to optional recrystallization as follows. Methanol (5.6 Kg, 8.3 L/Kg) and **Compound 13** (1.0 Kg) were charged to a glass-lined
 15 reactor. DBU (0.1 Kg) was added slowly. The crude was agitated for 1 h. THF (12.4 Kg, 13.9 L/Kg) was added slowly, and the resulting slurry was aged for 2 h. The product was isolated by filtration. The cake was washed with THF (2.6 Kg, 2.9 L/Kg), and dried under vacuum at 45 °C. **Compound 13** was isolated in 60% yield (1st crop). The mother liquor was distilled under vacuum until total volume became approximately 1 L/Kg. Two
 20 put/take distillations with methanol (2 × 2.8 Kg, 2 × 3.6 L/Kg) were performed and the solution was concentrated back to ~ 1 L/Kg. The crude was cooled to 20 °C. THF (4.8 Kg, 5.4 L/Kg) was added, and the resulting slurry was aged for 2 h. The product was isolated by filtration. The cake was washed with THF (1.0 Kg), and dried under vacuum at 45 °C. **Compound 13** was isolated in 25% yield (2nd crop).

25

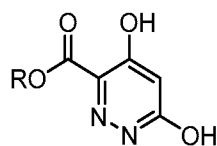
We Claim:

1. A process for the preparation of Compound I of the formula



comprising the steps of

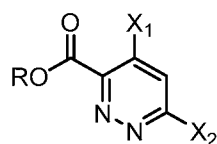
- a) reacting compound 1a of the formula,



Compound 1a

where R is C₁-C₆ alkyl or aryl;

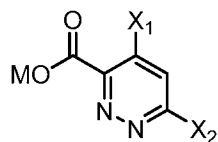
with activating reagents to afford Compound 2a of the formula,



Compound 2a

where X₁ and X₂ are independently halide or sulfonate; and R is defined as above,

- 20 b) subsequently reacting Compound 2a with an aqueous base to afford Compound 3a of the formula,

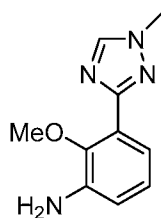


Compound 3a

where M is H, Li, Na, K, Cs, Ca, Mg, or Zn, and X₁ and X₂ are as defined above,

5

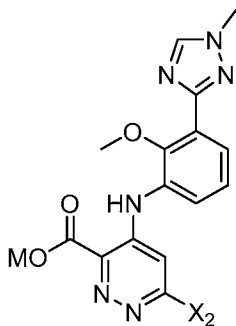
c) reacting Compound 3a, with Compound 7 of the formula



Compound 7

10

in a suitable solvent, and optionally in the presence of an acid, a base, or metal salts to afford Compound 8a of the formula,



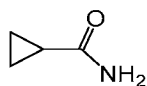
Compound 8a

15

where M and X₂ are defined as above,

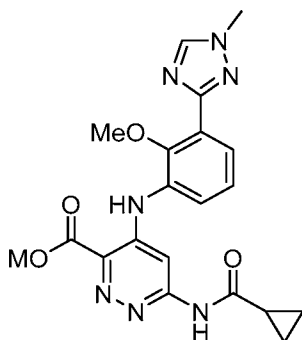
d) reacting Compound 8a with Compound 10 of the formula

20



Compound 10

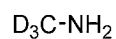
in the presence of a suitable transition metal catalyst, a ligand, one or more bases, and one
 5 or more suitable solvents to afford Compound 9a of the formula,



Compound 9a

10 where M is defined as above,

e) reacting Compound 9a with Compound 13, or a free base or salt thereof, of the
 formula

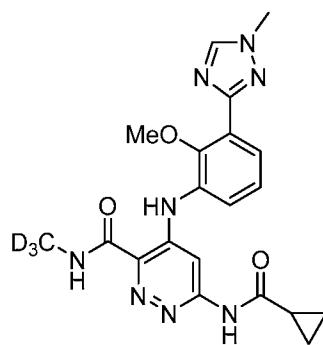


15

Compound 13

in the presence of one or more suitable activators, one or more suitable solvents, and
 optionally a base, to afford Compound I.

20 2. A process for the preparation of Compound I of the formula

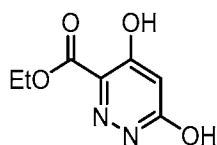


(I)

comprising the steps of

a) reacting compound 1 of the formula

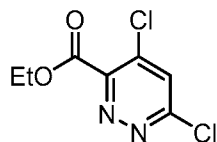
5



Compound 1

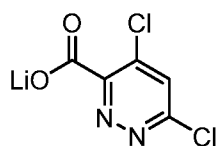
with POCl₃ and optionally an amine base, followed optionally by a buffered aqueous

10 workup to afford Compound 2 of the formula



Compound 2

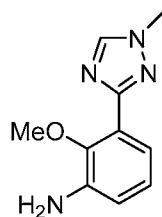
15 b) subsequently reacting Compound 2 with LiBr and DiPEA in water and acetonitrile to afford Compound 3 of the formula



Compound 3

20

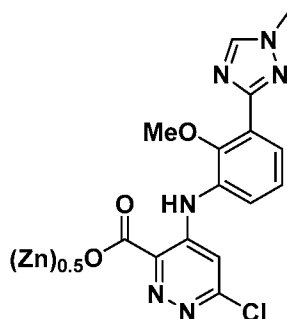
- c) reacting Compound 3, with Compound 7 of the formula



Compound 7

5

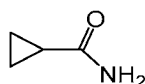
in the presence of zinc acetate in water and 2-propanol, to afford Compound 8 of the formula,



Compound 8

10 or a hydrate or solvate thereof;

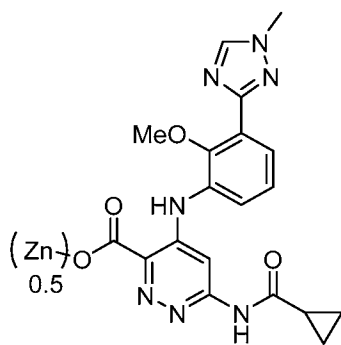
- d) reacting Compound 8 with Compound 10 of the formula



Compound 10

15

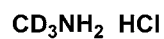
in a palladium catalyzed C-N coupling reaction in the presence of a phosphine ligand, and base, using a dual-base system comprised of potassium carbonate and DBU, followed optionally by isolation from aqueous acetic acid, to afford Compound 9 of the formula



Compound 9

or a hydrate or solvate thereof;

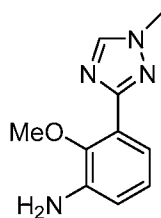
- e) reacting Compound 9 with EDC or other coupling agents and Compound 13 of the formula



Compound 13

- to afford Compound I, which may be further purified by crystallization from NMP/IPA.

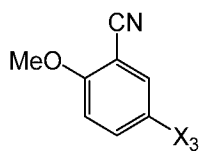
3. A process for preparing Compound 7 of the formula



Compound 7

comprising

- b) reacting compound 4a of the formula

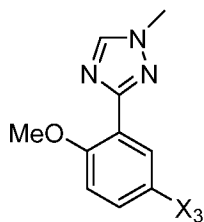


Compound 4a

where X₃ is Cl, Br, I or F;

with *N*-methyl-*N*-formylhydrazine and a suitable base to afford Compound 5a of the formula

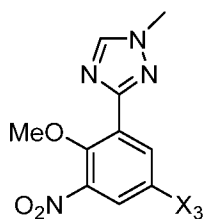
5



Compound 5a

b) which is then nitrated to afford Compound 6a of the formula

10

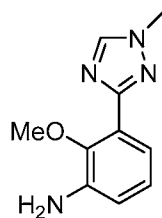


Compound 6a

c) which is subsequently reduced to afford Compound 7.

15

4. A process for preparing Compound 7 of the formula

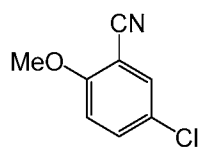


Compound 7

comprising

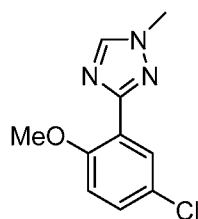
a) reacting compound 4 of the formula

20



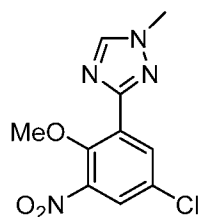
Compound 4

- with *N*-methyl-*N*-formylhydrazine in the presence of potassium *tert*-butoxide to afford
 5 Compound 5 of the formula



Compound 5

- b) which is then reacted with nitric acid in the presence of concentrated sulfuric acid
 10 to afford Compound 6 of the formula



Compound 6

- 15 c) which is subsequently reacted with hydrogen gas in the presence of Pd/C, sodium bicarbonate or sodium carbonate and methanol to afford Compound 7.

5. A process for preparing Compound 13 of the formula



- 20 or a salt thereof, comprising

- a) reacting d4-methanol of the formula



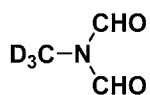
with activating reagents to afford compound 11a of the formula:



Compound 11a

5 where X₄ is independently halide or sulfonate,

b) which is then reacted with sodium diformylamide to afford Compound 12 of the formula



10

Compound 12

c) which is then hydrolyzed to afford Compound 13.

15 6. A process for preparing Compound 13 of the formula



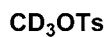
Compound 13

comprising

20 a) reacting d₄-methanol of the formula

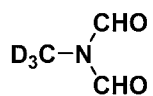


25 with tosyl chloride in the presence of aqueous sodium hydroxide to afford compound 11 of the formula:



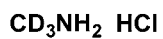
Compound 11

30 b) which is then reacted with sodium diformylamide to afford Compound 12 of the formula



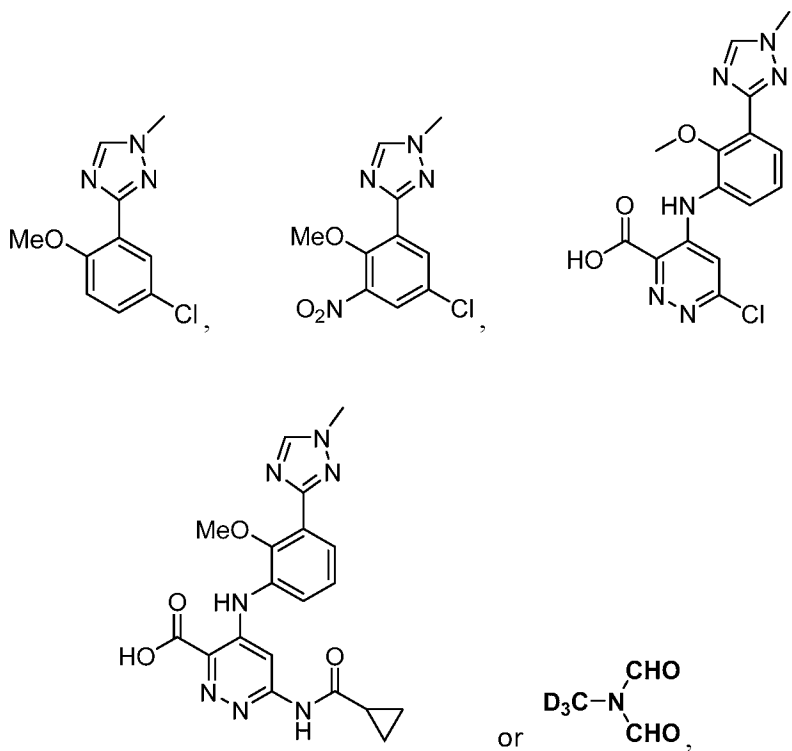
Compound 12

- c) which is then hydrolyzed in the presence of hydrochloride in methanol to afford
 5 Compound 13 as its hydrochloride salt of the formula



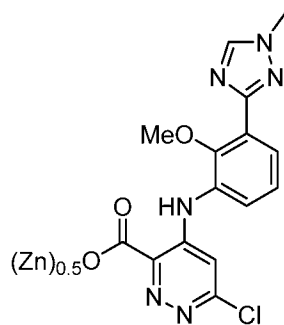
Compound 13.

- 10 7. A compound selected from the following



- 15 or a salt or hydrate thereof

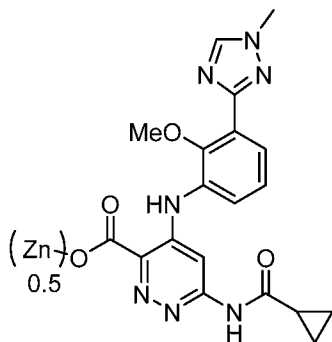
8. A compound according to Claim 7 which is



or a hydrate thereof.

9. A compound according to Claim 7 which is

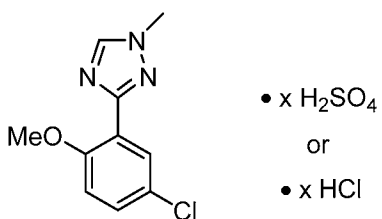
5



or a hydrate thereof.

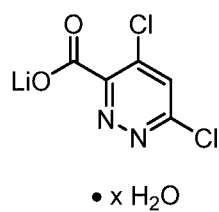
10. A compound according to Claim 7 which is

10

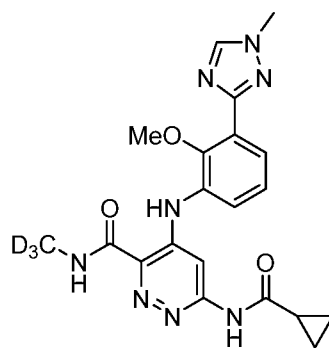


11. A compound of the formula

15



12. Compound I of the formula



5

prepared by the process of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/025100

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/12 A61K31/501 A61P29/00
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 A61K A61P

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.
X	US 9 505 748 B2 (BRISTOL-MYERS SQUIBB COMPANY [US]) 29 November 2016 (2016-11-29) cited in the application	12
A	column 4, lines 33-36; example 52 in columns 102-103; -----	1,2,8,9, 11



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

29 May 2018

Date of mailing of the international search report

09/08/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Wolf, Claudia

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/025100

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.:
because they relate to subject matter not required to be searched by this Authority, namely:
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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 8, 9, 11, 12(completely); 7(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 8, 9, 11, 12(completely); 7(partially)

a process for the preparation of compound of formula (I) and intermediates thereof

2. claims: 3, 4, 10(completely); 7(partially)

A process for preparing a compound 7 and intermediates thereof

3. claims: 5, 6(completely); 7(partially)

A process for preparing compound 13 and intermediates thereof

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/025100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 9505748	B2	29-11-2016	
		AR 094452 A1	05-08-2015
		AU 2013341186 A1	02-07-2015
		AU 2017201076 A1	09-03-2017
		BR 112015010102 A2	11-07-2017
		CA 2890981 A1	15-05-2014
		CL 2015001231 A1	28-08-2015
		CN 104884454 A	02-09-2015
		EA 201590917 A1	30-09-2015
		EP 2922846 A1	30-09-2015
		HK 1215255 A1	19-08-2016
		JP 2016506369 A	03-03-2016
		KR 20150081339 A	13-07-2015
		MA 38072 A1	29-07-2016
		PE 09442015 A1	20-06-2015
		PH 12015501004 A1	27-07-2015
		SG 10201706897T A	28-09-2017
		SG 10201706985U A	30-10-2017
		SG 11201503399X A	28-05-2015
		TW 201422593 A	16-06-2014
		US 2015299183 A1	22-10-2015
		US 2017022192 A1	26-01-2017
		UY 35126 A	30-05-2014
		WO 2014074661 A1	15-05-2014
		ZA 201504052 B	29-11-2017
