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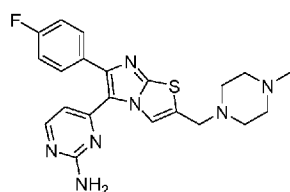
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(54) Title: NEW METHODS OF PRODUCING (2-AMINO-4-[6-(4-FLUOROPHENYL)-2-[(4-METHYL-1-PIPERAZINYLMETHYL)IMIDAZO[2,1-B]THIAZOL-5-YL]-PYRIMIDINE



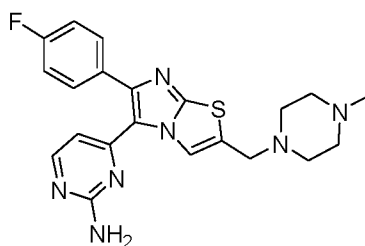
(I)

(57) Abstract: This invention is directed to improved processes for the preparation of (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl]imidazo[2,1-b]thiazol-5-yl]-pyrimidine of Formula (I).

NEW METHODS OF PRODUCING (2-AMINO-4-[6-(4-FLUOROPHENYL)-2-[(4-METHYL-1-PIPERAZINYL)METHYL]IMIDAZO[2,1-B]THIAZOL-5-YL]-PYRIMIDINE

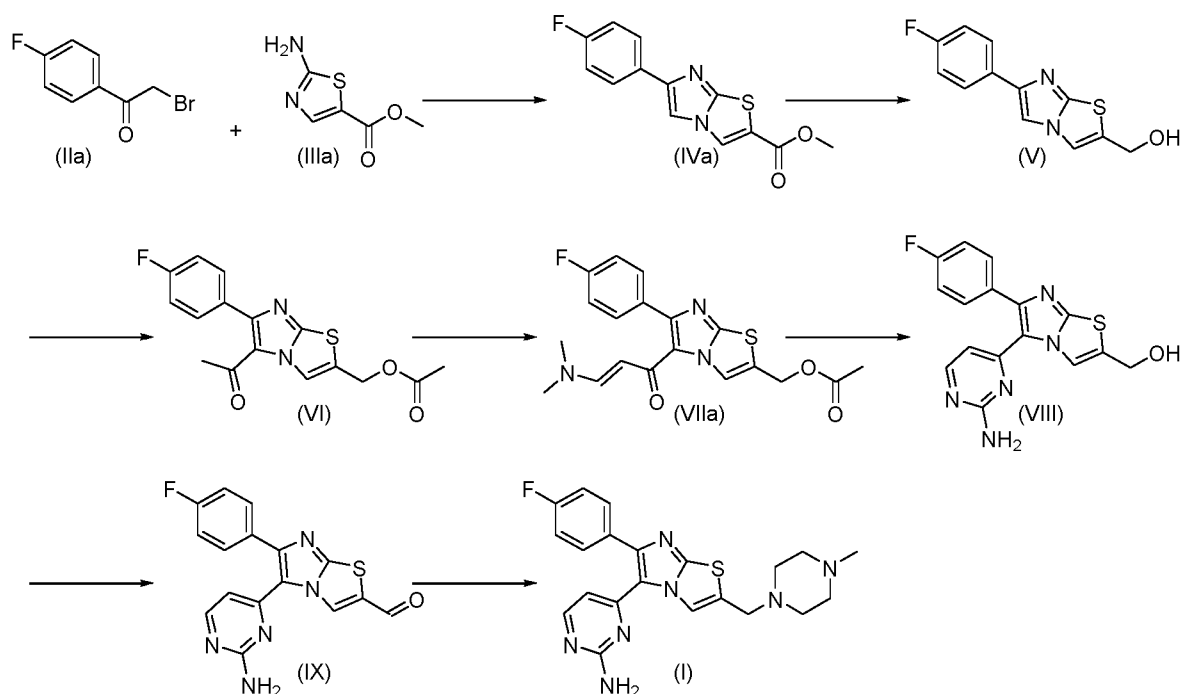
Background

5 Imidazothiazoles such as compound of Formula (I) have been claimed as mGluR1 antagonist for the treatment of schizophrenia by Ohta and co-inventors in WO2004016287, also as cGMP dependent protein kinase inhibitors for the treatment of cytokine mediated diseases and the prevention of protozoal diseases by Biftu and co-inventors in WO03/000682. The compound of Formula (I) has been shown to have good
10 *in vivo* efficacy against *Eimeria* spp infection in chickens.



Formula (I)

A seven steps synthesis of (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl]imidazo[2,1-b]thiazol-5-yl]-pyrimidine (I) has been already described
15 by Scribner in *Bioorg. Med. Chem. Lett.* **2008**, 18, 5263 (see also Scheme 1).

**Scheme 1**

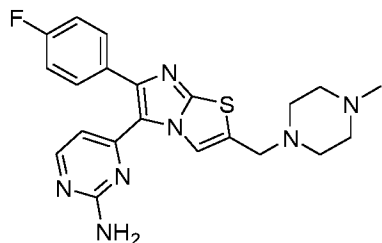
However, this synthesis method suffers from major inconveniences that preclude its application to the preparation of large quantities of compound. For example, the preparation of the intermediate methyl ester (IVa) from the starting materials (IIa) and (IIIa) is accompanied by the formation of the parent acid as side product. Moreover, the conversion of the alcohol (V) into the acylated ester (VI) performed in the presence of acetic anhydride under sulfuric acid catalysis proved very unreliable. Furthermore, oxidation of the intermediate alcohol (VIII) into the penultimate aldehyde (IX) is performed in the presence of harmful manganese dioxide. The overall yield of this synthetic pathway does not exceed 10%.

Summary of the Invention

Novel processes for the preparation of (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl]imidazo[2,1-b]thiazol-5-yl]-pyrimidine of Formula (I) have been discovered. These new processes are significantly shorter than the previously described synthesis and are composed of higher yielding and reliable steps. Therefore, the newly

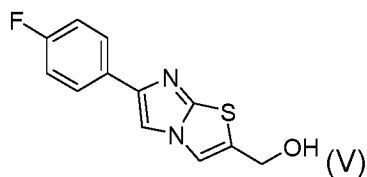
developed synthetic pathways are amenable to the production of large amount of compound of Formula (I).

An embodiment of the invention is a process to prepare a compound of Formula (I)

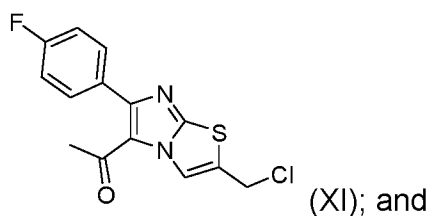


5 comprising

a. reacting a compound of Formula (V)



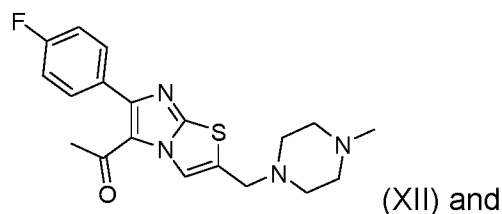
with acetyl chloride in an organic solvent to form a compound of Formula (XI).



10 b. converting the compound of Formula (XI) to the compound of Formula (I)

In an additional embodiment, the process further comprises

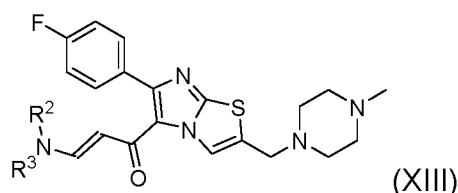
a. reacting the compound of Formula (XI) with 1-methyl piperazine in the presence of a base to form the compound of Formula (XII) or a salt thereof



converting the compound of Formula (XII) to the compound of Formula (I).

Another embodiment is a process further comprising

- a. reacting the compound of Formula (XII) or a salt thereof with a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent, preferably 1,1-dimethoxy-*N,N*-dimethylmethanamine to form the compound of Formula (XIII).



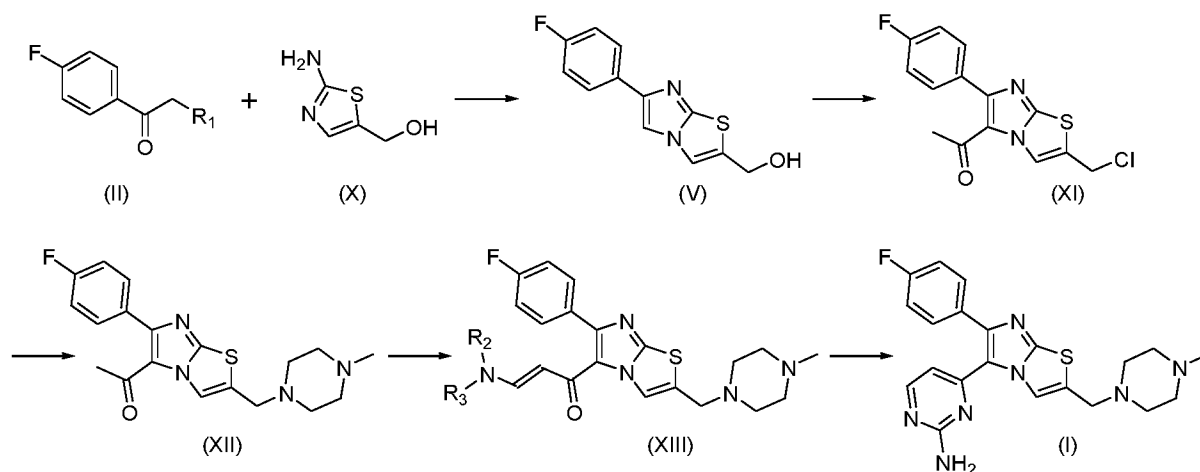
wherein R^2 and R^3 are independently C_1 to C_5 alkyl, preferably methyl; and

- b. converting the compound of Formula (XIII) to the compound of Formula (I).
- 10 In another embodiment, the process further comprises cyclocondensing the compound of Formula (XIII) with guanidine or a guanidinium salt to yield the compound of Formula (I).

Detailed Description

- 15 Applicants have developed a novel and efficient synthesis of (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl]imidazo[2,1-b]thiazol-5-yl]-pyrimidine of Formula (I) (scheme 2a). This method has a reduced number of steps and higher yields than the prior art methods of synthesizing this compound and is thus amenable to preparation of compound of Formula (I) on large scale.

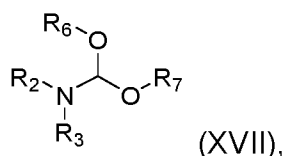
Scheme 2a – An embodiment of the invention



The cyclocondensation reaction leading to compound (V) is performed by reacting aminothiazolylmethanol (X) or a salt thereof with an acetophenone of Formula (II) bearing a leaving group R_1 . In one aspect of the invention, the leaving group R_1 is either halogen such as bromine, chlorine, iodine or a sulfonate such as mesylate or tosylate. In a subclass of the invention, R_1 is bromine or chlorine. The reactants are first stirred at ambient temperature in an organic solvent prior to the addition of a base. In an embodiment of the invention, the base is a trialkylamine such as *N*-methylmorpholine, ethyldiisopropylamine or triethylamine. In another embodiment of the invention, the base is triethylamine. The conversion of compound (V) into compound (XI) is achieved in the presence of an excess of acetyl chloride in an aprotic solvent at elevated temperature. In an embodiment of the invention, the excess of acetyl chloride is more than 1 equivalent. In an alternative embodiment, the excess of acetyl chloride is at least 2 equivalents. In another embodiment of the invention the excess of acetyl chloride is at least 3 equivalents. In another embodiment, the excess of acetyl chloride is at least 4 equivalents. In another embodiment, the excess of acetyl chloride is at least 5 equivalents. In one aspect of the invention the conversion is achieved under normal pressure. In another aspect of the invention the conversion is achieved under pressurized conditions with the pressure between about 1.5 bar and about 3.5 bar. In one part of the invention, the solvent is dioxane, THF, Methyl-THF, toluene, mesitylene, xylene, DMF, DMA or NMP. In an embodiment, the reaction temperature is between about 65 °C and about 200 °C. In a

sub-part of the invention, the solvent is NMP and the reaction temperature is between 130 and 160 °C.

The amination step towards compound (XII) is achieved by reacting compound (XI) with *N*-methylpiperazine or a salt thereof in the presence of a base. In one aspect of the invention, the base is potassium carbonate, potassium bicarbonate, sodium carbonate or sodium bicarbonate. In a sub-aspect of the invention, the base is potassium carbonate. A condensation reaction between compound (XII) or a salt thereof and a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent leads to compounds of formula (XIII). In one part of the invention the condensation is performed under normal pressure. In another part of the invention the condensation reaction is operated under pressurized conditions between about 1.3 bar and about 2.8 bar. In a part of the invention the 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent is 1,1-dimethoxy-*N,N*-dimethylmethanamine, 1,1-diethoxy-*N,N*-dimethylmethanamine, 1,1-dipropoxy-*N,N*-dimethylmethanamine, 1,1-diisopropoxy-*N,N*-dimethylmethanamine, 1-(dimethoxymethyl)pyrrolidine or 4-(dimethoxymethyl)morpholine. In a sub-part of the invention, the 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent is 1,1-dimethoxy-*N,N*-dimethylmethanamine. In an embodiment, the 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent is a compound of Formula (XVII)

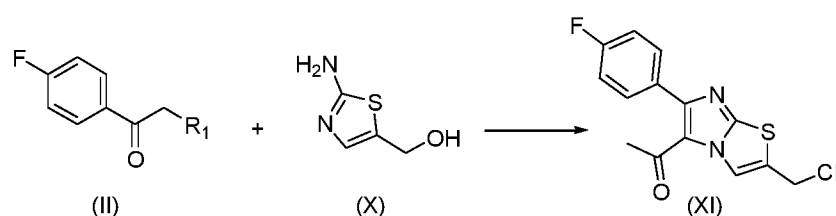


wherein R_2 , R_3 , R_6 and R_7 are each independently $\text{C}_1\text{-C}_5$ alkyl and wherein R_2 and R_3 may optionally form a ring taken together.

A cyclocondensation of guanidine or a guanidinium salt with a compound of formula (XIII) allows the formation of compound (I). In a part of the invention the guanidinium salts is guanidine hydrochloride, guanidine hydrobromide, guanidine sulfate, guanidine carbonate or guanidine phosphate. In a sub-part of the invention, the guanidinium salt is guanidine hydrochloride, guanidine hydrobromide or guanidine carbonate.

In addition, it has been discovered that the efficiency of the new synthetic pathway of scheme 2a can be further potentiated by performing two consecutive transformations without isolation of the intermediates. As illustrative examples of such telescoped processes, compound of Formula (XI) can be prepared from compounds of Formula (II) and (X) (scheme 2b) and the conversion of compound of Formula (XII) or a salt thereof into compound of Formula (I) can also be achieved in a single step (scheme 2c).

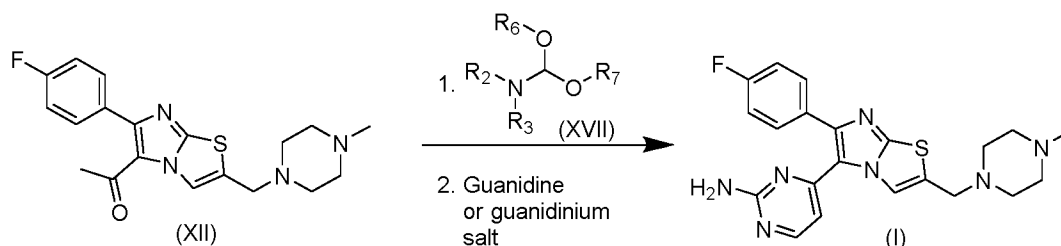
Scheme 2b



The conversion of compound (II) into compound (XI) is achieved by reacting a compound of Formula (II) with compound (X). The substitution reaction is performed at ambient temperature prior to the addition of a base. In an embodiment of the invention, the base is a trialkylamine such as *N*-methylmorpholine, ethyldiisopropylamine or triethylamine. In another embodiment of the invention, the base is triethylamine. After removal of the ammonium salts derived from the base, the condensation reaction is achieved at elevated temperatures. The resulting product is not isolated but rather is directly converted into compound (XI) in the presence of acetyl chloride in an aprotic solvent at elevated temperature. In a part of the invention, an excess of acetyl chloride is engaged in the reaction. In a sub-part of the invention at least 3 equivalents of acetyl chloride are engaged in the reaction. In an alternative embodiment, 4 equivalents of acetyl chloride are used. In another embodiment of the invention, 5 equivalents of acetyl chloride are reacted. In an embodiment, the conversion is achieved under normal pressure. In another aspect of the invention the conversion is achieved under pressurized conditions wherein the pressure is between about 1.5 bar to about 3.5 bar. In one part of the invention, the solvent is dioxane, THF, Methyl-THF, toluene, mesitylene, xylene, DMF, DMA or NMP. In an embodiment, the reaction temperature is between about 65 °C and about 200 °C.

In a sub-part of the invention, the solvent is NMP and the reaction temperature is between 130 and 160 °C.

Scheme 2c



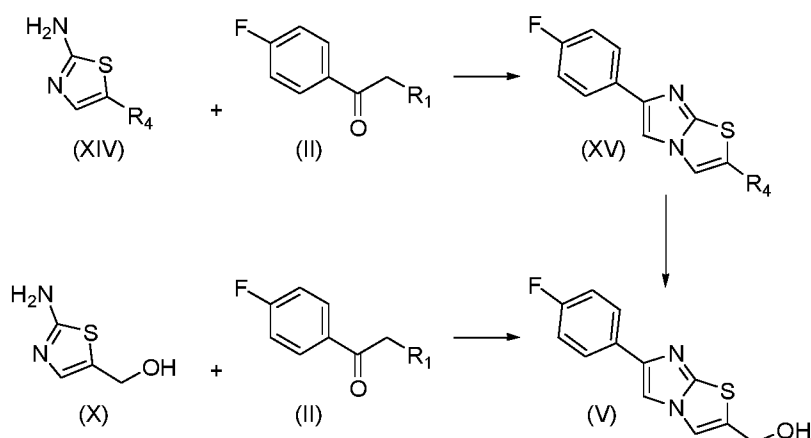
- 5 The conversion of compound (XII) or a salt thereof into compound (I) is achieved in one step by first reacting compound (XII) or a salt thereof with a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent (Compound (XVII) wherein R_2 , R_3 , R_6 and R_7 are each independently C_1 - C_5 alkyl, and wherein R_2 and R_3 may optionally form a ring taken together. R_2 , R_3 , R_6 and R_7 are each preferably methyl) in an organic solvent at elevated
- 10 temperature and in a second part of the experiment by adding a second organic solvent and either guanidine or a salt thereof to the reaction mixture to react further at elevated temperature. In an embodiment, the reaction temperature is between 65°C and 200 °C. Removal of the volatiles and recrystallization from a mixture of organic solvents deliver pure compound (I). In a part of the invention, the organic solvent used in the first part of
- 15 the experiment is DMF, DMA or NMP. In a sub-part of the invention, the organic solvent is DMA. In a class of the invention, the 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent is 1,1-dimethoxy-*N,N*-dimethylmethanamine, 1,1-diethoxy-*N,N*-dimethylmethanamine, 1,1-dipropoxy-*N,N*-dimethylmethanamine, 1,1-diisopropoxy-*N,N*-dimethylmethanamine, 1-(dimethoxymethyl)pyrrolidine or 4-(dimethoxymethyl)morpholine. In a sub-class of the
- 20 invention, the 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent is 1,1-dimethoxy-*N,N*-dimethylmethanamine. In one aspect of the invention, the organic solvent used in the second part of the reaction is an alkyl alcohol such as ethanol, propanol or isopropanol. In one embodiment of the invention, guanidine or a salt thereof such as guanidine hydrochloride, guanidine hydrobromide, guanidine sulfate, guanidine carbonate or

guanidine phosphate is added in the second part of the experiment for synthesizing compound (I).

In a sub-aspect of the invention, the organic solvent used in the second part of the experiment is ethanol. In one embodiment of the invention, the recrystallization of the crude product is performed using a mixture of ethyl acetate and of isopropanol.

As part of the present invention, new more efficient methods for preparing the compound of Formula (V) have been discovered. When compared to the prior art methods, the novel syntheses are either shorter and/or allow to isolate the intermediate of Formula (V) in higher yields (scheme 3).

10 Scheme 3 – Methods of producing Compound (V) of Scheme 2



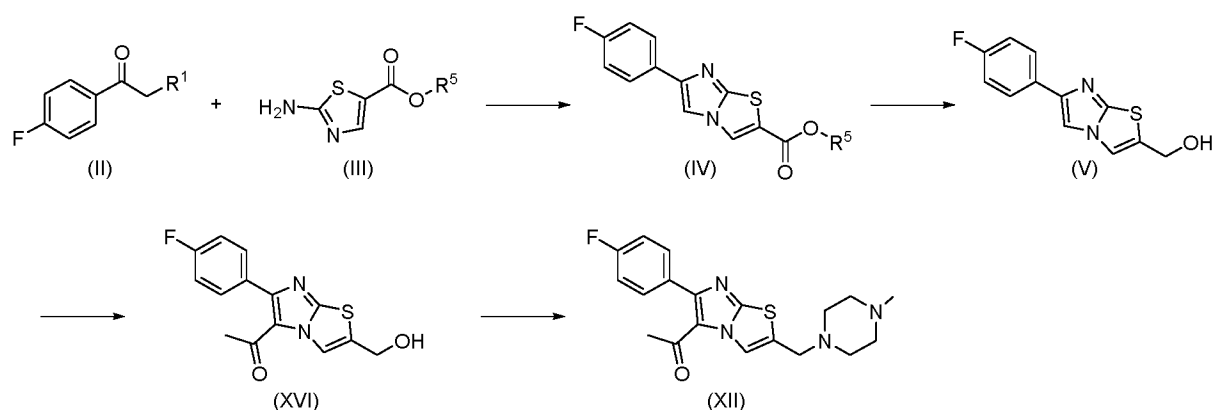
A cyclocondensation step of an aminothiazole of Formula (XIV) or a salt thereof with an acetophenone of Formula (II) bearing a leaving group R₁ leads to compounds of Formula (XV). In one aspect of the invention, the leaving group R₁ is halogen such as bromine, chlorine, iodine or a sulfonate such as mesylate or tosylate. In a sub-class of the invention, R₁ is bromine or chlorine. In another part of the invention, the substituting group R₄ is bromine or chlorine. In a sub-part of the invention, R₄ is bromine. In a further part of the invention, the cyclocondensation step towards compounds of Formula (XV) is performed in a polar non-protic organic solvent such as NMP, DMF or DMA. In cases where a salt of an aminothiazole (XIV) is engaged in the cyclocondensation step, a base such as sodium bicarbonate, potassium bicarbonate, potassium phosphate tribasic, 2,6-lutidine,

ethyldiisopropylamine or triethylamine is added to the reaction mixture. In a sub-case of the invention this base is sodium bicarbonate. The alkylation of compounds of Formula (XV) to compound (V) is performed in the presence of a strong base and of either formaldehyde or paraformaldehyde. In a class of the invention, the strong base is an alkylmagnesium halide, a lithium chloride complex thereof or an alkyl lithium. In a sub-class of the invention, the base is isopropylmagnesium chloride, *sec*-butylmagnesium chloride, isopropylmagnesium chloride lithium chloride complex or butyl lithium. In a further sub-class of the invention, the base is isopropylmagnesium chloride.

Alternative embodiment

- 10 In an alternative embodiment of the invention, compound (XII) can also be prepared from an intermediate of Formula (XVI). Compound (XVI) is derived from compound (V) which is obtained by the reduction of an intermediate of Formula (IV) (scheme 5).

Scheme 5

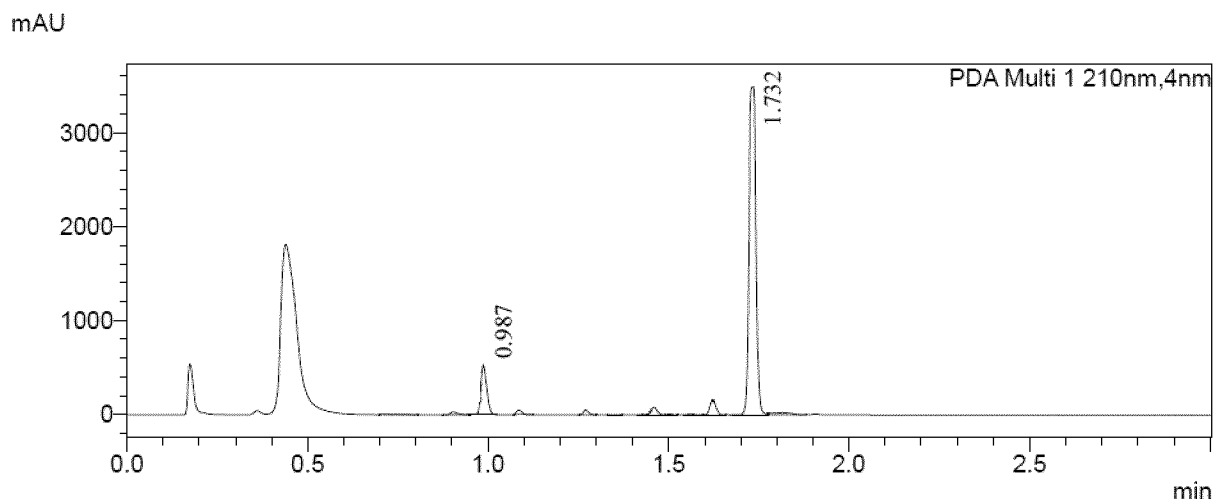


- 15 In an embodiment of the invention, the R_5 substituent is chosen from C_2 to C_5 alkyl. In a sub-embodiment of the invention, the R_5 substituent is chosen from C_2 to C_3 alkyl. In a further sub-embodiment of the invention, the R_5 substituent is C_2 alkyl.

As mentioned earlier, when the aminothiazole (IIIa) (R_5 is C_1 alkyl) is reacted with a compound of Formula (II), as it is known from the literature, the synthesis of the product of Formula (IVa) is accompanied by the formation of the corresponding acid as a side product. This side reaction does not only lower the yield but also complicates the

purification protocol. An illustrative example of a UV-chromatogram of a crude mixture of product (IVa) is shown in scheme 5a. Compound (IVa) at ret. time 1.732 min and parent acid side product at ret. time 0.987 min (solvent at retention. time about 0.45 min).

Scheme 5a – UV chromatogram of crude product (IVa) prepared from (II) and (IIIa)

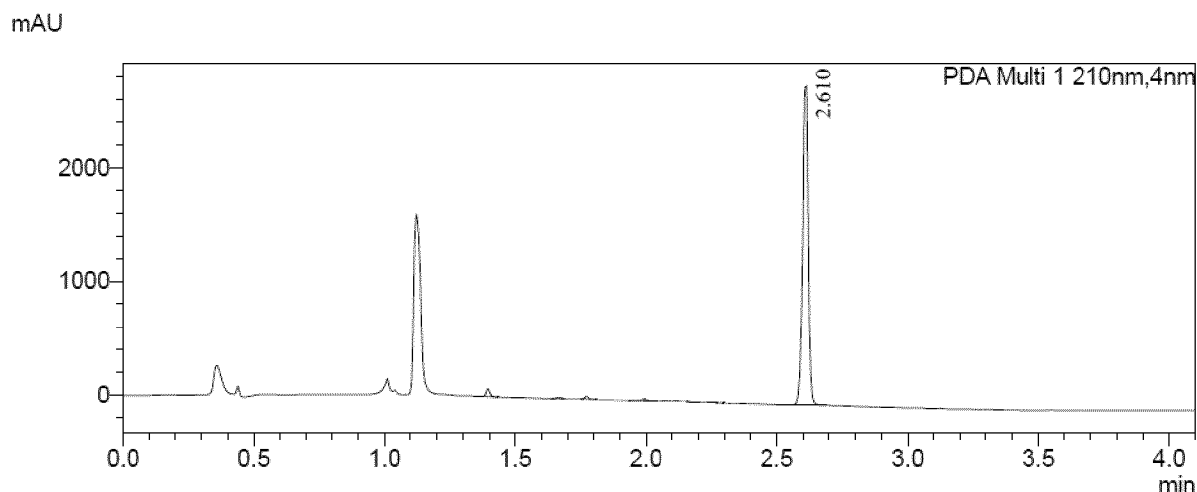


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Surprisingly, it has now been discovered that when a compound of Formula (III) where R_5 substituent is chosen from C_2 to C_5 alkyl is engaged in the same reaction, the formation of the acid side product previously observed when R_5 is C_1 alkyl does not take place. An illustrative example of a UV-chromatogram of a crude product of Formula (IVb) where R_5 is C_2 alkyl is shown in scheme 5b and attest for the absence of the acid side product at ret. time 0.987 min. Compound (IVb) at ret. time 2.610 min (solvent at ret. time about 1.15 min).

10

Scheme 5b – UV chromatogram of crude product (IVb) prepared from (II) and (IIIb)

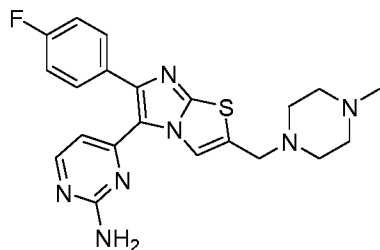


In a class of the invention, the reduction of a compound of Formula (IV) into compound (V) is performed in the presence of a reducing agent such as lithium aluminum hydride, diisobutyl aluminum hydride or sodium borohydride. In a part of the invention, the reducing agent is optionally associated to a Lewis acid. In a sub-part of the invention, the Lewis acid is selected from boron trifluoride diethyl etherate; zinc chloride or aluminum chloride. In a class of the invention, the reduction is performed in an organic solvent such as methanol, ethanol, isopropanol or tetrahydrofuran. In a sub-class of the invention, the organic solvent is either isopropanol or tetrahydrofuran. In an embodiment of the invention, the reduction is performed in the presence of sodium borohydride and of aluminum chloride in tetrahydrofuran.

In a part of the invention, the intermediate of Formula (XVI) is obtained by reacting compound (V) with acetic anhydride and by adding an aqueous solution of a base during the workup procedure. In a sub-part of the invention, the base is sodium hydroxide or potassium hydroxide.

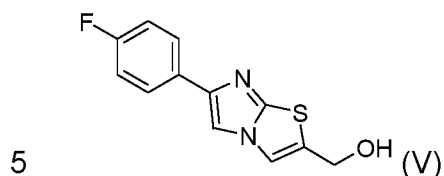
In an embodiment of the invention, the conversion of compound (XVI) into the intermediate (XII) is achieved by converting the alcohol group in Formula (XVI) into a sulfonate such as a tosylate or a mesylate and by reacting the sulfonate with *N*-methylpiperazine. In a sub-embodiment of the invention, the sulfonate is a mesylate. In a part of the invention, the conversion of the alcohol into the corresponding mesylate is performed at low temperature preferably at 0 °C.

An embodiment of the invention is a process to prepare a compound of Formula (I)

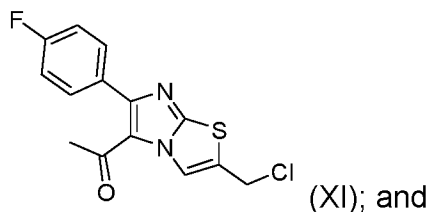


comprising

a. reacting a compound of Formula (V)



with acetyl chloride in an organic solvent to form a compound of Formula (XI).

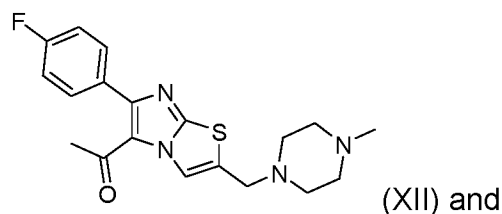


b. converting the compound of Formula (XI) to the compound of Formula (I).

10 In another embodiment, the solvent is selected from dioxane, THF, Methyl-THF, toluene, mesitylene, xylene, DMF, DMA and NMP, preferably, mesitylene, xylene or NMP, most preferably NMP.

In another embodiment, the process further comprises

c. reacting the compound of Formula (XI) with 1-methyl piperazine in the presence of a base to form the compound of Formula (XII)



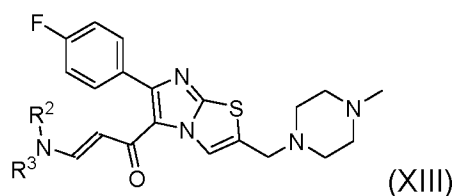
d. converting the compound of Formula (XII) to the compound of Formula (I).

In another embodiment, the base is selected from sodium carbonate, sodium bicarbonate, potassium bicarbonate, ethyldiisopropylamine, triethylamine or potassium carbonate,
5 preferably potassium carbonate.

In another embodiment, a solvent is used in step c and the solvent is selected from NMP, acetonitrile or dichloromethane, preferably acetonitrile and dichloromethane, most preferably acetonitrile.

In an additional embodiment, the process further comprises

- 10 a. reacting the compound of Formula (XII) with a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent, preferably 1,1-dimethoxy-*N,N*-dimethylmethanamine to form the compound of Formula (XIII).



wherein R^2 and R^3 are independently C_1 to C_5 alkyl, preferably methyl; and

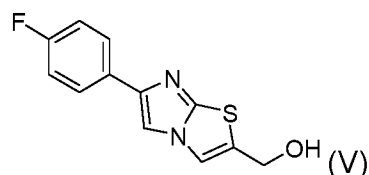
- 15 b. converting the compound of Formula (XIII) to the compound of Formula (I).

In an additional embodiment, a solvent is used in step a and the solvent is selected from *N,N*-dimethylacetamid, acetonitrile, THF, 1,1-dimethoxy-*N,N*-dimethylmethanamine, preferably acetonitrile and 1,1-dimethoxy-*N,N*-dimethylmethanamine, most preferably 1,1-dimethoxy-*N,N*-dimethylmethanamine.

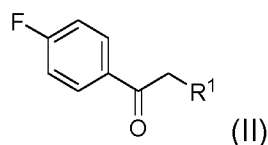
In an additional embodiment, the process further comprises cyclocondensing the compound of Formula (XIII) with guanidine or a guanidinium salt to yield the compound of Formula (I).

In an additional embodiment, the reaction is conducted in the presence of a base which
5 is selected from potassium carbonate and sodium ethoxide, preferably sodium ethoxide.

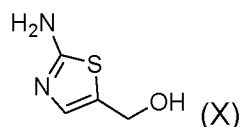
In an additional embodiment, the compound of Formula (V)



is formed by the process comprising reacting the compound of Formula (II)

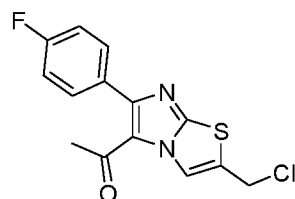


10 wherein R¹ is selected from halogen or sulfonate, preferably bromine, chlorine, iodine, mesylate or tosylate, with the compound of Formula (X)



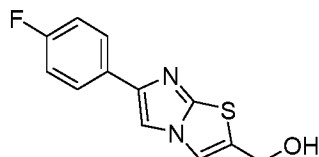
to yield the compound of Formula (V).

Another embodiment is a process to produce the compound of Formula (XI)



15

comprising reacting a compound of Formula (V)

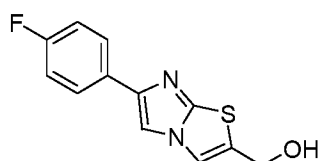


with acetyl chloride to form a compound of Formula (IV).

In an additional embodiment, the reaction to form the compound of Formula (XIII) is followed directly by the cyclocondensation reaction to form the compound of Formula (I) without isolation or purification of the compound of Formula (XIII).

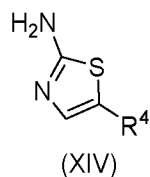
In an additional embodiment, the reaction to form the compound of Formula (V) is followed directly by reacting the compound of Formula (V) with acetyl chloride to form the compound of Formula (XI) without isolation or purification of the compound of Formula (V).

In another embodiment, the compound of Formula (V)



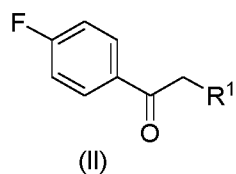
is formed by the process comprising

a. reacting a compound of Formula (XIV)



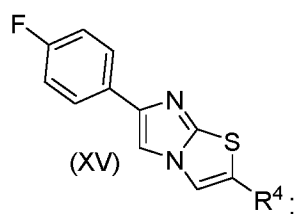
wherein R⁴ is bromo or chloro

with a compound of Formula (II)



wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate.

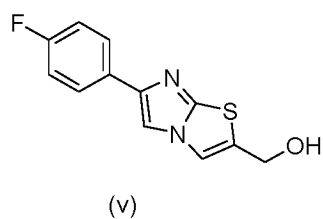
5 to yield the compound of Formula (XV)



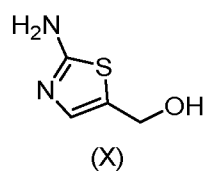
and

b. reacting the compound of Formula (XV) with isopropyl magnesium chloride and formaldehyde yield the compound of Formula (V).

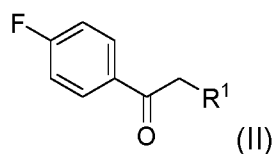
10 In an additional embodiment, the compound of Formula (V)



is formed by the process comprising reacting a compound of Formula (X)



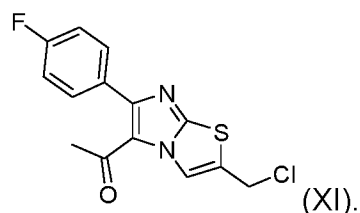
with a compound of Formula (II)



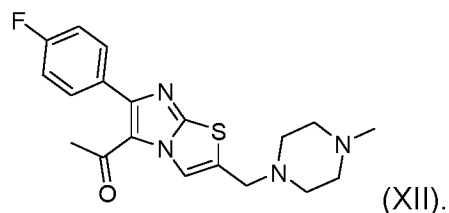
wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate.

5 to yield the compound of Formula (V).

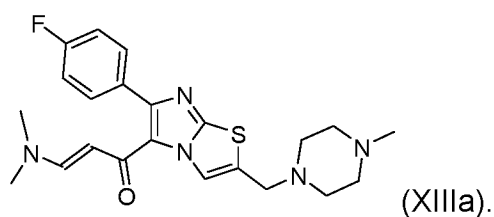
Another embodiment of the invention is a compound of Formula (XI)



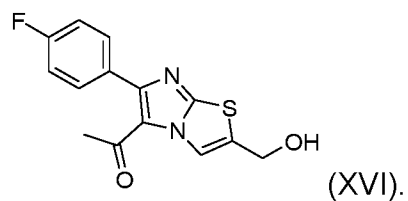
Another embodiment of the invention is a compound of Formula (XII)



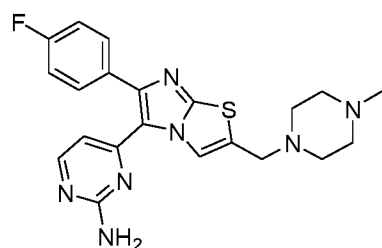
10 Another embodiment of the invention is a compound of Formula (XIII)



Another embodiment of the invention is a compound of Formula (XVI)

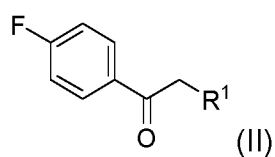


Another embodiment of the invention is a process to prepare a compound of Formula (I)



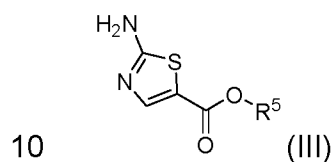
comprising

- 5 a. reacting a compound of Formula (II)



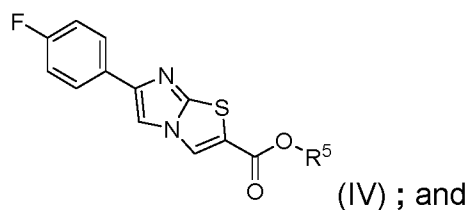
wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate,

with a compound of Formula (III)



wherein R⁵ is hydrogen, C₁ to C₅ alkyl, preferably C₂ to C₃, most preferred C₂.

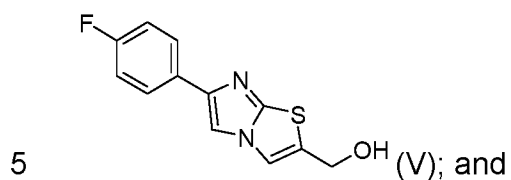
to yield a compound of Formula (IV)



- b. converting the compound of Formula (IV) to the compound of Formula (I).

In another embodiment, the process further comprises

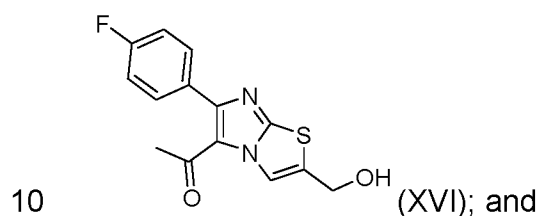
- a. reducing the compound of Formula (IV) to a compound of Formula (V)



- b. converting the compound of Formula (V) to the compound of Formula (I).

In another embodiment the process further comprises

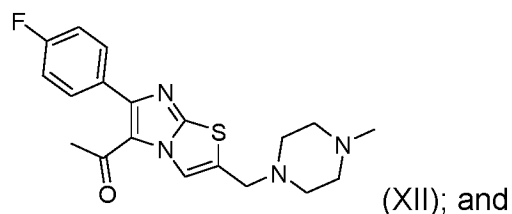
- a. reacting a compound of Formula (V) with acetic acid anhydride followed by saponification to form a compound of Formula (XVI)



- b. converting the compound of Formula (XVI) to the compound of Formula (I).

In another embodiment the process further comprises

- a. reacting the compound of Formula (XVI) with mesyl chloride followed by 1-methyl piperazine in the presence of a base to form the compound of Formula (XII) or salt thereof.



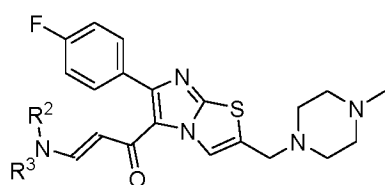
b. converting the compound of Formula (XII) to the compound of Formula (I).

In additional embodiment, the base is potassium carbonate or trimethylamine, preferably triethylamine.

5 In another embodiment, the salt of the compound of Formula (XII) is the dihydrochloride salt.

In another embodiment the process further comprises

a. reacting the compound of Formula (XII) with a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent, preferably 1,1-dimethoxy-*N,N*-dimethylmethanamine to
10 form the compound of Formula (XIII)

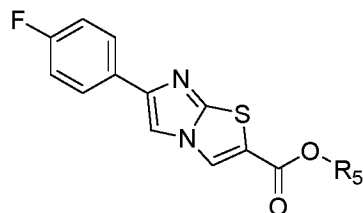


(XIII)

wherein R^2 and R^3 are independently C_1 to C_5 alkyl, preferably methyl; and

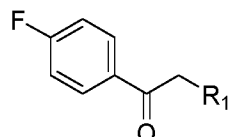
b. cyclocondensing the compound of Formula (XIII) with guanidine or a guanidinium
15 salt to yield the compound of Formula (I).

Another embodiment of the invention is a process to prepare a compound of Formula (IV) comprising



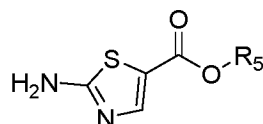
(IV)

reacting a compound of Formula (II)



5 (II)

with a compound of Formula (III)



(III)

to yield the compound of Formula (IV)

10 wherein R₁ is bromine or chlorine and R₅ is C₂ to C₅ alkyl, preferably C₂ alkyl.

Guanidine hydrochloride is also known as carbamimidoylazanium chloride (CAS # 50-01-1). Guanidine is also available as a free base and in other salt forms such as hydrobromide (CAS # 19244-98-5), hydrochloride (CAS # 50-01-1), sulfate (CAS # 594-14-9), carbonate (CAS # 593-85-1) and phosphate (CAS # 1763-07-1).

15 NMP is *N*-methyl-2-pyrrolidone (CAS # 872-50-4).

DMA is *N,N*-dimethylacetamide (CAS # 127-19-5).

DMF is *N,N*-dimethylformamide (CAS # 68-12-2).

THF is tetrahydrofuran (CAS # 109-99-9).

Diatomaceous earth (sometimes referred to by trademarked brand names such as Celite) is used in chemistry as a filtration aid, to filter very fine particles that would otherwise pass through or clog filters.

5 Methyl *tert*-butyl ether (also known as MTBE and *tert*-butyl methyl ether) is a solvent with a structural formula $(\text{CH}_3)_3\text{COCH}_3$ (CAS # 1634-04-4).

Methylene chloride (DCM, or dichloromethane) is a geminal organic compound with the formula CH_2Cl_2 (CAS # 75-09-2).

HPLC methods:

Method A

- 10
- Instrument: Agilent Technologies UHPLC/MSD 6130 B Series 1290
 - Column: Waters Column XP, 2.1 x 50mm Xbridge BEH C18 2.5 μ , T = 40 °C
 - Eluents: A: acetonitrile with 0.05 % (vol./vol.) formic acid. B: water with 0.05 % formic acid (vol./vol.)
 - Flow: 0.8 mL/min
- 15
- Gradient: From 2 to 100 % eluent A in 1.2 min, 0.5 min 100 % eluent A
 - Run time: 2.5 min
 - Detection: ESI/MS, positive and negative ions, Scan: 100-600 m/z; UV at 254 and 210 nm

Method B

- 20
- Instrument: Agilent Technologies UHPLC/MSD 6130 B Series 1290
 - Column: Waters Column XP, 2.1 x 50mm Xbridge BEH C18 2.5 μ , T = 40°C
 - Eluent A: acetonitrile; Eluent B: water with 0.1% (vol./vol.) ammonia
 - Flow: 0.8 mL/min

- Gradient: From 2% eluent A to 100% eluent A in 1.2 min, 0.5 min 100% eluent A
- Run time: 2.2 min
- Detection: ESI/MS, positive ions, Scan: 100-600 m/z; UV at 254nm and 210nm

Method C

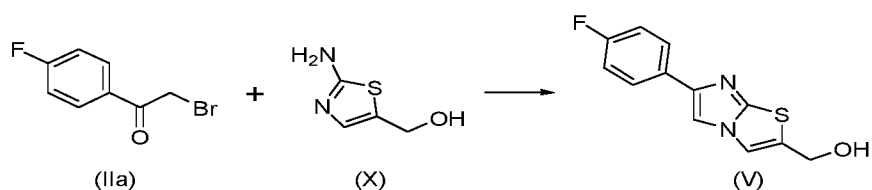
- 5
- Instrument: Agilent 1290 Infinity
 - Column: Ascentis Express C18 10x2.1 mm, 2.7 μ m, T = 40 °C
 - Eluent A: 0.1% formic acid (vol./vol.) in water, Eluent B: 0.1% formic acid (vol./vol.) in acetonitrile
 - Flow: 1.0 mL/min
- 10
- Gradient: 10 to 95% B over 6 min, then 2 min hold 95% B, then 95 to 10% B over 0.1 min, then 1.9 min hold at 10%B
 - Run time: 10 min
 - Detection: AJS ESI, positive ions, Scan: 100 to 1000 m/z, UV at 210 nm and 254 nm

15 Method D

Same as method C but gradient 10 to 50% B over 6 min, then 50 to 95% B over 0.3 min, then 1.7 min hold 95%B, then 95 to 10% B over 0.1 min, then 1.9 min hold at 10%B.

- 20
- ^1H - and ^{13}C -NMR-data were recorded either with a Bruker Avance III 300 spectrometer (^1H -NMR: 300 MHz; ^{13}C -NMR: 75 MHz) equipped with a PA BBO 300S1 BBF-H-D-05-Z probe head or with a Bruker Avance III HD 600 spectrometer (^1H -NMR: 600 MHz; ^{13}C -NMR: 150 MHz) equipped with a CPP BBO 600S3 BB-H&F-D-05 Z ET probe head

Examples

Preparation of (6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol

(2-Aminothiazol-5-yl)methanol (100 g, 755 mmol) was dissolved in *N*-methylpyrrolidone
5 (700 mL), 2-bromo-1-(4-fluorophenyl)ethanone (168 g, 770 mmol) was added and the
reaction mixture was stirred over night at room temperature. After cooling to below 20°C
triethylamine (111 mL, 793 mmol) was added dropwise and the resulting reaction mixture
was allowed to reach room temperature and was stirred for 1 h. The formed precipitates
were separated by filtration and washed with NMP (100 ml). The clear filtrate was heated
10 to 105°C and stirred for 100 min. The reaction mixture was cooled down to room
temperature and was slowly poured into water (4 L) to induce precipitation. The mixture
was aged at room temperature overnight. The formed precipitate was collected by
filtration, washed with cold water (3 x 1 L), pre-dried by suction and finally dried under
reduced pressure at 40°C in a drying oven to afford crude desired product (168.8 g, 600
15 mmol).

Crude (6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol (168 g, 597 mmol) was
suspended in a 7:3 (v/v) mixture of ethanol / water (800 mL) and the resulting mixture
was heated to 90°C until a clear solution was obtained. Heating was stopped and the
mixture was allowed to slowly cool down to room temperature under stirring. The mixture
20 was aged in an ice bath for 1 h. The formed precipitate was collected by filtration, the wet
cake was washed with a 7:3 (v/v) mixture of ethanol / water (300 mL), pre-dried by suction
and was finally dried under reduced pressure at 40°C in a drying oven.

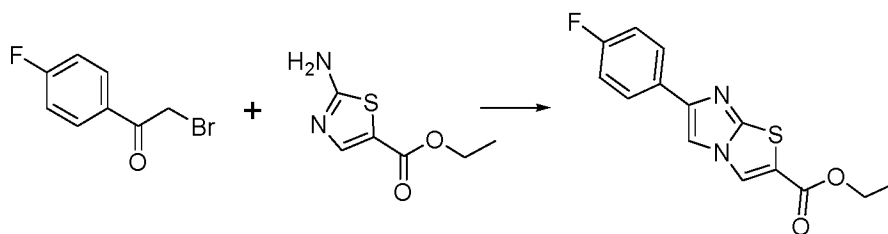
The mother liquor and the washing liquor are combined and evaporated to dryness,
dissolved in hot ethanol (160 mL) and charcoal is added (5 g). The mixture is heated to
25 reflux for 30 minutes and hot filtrated over a Celite bed. The filtrate is evaporated to

dryness and the precipitate is recrystallized from ethanol/water 7:3 v/v (160 mL). After filtration the precipitate is washed with cold ethanol/water 7:3 v/v (80 mL). pre-dried by suction and finally dried under reduced pressure at 40°C in a drying oven (136 g, 537 mmole)

- 5 ^1H NMR (600 MHz, DMSO) δ (ppm): 8.15 (1H, s), 7.91 - 7.72 (3H, m), 7.21 (2H, J = 8.9 Hz, t), 5.68 (1H, J = 5.8 Hz, t), 4.60 (2H, J = 5.8 Hz, dd).

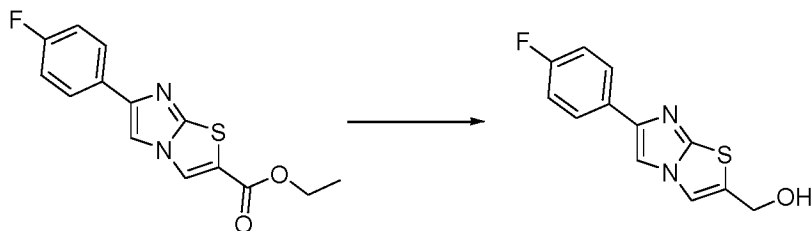
LC/MS (Method A): R_t = 0.78 min, m/z 249

Alternative preparation of (6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol



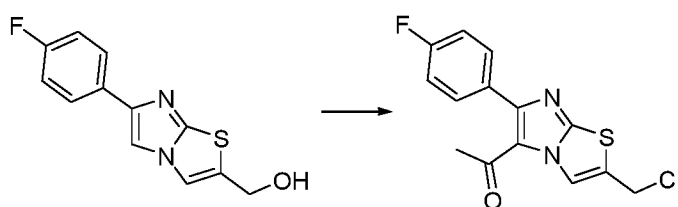
- 10 Step 1: to a clean reactor under an inert atmosphere was charged ethyl 2-aminothiazole-5-carboxylate (1.70 kg, 9.88 mol) *N*-methylpyrrolidone (17 L) followed by 2-bromo-1-(4-fluorophenyl)ethan-1-one (2.14 kg, 9.88 mol). The reaction was aged at room temperature overnight. The reaction mixture was allowed to warm to 80°C followed by aging for an additional 3 h at this temperature. The mixture was then cooled to 0°C before
- 15 water (25.5 L) was added and the slurry aged for 30 min at 0°C. The slurry was then filtered and the cake washed with water (22 L). The obtained solid was dried to afford ethyl 6-(4-fluorophenyl)imidazo[2,1-b]thiazole-2-carboxylate as an off-white solid (2.47 kg, 8.30 mol).

- ^1H NMR (DMSO) δ (ppm) 8.73 (1H, s), 8.20 (1H, s), 7.88 (2H, dd, J = 5.4, 8.7 Hz), 7.22 (2H, t, J = 9.0 Hz), 4.31 (2H, q, J = 7.2 Hz), 1.30 (3H, t, J = 7.2 Hz).
- 20



Step 2: to a clean reactor under an inert atmosphere were charged ethyl 6-(4-fluorophenyl) imidazo[2,1-b]thiazole-2-carboxylate (2.32 kg, 7.99 mol) and tetrahydrofuran (23 L). The solution was cooled to 0°C and a 1.5 M solution of diisobutyl
 5 aluminum hydride in toluene (13.3 L, 19.9 mol) was added whilst maintaining the internal temperature at 0°C. The resulting mixture was aged at 0°C for an additional 2 h. The reaction mixture was added into aqueous 2 M hydrochloric acid (11.6 L) while maintaining an internal temperature below 10°C. Upon addition, the reaction mixture was then allowed to warm to room temperature and the two layers are separated. The organic phase was
 10 then diluted with toluene (20 L) and concentrated to a volume of about 10 L, This process was repeated three times until no tetrahydrofuran remained. The obtained slurry was filtered and the isolated solid was dried to give (6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol as a light yellow solid. (1.84 kg, 7.19 mol).

Preparation of 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone
 15



To a clean reactor under an inert atmosphere was charged (6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol (1.73 kg, 6.61 mol) followed by *N*-methylpyrrolidone (17 L). Acetyl chloride (3.61 kg, 46.27 mol) was charged to the vessel at room temperature
 20 and the solution was heated to 130-140 °C. The reaction mixture was aged at this temperature for 42 h. The reaction mixture was then cooled to 0 °C and 6 M NaOH (11.8 L) was added while maintaining the temperature below 20 °C. At the end of addition, the

pH reaches between 8-9. The resulting slurry was then diluted with water (5.2 L) and was aged for 1 h at room temperature. The mixture was cooled to below 15 °C and is filtered. The filter cake was washed with water (8.5 L) and with a 5 to 1 (vol./vol.) mixture of methanol and water (17 L). The resulting solid was dried to give 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone as a dark beige solid, (1.79 kg, 4.96 mol).

Alternative preparation of 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone

(6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol (10 g, 38.9 mmol) was dissolved in *N*-methylpyrrolidone (100 mL). Acetyl chloride (13.87 mL; 194 mmol) was added and the reaction mixture was heated to 160 °C. The conversion to 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone was monitored by HPLC and acetylchloride was added in case the conversion of the starting material was not complete. The reaction mixture was cooled to room temperature and was carefully added under ice bath cooling to a mixture of aqueous 6 M sodium hydroxide (70 mL) and water (430 mL) by keeping the temperature below 20°C. The suspension was aged overnight with stirring. The formed precipitate was collected by filtration, is washed with water (250 mL) until pH of the filtrate is neutral, the wet cake was pre-dried by suction and was finally dried under reduced pressure at 40°C in a drying oven to afford 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone as crude product (12.2 g, 33.2 mmol).

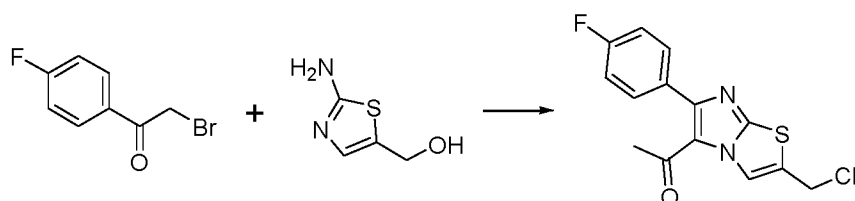
Crude 1-(6-(4-Fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone (6.1 g, 16.60 mmol) was dissolved in warm ethanol (120 mL), charcoal (1.2 g) was added and the mixture was heated to reflux under stirring for 30 min. The hot mixture was filtered through a Celite bed, the Celite bed was rinsed with hot ethanol (2 × 60 mL). The combined filtrates were evaporated to dryness under reduced pressure. The obtained solid was dissolved in a hot 9:1 (v/v) mixture of ethanol / water (85 mL). After a clear solution was obtained, the solution was allowed to slowly reach room temperature under stirring. The temperature was adjusted to below 5°C with the help of an ice bath and the mixture was stirred for 1 h at this temperature. The formed precipitate was collected by

filtration, the wet cake was washed with a 1:1 (v/v) mixture of ethanol / water (20 mL), was pre-dried by suction and was finally dried under reduced pressure at 40°C in a drying oven to afford pure 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone (4.4 g, 13.92 mmol).

- 5 ¹H NMR (600 MHz, DMSO) δ (ppm): 8.68 (1H, m), 7.74 - 7.64 (2H, m), 7.39 - 7.30 (2H, m), 5.19 (2H, s), 2.12 (3H, s).

LC/MS (Method A): R_t = 1.08 min; m/z 309

Alternative preparation of 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone



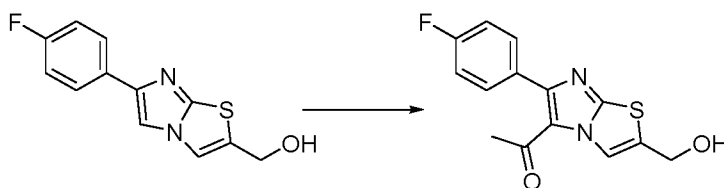
10

- (2-Aminothiazol-5-yl)methanol (10 g, 66.1 mmol) is dissolved in *N*-methylpyrrolidone (100 mL), 2-bromo-1-(4-fluorophenyl)ethan-1-one (15.84 g, 72.8 mmol) was added and the resulting mixture was stirred overnight at room temperature. After cooling to below 5°C triethylamine (11.06 mL, 79 mmol) was added dropwise and the mixture was aged at room temperature for 2 h. The formed precipitate was collected by filtration and the wet cake was rinsed with *N*-methylpyrrolidone (30 mL). The combined filtrates were diluted with *N*-methylpyrrolidone (50 mL), and the resulting mixture was heated to 105°C and reacted at this temperature for 2 h. After cooling to below 80 °C, acetyl chloride (25 mL, 350 mmol) was added. The reaction mixture was heated to 170 °C and was reacted at this temperature overnight. After 20 h reaction time the mixture was cooled to room temperature and was added dropwise to a pre-chilled mixture of aqueous 6 M sodium hydroxide (126 mL) and water (775 mL). The resulting suspension was aged at below 5°C for 1 h. The formed fine precipitate was collected by pressure filtration. The wet cake was washed with water (2 × 250 mL) and dried at 40°C in a drying cabinet under reduced pressure to afford the crude desired product.
- 15
- 20
- 25

The isolated crude product was dissolved in warm ethanol (370 mL). Charcoal (2.78g) was added and the mixture was heated to reflux for 30 min. The reaction mixture was hot filtrated over a Celite bed which was rinsed with hot ethanol (2 × 75 mL). The combined filtrates were evaporated to dryness. This procedure was repeated twice and a brown solid was isolated (14.2 g). The isolated solid was recrystallized from ethanol/water 90:10 (105 mL) and aged below 5°C for 2 h. The precipitate was separated by filtration, washed twice with cold ethanol/water 1:1 (100 mL each) and dried under reduced pressure at 40°C to afford 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone (7.88 g, 24.64 mmol).

LC/MS (Method A): R_t = 1.09 min; m/z 309

Preparation of 1-(6-(4-fluorophenyl)-2-(hydroxymethyl)imidazo[2,1-b]thiazol-5-yl)ethanone



(6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol (300 g; 1.21 mol) was suspended in a mixture of acetic anhydride (3.42 L, 36.2 mol) and sulfuric acid (64.4 mL, 1.21 mol) and the reaction mixture is heated to 135°C under stirring. The reaction mixture was aged at 135°C for 8 h. After cooling to room temperature, the brown reaction mixture was pressure filtered and the residue was rinsed twice with tetrahydrofuran (1 L each). The combined filtrates were evaporated under reduced pressure giving 5-acetyl-6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methyl acetate (304 g, 869 mmol) as crude product.

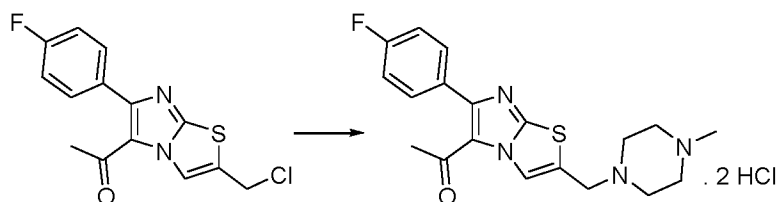
LC/MS (Method A): R_t = 1.02 min; m/z 333

The crude product (304 g, 869 mmol) was suspended in tetrahydrofuran (1.5 L). Aqueous 4N sodium hydroxide (1.1 L, 4.4 mol) was added and the mixture was stirred at 45°C for 3 h. After separation of the phases, the organic layer was washed with warm brine (700

mL). The organic layer was dried over sodium sulfate, was filtered and was concentrated to dryness under reduced pressure to afford pure 1-(6-(4-fluorophenyl)-2-(hydroxymethyl)imidazo[2,1-b]thiazol-5-yl)ethanone (164 g, 554 mmol).

LC/MS (Method A): R_t = 0.86; m/z 291

5 **Preparation of 1-(6-(4-fluorophenyl)-2-((4-methyl-piperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl) ethanone dihydrochloride**

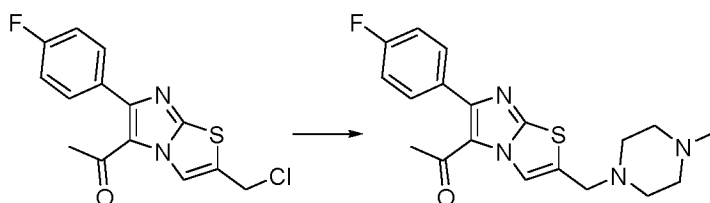


To a clean reactor under an inert atmosphere were charged 1-(6-(4-fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone (1.7 kg, 5.52 mol) and *N*-methylpyrrolidone (17 L). Methylpiperazine (0.56 kg, 6.62 mol) was then added followed by potassium phosphate (1.49 kg, 8.28 mol). The resulting mixture was allowed to age at room temperature for 18 h. The reaction mixture was then treated with aqueous 2 M hydrochloric acid (17 L) while maintaining an internal temperature between below 20 °C. After completion of the addition, a pH of 1 to 2 was usually recorded. The reaction mixture was then further diluted by the addition of water (17 L) and ethyl acetate (17 L) and the resulting mixture was filtered. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 x 17 L). The aqueous phase was then diluted by the addition of water (17 L) and ethylacetate (17 L) and the pH was adjusted to between 11-12 using aqueous 5 M NaOH while maintaining an internal temperature below 20 °C. The layers were separated and the aqueous phase was extracted with additional ethyl acetate (17 L). The combined organic streams were filtered by a polish filtration to remove insoluble material. The filtrate was then treated with a 4 M hydrochloric acid solution in methanol (8.5 L) which was added at a rate allowing to keep an internal temperature below 20 °C. The resulting solids were filtered and the cake was washed with methanol (8.5 L). The resulting solid was dried to afford 1-(6-(4-fluorophenyl)-2-((4-methyl-

piperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl) ethanone dihydrochloride as an off-white solid (1.64 kg, 4.22 mol).

¹H NMR (600 MHz, D₂O) δ (ppm): 8.52 (s, 1H), 7.45-7.39 (m, 2 H), 7.13 (t, 2 H, *J* = 6.6 Hz), 4.39 (s, 2 H), 3.85-3.02 (m, 8 H), 2.91 (s, 3H), 2.00 (s, 3H). ¹³C-NMR (D₂O) δ (ppm):
 190.1, 164.9, 162.4, 152.7, 150.9, 132.0, 131.9, 127.1, 124.7, 124.6, 124.0, 115.8, 115.6,
 52.9, 51.4, 48.6, 42.8, 27.7

Preparation of 1-(6-(4-fluorophenyl)-2-((4-methyl-piperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl) ethanone

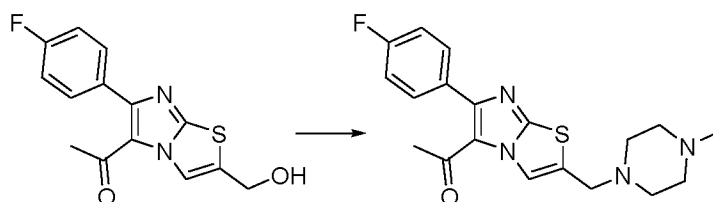


1-(6-(4-Fluorophenyl)-2-(chloromethyl)imidazo[2,1-b]thiazol-5-yl)ethanone (4.00 g, 12.67 mmol) was suspended in acetonitrile (80 mL) and the resulting mixture was warmed up to 55°C until a clear solution was obtained. Potassium carbonate (2.65 g, 19.17 mmol) was added, followed by 1-methylpiperazine (2.86 mL, 25.5 mmol). The reaction mixture was stirred between 53 and 55°C for 3 h and 45 min before cooling to room temperature.
 The solids were separated by filtration and were washed with acetonitrile. The filtrate was combined with the rinses and evaporated to dryness under reduced pressure. After a short time, crystallization of the viscous oil was observed. The crude product was dissolved in dichloromethane (50 mL) and the resulting solution was extracted with aqueous 0.5 M hydrochloric acid (2 × 50 mL). In the combined aqueous layers (pH < 1) a precipitate developed, which was separated by filtration. The filtrate was adjusted to pH 10 with aqueous 4 M sodium hydroxide, and was kept at a temperature below 15°C. A white precipitate formed, was separated by filtration, and was washed with water (50 mL), pre-dried by suction and finally dried under reduced pressure at 30°C in a drying oven to afford 1-(6-(4-fluorophenyl)-2-((4-methyl-piperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl) ethanone (3.88 g, 10.1 mmol).

^1H NMR (600 MHz, DMSO) δ (ppm): 8.40 (1H, s), 7.74 - 7.62 (2H, m), 7.40 - 7.27 (2H, m), 3.75 (2H, s), 2.41 - 2.23 (4H, m), 2.15 (3H, s), 2.10 (3H, s).

LC/MS (Method B): R_t = 1.00 min; m/z 373

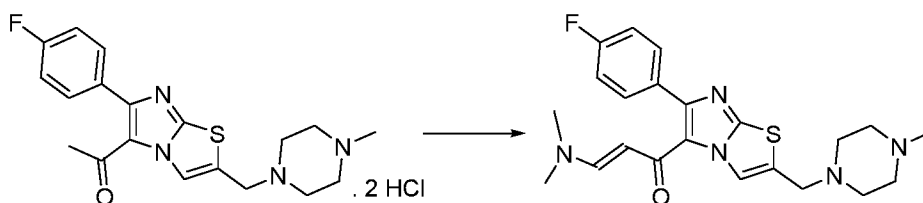
Alternative preparation of 1-(6-(4-fluorophenyl)-2-((4-methyl-piperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl) ethanone



1-(6-(4-Fluorophenyl)-2-(hydroxymethyl)imidazo[2,1-b]thiazol-5-yl)ethanone (164 g, 554 mmol) was suspended in dichloromethane (3.3 L) and triethylamine (231 mL, 1.66 mol) was added. The resulting suspension was cooled to 0°C and methanesulfonyl chloride (86 mL, 1.11 mol) was added dropwise within 20 min, while keeping the temperature of the reaction mixture below 3°C. After aging the reaction mixture for 1 h at 0°C, *N*-methylpiperazine (248 mL, 2.21 mol) was added dropwise within 15 min, while keeping the temperature of the reaction mixture below 3°C. The reaction mixture was aged at 0 to 3°C for 10 min, followed by aging overnight at room temperature. The reaction mixture was diluted with water (2.5 L) and the layers were separated. The organic layer was washed with aqueous half saturated sodium bicarbonate (2.5 L) and was concentrated under reduced pressure to afford 1-(6-(4-fluorophenyl)-2-((4-methyl-piperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl) ethanone (162 g, 418 mmol).

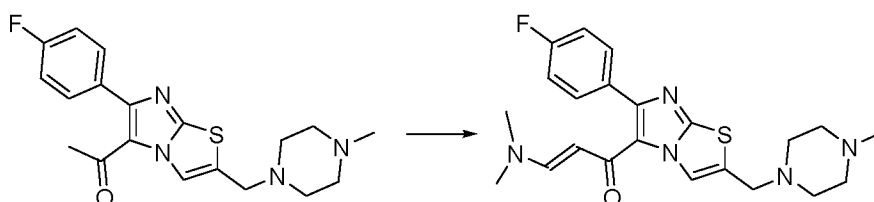
LC/MS (Method A): R_t = 0.70 min; m/z 373

Preparation of (*E*)-3-(dimethylamino)-1-(6-(4-fluorophenyl)-2-((4-methylpiperazin-1-yl) methyl) imidazo[2,1-b]thiazol-5-yl) prop-2-en-1-one



A mixture of 1-(6-(4-Fluorophenyl)-2-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl)ethan-1-one dihydrochloride (5 g, 11.0 mmol) and of a 25% (w/w) solution of sodium methoxide in methanol (7.14 g, 33.0 mmol) was stirred in ethanol (40 mL) for 10 min. 1,1-Dimethoxy-*N,N*-dimethylmethanamine (7.78 mL, 55.1 mmol) was added, the temperature was raised to 80 °C and the reaction mixture was stirred at this temperature for 16 h. The heating was stopped, the reaction mixture was allowed to reach room temperature and was filtered. The volume of the filtrate was reduced to about 20 mL and ethyl acetate (50 mL) and water (40 mL) were added. The obtained precipitate was filtered and dried under reduced pressure at 40 °C. The filtrate was decanted, the aqueous phase was extracted with ethyl acetate (50 mL) which was combined with the organic phase. The combined organic layers were concentrated under reduced pressure. The two crops were combined to afford (*E*)-3-(dimethylamino)-1-(6-(4-fluorophenyl)-2-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl)prop-2-en-1-one (4.57 g, 9.9 mmol).

Alternative preparation of (*E*)-3-(dimethylamino)-1-(6-(4-fluorophenyl)-2-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl)prop-2-en-1-one



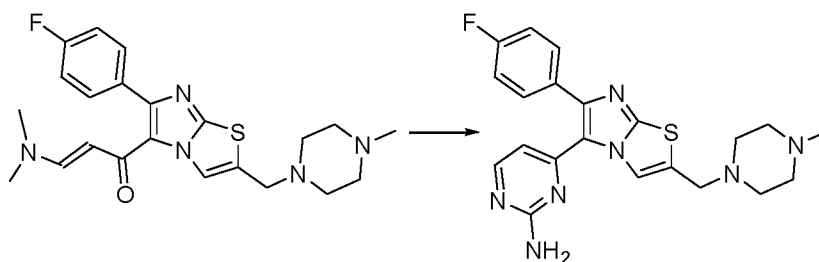
1-(6-(4-Fluorophenyl)-2-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl)ethan-1-one (3.0 g, 7.81 mmol) and 1,1-dimethoxy-*N,N*-dimethylmethanamine (38.6 mL, 273 mmol) were heated to 115°C and stirred over night. After cooling to room temperature the reaction mixture was stirred again over night. After cooling to below 5°C for 2 h, a precipitate formed, was separated by filtration, was washed with methyl-tert-

butylether and was dried by suction to afford (*E*)-3-(dimethylamino)-1-(6-(4-fluorophenyl)-2-((4-methylpiperazin-1-yl) methyl) imidazo[2,1-b]thiazol-5-yl) prop-2-en-1-one (2.70 g, 6.16 mmol).

¹H NMR (600 MHz, DMSO) δ (ppm): 8.33 (s, 1H), 7.64 (dd, J = 5.6, 8.8 Hz, 2H), 7.58 (d, J = 12.3 Hz, 1H), 7.29 (t, J = 8.9 Hz, 2H), 4.99 (d, J = 12.4 Hz, 1H), 3.73 - 3.69 (m, 2H), 3.04 (br s, 3H), 2.45 (br s, 3H), 2.42 - 2.23 (m, 4H), 2.16 (s, 3H).

LC/MS (Method B): R_t = 0.96 min; m/z 428

Preparation of (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl]imidazo[2,1-b]thiazol-5-yl]-pyrimidine



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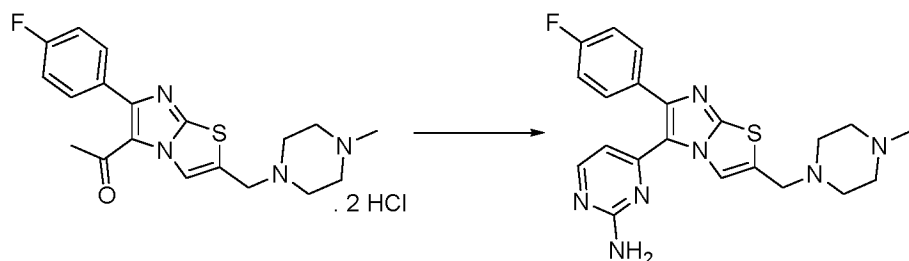
(*E*)-3-(Dimethylamino)-1-(6-(4-fluorophenyl)-2-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl)prop-2-en-1-one (1.00 g, 2.34 mmol) was dissolved in ethanol (10 mL), guanidine hydrochloride (1.12 g, 11.69 mmol) and sodium ethoxide (0.50 g, 7.02 mmol) were added and the reaction mixture was stirred at reflux for 2 h and 45 min. After cooling to room temperature, the suspension was stirred in an ice bath for 1 h. The formed precipitate was separated by filtration, was washed with methyl-*tert*-butylether, was pre-dried by suction and was finally dried under reduced pressure at 40°C in a drying oven. The crude product was suspended in a 10:1 (v/v) mixture of water/ethanol (10 mL) and was stirred at room temperature for 1 h. The solid was separated by filtration, was washed with water, was pre-dried by suction and finally dried under reduced pressure at 40°C in a drying oven to afford (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl] imidazo[2,1-b]thiazol-5-yl]-pyrimidine (0.86 g, 2.03 mmol).

20

^1H NMR (600 MHz, DMSO) δ (ppm): 8.83 (1H, s), 8.05 (1H, d, $J=5.3$ Hz), 7.64 - 7.61 (2H, m), 7.33 - 7.29 (2H, m), 6.95 - 6.75 (2H, b), 6.28 (1H, d, $J=5.3$ Hz), 3.72 (2H, s), 2.70 - 2.20 (8H, m), 2.17 (3H, s)

LC/MS (Method A): R_t = 0.643 min; m/z 424

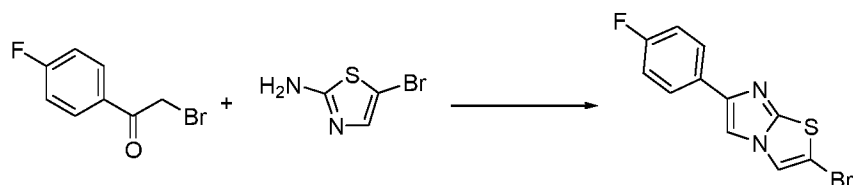
5 **Alternative preparation of (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl]imidazo[2,1-b]thiazol-5-yl]-pyrimidine**



To a clean reactor under an inert atmosphere were charged 1-(6-(4-fluorophenyl)-2-((4-methyl-piperazin-1-yl)methyl)imidazo[2,1-b]thiazol-5-yl) ethanone dihydrochloride (1560 g, 3.41 mol) and ethanol (13 L). A 25% w/w solution of sodium methoxide in methanol (2208 g, 10.22 mol) was added and the resulting mixture was stirred 10 min. 1,1-Dimethoxy-*N,N*-dimethylmethanamine (2028 g, 17.04 mol) was added and the mixture was then heated to 80 °C and was aged at this temperature for 24 h. The reaction mixture was allowed to cool to room temperature. Guanidine hydrochloride (1627 g, 17.04 mol), a 25% w/w solution of sodium methoxide in methanol (3681 g, 17.04 mol) and water (123 g, 6.82 mol) were charged to the reactor and the mixture was again heated to 80 °C. The reaction mixture was aged for an additional 4 h at this temperature before being allowed to cool to 60 °C and water (62.4 L) was added. The total volume was reduced from about 85 L to 70 L at about 40 °C in 4 h under reduced pressure. The resulting mixture was cooled to 20 °C. The solid formed was collected by filtration and the wet cake was washed with water (7.8 L). The solid was dried and was then slurried in methanol (10 L) for 2 h at 0 °C. After filtration, the cake was washed with methanol (1.25 L) and water (2.5 L). The solid was then dried to afford (2-amino-4-[6-(4-fluorophenyl)-2-[(4-methyl-1-piperazinyl)methyl]imidazo[2,1-b]thiazol-5-yl]-pyrimidine as an off-white solid (1188 g, 2.77 mol).

¹H-NMR (600 MHz, DMSO) δ (ppm): 8.82 (s, 1H), 8.04 (d, 1H, *J* = 5.3 Hz), 7.64 - 7.55 (m, 2H), 7.33 - 7.25 (m, 2H), 6.81 (br, 2H), 6.28 (d, 1H, *J* = 5.3 Hz), 3.72 (s, 2H), 2.71-2.21 (m, 8H), 2.17 (s, 3H). ¹³C-NMR (DMSO) δ (ppm): 163.9, 163.8, 161.4, 158.6, 156.3, 151.2, 147.1, 131.8, 131.8, 131.7, 131.7, 130.8, 120.9, 116.1, 115.9, 105.7, 55.2, 55.0, 52.9, 46.1.

Preparation of 2-bromo-6-(4-fluorophenyl)imidazo[2,1-b]thiazole

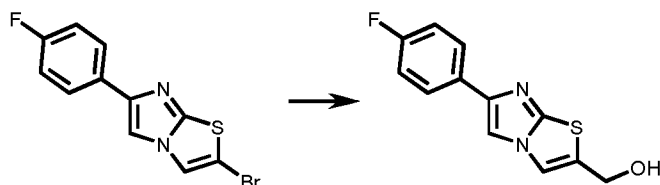


5-Bromothiazol-2-amine (2.50 g, 12.7 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (2.84 g, 12.7 mmol) were placed under nitrogen atmosphere and dry *N*-methylpyrrolidone (25 mL) was added. The resulting clear solution was stirred at ambient temperature over night. The reaction mixture was heated to about 100°C for 1 h, then cooled down to room temperature and placed into an ice bath. Aqueous 1M sodium hydroxide was added over 15 min while not exceeding a temperature of 10°C, until pH 11-12 was reached (about 15 mL were added). A precipitate formed. The mixture was diluted with water (35 mL) which was added with a dropping funnel over 35 min at 5°C. The resulting suspension was stirred at about 0°C for 40 min. The suspension was filtered and the solids were washed with water (7.5 mL). The wet cake was pre-dried by suction for 90 min, and then dried for 24 h under vacuum at 40 °C with a nitrogen sweep to afford 2-bromo-6-(4-fluorophenyl)imidazo[2,1-b]thiazole (3.57 g, 10.9 mmol).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.78-7.72 (m, 2H), 7.60 (s, 1H), 7.45 (s, 1H), 7.12-7.05 (m, 2H).

LC/MS (Method C): *R*_t = 3.171 min; *m/z* 297

Alternative preparation of (6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol



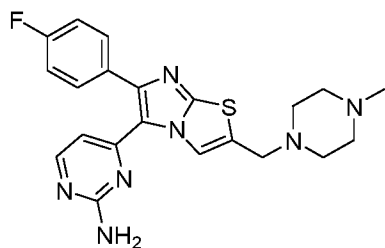
Dry tetrahydrofuran (10 mL) was introduced in a dry round bottom flask under inert atmosphere. A 2 M solution of isopropylmagnesium chloride in tetrahydrofuran (5 mL, 10 mmol) was added and the resulting solution was cooled to about -15°C. To this solution
5 was added over 25 min a solution of 2-bromo-6-(4-fluorophenyl)imidazo[2,1-b]thiazole (2.7 g, 9.1 mmol) in dry tetrahydrofuran (54 mL) while maintaining the temperature at about -15°C. Paraformaldehyde (355 mg, 11.8 mmol) was then added in one portion to the reaction mixture at -15°C under slight positive nitrogen pressure. The reaction mixture was allowed to reach room temperature and was stirred at this temperature for
10 10 min before being heated up to 40°C to be stirred at this temperature for 80 min. The obtained suspension was cooled to room temperature over 10 min, then cooled with the help of an ice-water bath, prior to the addition of aqueous 15% (wt.) citric acid (27 mL) and of dichloromethane (40 mL). The aqueous layer was separated and was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with
15 aqueous half-saturated sodium bicarbonate (2 × 27 mL) were concentrated to dryness under reduced pressure and the obtained residue was purified by column chromatography on silica gel (1 to 10% (vol.) methanol gradient in dichloromethane) to give pure (6-(4-fluorophenyl)imidazo[2,1-b]thiazol-2-yl)methanol (1.57 g, 6.32 mmol).

¹H NMR (400 MHz, DMSO) δ (ppm): 8.14 (s, 1H), 7.88-7.82 (m, 3H), 7.25-7.18 (m, 2H),
20 5.68 (t, J = 8.0 Hz, 1H), 4.60 (dd, J = 8.0, 1.5 Hz, 2H).

LC/MS (Method C): R_t = 2.510 min; m/z 249

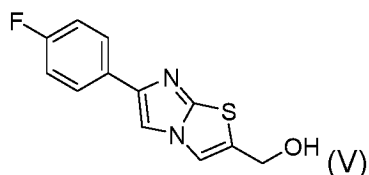
The following are numbered embodiments of the invention:

1. A process to prepare a compound of Formula (I)

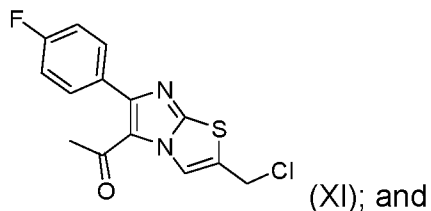


comprising

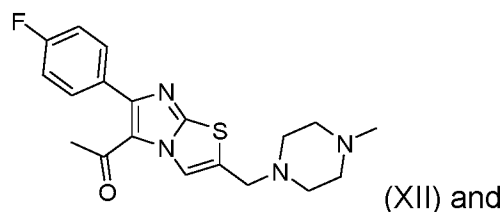
- 5 a. reacting a compound of Formula (V)



with acetyl chloride in an organic solvent to form a compound of Formula (XI).



- b. converting the compound of Formula (XI) to the compound of Formula (I).
- 10 2. The process of claim 1, wherein the solvent is selected from dioxane, THF, Methyl-THF, toluene, mesitylene, xylene, DMF, DMA and NMP.
3. The process of claims 1 or 2, further comprising
 - a. reacting the compound of Formula (XI) with 1-methyl piperazine in the presence of a base to form the compound of Formula (XII) or a salt thereof



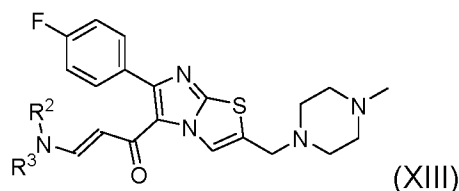
b. converting the compound of Formula (XII) to the compound of Formula (I).

4. The process of claim 3, wherein the base is selected from sodium carbonate, sodium bicarbonate, potassium bicarbonate, ethyldiisopropylamine, triethylamine and potassium carbonate.

5. The process of claims 3 or 4, wherein a solvent is used in step a and the solvent is selected from NMP, acetonitrile and dichloromethane.

6. The process of any one of claims 3-5, further comprising

a. reacting the compound of Formula (XII) or a salt thereof with a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent, preferably 1,1-dimethoxy-*N,N*-dimethylmethanamine to form the compound of Formula (XIII).



wherein R² and R³ are independently C₁ to C₅ alkyl, preferably methyl; and

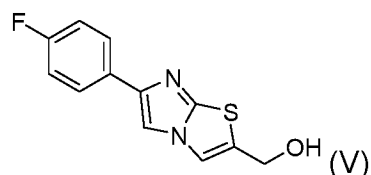
b. converting the compound of Formula (XIII) to the compound of Formula (I).

7. The process of claim 6, wherein a solvent is used in step a and the solvent is selected from *N,N*-dimethylacetamide, acetonitrile, THF, and 1,1-dimethoxy-*N,N*-dimethylmethanamine.

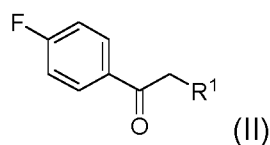
8. The process of anyone of claims 6-7, further comprising cyclocondensing the compound of Formula (XIII) with guanidine or a guanidinium salt to yield the compound of Formula (I).

9. The process of claim 8, wherein the reaction is conducted in the presence of a base
5 which is selected from potassium carbonate and sodium ethoxide.

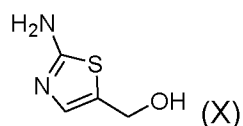
10. The process of any one of claims 1-9, wherein the compound of Formula (V)



is formed by the process comprising reacting the compound of Formula (II)

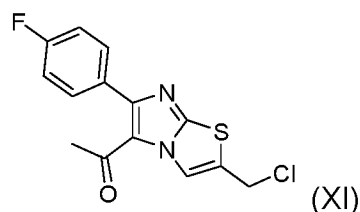


10 wherein R¹ is selected from halogen and sulfonate with the compound of Formula (X)

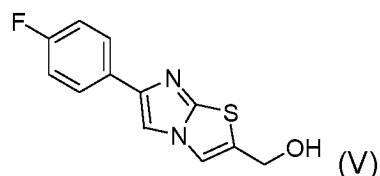


to yield the compound of Formula (V).

11. A process to produce the compound of Formula (XI)



15 comprising reacting a compound of Formula (V)

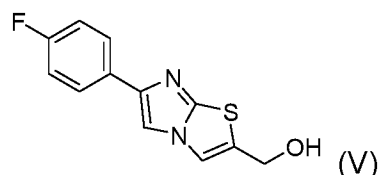


with acetyl chloride to form a compound of Formula (XI).

12. The process of claim 8, wherein the reaction to form the compound of Formula (XIII) is followed directly by the cyclocondensation reaction with guanidine or a salt thereof to form the compound of Formula (I) without isolation or purification of the compound of Formula (XIII).

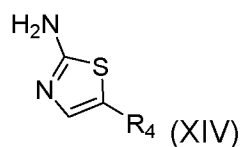
13. The process of claim 10, wherein the reaction to form the compound of Formula (V) is followed directly by reacting the compound of Formula (V) with acetyl chloride to form the compound of Formula (XI) without isolation or purification of the compound of Formula (V).

14. The process of any one of claims 1-9 and 12-13, wherein the compound of Formula (V)



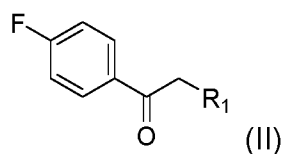
is formed by the process comprising

a. reacting a compound of Formula (XIV)



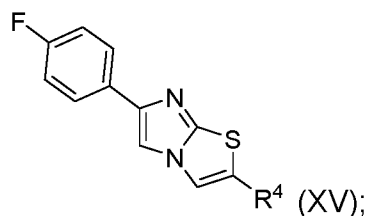
wherein R⁴ is bromo or chloro

with a compound of Formula (II)



wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate.

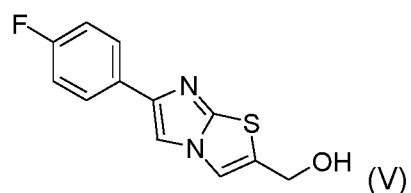
5 to yield the compound of Formula (XV)



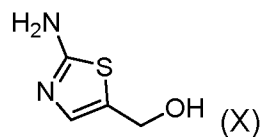
and

b. reacting the compound of Formula (XV) with isopropyl magnesium chloride and formaldehyde yield the compound of Formula (V).

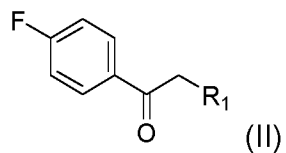
10 15. The process of claim 1, wherein the compound of Formula (V)



is formed by the process comprising reacting a compound of Formula (X)



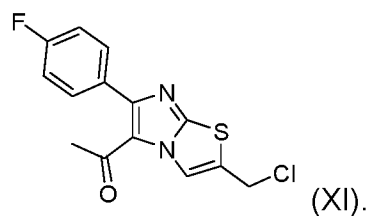
with a compound of Formula (II)



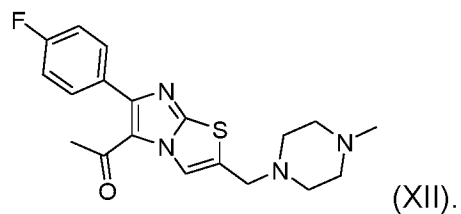
wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate.

to yield the compound of Formula (V).

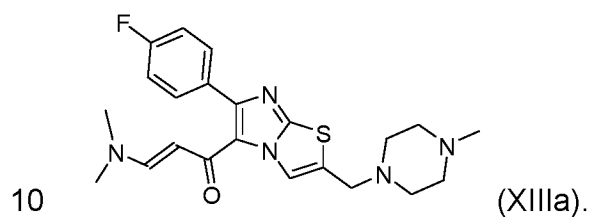
5 16. The compound of Formula (XI)



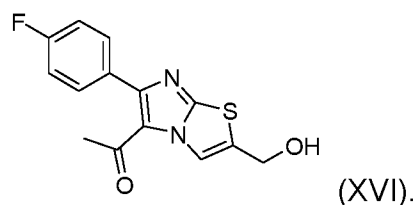
17. The compound of Formula (XII)



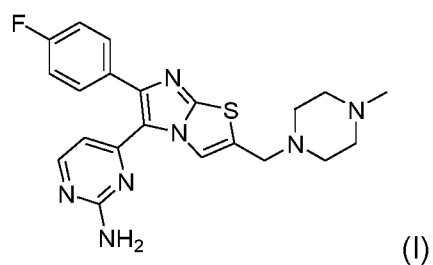
18. The compound of Formula (XIIIa)



19. The compound of Formula (XVI)

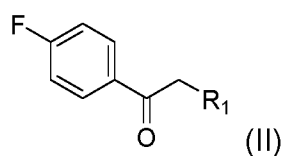


20. A process to prepare a compound of Formula (I)



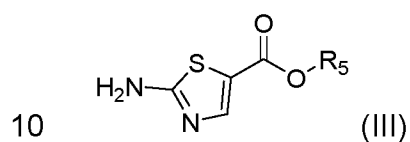
comprising

5 a. reacting a compound of Formula (II)



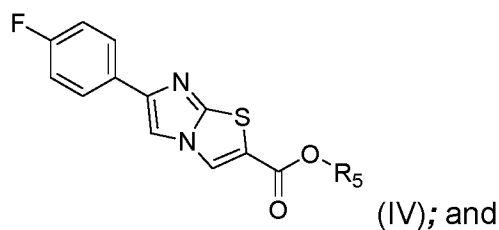
wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate,

with a compound of Formula (III)



wherein R⁵ is hydrogen, C₁ to C₅ alkyl, preferably C₂ to C₃, most preferred C₂

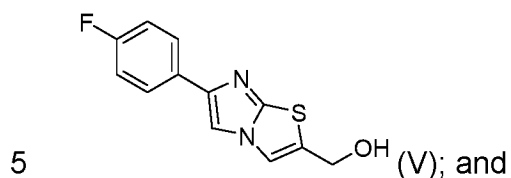
to yield a compound of Formula (IV)



b. converting the compound of Formula (IV) to the compound of Formula (I).

21. The process of claim 20, further comprising

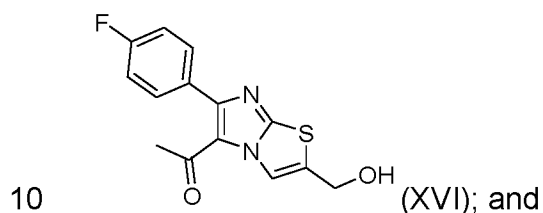
a. reducing the compound of Formula (IV) to a compound of Formula (V)



b. converting the compound of Formula (V) to the compound of Formula (I).

22. The process of claim 21, further comprising

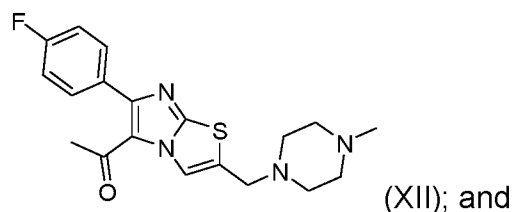
a. reacting a compound of Formula (V) with acetic acid anhydride followed by saponification to form a compound of Formula (XVI)



b. converting the compound of Formula (XVI) to the compound of Formula (I).

23. The process of claim 22, further comprising

a. reacting the compound of Formula (XVI) with mesyl chloride followed by 1-methyl piperazine in the presence of a base to form the compound of Formula (XII).

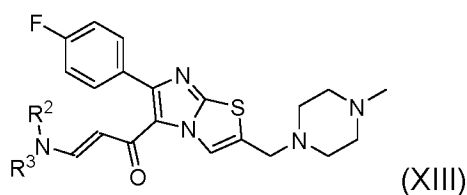


b. converting the compound of Formula (XII) to the compound of Formula (I).

24. The process of claim 23, wherein the base is potassium carbonate or trimethylamine, preferably triethylamine.

5 25. The process of claim 23 or 24, further comprising

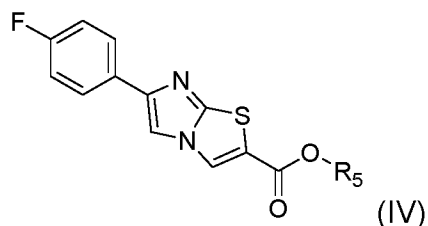
a. reacting the compound of Formula (XII) with a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent, preferably 1,1-dimethoxy-*N,N*-dimethylmethanamine to form the compound of Formula (XIII)



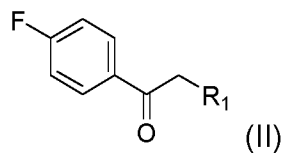
10 wherein R² and R³ are independently C₁ to C₅ alkyl, preferably methyl; and

b. cyclocondensing the compound of Formula (XIII) with guanidine or a guanidinium salt to yield the compound of Formula (I).

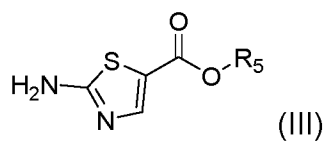
26. A process to prepare a compound of Formula (IV) comprising



15 reacting a compound of Formula (II)



with a compound of Formula (III)



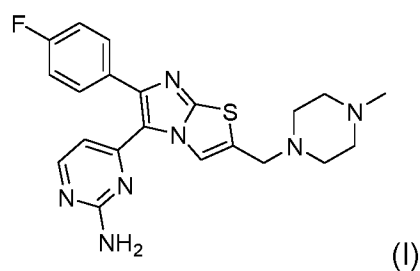
to yield the compound of Formula (IV)

- 5 wherein R_1 is bromine or chlorine and R_5 is C_2 to C_5 alkyl, preferably C_2 alkyl.

27. The process of any one of claims 3-5 wherein, the salt of the compound of Formula (XII) is the dihydrochloride salt.

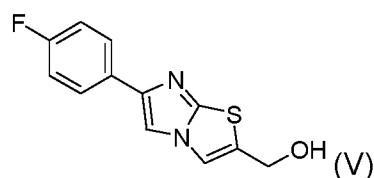
Claims

1. A process to prepare a compound of Formula (I)

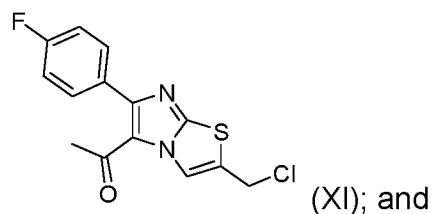


comprising

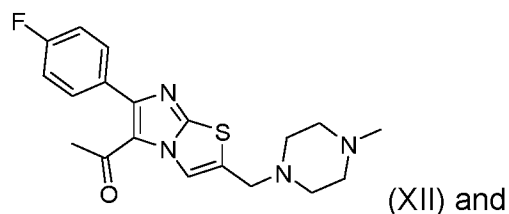
- 5 a. reacting a compound of Formula (V)



with acetyl chloride in an organic solvent to form a compound of Formula (XI).



- b. converting the compound of Formula (XI) to the compound of Formula (I).
- 10 2. The process of claim 1, wherein the solvent is selected from dioxane, THF, methyl-THF, toluene, mesitylene, xylene, DMF, DMA and NMP.
3. The process of claims 1 or 2, further comprising
- a. reacting the compound of Formula (XI) with 1-methyl piperazine in the presence of a base to form the compound of Formula (XII)



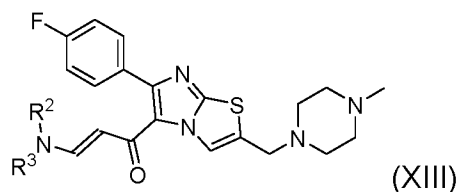
b, converting the compound of Formula (XII) to the compound of Formula (I).

4. The process of claim 3, wherein the base is selected from sodium carbonate, sodium bicarbonate, potassium bicarbonate, ethyldiisopropylamine, triethylamine and potassium carbonate.

5. The process of claims 3 or 4, wherein a solvent is used in step a and the solvent is selected from NMP, acetonitrile and dichloromethane.

6. The process of any one of claims 3-5, further comprising

a. reacting the compound of Formula (XII) or a salt thereof with a 1,1-dialkoxy-*N,N*-dialkylmethanamine reagent, preferably 1,1-dimethoxy-*N,N*-dimethylmethanamine to form the compound of Formula (XIII).



wherein R^2 and R^3 are independently C_1 to C_5 alkyl, preferably methyl; and

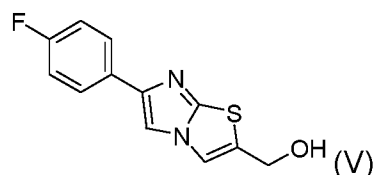
b. converting the compound of Formula (XIII) to the compound of Formula (I).

7. The process of claim 6, wherein a solvent is used in step a and the solvent is selected from *N,N*-dimethylacetamide, acetonitrile, THF, and 1,1-dimethoxy-*N,N*-dimethylmethanamine.

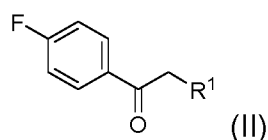
8. The process of anyone of claims 6-7, further comprising cyclocondensing the compound of Formula (XIII) with guanidine or a guanidinium salt to yield the compound of Formula (I).

9. The process of claim 8, wherein the reaction is conducted in the presence of a base
5 which is selected from potassium carbonate and sodium ethoxide.

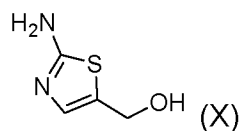
10. The process of any one of claims 1-9, wherein the compound of Formula (V)



is formed by the process comprising reacting the compound of Formula (II)

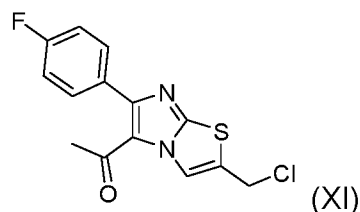


10 wherein R¹ is selected from halogen and sulfonate with the compound of Formula (X)

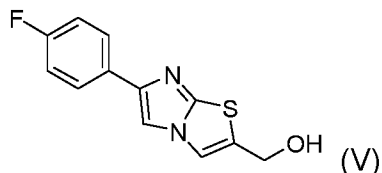


to yield the compound of Formula (V).

11. A process to produce the compound of Formula (XI)



15 comprising reacting a compound of Formula (V)

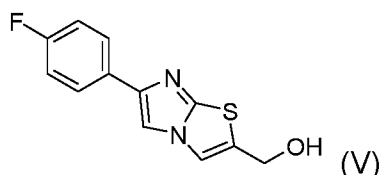


with acetyl chloride to form a compound of Formula (XI).

12. The process of claim 8, wherein the reaction to form the compound of Formula (XIII) is followed directly by the cyclocondensation reaction with guanidine or a salt thereof to form the compound of Formula (I) without isolation or purification of the compound of Formula (XIII).

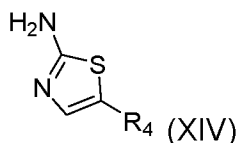
13. The process of claim 10, wherein the reaction to form the compound of Formula (V) is followed directly by reacting the compound of Formula (V) with acetyl chloride to form the compound of Formula (XI) without isolation or purification of the compound of Formula (V).

14. The process of any one of claims 1-9 and 12-13, wherein the compound of Formula (V)



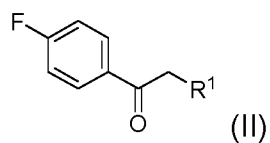
is formed by the process comprising

15 a. reacting a compound of Formula (XIV)



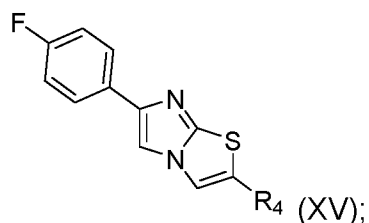
wherein R⁴ is bromo or chloro

with a compound of Formula (II)



wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate.

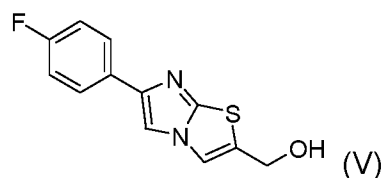
5 to yield the compound of Formula (XV)



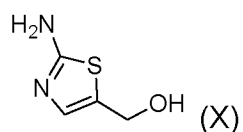
and

b. reacting the compound of Formula (XV) with isopropyl magnesium chloride and formaldehyde yield the compound of Formula (V).

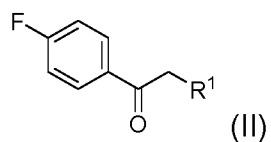
10 15. The process of claim 1, wherein the compound of Formula (V)



is formed by the process comprising reacting a compound of Formula (X)



with a compound of Formula (II)



wherein R¹ is a halogen or a sulfonate, preferably bromine, chlorine, iodide, mesylate or tosylate.

to yield the compound of Formula (V).

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2019/086310

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D513/04
 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	SCRIBNER A ET AL: "Synthesis and biological activity of anticoccidial agents: 5,6-Diarylimidazo[2,1-b][1,3]thiazoles", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 18, no. 19, 1 October 2008 (2008-10-01), pages 5263-5267, XP025433914, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2008.08.063 [retrieved on 2008-08-22] cited in the application scheme 1; compound 10 ----- -/-	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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 January 2020

Date of mailing of the international search report

11/02/2020

Name and mailing address of the ISA/

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

Authorized officer

Österle, Carmen

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/086310

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 2 682 395 A1 (ESTEVE LABOR DR [ES]) 8 January 2014 (2014-01-08) schemes; examples -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/086310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2682395	A1	08-01-2014	CA 2878339 A1 09-01-2014
			CN 104520304 A 15-04-2015
			EP 2682395 A1 08-01-2014
			EP 2870164 A1 13-05-2015
			ES 2607183 T3 29-03-2017
			HK 1210149 A1 15-04-2016
			JP 6401156 B2 03-10-2018
			JP 2015521994 A 03-08-2015
			PT 2870164 T 21-12-2016
			US 2015166574 A1 18-06-2015
			WO 2014006130 A1 09-01-2014
