

ABSTRACT

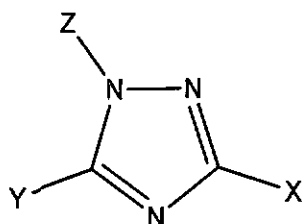
A NOVEL PROCESS FOR SYNTHESIS OF DEFERASIROX

The invention relates to metal mediated synthesis of Deferasirox 4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl] benzoic acid, [I], an iron chelating agent, synthesized from 1, 2, 4-triazole. The process involves Preparation of 3,5-dibromo-1H-1,2,4-triazole (II) from 1,2,4 triazole; reaction of compound (II) with benzyl bromide to form 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III); reaction of compound (III) and (2-methoxyphenyl)boronic acid to give 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV); compound (IV) being reacted with suitable reactants to give compound (V); reacting compound (V) with (4-(methoxycarbonyl)phenyl)boronic acid to give compound (VI); and deprotection of compound (VI) to give compound [I]. A further process involves preparation of 3,5-dibromo 1H-1,2,4-triazole (II) from 1,2,4-triazole; reacting 3,5-dibromo 1H-1,2,4-triazole (II) and (4-(methoxycarbonyl)phenyl)boronic acid to form methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) ; reaction of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) and (2-methoxyphenyl)boronic acid to form Synthesis of 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI); deprotection of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) to form deferasirox (I). The invention also includes intermediates formed in the process of preparation of Deferasirox.

12 SEP 2013

WE CLAIM:

1. Compounds of the formula having following structure,



Compound (IV) when X=Y= O-methoxyphenyl & Z= Benzyl

Compound (V) when X=Y= O-methoxyphenyl & Z= H

Compound (VI) when X=Y= O-methoxyphenyl & Z= Benzoic acid ester

Compound (VII) when X=Y= Br & Z= Benzoic acid ester

Compound (IX) when X=Br, Y= O-methoxyphenyl & Z= Benzyl

Compound (X) when X= O-methoxyphen, Y= Br & Z= Benzyl

Compound (XI) X=H, Y= O-methoxyphenyl & Z= Benzyl

Compound (XII) X=O-methoxyphenyl, Y=H & Z= Benzyl

2. A process for the synthesis of Deferasirox[I] comprising;

- a) Preparation of 3,5-dibromo-1H-1,2,4-triazole (II) from 1,2,4 triazole;
- b) reaction of compound (II) with benzyl bromide to form 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III);
- c) reaction of compound (III) and (2-methoxyphenyl)boronic acid to give 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV);
- d) compound (IV) being reacted with suitable reactants to give compound (V);
- e) reacting compound (V) with (4-(methoxycarbonyl)phenyl)boronic acid to give compound (VI); and
- f) deprotection of compound (VI) to give compound [I].

3. The process according to claim 2, wherein preparation of compound (II) from 1,2,4-triazole mentioned in step a) is carried out in dichloromethane/ water biphasic mixture employing bromine and aqueous solution of sodium hydroxide.
4. The process according to claim 2, wherein reaction of 3,5-dibromo 1H-1,2,4-triazole (II) and benzyl bromide as mentioned in step b) for formation of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) is carried out in presence of suitable base selected from triethyl amine, Hunig's base, potassium carbonate, sodium carbonate; preferably Hunig's base and in organic solvent such as acetonitrile at temperature 80°C.
5. The process according to claim 2, wherein reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) and (2-methoxyphenyl)boronic acid as mentioned in step c) for formation of 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV) is carried out through Palladium catalyzed Suzuki coupling reaction in suitable organic solvent and in presence of suitable base.
6. The process according to claim 5, wherein palladium catalytic system for Suzuki reaction is selected from palladium acetate/tricyclohexyl phosphine, tris(dibenzylideneacetone)dipalladium and bis(triphenylphosphine)palladium(II) dichloride, palladium acetate/di(1-adamantyl)benzylphosphine hydroiodide; preferably palladium acetate/tricyclohexyl phosphine.
7. The process according to claim 5, wherein organic solvent is selected from n-propanol, isopropanol, dimethyl acetamide, preferably dimethyl acetamide.
8. The process according to claim 5, wherein base is selected from triethyl amine, Hunig's base, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, preferably Hunig's base and potassium tert-butoxide.

9. The process according to claim 2, wherein reaction of 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV) as mentioned in step d) for formation of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (V) is through hydrogenolysis using noble metal catalyst such as 5-10% palladium on carbon, palladium hydroxide; preferably 10% palladium on carbon at reaction temperature 25⁰C, under hydrogen pressure of 7-10 kg; in organic solvent such ethanol.

10. The process according to claim 2, wherein reaction of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (V) and (4-(methoxycarbonyl)phenyl)boronic acid as mentioned in step e) for formation of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) is through using copper catalyzed Chan-Lam coupling reaction in suitable organic solvent and in presence of suitable base.

11. The process according to claim 10, wherein copper salt used in Chan-Lam coupling reaction is selected from copper (I) chloride, copper(I) acetate, copper (II) chloride, copper (II) triflate & copper (II) acetate, preferably copper (II) acetate.

12. The process according to claim 10, wherein organic solvent used is selected from dichloromethane, Dimethylformamide, dioxane, preferably dichloromethane.

13. The process according to claim 10, wherein base used is selected from triethyl amine, Hunig's base, pyridine, preferably pyridine.

14. The synthesis of Deferasirox from methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate as mentioned in step f) of claim 2 is carried out in presence of 2-(diethylamino)ethanethio in organic solvent and in presence of base at 140-160 ⁰C; preferably at 150⁰C

15. The process according to claim 14, wherein organic solvent is selected from Dimethylformamide, N-methyl pyrrolidone, tetrahydrofuran, dimethylsulfoxide, preferably dimethylformamide.

16. The process according to claim 14, wherein base used is selected from potassium tert-butoxide, sodium tert-butoxide, sodium hydroxide, potassium hydroxide, preferably sodium tert-butoxide.

17. A process for the synthesis of Deferasirox[I] comprising;

- a) preparation of 3,5-dibromo 1H-1,2,4triazole (II) from 1,2,4-triazole;
- b) reacting 3,5-dibromo 1H-1,2,4triazole (II) and (4-(methoxycarbonyl)phenyl)boronic acid to form methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) ;
- c)) reaction of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) and (2-methoxyphenyl)boronic acid to form Synthesis of 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI);
- d) deprotection of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) to form deferasirox (I)

18. The process according to claim 17, wherein synthesis of compound (II) from 1,2 4-triazole mentioned in step a) is carried out in dichloromethane/ water biphasic mixture employing bromine and aqueous solution of sodium hydroxide at 10-15 °C.

19. The process according to claim 17, wherein reaction of 3,5-dibromo 1H-1,2,4triazole (II) and (4-(methoxycarbonyl)phenyl)boronic acid as mentioned in step b) for preparation of methyl

4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) is carried through using copper catalyzed Chan-Lam coupling reaction in suitable organic solvent and in presence of suitable base.

20. The process according to claim 19, wherein copper salt used in Chan-Lam coupling reaction is selected from copper (I) chloride, copper(I) acetate, copper (II) chloride, copper (II) triflate & copper (II) acetate, preferably copper (II) acetate.

21. The process according to claim 19, wherein organic solvent is selected from dichloromethane, Dimethylformamide, dioxane, preferably dichloromethane.

22. The process according to claim 19, wherein base is selected from triethyl amine, Hunig's base, pyridine, preferably pyridine.

23. The process according to claim 17, wherein reaction of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) and (2-methoxyphenyl)boronic acid as mentioned in step c) for formation of 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) is carried through palladium catalyzed Suzuki coupling reaction in suitable organic solvent in presence of suitable base.

24. The process according to claim 23, wherein palladium catalytic system for Suzuki reaction is selected from palladium acetate/tricyclohexyl phosphine, tris(dibenzylideneacetone)dipalladium and bis(triphenylphosphine)palladium(II) dichloride, palladium acetate/di(1-adamantyl)benzylphosphine hydroiodide, preferably palladium acetate/di(1-adamantyl)benzylphosphine hydroiodide

25. The process according to claim 23, wherein organic solvent is selected from n-propanol, iso-propanol, dimethyl acetamide, preferably dimethyl acetamide.

26. The process according to claim 23, wherein base is selected from triethyl amine, Hunig's base, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, preferably Hunig's base and potassium tert-butoxide.
27. The process according to claim 17, wherein deprotection of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate as mentioned in step d) for formation of 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) is carried out in presence of 2-(diethylamino)ethanethio in organic solvent and in presence of base at 140-160 °C; preferably at 150°C
28. The process according to claim 27, wherein organic solvent is selected from Dimethylformamide, N-methyl pyrrolidone, Tetrahydrofuran, Dimethylsulfoxide, preferably dimethylformamide.
29. The process according to claim 27, wherein base is selected from potassium tert-butoxide, sodium tert-butoxide, sodium hydroxide, potassium hydroxide; preferably sodium tert-butoxide.
30. A process for the preparation of compound (IV) comprising reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) with (2-methoxyphenyl)boronic acid in the presence of suitable palladium catalyst, a suitable base and a suitable solvent.
31. A process for the preparation of compound (V) comprising debenzylation of 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (IV) using noble metal catalyst.
32. A process for the preparation of compound (VI) comprising copper-mediated cross coupling of compound (V) with (4-(methoxycarbonyl)phenyl)boronic acid in presence of suitable solvent and suitable base.

33. The process for preparation of compound (VII) comprising copper-mediated cross coupling of compound (II) with (4-(methoxycarbonyl)phenyl)boronic acid in presence of suitable solvent and base.

34. A process for the preparation of compound (IX) or (X) comprising Suzuki coupling of compound (III) with (2-methoxyphenyl)boronic acid in presence of palladium catalyst, ligand, organic solvent and a base.

35. A process for the preparation of compounds (XI) or (XII) comprising Suzuki coupling of compound (III) with (2-methoxyphenyl)boronic acid in presence of palladium catalyst, organic solvent and a base.

Dated this 12th day of September 2013



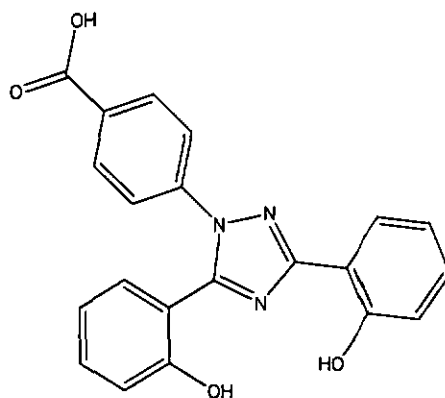
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Of S. Majumdar & Co.
(Applicant's Agent)

Field of the Invention:

This present invention relates to metal mediated synthesis of Deferasirox, an iron chelating agent, synthesized from 1, 2, 4-triazole.

Background of the Invention:

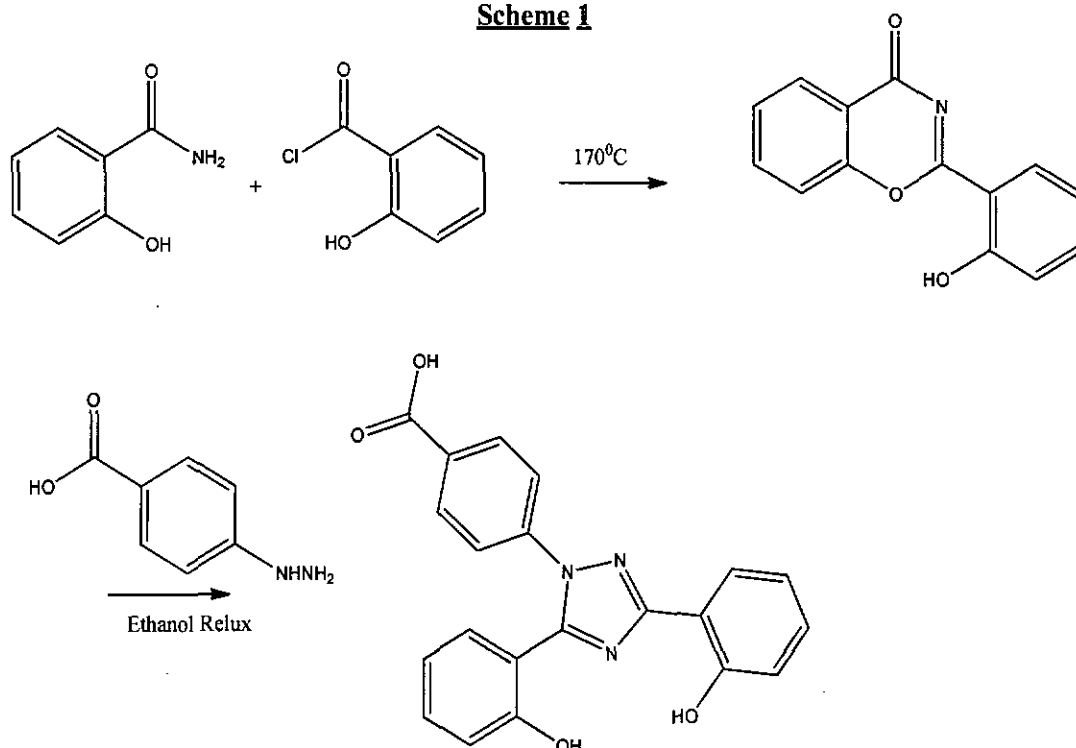
Deferasirox-4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl] benzoic acid, [I], is an iron-chelator and is prescribed for treatment of liver diseases in which iron plays a role of pathogenesis and also for treatment of Friedreich Ataxia resulting from intracellular mishandling of iron.



[I]

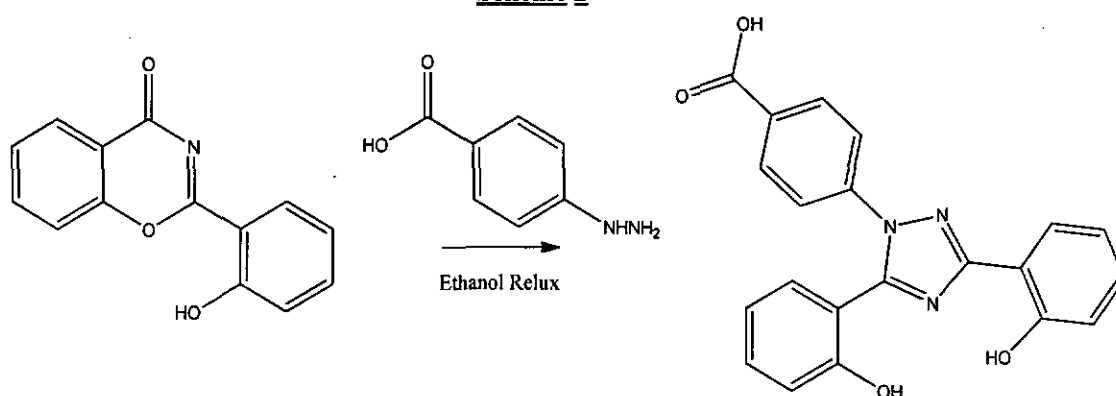
U. S. patent No. 6,465,504 discloses the process for synthesis of compound [I], involving condensation of salicylamide with salicyloyl chloride to obtain 2-(2-hydroxyphenyl)-ben[e][1,3]oxazin-4-one by heating at 170°C, which on reaction with 4-hydrazinobenzoic acid gave compound [I] (Scheme 1).

Scheme 1

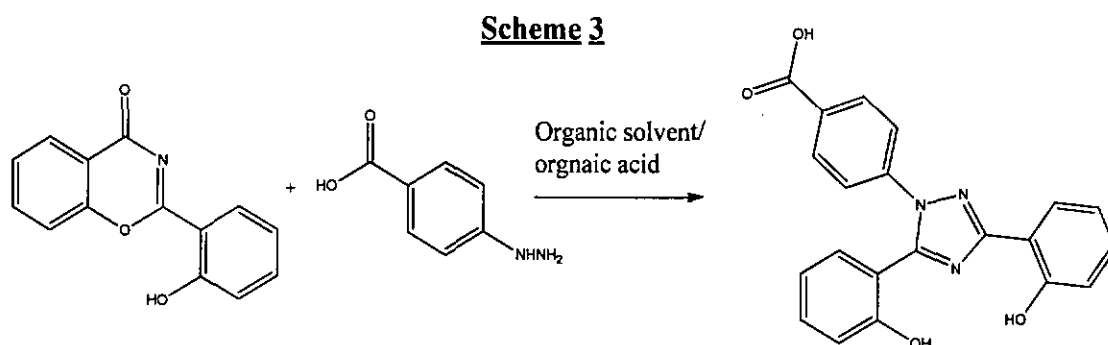


WO2003/053986discloses the process for synthesis of compound [I] involving, dissolving 4-hydrazinobenzoic acid in ethanol at reflux temperature and adding to this solution, solid 2-(2-hydroxyphenyl)-benzo-4H-[1,3]-oxazin-4-one at reflux temperature(scheme 2). Addition of solid material at reflux temperature is not desirable at industrial scale.

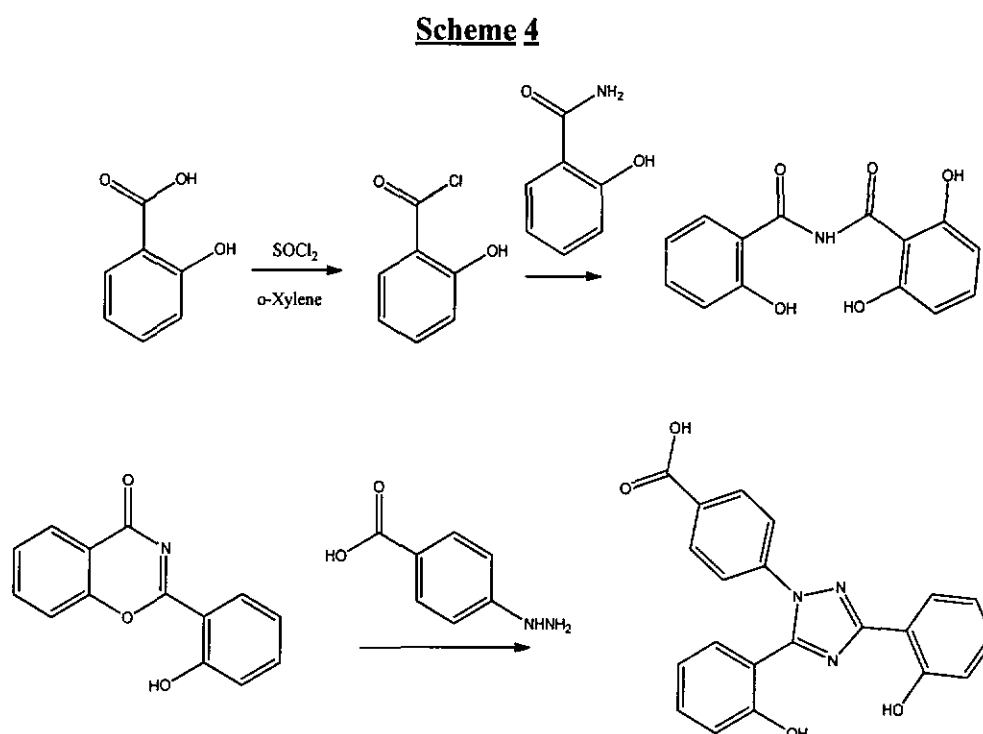
Scheme 2



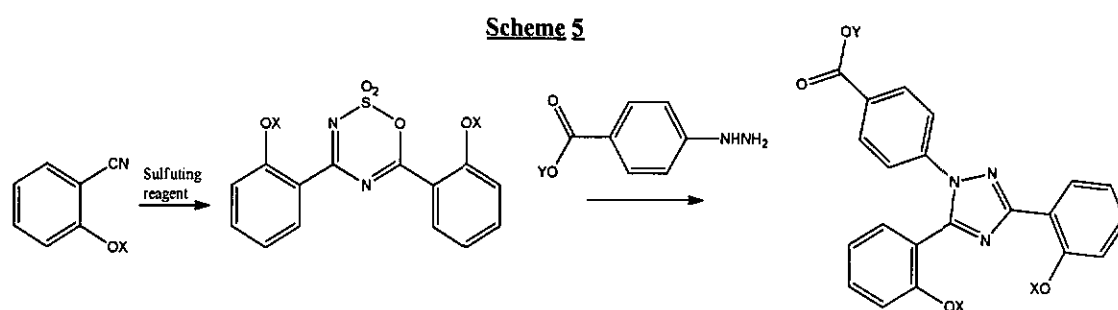
WO 2009/094956 discloses process for synthesis of compound [I] through reaction between 4-hydrazinobenzoic acid and 2-(2-hydroxyphenyl)-benzo-4H-[1,3]-oxazin-4-one in presence of organic acid such as propionic acid, trichloroacetic acid and methoxypropionic acid optionally with an organic solvent (Scheme 3).



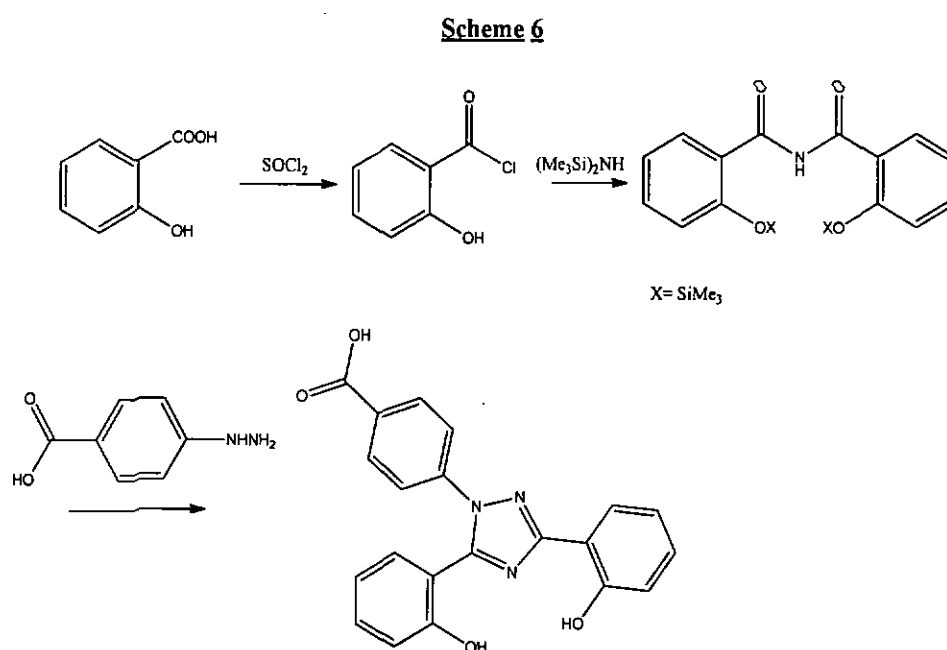
WO2010/023685 discloses improved process for the preparation of crystalline form of 2-(2-hydroxyphenyl) benz (e) [1,3] oxazin 4-one through condensation of salicyloyl chloride and salicylamide in presence of organic solvent (Scheme 4) .



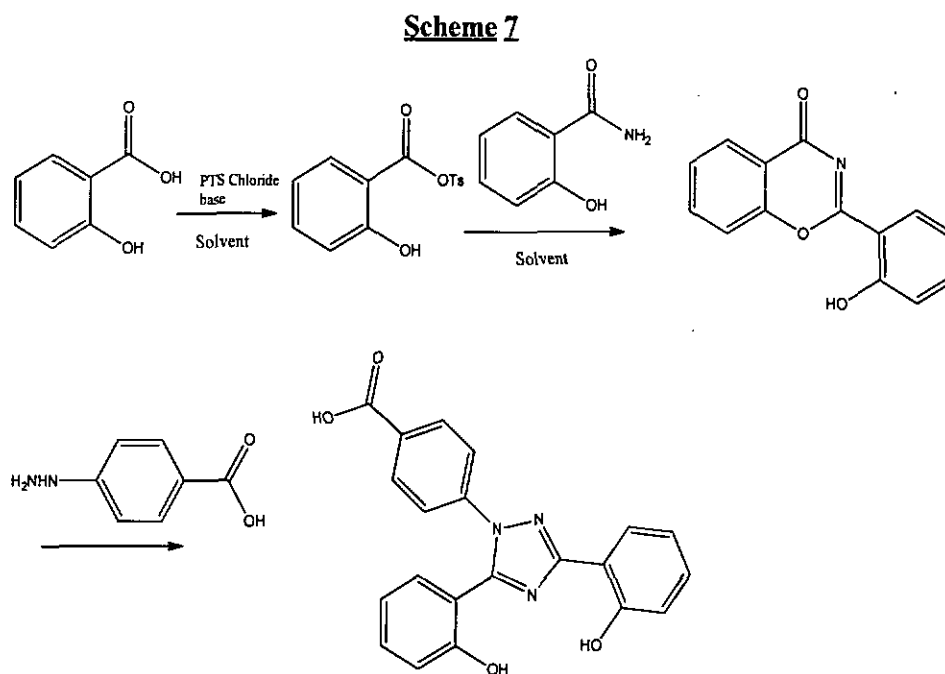
WO2011/070560 describes process for synthesis of compound [I] through reaction of 2-acetoxybenzonitrile with dioxane-sulfur trioxide complex to obtain the corresponding sulfur intermediate, which upon reaction with 4-hydrazinobenzoic acid ethyl ester yielded the desired compound (Scheme 5). It is needless to mention that sulfur trioxide is a hazardous gas and requires special precaution to handle at industrial scale.



In the same patent alternative process for synthesis of compound [I] through reaction of salicyloyl chloride with hexamethyldisilazane to obtain 2-hydroxy-N-(2-hydroxybenzoyl)benzamide di (silyl) imide has been described, which upon reaction with 4-hydrazinobenzoic acid yield desired compound (Scheme 6).

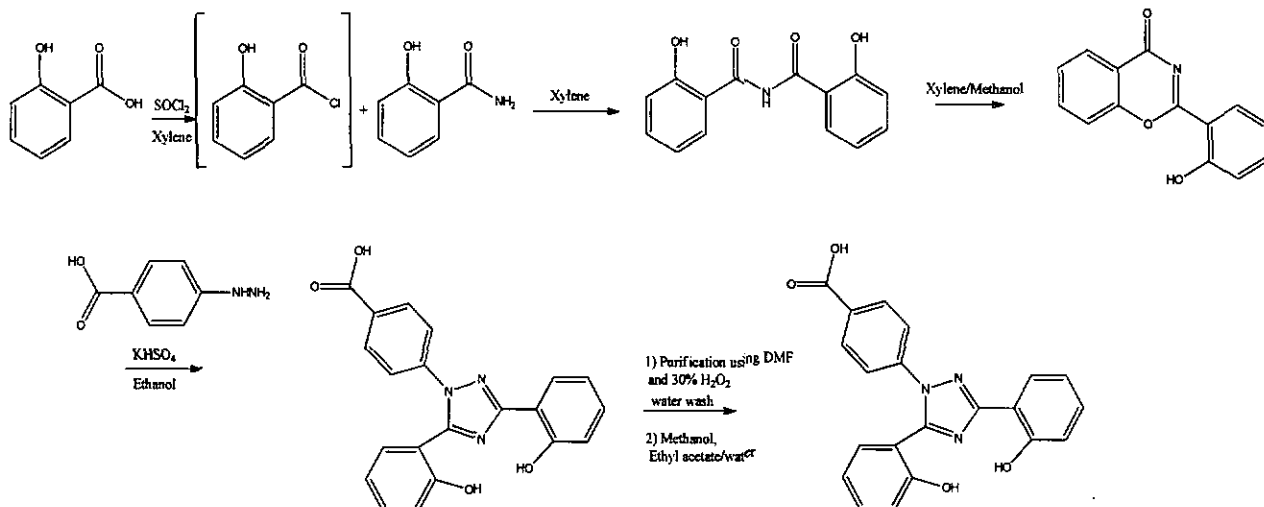


WO2012025935 discloses the process for synthesis of compound [I] as shown in scheme 7. In the said patent application salicylic acid is reacted with tosyl chloride to obtain tosyl intermediate, which on reaction with salicylamide yield cyclic intermediate, which was further converted to compound [I] on reaction with 4-hydrazinobenzoic acid.



WO2012/069946 discloses the process for synthesis of compound [I] from salicylic acid and salicylamide as shown in scheme 8. Crude Deferasirox was further purified using DMF and 30% aqueous hydrogen peroxide to obtain Deferasirox free 4-hydrazinebenzoic acid, which was further crystallized to obtain pure Deferasirox.

Scheme 8



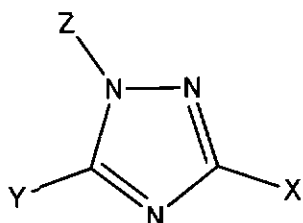
All the above mentioned processes for synthesis of compound [I] revolve around the condensation of salicylamide with salicyloyl chloride which involves evolution of corrosive/hazardous gaseous hydrochloric acid, elevated reaction temperature and most importantly poor overall yield makes the process not very desirable on an industrial scale. In addition, all these processes make use of 4-hydrazinobenzoic acid as one of the key starting material, which is carcinogenic in nature.

Thus there is a need for development of a process for Deferasirox, which would overcome the above drawbacks.

Summary of Invention

In accordance with one embodiment, the present invention provides, synthesis of 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV) through Suzuki coupling reaction between 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) and (2-methoxyphenyl)boronic acid, which is further converted to compound [I].

In accordance with another aspect are the various intermediates in the process of the present invention as under. Compounds of the formula having following structure,



- Compound (IV) when X=Y= O-methoxyphenyl & Z= Benzyl
- Compound (V) when X=Y= O-methoxyphenyl & Z= H
- Compound (VI) when X=Y= O-methoxyphenyl & Z= Benzoic acid ester
- Compound (VII) when X=Y= Br & Z= Benzoic acid ester
- Compound (IX) when X=Br, Y= O-methoxyphenyl & Z= Benzyl
- Compound (X) when X= O-methoxyphen, Y= Br & Z= Benzyl
- Compound (XI) X=H, Y= O-methoxyphenyl & Z= Benzyl
- Compound (XII) X=O-methoxyphenyl, Y=H & Z= Benzyl

In accordance with a further embodiment the present invention provides a process for the preparation of compound (IV) comprising reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) with (2-methoxyphenyl)boronic acid in the presence of suitable palladium catalyst, a suitable base and a suitable solvent

In accordance with another embodiment, the present invention provides synthesis of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (V) through debenzylation of compound (IV) with noble metal catalyst and in presence of hydrogen. This compound V is used as intermediate which is further converted to compound [I].

In accordance with another embodiment, the present invention provides synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) via Chan-Lam coupling reaction between (4-(methoxycarbonyl)phenyl)boronic acid and compound (V), which is further converted to compound [I].

In accordance with another embodiment, the present invention provides, synthesis of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) through Chan-Lam coupling reaction between (4-(methoxycarbonyl)phenyl)boronic acid and 3,5-dibromo-1H-1,2,4-traizole (II). This is another intermediate which is further converted to compound [I].

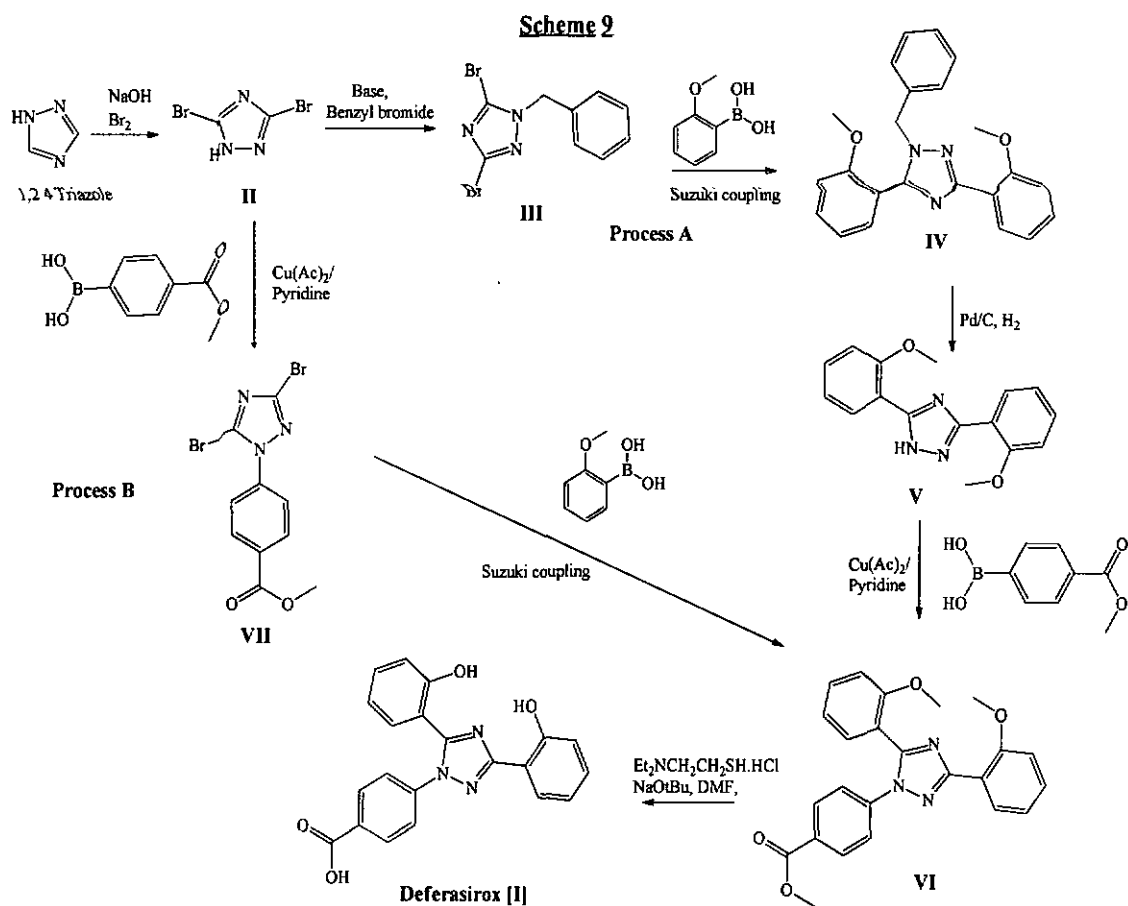
In accordance with another embodiment, the present invention provides synthesis methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) through Suzuki coupling reaction between methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) and (2-methoxyphenyl)boronic acid, which is further converted to compound [I].

In accordance with another embodiment, the present invention provides a process for the preparation of compound (IX) or (X) comprising Suzuki coupling of compound (III) with (2-methoxyphenyl)boronic acid in presence of palladium catalyst, ligand, organic solvent and a base.

In accordance with another embodiment, the present invention provides a process for the preparation of compounds (XI) or (XII) comprising Suzuki coupling of compound (III) with (2-methoxyphenyl)boronic acid in presence of palladium catalyst, organic solvent and a base.

In accordance with another embodiment, the present invention provides synthesis of compound [I] through demethylation by 2-(diethylamino)ethanethiol in presence of a base.

The present invention provides the metal mediated process for synthesis of Deferasirox through two different processes referred herein as process A and process B. The overall reaction scheme is shown in **Scheme 9**.



Detail Description:

The present invention relates to synthesis of compound [I] through sequence of various metal mediated coupling reactions.

Generally Suzuki coupling reaction is a palladium-catalyzed cross-coupling reaction between different types of organoboron compounds and various organic electrophiles including halides or triflates in the presence of a base. This reaction is a versatile method and has wide application for formation of C-C bond and has been widely practiced in art. Recently, other transition metals such as nickel catalyzed Suzuki reactions have been reported.

In one embodiment, the present invention provides the Suzuki coupling reactions between (2-methoxyphenyl)boronic acid with derivatives of 3,5-dibromo-1*H*-1,2,4-triazole compounds.

In another embodiment, the present invention provides the process for synthesis of Deferasirox(I), as depicted in Scheme A, comprising;

a) reaction of 1,2,4 triazole with bromine and aqueous sodium hydroxide solution to obtain 3,5-dibromo-1*H*-1,2,4-triazole (II);

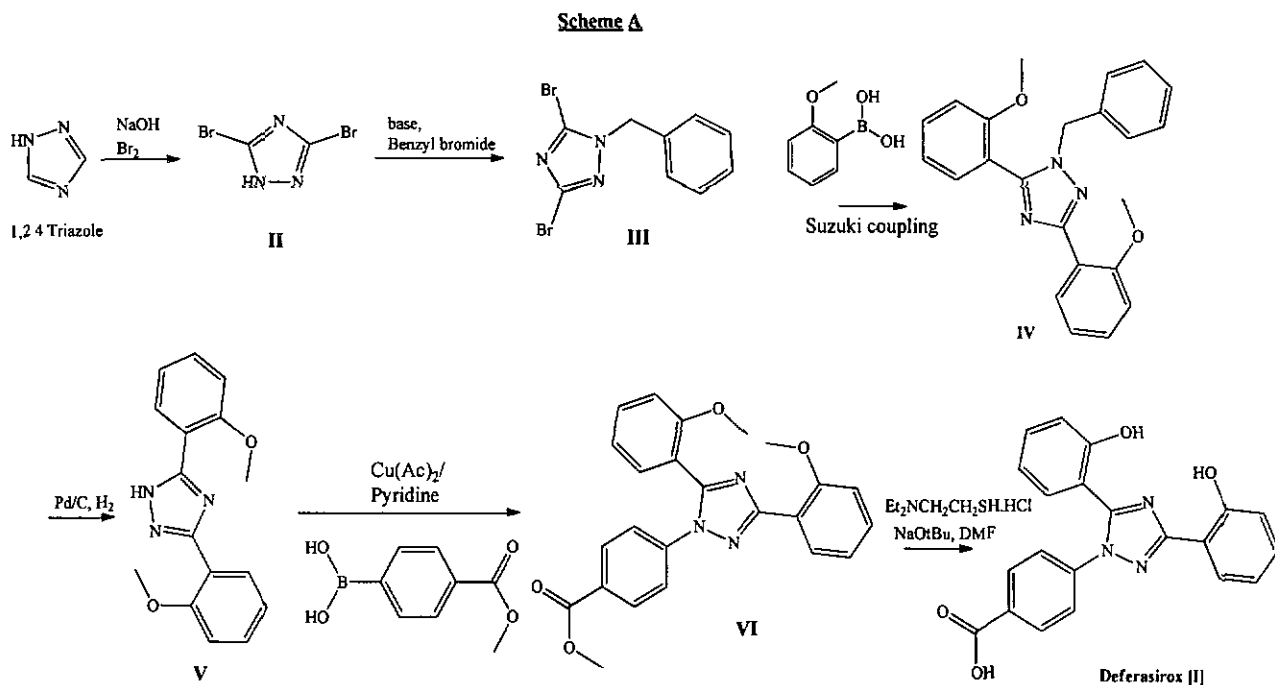
b) reaction of compound (II) with benzyl bromide in presence of suitable organic or inorganic base and in suitable organic solvent gives 1-benzyl-3,5-dibromo-1*H*-1,2,4-triazole (III);

c) Suzuki coupling reaction of compound (III) and (2-methoxyphenyl)boronic acid gives 1-benzyl-3,5-bis[2-methoxyphenyl]-1*H*-1,2,4-triazole (IV);

d) *N*-de-benzylation of compound (IV) with suitable noble metal catalyst in presence of hydrogen in alcohol solvent gives compound (V);

e) copper-mediated cross coupling of compound (V) with (4-(methoxycarbonyl)phenyl)boronic acid gives compound (VI) in presence of suitable solvent and suitable base; and

f) deprotection of compound (VI) in presence of 2-(diethylamino)ethanethiol gives compound [I] in presence of organic solvent and base.



The reaction according to step (a) is carried out in organic solvent selected from dichloromethane, chloroform, dichloroethane, water or mixture thereof; preferably dichloromethane and/or water; most preferably mixture of dichloromethane/water.

The reaction according to step (b) is carried out in presence of suitable organic or inorganic base like triethylamine, Hunig's base, potassium carbonate, sodium carbonate and the like; preferably triethylamine and Hunig's base, most preferably Hunig's base.

The reaction according to step (b) is carried out in presence of organic solvents like acetonitrile, dichloromethane; preferably acetonitrile.

The reaction according to step (b) is carried out at room temperature to reflux temperature depending on the solvent used.

The reaction according to step (c) is carried out in presence of suitable palladium catalyst, suitable base and suitable solvent.

The palladium catalytic system used in step (c) is selected from palladium acetate/tricyclohexyl phosphine, tris(dibenzylideneacetone)dipalladium and bis(triphenylphosphine)palladium (II) dichloride, palladium acetate/di(1-adamantyl)benzylphosphine hydrochloride; most preferably palladium acetate/tricyclohexyl phosphine.

The organic solvent used in step (c) is selected from alcohol like n-propanol, iso-propanol and the like; dipolar aprotic solvents such as dimethylacetamide, dimethylformamide, dimethyl sulfoxide and the like; preferably dimethylacetamide.

The reaction according to step (c) is carried out in presence of suitable base such as organic or inorganic base. The organic bases such as triethylamine, Hunig's base and the like; the inorganic bases are selected from potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, sodium tert-butoxide and the like; preferably Hunig's base and potassium tert-butoxide.

The reaction according to step (d) is carried out using noble metal catalysts such as palladium on carbon, palladium hydroxide and the like; preferably 10% palladium on carbon.

The solvent used in step (d) is selected from methanol, ethanol, n-propanol, iso-propanol and the like; most preferably ethanol.

The copper salt used according to step (e) is selected from copper (I) chloride, copper (I) acetate, copper (II) chloride, copper (II) acetate, and copper (II) triflate; most preferably copper (II) acetate.

The solvent used according to step (e) is selected from dichloromethane, dimethylformamide, dioxane, and the like; most preferable dichloromethane.

The base used according to step (e) is selected from triethylamine, Hunig's base, pyridine and the like; most preferably pyridine.

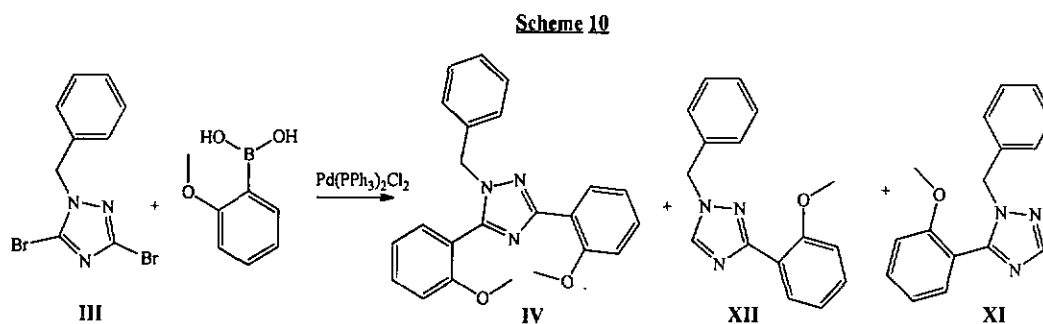
The process according to step (f) is carried in presence of suitable solvent selected from dimethylformamide, N-methyl pyrrolidone, tetrahydrofuran, dimethylsulfoxide and the like; preferably dimethylformamide.

The process according to step (f) is carried out at temperature ranges from 70°C to 200°C, preferably 100°C to 150°C; most preferable reaction is carried out at 150°C.

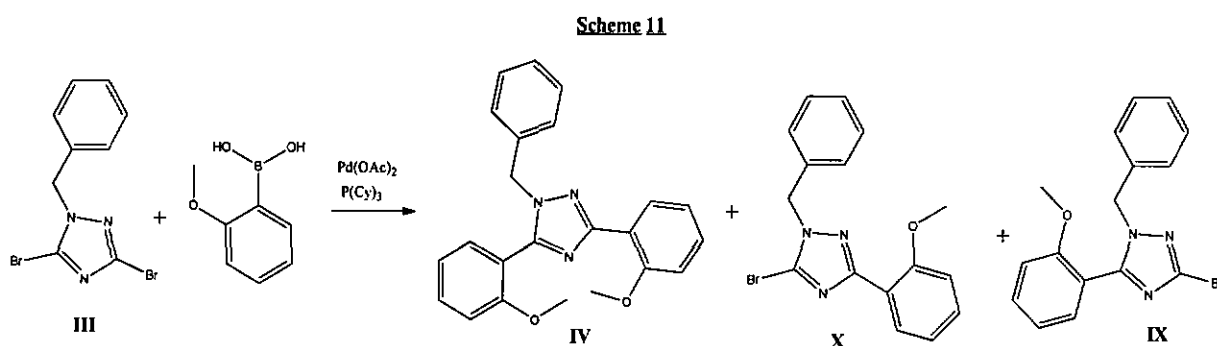
The process according to step (f) is carried out in presence of suitable base selected from potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydroxide, potassium hydroxide and the like; preferably sodium *tert*-butoxide.

Suzuki coupling reaction employing the bis(triphenylphosphine)palladium(II) dichloride in presence of organic base such as Hunig's base and inorganic bases such as potassium *tert*-butoxide in *n*-propanol gave 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole in 40 % isolated yield

as well as mixture of mono debrominated product, 1-benzyl-5-(2-methoxyphenyl)-1H-1,2,4-triazole/1-benzyl-3-(2-methoxyphenyl)-1H-1,2,4-triazole as shown in **Scheme 10**.



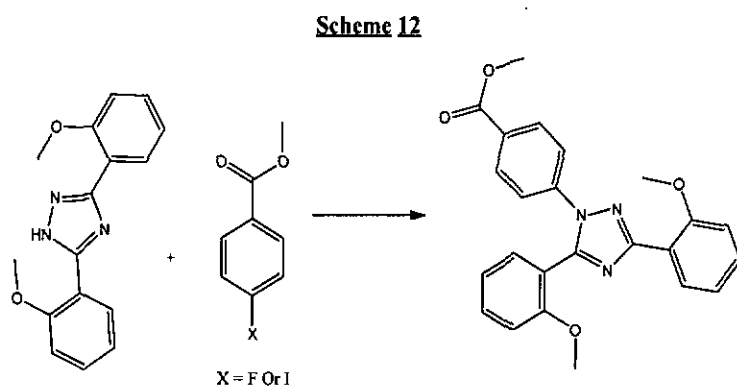
When Suzuki coupling reaction was carried out with the catalyst system consisting of $\text{Pd}_2(\text{dba})_3$ or $\text{Pd}(\text{OAc})_2$ and the necessary ligand such as tricyclohexyl phosphine, 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole was obtained in 50% isolated yield and mixture of mono coupled Suzuki product *i.e.* 1-benzyl-5-bromo-3-(2-methoxyphenyl)-1H-1,2,4-triazole and 1-benzyl-3-bromo-5-(2-methoxyphenyl)-1H-1,2,4-triazole was obtained in 30% yield as shown in **Scheme 11**.



1-Benzyl-5-bromo-3-(2-methoxyphenyl)-1H-1,2,4-triazole (X) and 1-benzyl-3-bromo-5-(2-methoxyphenyl)-1H-1,2,4-triazole (IX) could be converted to compound [VI] through Suzuki coupling employing the similar reaction condition, resulting in an increase in yield.

The nucleophilic displacement reaction of 4- fluoro benzoic acid methyl ester and anion of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole as well as Buchwald-Hartwig cross coupling reaction between 4- iodo benzoic acid methyl ester and 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole gave unsatisfactory yield towards the desired product(Scheme 12),thus alternative reaction scheme was employed such as,

- 1) Sodium hydride and 4- fluoro benzoic acid methyl ester,
- 2) *n*-Butyl lithium and 4- fluoro benzoic acid methyl ester,
- 3) Tris(dibenzylideneacetone)dipalladium and 4-iodo benzoic acid methyl ester
- 4) Copper(I) iodide and bipyridine and 4-iodo benzoic acid methyl ester.



De-methylation of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate to obtain compound [I] was achieved using 2-(diethylamino)ethanethiol, in presence of base and organic solvent at reaction temperature of about 150°C.

De-methylation reaction is carried out using base such as potassium tert-butoxide, sodium tert-butoxide, sodium hydroxide and the like;

De-methylation reaction is carried out in presence of organic solvents such as dimethylformamide, N-methyl pyrrolidone, dimethylsulfoxide and the like.

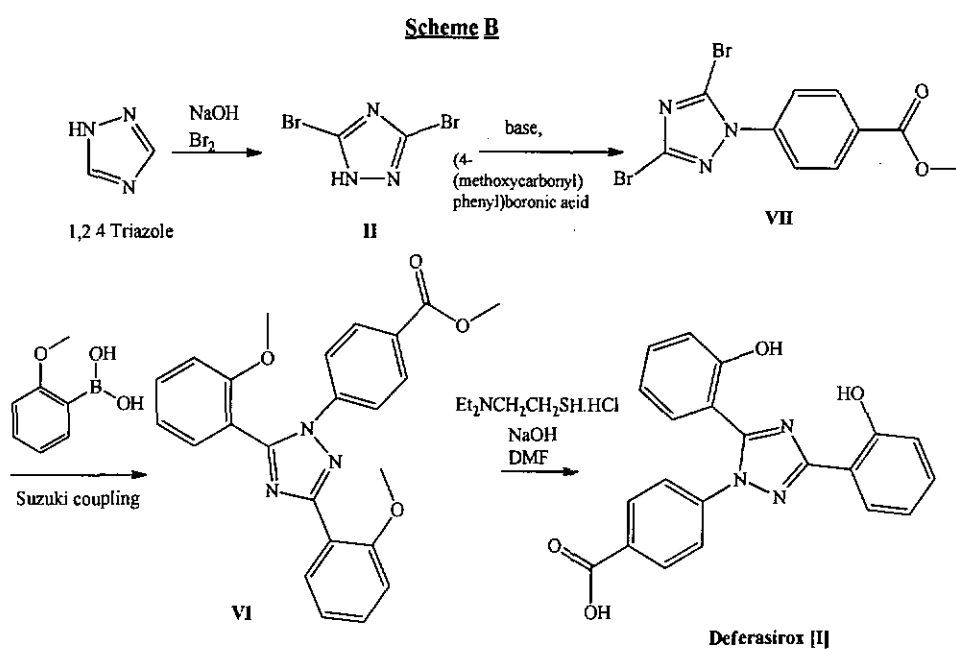
In another embodiment, the present invention provides the process for synthesis of Deferasirox(I), as per Scheme (B), comprising;

a) reaction of 1,2,4 triazole with bromine and aqueous sodium hydroxide solution to obtain 3,5-dibromo-1H-1,2,4-triazole (II);

b) copper-mediated cross coupling of compound (II) with (4-(methoxycarbonyl)phenyl)boronic acid in presence of suitable solvent and base gives compound (VII);

c) Suzuki coupling reaction of compound (VII) and (2-methoxyphenyl)boronic acid gives compound (VI); and

d) deprotection of compound (VI) in presence of 2-(diethylamino)ethanethiol, organic solvent and base gives compound [I].



The reaction according to step (a) is carried out in organic solvent selected from dichloromethane, chloroform, dichloroethane, water or mixture thereof; preferably dichloromethane and/or water; most preferably mixture of dichloromethane/water.

The copper salt used according to step (b) is selected from copper (I) chloride, copper (I) acetate, copper (II) chloride, copper (II) acetate, and copper (II) triflate; most preferably copper (II) acetate.

The solvent used according to step (b) is selected from dichloromethane, dimethylformamide, dioxane, and the like; most preferable dichloromethane.

The base used according to step (b) is selected from triethylamine, Hunig's base, pyridine and the like; most preferably pyridine.

The reaction according to step (c) is carried out in presence of suitable palladium catalyst, suitable base and suitable solvent.

The palladium catalytic system used in step (c) is selected from palladium acetate/tricyclohexyl phosphine, tris(dibenzylideneacetone)dipalladium and bis(triphenylphosphine)palladium (II) dichloride, palladium acetate/di(1-adamantyl)benzylphosphine hydrochloride; most preferably palladium acetate/tricyclohexyl phosphine.

The organic solvent used in step (c) is selected from alcohol like n-propanol, iso-propanol and the like; dipolar aprotic solvents such as dimethylacetamide, dimethylformamide, dimethyl sulfoxide and the like; preferably dimethylacetamide.

The reaction according to step (c) is carried out in presence of suitable base such as organic or inorganic base. The organic bases such as triethylamine, Hunig's base and the like; the inorganic bases are selected from potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, sodium tert-butoxide and the like' preferably Hunig's base and potassium tert-butoxide.

The process according to step (d) is carried in presence of suitable solvent selected from dimethylformamide, N-methyl pyrrolidone, tetrahydrofuran, dimethylsulfoxide and the like; preferably dimethylformamide.

The reaction according to step (d) is carried out at 70° to 200°C, preferably 100° to 150°C; most preferably reaction is carried out at 150°C.

The process according to step (d) is carried out in presence of suitable base selected from potassium tert-butoxide, sodium tert-butoxide, sodium hydroxide, potassium hydroxide and the like; preferably sodium tert-butoxide.

Suzuki coupling reaction in presence of catalytic system obtained from palladium acetate and tricyclohexyl phosphine gave the desired product in low yield. However, when reaction was carried out in presence of catalytic system obtained from di(1-adamantyl)-*n*-butylphosphine hydriodide and palladium acetate, it gave the desired product in satisfactory yield.

De-methylation of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate to obtain compound [I] was achieved using 2-(diethylamino)ethanethiol, in presence of base and organic solvent at reaction temperature of about 150°C.

De-methylation reaction is carried out using bases such as potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydroxide and the like;

De-methylation reaction is carried out in presence of organic solvents such as dimethylformamide, N-methyl pyrrolidone, dimethylsulfoxide and the like.

The following examples are meant to illustrate, but in no way to limit, the claimed invention.

Analytical Methods:

The purity was determined by HPLC using a Shimadzu LC 2010 system equipped with a column (Purosphere star RP-18e (4.6 × 150mm), 5µm), column oven temperature 25°C and UV-visible detector (UV at 340nm). Mobile phase was buffer: acetonitrile (55:45) with flow rate 3.0 mL⁻¹, injection volume 20 µL. NMR spectra were obtained at 200 and 400 MHz using Bruker instruments, with CDCl₃ as solvent unless otherwise stated. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (δ = 0 ppm). IR spectra were recorded on Perkin-Elmer Spectrum (Model: Spectrum 100) and absorption bands are given in cm⁻¹.

Example 1: Synthesis of 3,5-dibromo-1*H*-[1,2,4] triazole [II]

To a solution of 1,2,4-triazole (27.6 g) in dichloromethane (80 mL) was added solution of bromine in dichloromethane (50%v/v, 80 mL) and aqueous solution of sodium hydroxide (50% w/v, 96 mL) was added slowly as well as simultaneously at such rate that the temperature was kept between 10- 15°C. After complete addition, reaction was further stirred at 25 °C for 12 h. Then, 6 N aqueous hydrochloride was added and stirred for 1 h to precipitate out solid material, which was filtered under vacuum and dried under vacuum at 50°C to obtain off-white solid product in 90% isolated yield. The product was used without further purification.

Melting point: 204.8 -206.0 (lit⁹ mp: 211-212°C); PXRD [2θ] (Cu K_{α1} = 1.54060 Å, K_{α2} = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV):8.13, 15.14, 15.69, 17.49, 21.85, 23.21, 26.21, 26.36, 26.70, 29.50, 30.53, 31.80, 34.50, 35.39, 37.511, 38.688.

Example 2: Synthesis of 1-benzyl-3,5-dibromo-3,5-Dibromo-1H-[1,2,4] triazole [III]

To a solution of 3,5-dibromo-1H-[1,2,4] triazole (15 g) in acetonitrile (80 mL) was slowly added N,N-diisopropylethylamine (8.0 g) and solution of benzyl bromide (12.4 g) in dimethylformamide (15 mL). Resulting reaction mixture was stirred for 12 h at 80°C. Reaction was monitored on TLC for completion. After completion of reaction solvent was evaporated under reduced pressure to obtain residue water was added and extracted with dichloromethane (3x 100 mL). Combined organic layer was dried over magnesium sulphate and evaporated to obtain crude product, which was further purified through column chromatography to obtain white solid product in 80 % yield.

¹H NMR (CDCl₃, 400 MHz): δ 5.32 (s, 2H), 7.31-7.39 (m, 5H). ¹³C NMR (CDCl₃, 100 MHz): δ 53.7, 128.0, 128.8, 129.0, 129.4, 133.6, 140.3; ; PXRD [2θ] (Cu K_{α1} = 1.54060 Å, K_{α2} = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 10.53, 13.00, 14.63, 15.64, 15.91, 16.5, 18.80, 19.83, 20.33, 21.14, 24.46, 26.144, 28.10, 28.54, 28.76, 29.48, 30.89, 31.55, 32.09, 33.33, 35.47; IR 3088, 29.48, 15.86, 14.96, 1453, 1434, 1416, 1259, 1059

Melting point: 67.4-68.5 (lit⁹ mp: 64-66 °C)

Example 3: Synthesis of 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole [IV] by Suzuki coupling reaction [bis(triphenylphosphine)palladium(II) dichloride]

To a solution of 2-methoxy phenyl boronic acid (6.0 g) in *n*-propanol, diisopropyl ethyl amine (Hunig's base; 10 mL), Pd(PPh₃)₂Cl₂ (0.2 g) and potassium *tert*-butoxide (6.36 g) was added. A solution of 1-benzyl-3,5-dibromo-1H-[1,2,4] triazole (4.5 g) in *n*-propanol (100 mL) was added to above reaction mixture. Resulting reaction mixture was stirred at 115°C for 14 h. After cooling down, solvent was evaporated under reduced pressure and residue was suspended in 10% aqueous sodium hydroxide solution (20 mL). Aqueous phase was extracted with ethyl

acetate (3x50mL). The organic phases were combined, dried over anhydrous sodium sulfate and evaporated by a rotary evaporator to obtain crude product. Further purification was done by silica gel column chromatography using silica gel (100-200 mesh) as stationary phase and ethyl acetate/hexane(2:8) as mobile phase to obtain pure product 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (2.13 g 40% yield) as semi-solid material and also other product such 1-benzyl-3-(2-methoxyphenyl)-1H-1,2,4-triazole/1-benzyl-5-(2-methoxyphenyl)-1H-1,2,4-triazole (1.5 g) was obtained as semi-solid material.

1-Benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole: ^1H NMR (CDCl_3 , 400 MHz): δ 3.62(s, 3H), 3.90(s, 3H), 5.30(s, 2H), 6.93 (d, 1H), 6.99-7.04 (m, 3H), 7.11(d, 2H), 7.20-7.27 (m, 3H), 7.35(t, 1H), 7.42(d, 2H), 8.01(d, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 52.7, 55.2, 56.0, 111.0, 111.7, 117.4, 120.5, 120.54, 120.8, 127.4, 127.5, 127.7, 127.8, 128.1, 128.3, 130.2, 131.1, 131.8, 131.9, 136.2, 152.9, 157.1, 157.4, 160.0. **MS (EI):** $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2$; Exact Mass: 371.16, Observed Mass: 372.15

1-Benzyl-5-(2-methoxyphenyl)-1H-1,2,4-triazole(XI): ^1H NMR (CDCl_3 , 400 MHz): δ 3.72 (s, 3H), 5.19 (s, 2H), 6.99 (d, 1H), 7.04-7.10 (m, 3H), 7.28-7.31 (m, 3H), 7.36-7.39 (m, 1H), 7.48-7.53 (m, 1H), 8.25 (s, 1H). **MS (EI):** $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}$; Exact Mass: 265.12.03, Observed Mass: 266.35

1-Benzyl-3-(2-methoxyphenyl)-1H-1,2,4-triazole (XII): ^1H NMR (CDCl_3 , 400 MHz): δ 3.72 (s, 3H), 5.19 (s, 2H), 6.99 (d, 1H), 7.04-7.10 (m, 3H), 7.28-7.31 (m, 3H), 7.36-7.39 (m, 1H), 7.48-7.53 (m, 1H), 8.25 (s, 1H). **MS (EI):** $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}$; Exact Mass: 265.12.03, Observed Mass: 266.35

Example 4: Synthesis of 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole [IV] by Suzuki coupling reaction (palladium acetate and tricyclohexyl phosphine)

To a solution of 1-benzyl-3,5-dibromo-1H-[1,2,4] triazole (5.0 g) in dimethyl acetamide (67.5 g) under nitrogen atmosphere, 2-methoxy phenyl boronic acid (5.3 g) was added. A solution was stirred under nitrogen atmosphere for degassing for 30 min, after which potassium carbonate (5.5 g), tricyclohexyl phosphine (0.89 g) and palladium acetate (0.356 g) was added. Resulting reaction mixture was initially stirred for 30 min at 25°C and then at 130°C for 14 h. Reaction was monitored on TLC. After completion of reaction, it was cooled to room temperature and solvent was evaporated under reduced pressure and residue was suspended in 10% aqueous sodium hydroxide solution (20 mL). Aqueous phase was extracted with ethyl acetate (3x50mL) The organic phases were combined, dried over anhydrous sodium sulfate and evaporated by a rotary evaporator to obtain crude product. Further purification was done by silica gel (100-200 mesh) as stationary phase and ethyl acetate:n-hexane (2:8) as mobile phase to obtain product 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (3.25g, 55% yield) as semi-solid material and 1-benzyl-3-(2-methoxyphenyl)-1H-1,2,4-triazole/1-benzyl-5-(2-methoxyphenyl)-1H-1,2,4-triazole (1.42g 30%).

1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole: ¹H NMR (CDCl₃, 400 MHz): δ 3.62(s, 3H), 3.90(s, 3H), 5.30(s, 2H), 6.93 (d, 1H), 6.99-7.04 (m, 3H), 7.11(d, 2H), 7.20-7.27 (m, 3H), 7.35(t, 1H), 7.42(d, 2H), 8.01(d, 1H): ¹³C NMR (CDCl₃, 100 MHz): δ 52.7, 55.2, 56.0, 111.0, 111.7, 117.4, 120.5, 120.54, 120.8, 127.4, 127.5, 127.7, 127.8, 128.1, 128.3, 130.2, 131.1, 131.8, 131.9, 136.2, 152.9, 157.1, 157.4, 160.0. MS (EI): C₂₃H₂₁N₃O₂; Exact Mass: 371.16, Observed Mass: 372.15; PXRD [2θ] (Cu K_{α1} = 1.54060 Å, K_{α2} = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 8.09, 8.96, 12.30, 14.84, 16.43, 17.60, 17.93, 18.88, 20.92, 22.29, 24.70, 15.59, 30.02, 30.31.

1-Benzyl-3-bromo-5-(2-methoxyphenyl)-1H-1,2,4-triazole (IX): ^1H NMR (CDCl_3 , 400 MHz): δ 3.72 (s, 3H), 5.19 (s, 2H), 6.99 (d, 1H), 7.04-7.10 (m, 3H), 7.28-7.31 (m, 3H), 7.36-7.39 (m, 1H), 7.48-7.53 (m, 1H). MS (EI): $\text{C}_{16}\text{H}_{14}\text{BrN}_3\text{O}$; Exact Mass: 343.03, Observed Mass: 343.6 & 345.6 (bromo pattern)

1-Benzyl-5-bromo-3-(2-methoxyphenyl)-1H-1,2,4-triazole (X): ^1H NMR (CDCl_3 , 400 MHz): δ 3.72 (s, 3H), 5.19 (s, 2H), 6.99 (d, 1H), 7.04-7.10 (m, 3H), 7.28-7.31 (m, 3H), 7.36-7.39 (m, 1H), 7.48-7.53 (m, 1H). MS (EI): $\text{C}_{16}\text{H}_{14}\text{BrN}_3\text{O}$; Exact Mass: 343.03, Observed Mass: 343.6 & 345.6 (bromo pattern)

Example 5: Synthesis of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (V) from 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (IV)

1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (2.8 g) was dissolved in ethanol (50 mL) at RT and transferred to a Parr autoclave reactor. Palladium on carbon (0.28 g) was added to the reaction mass which was then flushed twice with nitrogen and once with hydrogen. Subsequently, a hydrogen pressure of 5-7 kg/cm^2 was maintained for 12 h at RT. Reaction was monitored on TLC. After completion of reaction, palladium on carbon was filtered through a Celite bed. The mother liquor was concentrated under reduced pressure to give crude product 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole, which was further purified through column chromatography using silica gel (100-200 mesh) as stationary phase and ethyl acetate: hexane (30:70) as mobile phase to obtain pure product as light yellow solid (1.9g, 90%)

3,5-Bis(2-methoxyphenyl)-1H-1,2,4-triazole: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 3.92(s, 6H), 7.14(t, 2H), 7.25(d, 2H), 7.57(t, 2H), 7.97 (d, 2H), 9.0(bs, 1H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ

56.4, 112.7, 114.6, 121.2, 130.6, 133.2, 152.5, 157.5 MS (EI): $C_{16}H_{15}N_3O_2$ Exact Mass: 281.12, Observed Mass: 282.10; Melting point: 197.8-200.8°C; PXRD $[2\theta]$ (Cu $K_{\alpha 1}$ = 1.54060 Å, $K_{\alpha 2}$ = 1.54443 Å, K_{β} = 1.39225 Å; 40 mA, 45 kV): 5.15, 7.70, 9.51, 10.3, 10.62, 12.55, 14.15, 15.45, 15.94, 17.29, 19.35, 19.45, 19.85, 21.31, 21.72, 23.02, 23.19, 24.17, 24.82, 25.15, 25.82, 26.21, 27.08, 28.41, 29.68, 31.74, 32.67, 35.94.

Example 6: Synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) (Chan-Lam Coupling reaction):

To a solution of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (0.5 g) in dichloromethane (40 mL) was added (4-(methoxycarbonyl)phenyl)boronic acid (0.64g), copper(II) acetate (0.75 g), pyridine (2.0g) and 4A molecular sieve. The resulting reaction was stirred for 14 h at 25°C and after completion of reaction, reaction mass was filtered through a Celite bed to remove inorganic mass. The mother liquor was concentrated under reduced pressure to give crude product methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate, which was further purified through column chromatography using silica gel (100-200 mesh) as stationary phase and ethyl acetate: hexane (30:70) as mobile phase to obtain pure product as off-white solid (0.44 g, 60%)

1H NMR ($CDCl_3$, 400 MHz): δ 3.32(s, 3H), 3.93(s, 3H), 3.98(s, 3H), 6.82 (d, 1H), 7.05-7.14 (m, 3H), 7.41-7.49 (m, 4H), 7.71 (d, 1H), 8.01-8.07(m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.4, 54.9, 56.9, 111.3, 111.7, 117.9, 119.8, 120.7, 121.2, 122.8, 129.1, 130.3, 130.5, 130.8, 131.3, 131.6, 132.3, 142.8, 152.2, 156.6, 157.7, 160.9, 166.4. MS (EI): $C_{24}H_{21}N_3O_4$: Exact Mass: 415.15, Observed Mass: 415.95

Example 7: Synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) (Buchwald-Hartwig coupling reaction)

To a solution of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (0.2g) in DMF(15 mL) was added copper (I) iodide (0.5 g), bipyridine (0.3 g) and potassium phosphate (0.3 g) at 30⁰C. The resulting reaction mixture was added to a solution of 4-iodomethyl benzoate (0.25 g) in DMF (10 mL) and stirred for 24 h at 150⁰C. Reaction was monitored on TLC for formation of product with authentic product.

Example 8: Synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) (Buchwald-Hartwig coupling reaction)

To a solution of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (0.2g) in DMF(15 mL) was added Pd₂(dba)₃ (0.03 g) and sodium methoxide (0.1 g) at 30⁰C. The resulting reaction mixture was added to a solution of 4-iodomethyl benzoate (0.25 g) in DMF (10 mL) and stirred for 24 h at 100⁰C. Reaction was monitored on TLC for formation of product with authentic product.

Example 9: Synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI)

A solution of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (0.1g) in dimethyl sulfoxide (15 mL) was added to sodium hydride (0.02 g) at 30⁰C under nitrogen atmosphere. To the resulting reaction mixture was added to solution of 4-fluoromethyl benzoate (0.25 g) in dimethyl sulfoxide (10 mL) was added and stirred for 10 h at 80 ⁰C. Reaction was monitored on TLC for formation of product with authentic product.

Example 10: Synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI)

To a solution of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (0.1g) in dioxane (15 mL) was added 2M solution of n-butyl lithium in cyclohexane (1 mL) at -30⁰C. The resulting reaction mixture was added to a solution of 4-fluoromethyl benzoate (0.25 g) in dioxane (10 mL) and stirred for 10 h at 0⁰C. Reaction was monitored on TLC for formation of product with authentic product.

Example 11: Synthesis of Deferasirox [I]

To a solution of 2-(diethylamino)ethanethiol (2.7g) in dimethylformamide (27 mL) under nitrogen atmosphere was added sodium *tert*-butoxide (3.0g) at 0⁰C. To this resulting solution methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (2.1 g) was added and stirred the reaction mixture at 150⁰C for 2 h. Reaction was monitored on TLC. After cooling to 25⁰C, water (150 mL) was added. Resulting mixture was extracted with ethyl acetate (3X50 mL). The combined organic layer was dried over anhydrous sodium sulphate and solvent was evaporated under reduced pressure to obtain Deferasirox (1.7 g) as off-white solid (yield: 76%)

Example 12: Synthesis of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII)

To a solution of 3,5-dibromo 1,2,4 triazole (2.8 g) in dichloromethane (40 mL) was added (4-(methoxycarbonyl)phenyl)boronic acid (2.0g), copper(II) acetate (4.0 g), pyridine (1.75g) and 4Å molecular sieve. Stirred the resulting reaction for 14 h at 25⁰C and after completion of reaction, reaction mass was filtered through a Celite bed to remove inorganic mass. The mother liquor was concentrated under reduced pressure to give crude product methyl 4-(3,5-dibromo-

1H-1,2,4-triazol-1-yl)benzoate, which was further purified through column chromatography using silica gel (100-200 mesh) as stationary phase and ethyl acetate: hexane (30:70) as mobile phase to obtain pure product as off-white solid (2.75 g, 60 %).

Methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate: FTIR (neat): 2957, 1724, 1607, 1510, 1447, 1391, 1311, 1295, 1266, 1118, 1003, 857, 769 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 3.97(s, 3H), 7.69 (d, 2H), 8.21 (d, 2H), ^{13}C NMR (CDCl_3 , 100 MHz): δ 52.7, 124.38, 129.2, 130.9, 130.9, 131.4, 139.3, 141.9, 165.7 MS (EI): $\text{C}_{10}\text{H}_7\text{Br}_2\text{N}_3\text{O}_2$: Exact Mass: 361.89 (100%), Observed Mass : 361.90 (dibromo pattern). Melting point: 139.2-140.9 $^\circ\text{C}$; PXRD $[2\theta]$ (Cu $K_{\alpha 1}$ = 1.54060 Å, $K_{\alpha 2}$ = 1.54443 Å, K_{β} = 1.39225 Å; 40 mA, 45 kV): 3.79, 5.05, 7.38, 3.00, 9.49, 11.16, 14.71, 15.24, 15.95, 17.42, 21.56, 21.87, 22.00, 22.31, 24.19, 24.75, 26.41, 27.83, 30.81, 31.58, 33.68, 36.79, 37.16, 39.05.

Example 13: Synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate through Suzuki coupling reaction between compound (VII) and (2-methoxyphenyl)boronic acid

To a solution of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate(1.5 g) in dimethyl acetamide (67.5 g) under nitrogen atmosphere, 2-methoxy phenyl boronic acid (2.52 g) was added. The solution was stirred under nitrogen atmosphere for degassing for 30 min, after which potassium carbonate (1.43 g), tricyclohexyl phosphine (0.234 g) and palladium acetate (0.093 g) were added. Resulting reaction mixture was initially stirred for 30 min at 25 $^\circ\text{C}$ and then at 135 $^\circ\text{C}$ for 14 h. Reaction was monitored on TLC and product was confirmed by matching with authentic sample in TLC as well HPLC.

Example 14: Synthesis of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate through Suzuki coupling reaction between (VII) and (2-methoxyphenyl)boronic acid

To a solution of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate(02 g) in dimethyl acetamide (25 mL) under nitrogen atmosphere, 2-methoxy phenyl boronic acid (0.52 g) was added. The solution was stirred under nitrogen atmosphere for degassing for 30 min, after which potassium carbonate (0.43 g), di(1-adamantyl)-*n*-butylphosphine hydriodide (0.234 g) and palladium acetate (0.093 g) were added. Resulting reaction mixture was initially stirred for 30 min at 25⁰C and then at 135⁰C for 14 h. Reaction was monitored on TLC and product was confirmed by matching with authentic sample in TLC as well HPLC.

Example 15: Methyl 4-(1H-1,2,4-triazol-1-yl)benzoate [VIII]

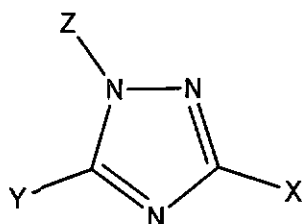
To a solution of 1,2,4-triazole (15 g) in acetonitrile (80 mL) were slowly added sodium methoxide (8.0 g) and solution of 4-fluoro benzoic acid methyl ester (12.4 g) in acetonitrile (15mL). Resulting reaction mixture was stirred for 12 h at 80 ⁰C. Reaction was monitored on TLC for completion. After completion of reaction solvent was evaporated under reduced pressure to the obtained residue water was added and extracted with dichloromethane (3x 100 mL). Combined organic layer was dried over magnesium sulphate and evaporated to obtain crude product, which was further purified through column chromatography to obtain white solid product in 80 % yield.

FTIR (neat): 2876, 1720, 1660, 1440, 1278, 1102, 768 cm⁻¹; **¹H NMR (DMSO-D₆, 400 MHz):** δ 3.86(s, 3H), 7.94 (s, 1H), 8.01 (d, 2H), 8.11 (d, 2H), 8.26 (s, 1H); **¹³CNMR (CDCl₃, 100 MHz):**

δ 52.7, 119.5, 128.9, 131.3, 140.5, 143.3, 153.3, 165.8 ; **MS (EI):** C₁₀H₉N₃O₂: Exact Mass: 203.07,
Observed Mass: 203.95

WE CLAIM:

1. Compounds of the formula having following structure,



Compound (IV) when X=Y= O-methoxyphenyl & Z= Benzyl

Compound (V) when X=Y= O-methoxyphenyl & Z= H

Compound (VI) when X=Y= O-methoxyphenyl & Z= Benzoic acid ester

Compound (VII) when X=Y= Br & Z= Benzoic acid ester

Compound (IX) when X=Br, Y= O-methoxyphenyl & Z= Benzyl

Compound (X) when X= O-methoxyphen, Y= Br & Z= Benzyl

Compound (XI) X=H, Y= O-methoxyphenyl & Z= Benzyl

Compound (XII) X=O-methoxyphenyl, Y=H & Z= Benzyl

2. A process for the synthesis of Deferasirox[I] comprising;

- a) Preparation of 3,5-dibromo-1H-1,2,4-triazole (II) from 1,2,4 triazole;
- b) reaction of compound (II) with benzyl bromide to form 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III);
- c) reaction of compound (III) and (2-methoxyphenyl)boronic acid to give 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV);
- d) compound (IV) being reacted with suitable reactants to give compound (V);
- e) reacting compound (V) with (4-(methoxycarbonyl)phenyl)boronic acid to give compound (VI); and
- f) deprotection of compound (VI) to give compound [I].

3. The process according to claim 2, wherein preparation of compound (II) from 1,2,4-triazole mentioned in step a) is carried out in dichloromethane/ water biphasic mixture employing bromine and aqueous solution of sodium hydroxide.
4. The process according to claim 2, wherein reaction of 3,5-dibromo 1H-1,2,4-triazole (II) and benzyl bromide as mentioned in step b) for formation of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) is carried out in presence of suitable base selected from triethyl amine, Hunig's base, potassium carbonate, sodium carbonate; preferably Hunig's base and in organic solvent such as acetonitrile at temperature 80°C.
5. The process according to claim 2, wherein reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) and (2-methoxyphenyl)boronic acid as mentioned in step c) for formation of 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV) is carried out through Palladium catalyzed Suzuki coupling reaction in suitable organic solvent and in presence of suitable base.
6. The process according to claim 5, wherein palladium catalytic system for Suzuki reaction is selected from palladium acetate/tricyclohexyl phosphine, tris(dibenzylideneacetone)dipalladium and bis(triphenylphosphine)palladium(II) dichloride, palladium acetate/di(1-adamantyl)benzylphosphine hydroiodide; preferably palladium acetate/tricyclohexyl phosphine.
7. The process according to claim 5, wherein organic solvent is selected from n-propanol, isopropanol, dimethyl acetamide, preferably dimethyl acetamide.
8. The process according to claim 5, wherein base is selected from triethyl amine, Hunig's base, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, preferably Hunig's base and potassium tert-butoxide.

9. The process according to claim 2, wherein reaction of 1-benzyl-3,5-bis[2-methoxyphenyl]-1H-1,2,4-triazole (IV) as mentioned in step d) for formation of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (V) is through hydrogenolysis using noble metal catalyst such as 5-10% palladium on carbon, palladium hydroxide; preferably 10% palladium on carbon at reaction temperature 25⁰C, under hydrogen pressure of 7-10 kg; in organic solvent such ethanol.

10. The process according to claim 2, wherein reaction of 3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (V) and (4-(methoxycarbonyl)phenyl)boronic acid as mentioned in step e) for formation of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) is through using copper catalyzed Chan-Lam coupling reaction in suitable organic solvent and in presence of suitable base.

11. The process according to claim 10, wherein copper salt used in Chan-Lam coupling reaction is selected from copper (I) chloride, copper(I) acetate, copper (II) chloride, copper (II) triflate & copper (II) acetate, preferably copper (II) acetate.

12. The process according to claim 10, wherein organic solvent used is selected from dichloromethane, Dimethylformamide, dioxane, preferably dichloromethane.

13. The process according to claim 10, wherein base used is selected from triethyl amine, Hunig's base, pyridine, preferably pyridine.

14. The synthesis of Deferasirox from methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate as mentioned in step f) of claim 2 is carried out in presence of 2-(diethylamino)ethanethio in organic solvent and in presence of base at 140-160 ⁰C; preferably at 150⁰C

15. The process according to claim 14, wherein organic solvent is selected from Dimethylformamide, N-methyl pyrrolidone, tetrahydrofuran, dimethylsulfoxide, preferably dimethylformamide.

16. The process according to claim 14, wherein base used is selected from potassium tert-butoxide, sodium tert-butoxide, sodium hydroxide, potassium hydroxide, preferably sodium tert-butoxide.

17. A process for the synthesis of Deferasirox[I] comprising;

- a) preparation of 3,5-dibromo 1H-1,2,4triazole (II) from 1,2,4-triazole;
- b) reacting 3,5-dibromo 1H-1,2,4triazole (II) and (4-(methoxycarbonyl)phenyl)boronic acid to form methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII);
- c) reaction of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) and (2-methoxyphenyl)boronic acid to form Synthesis of 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI);
- d) deprotection of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) to form deferasirox (I)

18. The process according to claim 17, wherein synthesis of compound (II) from 1,2,4-triazole mentioned in step a) is carried out in dichloromethane/ water biphasic mixture employing bromine and aqueous solution of sodium hydroxide at 10-15 °C.

19. The process according to claim 17, wherein reaction of 3,5-dibromo 1H-1,2,4triazole (II) and (4-(methoxycarbonyl)phenyl)boronic acid as mentioned in step b) for preparation of methyl

4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) is carried through using copper catalyzed Chan-Lam coupling reaction in suitable organic solvent and in presence of suitable base.

20. The process according to claim 19, wherein copper salt used in Chan-Lam coupling reaction is selected from copper (I) chloride, copper(I) acetate, copper (II) chloride, copper (II) triflate & copper (II) acetate, preferably copper (II) acetate.

21. The process according to claim 19, wherein organic solvent is selected from dichloromethane, Dimethylformamide, dioxane, preferably dichloromethane.

22. The process according to claim 19, wherein base is selected from triethyl amine, Hunig's base, pyridine, preferably pyridine.

23. The process according to claim 17, wherein reaction of methyl 4-(3,5-dibromo-1H-1,2,4-triazol-1-yl)benzoate (VII) and (2-methoxyphenyl)boronic acid as mentioned in step c) for formation of 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) is carried through palladium catalyzed Suzuki coupling reaction in suitable organic solvent in presence of suitable base.

24. The process according to claim 23, wherein palladium catalytic system for Suzuki reaction is selected from palladium acetate/tricyclohexyl phosphine, tris(dibenzylideneacetone)dipalladium and bis(triphenylphosphine)palladium(II) dichloride, palladium acetate/di(1-adamantyl)benzylphosphine hydroiodide, preferably palladium acetate/di(1-adamantyl)benzylphosphine hydroiodide

25. The process according to claim 23, wherein organic solvent is selected from n-propanol, isopropanol, dimethyl acetamide, preferably dimethyl acetamide.

26. The process according to claim 23, wherein base is selected from triethyl amine, Hunig's base, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, preferably Hunig's base and potassium tert-butoxide.
27. The process according to claim 17, wherein deprotection of methyl 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate as mentioned in step d) for formation of 4-(3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzoate (VI) is carried out in presence of 2-(diethylamino)ethanethio in organic solvent and in presence of base at 140-160 °C; preferably at 150°C
28. The process according to claim 27, wherein organic solvent is selected from Dimethylformamide, N-methyl pyrrolidone, Tetrahydrofuran, Dimethylsulfoxide, preferably dimethylformamide.
29. The process according to claim 27, wherein base is selected from potassium tert-butoxide, sodium tert-butoxide, sodium hydroxide, potassium hydroxide; preferably sodium tert-butoxide.
30. A process for the preparation of compound (IV) comprising reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole (III) with (2-methoxyphenyl)boronic acid in the presence of suitable palladium catalyst, a suitable base and a suitable solvent.
31. A process for the preparation of compound (V) comprising debenzylation of 1-benzyl-3,5-bis(2-methoxyphenyl)-1H-1,2,4-triazole (IV) using noble metal catalyst.
32. A process for the preparation of compound (VI) comprising copper-mediated cross coupling of compound (V) with (4-(methoxycarbonyl)phenyl)boronic acid in presence of suitable solvent and suitable base.

33. The process for preparation of compound (VII) comprising copper-mediated cross coupling of compound (II) with (4-(methoxycarbonyl)phenyl)boronic acid in presence of suitable solvent and base.

34. A process for the preparation of compound (IX) or (X) comprising Suzuki coupling of compound (III) with (2-methoxyphenyl)boronic acid in presence of palladium catalyst, ligand, organic solvent and a base.

35. A process for the preparation of compounds (XI) or (XII) comprising Suzuki coupling of compound (III) with (2-methoxyphenyl)boronic acid in presence of palladium catalyst, organic solvent and a base.

Dated this 12th day of September 2013



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