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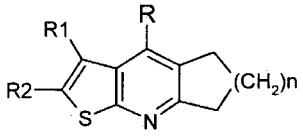
(54) **Title**: THIENOPYRIDINES AS PHARMACOLOGICALLY ACTIVE AGENTS



(I)

(57) **Abstract**: The present invention provides compounds and pharmaceutically acceptable salts thereof methods for synthesizing thienopyridines and methods for inhibiting TNF- α activity for the treatment of cancer, asthma, arthritis, diabetes and inflammation. Provided- are compounds of formula (I).

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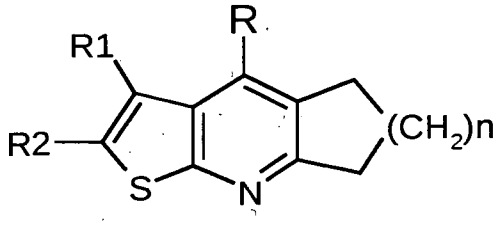
AMENDED CLAIMS
received by the Internationnal Bureau on 18 August 2010 (18.08.10)

1. Thienopyridine compounds of the formula I below



Formula I

where n is 1, 2, 3 or 4,

R1 and R2 are independently selected from the group consisting of , alkyl excluding CH_3 and aryl; wherein, when R1 is aryl R2 is not aryl and when R2 is aryl R1 is not aryl; or R1+R2 is selected from cyclopentyl, cycloheptyl, bicycloalkyl, and alkyl of more than 2 carbon chains;

R is selected from the group consisting of amine, sulfonamide, sulfonyl alkyl, alkyl or cycloalkyl, aryl, hydroxamate, and heterocyclic moieties;

the said heterocyclic moiety is selected from imidazole, triazole, tetrazole, pyridine, benzimidazole, quinazoline, quinoline, thiophene, thienopyrimidine, thienopyridine, acridine, indole, pyrrole and benzofuran and pharmaceutically acceptable salts thereof.

2. A thienopyridine compound as claimed in claim 1 wherein the ring is a substituted ring wherein the substituents are selected from the group consisting of –H, -(C_1-C_3) alkyl, -O(C_1-C_3) alkyl, -F, -CF_3, -NH_2, - $N(CH_3)$, -$N(CH_3)_2$, -SH, -SCH_3, -SCH_2CH_3 and any combination thereof.

3. A compound as claimed in claim 1 selected isomers of compounds of the general formula I, inclusive of their stereoisomeric forms, polymorphs, acid addition salts, base addition salts, and prodrugs thereof.

4. A compound as claimed in any preceding claim wherein the acid addition salt is selected from the group consisting of acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, napthelene-2-benzoate, isobutyrate, phenylbutyrate, b-hydroxybutyrate, butyne-1-4-dioate, hexyne-1-4-dioate, caprate, caprylate, cinnamate, citrate, formate, fumerate, glycollate, heptanoate, hippurate, lactate, maleate, malate, hydroxymaleate, malonate, madelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, and tartarate.

5. A compound as claimed in any preceding claim wherein the acid addition salt is selected from the group consisting of hydrocloride, hydrobromide, citrate and oxalate.

6. A compound as claimed in claims 1 to 3 wherein the basic addition salts are formed from inorganic bases selected from the group consisting of sodium, potassium, lithium, calcium, aluminium, ammonium, barium, zinc, and magnesium.

7. A compound as claimed in claims 1 to 3 wherein the basic addition salt is selected from the group consisting salts obtained from an organic base selected in turn from the group consisting of N-N'-dibenzylethelynediamine, choline, diethanolamine, ethelenediamine, N-methylglucamine, triethylamine, dimethylamine and procaine.

8. A compound as claimed in claims 1 to 3 wherein the salt is an amine salt such as an arginate.

9. A compound as claimed in claims 1 to 3 wherein the prodrug is selected from the group obtained by conjugation of compounds of formula I with sugar moieties with suitable spacers, and alkyl esters obtained by reaction of the parent acid with a suitable alcohol, or amides obtained by reaction of parent acidic compound with a suitable amine.

10. A compound as claimed in any preceding claim wherein aryl is selected from phenyl, biphenyl, benzyl, naphthyl, anthryl, phenanthryl, fluorenyl and indenyl.

11. A compound as claimed in any of claims 1 to 10 wherein the heterocycle is selected from the group consisting of imidazole, triazole, tetrazole, indole, and pyrrole.

12. A compound as claimed in claim 11, wherein the heterocycle has one or more heteroatoms selected from O, S and N in the aromatic ring.

13. A compound as claimed in claim 1 wherein the compound is 2,3,6,7,8,9-hexahydro-1*H*-benzo[4,5]thieno[2,3-*b*]cyclopenta[*e*]pyridin-10-amine.

14. A compound as claimed in claim 1 wherein the compound is 2,3,4,7,8,9,10,11-octahydro-1*H*-benzo[4,5] thieno[2,3-*b*] cyclohepta [*e*]pyridin-12-amine.

15. A compound as claimed in claim 1 wherein the compound is 1,2,3,6,7,8-hexahydrocyclopenta[*b*]cyclopenta[4,5]thieno[3,2-*e*]pyridin-9-amine.

16. A compound as claimed in claim 1 wherein the compound is 2,3,6,7,8,9-hexahydro-1*H*-cyclopenta[4,5]thieno[2,3-*b*]quinolin-10-amine.

17. A compound as claimed in claim 1 wherein the compound is 7-methyl-2,3,6,7,8,9-hexahydro-1*H*-cyclopenta[4,5]thieno[2,3-*b*]quinolin-10-amine.

18. A compound as claimed in claim 1 wherein the compound is 1,2,3,6,7,8,9,10-octahydrocyclohepta[*b*]cyclopenta[4,5]thieno [3,2- *e*] pyridine -11-amine.

19. A compound as claimed in claim 1 wherein the compound is 2,3,6,7,8,9,10,11-octahydro-1*H*-cycloocta[*b*]cyclopenta[4,5]thieno[3,2-*e*]pyridin-12-amine.

20. A compound as claimed in claim 1 wherein the compound is 1,2,3,6,7,8,9,10-octahydrocyclohepta[4,5]thieno[2,3-*b*]cyclopenta[*e*]pyridin-11-amine.

21. A compound as claimed in claim 1 wherein the compound is 2,3,4,7,8,9,10,11-octahydro-1*H*-cyclohepta[4,5]thieno[2,3-*b*]quinolin-12-amine.

22. A compound as claimed in claim 1 wherein both R1+R2 is alkyl.

23. A compound as claimed in claim 1 wherein R1+R2 is selected from the group consisting of , $-(CH_2)_3-$, $-(CH_2)_5-$.

24. A compound as claimed in claims 1 and 28 wherein n is 1, 2 or 3.

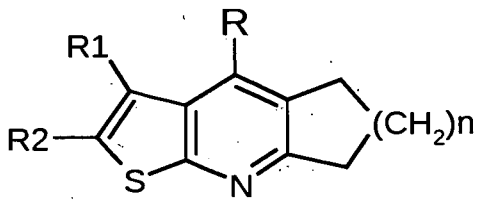
25. A compound as claimed in claims 1 and 30 wherein n is 1, 2 or 3.

26. A compound as claimed in claim 1 to 30 wherein R is NH_2.

27. . A method for the preparation of a compound of general formula I, said method comprising

(a) synthesizing 2-amino 3-cyano thiophene;

(b) reacting the 2-amino 3-cyano thiophene with a cyclic ketone under conditions suitable to obtain the corresponding product of formula I



Formula I

where n is 1, 2, 3 or 4

R1 and R2 are independently selected from the group consisting of alkyl excluding CH_3 and aryl; wherein, when R1 is aryl R2 is not aryl and when R2 is aryl R1 is not aryl; or R1+R2 is selected from cyclopentyl, cycloheptyl, bicycloalkyl, and alkyl;

R is selected from the group consisting of amine, sulfonamide, sulfonyl alkyl, alkyl or cycloalkyl, aryl, hydroxamate, and heterocyclic moieties;

wherein the heterocyclic moiety is selected from imidazole, triazole, tetrazole, pyridine, benzimidazole, quinazoline, quinoline, thiophene, thienopyrimidine, thienopyridine, acridine, pyrrole, indole and benzofuran and pharmaceutically acceptable salts thereof.

28. A method as claimed in claim 34 wherein the reaction with cyclic ketone is carried out by formation of a zinc chloride complex, followed by treatment with a base to precipitate the product from the complex, followed by separation and purification, and if desired, conversion to the desired ester, or salt form.

29. A method as claimed in claims 34 and 35 wherein the reaction with zinc chloride is carried out by heating under reflex for a time suitable to form a complex.

30. A method as claimed in claims 34 to 36 wherein the thiophene and the cyclic ketone are reacted at a molar ratio of 1:2.

31. A method as claimed in any of claims 34 to 37 wherein the base is NaOH.

32. A method as claimed in any of claims 34 to 38 wherein the 2-amino, 3-cyano thiophene is prepared by reacting sulphur, melanonitrile and respective ketone in the presence of an alcohol under stirring.

33. A method as claimed in any of claims 34 to 39 wherein the compound of formula I is reacted with an equimolar amount or an excess of acid in a neat or in a suitable inert solvent to form the corresponding acid addition salt.

34. A method as claimed in claim 40 wherein the acid is selected from the group consisting of hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, aliphatic mono and dicarboxylic acid, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids.

35. A method as claimed in any of claims 34 to 39 wherein the compound of formula I is reacted in an inert suitable solvent or a neat solvent with an equimolar or excess amount of a base to form the corresponding base addition salt.

36. A method as claimed in claim 42 wherein the base is selected from sodium, potassium, lithium, calcium, aluminium, ammonium, barium, zinc, magnesium, N-N'-dibenzylethelynediamine, choline, diethanolamine, ethelenediamine, N-methylglucamine, triethylamine, dimethylamine, and procaine, and amino acids to obtain the respective basic addition salts.

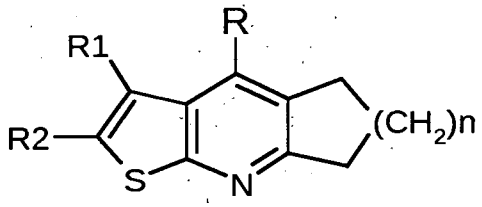
37. A method as claimed in any of claims 34 to 41 wherein the salt is formed by sending the dry acidic gas into the methanolic solution of the compound.

38. A method as claimed in any of claims 34 to 39 wherein the prodrug is obtained by conjugation of compounds of formula (I) with sugar moieties adding suitable spacers, or alkyl esters prepared by the reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with suitable amine.

39. A pharmaceutical composition comprising the compound of formula I or a salt or ester

or prodrug form thereof with one or more pharmaceutically acceptable excipients.

40. A pharmaceutical composition comprising the compound of formula I



where n is 1, 2, 3 or 4,

R1+R2 are independently selected from the group consisting of alkyl excluding CH_3 and aryl; wherein, when R1 is aryl R2 is not aryl and when R2 is aryl R1 is not aryl; or R1+R2 is selected from cyclopentyl, cycloheptyl, bicycloalkyl, and alkyl of more than 2 carbon chains;

R is selected from the group consisting of amine sulfonamide, sulfonyl alkyl, alkyl or cycloalkyl, aryl, hydroxamate, and heterocyclic moieties;

wherein the said heterocyclic moiety is selected from imidazole, triazole, tetrazole, pyridine, benzimidazole, quinazoline, quinoline, thiophene, thienopyrimidine, thienopyridine, acridine, indole, pyrrole and benzofuran and pharmaceutically acceptable salts thereof

with a conventional active agent for treatment of diabetes, cancer, arthritis or inflammation.

41. A composition as claimed in claim 47, wherein het additional active selected from the group consisting of alkylating agents, antimetabolites, antibiotics, immunomodulating agents, nucleotide derivatives, cyclin dependent kinase inhibitors, interferon like agents and histone deacytalase inhibitors.

42. A composition as claimed in claim 47 wherein the additional active is selected from the group consisting of COX-II inhibitors such as nimuselide, celocoxib, etorocoxib, and

valdicoxib.

43. A composition as claimed in claim 47 wherein the additional active is selected from the group consisting of sulphonylureas, Biguanides, Meglitinides, Glitazones, and -Glucosidase Inhibitors.

44. A composition as claimed in any of claims 46 to 50 wherein the pharmaceutically acceptable excipients are selected from the group consisting of pharmaceutically acceptable carrier or diluent.

45. A composition as claimed in claim 51 wherein the carrier or diluents is selected from the group consisting of water, salt solutions, alcohols, polyethylene glycols, polyhydroxy ethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, sucrose, cyclodextrin, amylose, magnesium stereate, talc, agar, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides, fatty acid diglycerides, polyoxyethylene, hydroxymethylcellulose, and polyvinylpyrrolidine.

STATEMENT UNDER ARTICLE 19 (1)

With reference to the search report and written opinion of the International Searching Authority [ISA/EP], we are suitably amending the claims to establish the novelty and inventive step in present invention.

- Claims 2-12, 17, 20-27, 29-33, 35-46 and 48-52 remain unchanged.
- Claims 13-16, 18-19 and 28 have been deleted.
- Claims 1, 30, 34 and 47 have been suitably amended.
- Claims 17 -52 have been renumbered.
- Any additions in the claims have been indicated by underline and any deletion in the claims have been indicated by strike through.

The amended claims do not go beyond the disclosure of the international application as filed and have no impact on the description and drawings as filed.