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FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

AND

The Patents Rules, 2003

COMPLETE SPECIFICATION

(See section 10 and rule13)

1. TITLE OF THE INVENTION:

"Triaminotriazine Picolinonitrile Derivatives As Potent Reverse Transcriptase Inhibitor of HIV-1"

2. APPLICANT:

(a) NAME: Shri Chhatrapti Shivaji College (affiliated to Dr. Babasaheb Ambedkar Marathwada University, Auranagabad, Maharashtra, India.)

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(b) NATIONALITY: Indian Academic research Institution

(c) ADDRESS: 73, G Block, Bhosari Industrial Estate, Bhosari, Pune-411026, Maharashtra, India.

3.PREAMBLE TO THE DESCRIPTION:

The following specification particularly describes the invention and the manner in which it is to be performed.

Technical field of the invention

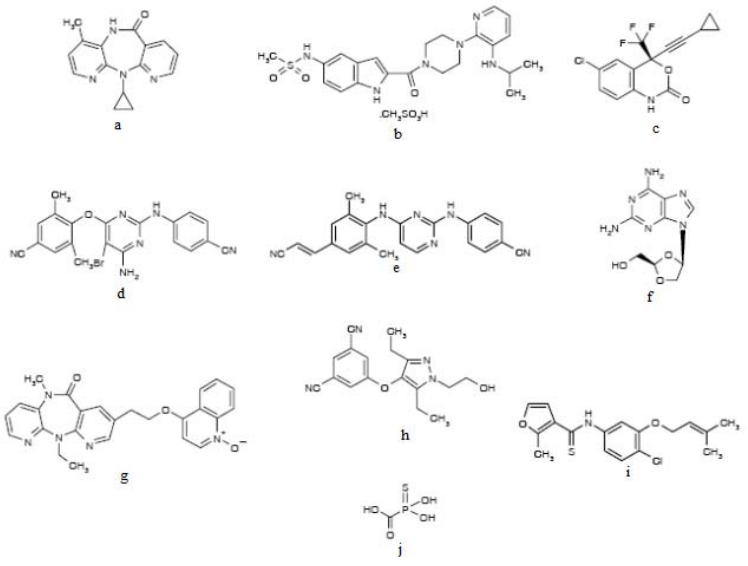
The present invention relates to triamino triazine picolinonitriles of formula- I useful for treating or reducing the severity of hyperproliferative diseases by inhibiting metastasis, or in the treatment or prevention of human immunodeficiency virus (HIV) infections. The invention further relates to process for preparation of compounds of formula-I and pharmaceutical composition thereof.

Background and prior art

The human immunodeficiency virus type 1 (HIV-1) is a retrovirus belonging to the Retroviridae family that was first identified in 1983 and was shown to be the cause of acquired immune deficiency syndrome (AIDS).

Highly active antiretroviral therapy (HAART) incorporating at least three antiretroviral agents has been the standard therapy for HIV/AIDS for more than 10 years. HAART includes protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), entry inhibitors and integrase inhibitors.

FDA approved NNRTIs for the treatment of HIV/AIDS include (a)Nevirapine, (b)Delavirdinemesilate, (c)Efavirenz, (d)Etravirine, (e)Rilpivirine, (f)Amdoxovir, (g)BILR-355 (BILR-355-BS), (h)UK-453061, (i) UC-781 and (j)Thiofoscarnet (ANX-201).



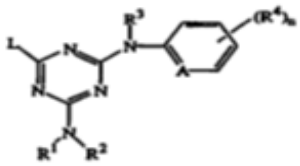
The highly specific NNRTIs are however associated with the rapid emergence of resistance mutations that surround the NNRTI binding pocket, thus rendering the molecules ineffective. Also, extensive cross-resistance is well documented among the available NNRTIs. Combination therapy has also led to the development of adherence problems, reduced antiretroviral activity and drug toxicity.

In continuation to develop new potent, selective and non-toxic anti HIV agents, scientists worldwide found a new class of compounds belonging to s-tirazines, which are known for their anti-inflammatory, antispasmodic, diuretic and for modifying adreno-cortico hormone secretion, with promising antiviral and anti HIV activity.

Among the triazine compounds that belong to NNRTI category, diaryltriazine analogues (DATAs) and diarylpyrimidine analogues (DAPYs) are known for their activity against wild-type and various mutant strains of HIV-1.

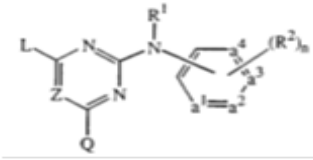
WO 99/50250 and WO 00/27825 disclose substituted amino pyrimidine derivatives which are used in the systemic treatment and prophylaxis of HIV infection. They function by blocking the multiplication process of HIV particularly they block the reverse transcriptase enzyme that plays a vital role in the viral multiplication process.

WO99/50256 discloses 1,3,5 trisubstituted triazine derivatives having HIV replication inhibiting properties.



wherein A may be selected from N; R^3 is H; , R^4 is –CN, L is –X-R^5 , R^5 is (un) substituted phenyl; R_1 and R^2 represent amino, or R^1 and R^2 taken together may form pyrrolidinyl, morpholidinyl. WO'256 however specifically relates to triazine benzonitrile compounds.

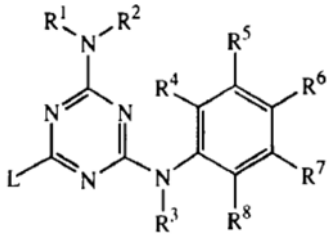
WO01/85700 also relates to substituted amino triazine derivatives having HIV replication inhibiting properties of the formula given below.



wherein, -a'=a^2-a^3=a^4-represents a bivalent radical of formula -N=CH-CH=CH-; R^2 is cyano, Q is selected from halo, amino C_1-C_6 alkyl, C_1-C_6 alkyloxy, hetero which is pyrazolidinyl, L is –X-R^3 , R^3 is (un) substituted phenyl.

The compounds disclosed in WO'256 and WO'700 inhibit replication of HIV virus in the human T-4 cells via an interaction with HIV reverse transcriptase enzyme.

EP0834507 discloses substituted diamino triazine derivatives having HIV replication inhibiting properties.



wherein the variables are as described in the patent.

With a need to improve antiretroviral activity against both wild-type and drug-resistant HIV and to overcome the drawback of the currently used compounds which are toxic and have poor bioavailability, and further with the promising biological activity of triazine scaffold, the present invention focusses in designing triazine derivatives by introducing a pyridine moiety in the side chain. Introducing a pyridine ring increases the polarity and subsequently the bioavailability of the compounds thus enhancing the treatment of HIV with convenience.

Further, the invention is based on the unexpected finding that the compounds described herein below are antagonists of the chemokine CXCR4 receptor which are useful to mediate the medical condition that is modulated by CXCR4 receptor signalling, and in

particular for treating or reducing the severity of hyperproliferative diseases by inhibiting metastasis, or in the treatment or prevention of HIV infections.

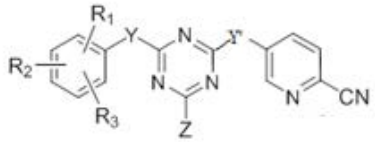
Summary of the invention

It is therefore the primary object of the present invention to provide novel triamino triazine compounds by introducing a polar pyridine moiety in the side chain for the treatment or prevention of HIV infections and for treating or reducing the severity of hyperproliferative diseases.

The other object is to provide novel triamino triazine compounds with a polar pyridine moiety in the side chain with reduced toxicity and increased bioavailability.

Yet another object of the invention is to provide a process for synthesis of novel triamino triazine compounds with a polar pyridine moiety in the side chain under mild conditions.

In an aspect, the present invention provides triamino triazine picolinonitriles of formula-I or its pharmaceutically acceptable addition salts or enantiomers or mixtures of enantiomers or stereoisomers or racemates or solvates or hydrates useful for treating or reducing the severity of hyper proliferative diseases by inhibiting metastasis, or in the treatment or prevention of HIV infections with reduced toxicity, comprising ;



(I)

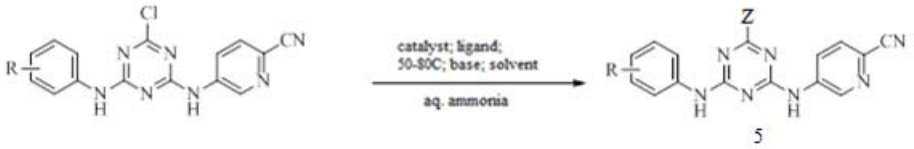
wherein, Y and Y' represent NH,

'Z' independently is selected from hydrogen, halo, NH_2, NMe_2, OMe, NH-Ar, morpholine, piperidine, pyrolidine, NHR', COOH or COOR';

R_1, R_2 and R_3 independently are selected from hydrogen, , alkyl, cycloalkyl, aryl, heteroaryl, acyl, halo, OH, OR', NH_2, NHR', SR', COOH, COOR', wherein R' independently is selected from straight or branched alkyl, cyclic alkyl or aralkyl, aryl or heteroaryl groups.

In another aspect, the present invention provides a process for preparation of compounds of formula-I comprising catalytic coupling of 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile (**formula -5**)with a suitable reagent in presence of a base, ligand as promoter and solvent at a temperature in the range of 50-80°C. The suitable reagent is optimised by selecting the appropriate catalyst and promoter ligand to improve the yield and selectivity.

Accordingly, the suitable reagent is selected from aq. ammonia, or an amino derivative of general formula NHR"'; wherein R"' is selected from (un) substituted or substituted alkyl, cycloalkyl, aryl, heteroaryl; preferably the reagent is aq. ammonia. The catalyst is selected from copper catalyst such as Cu(I) chloride, Cu(I) iodide, $CuSO_4.5H_2O$, $[CuBr(PPh_3)_2]$ and the like. The ligand as promoter is selected from 1,10-phenanthroline, picolinic acid, 4-hydroxy-proline and N,N-dimethylglycine. The solvent is selected from polar aprotic solvent.



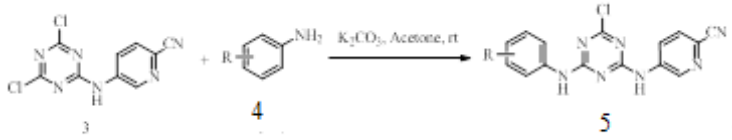
wherein 'Z' independently is selected from hydrogen, halogen, NH_2, NMe_2, OMe, NH-Ar, morpholine, piperidine, pyrolidine, NHR', COOH or COOR'; and

R independently is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, acyl, halogen, OH, OR, NH_2, NHR', SR', COOH, COOR'; wherein R' is selected from straight or branched alkyl, cyclic alkyl, aralkyl, aryl or heteroaryl groups.

In another aspect, the compound of formula -5 was prepared from cyanuric chloride by a process described in WO99/50256. Accordingly, the process for preparation of triamino triazine picolinonitriles of formula- I or its pharmaceutically acceptable addition salt under mild conditions comprises;

1. Adding cyanuric chloride **(1)** to 5-amino-picolinonitrile (**2**) in presence of a solvent at a temperature 0-5°C with constant stirring to obtain 5-(4, 6-dichloro-1,3,5-triazin-2-yl amino) picolinonitrile (**3**);
2. Reacting 5-(4,6-dichloro-1,3,5-triazin-2-ylamino) picolinonitrile (**3**) with substituted phenyl amine of **formula -4** in presence of a base and solvent at room

temperature to obtain 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile of **formula -5** and optionally converting to its salt;



wherein R is as defined above; and

3. catalytic coupling of compound of **formula -5** with a suitable reagent in presence of a base, ligand and solvent at ambient temperature to obtain compounds of formula- I.

In yet another aspect, the present invention provides pharmaceutical composition comprising triamino triazine picolinonitriles of formula- I or its pharmaceutically acceptable addition salt along with pharmaceutically acceptable excipients for treating or reducing the severity of hyperproliferative diseases by inhibiting metastasis, or in the treatment or prevention of HIV infections.

Detailed description of the invention

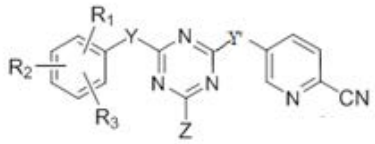
The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

As used herein , the pharmaceutically acceptable addition salts as mentioned hereinabove and herein after are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula-I are able to form. The compounds of formula-I which have basic properties can be converted to their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids.

With the need for new antiretroviral agents that can enhance bioavailability, reduce toxicity and improve antiretroviral activity against both wild-type and drug-resistant HIV, the present invention provides triamino triazine derivatives by introducing a pyridine moiety in the side chain to achieve the desired properties and activity.

The invention further provides a process for the synthesis of triamino triazine derivatives with a pyridine ring in the side chain. The process of the present invention further uses promoter ligand that facilitates to complete the reaction at an ambient temperature in the range of 50-80°C.

In an embodiment, the present invention relates to triamino triazine picolinonitriles of formula- I or its pharmaceutically acceptable acid addition salts or enantiomers or mixtures of enantiomers or stereoisomers or racemates or solvates or hydrates useful for treating or reducing the severity of hyperproliferative diseases by inhibiting metastasis, or in the treatment or prevention of HIV infections with reduced toxicity, comprising;



(I)

wherein, Y and Y' represent NH,

'Z' independently is selected from hydrogen, halo, NH_2, NMe_2, OMe, NH-Ar, morpholine, piperidine, pyrolidine, NHR', COOH or COOR';

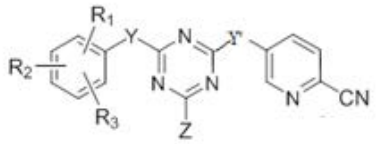
R_1, R_2 and R_3 independently are selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, acyl, halo, OH, OR', NH_2, NHR', SR', COOH, COOR', wherein R' independently is selected from straight or branched alkyl, cyclic alkyl or aralkyl, aryl or heteroaryl groups.

In another embodiment, compounds of formula-I or its pharmaceutically acceptable acid addition salts comprises;

i. 5-(4-chloro-6-(p-tolylamino)-1, 3, 5-triazin-2-ylamino) picolinonitrile ;
ii. 5-(4-chloro-6-(3-methoxyphenylamino)-1, 3, 5-triazin-2-ylamino) picolinonitrile;
iii. 5-(4-amino-6-(p-tolylamino)-1,3,5-triazin-2-ylamino)picolinonitrile;
iv. 5-(4-amino-6-(3-methoxyphenylamino)-1,3,5-triazin-2-ylamino)picolinonitrile;
v. 5-(4-amino-6-(mesitylamino)-1, 3, 5-triazin-2-ylamino) picolinonitrile;
vi. 5-(4-morpholino-6-(p-tolylamino)-1,3,5-triazin-2-ylamino)picolinonitrile;

We claim;

1. Triamino triazine picolinonitriles of formula- I or its pharmaceutically acceptable addition salts or enantiomers or mixtures of enantiomers or stereoisomers or racemates or solvates or hydrates comprising ;



(I)

wherein, Y and Y' represent NH,

'Z' independently is selected from hydrogen, halogen, NH_2, NMe_2, OMe, NH-Ar, morpholine, piperidine, pyrolidine, NHR, COOH or COOR;

R_1, R_2 and R_3 independently are selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, acyl, halogen, OH, OR, NH_2, NHR, SR, COOH, COOR; 'R' independently is selected from straight or branched alkyl, cyclic alkyl or aralkyl, aryl or heteroaryl groups.

2. The triamino triazine picolinonitriles according to claim 1, comprising;
    i. 5-(4-chloro-6-(p-tolylamino)-1, 3, 5-triazin-2-ylamino) picolinonitrile ;
    ii. 5-(4-chloro-6-(3-methoxyphenylamino)-1,3,5-triazin-2-ylamino)picolino nitrile;
    iii. 5-(4-amino-6-(p-tolylamino)-1,3,5-triazin-2-ylamino)picolinonitrile;
    iv. 5-(4-amino-6-(3-methoxyphenylamino)-1,3,5-triazin-2-ylamino)picolino nitrile;
    v. 5-(4-amino-6-(mesitylamino)-1, 3, 5-triazin-2-ylamino) picolinonitrile;
    vi. 5-(4-morpholino-6-(p-tolylamino)-1,3,5-triazin-2-ylamino)picolinonitrile;
    vii. 5-(4-(4-fluorophenylamino)-6-morpholino-1,3,5-triazin-2-ylamino) picolino nitrile;
    viii. 5-(4-(3-methoxyphenylamino)-6-(piperidin-1-yl)-1,3,5-triazin-2yl amino) picolinonitrile;
    ix. 5-(4-(3-methoxyphenylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazin-2ylamino) picolinonitrile;

x. 5-(4-(2-methoxyethylamino)-6-(p-tolylamino)-1,3,5-triazin-2ylamino) picolinonitrile;
xi. 5-(4-(phenylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazin-2ylamino) picolinonitrile;
xii. 5-(4-(2-methoxyethylamino)-6-(phenylamino)-1,3,5-triazin-2ylamino)picolino nitrile;
xiii. 5-(4-(phenylamino)-6-(piperidin-1-yl)-1,3,5-triazin-2-ylamino) picolinonitrile;
xiv. 5-(4-(phenylamino)-6-(morpholine-1-yl)-1,3,5-triazin-2-ylamino) picolinonitrile;
xv. 5-(4-amino-6-(phenylamino)-1,3,5-triazin-2- ylamino) picolinonitrile;
xvi. 5-(4-chloro-6-(mesityl amino)-1,3,5-triazin-2-ylamino) picolinonitrile.

3. The triamino triazine picolinonitriles according to claim 2, comprising;

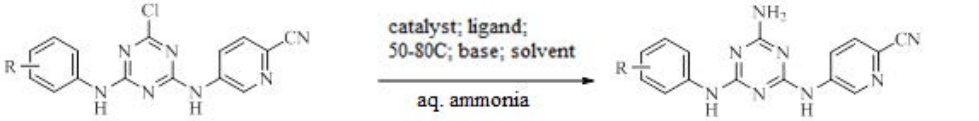
i. 5-(4-chloro-6-(mesityl amino)-1,3,5-triazin-2-ylamino) picolinonitrile;
ii. 5-(4-amino-6-(mesitylamino)-1, 3, 5-triazin-2-ylamino) picolinonitrile

4. A process for preparation of compounds of formula-I or its pharmaceutically acceptable addition salts according to claim 1, comprising catalytic coupling of 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile of formula-5 with a suitable reagent in presence of a base, ligand as promoter and solvent at an ambient temperature in the range of 50-80°C;

5

wherein 'Z' independently is selected from hydrogen, halogen, NH_2, NMe_2, OMe, NH-Ar, morpholine, piperidine, pyrolidine, NHR', COOH or COOR'; and
R independently is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, acyl, halogen, OH, OR, NH_2, NHR', SR', COOH, COOR'; wherein R' is selected from straight or branched alkyl, cyclic alkyl, aralkyl, aryl or heteroaryl groups.

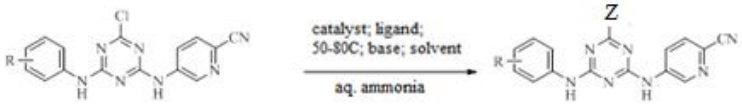
5. The process according to claim 4, comprising catalytic coupling of 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile of formula-5(a-e) with aqueous ammonia in presence of a base, ligand as promoter and solvent at an ambient temperature in the range of 50-80°C to obtain compounds of formula 7(a-e) and optionally converting to acid salts thereof;



5(a-e) R = 5a) 4-F; 5b) 4-OMe; 5c) 4-CH_3; 5d) 3-OMe; 5e) 2,4,6-CH_3.

7(a-e) R = 7a) 4-F; 7b) 4-OMe; 7c) 4-CH_3; 7d) 3-OMe; 7e) 2,4,6-CH_3.

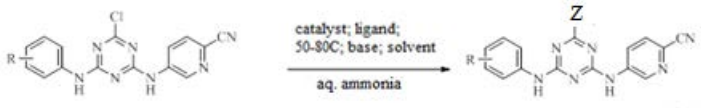
6. The process according to claim 4, comprising catalytic coupling of 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile of formula-5(a-e) with piperidine in presence of a base, ligand as promoter and solvent at an ambient temperature in the range of 50-80°C to obtain compounds of formula 10(a-e) and optionally converting to acid salts thereof.



5(a-e) R = 5a) 4-F; 5b) 4-OMe; 5c) 4-CH_3; 5d) 3-OMe; 5e) 2,4,6-CH_3.

11(a-e) Z = piperidine
R = 11a) 4-F; 11b) 4-OMe; 11c) 4-CH_3; 11d) 3-OMe; 11e) 2,4,6-CH_3.

7. The process according to claim 3, comprising catalytic coupling of 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile of formula-5(a-e) with morpholine in presence of a base, ligand as promoter and solvent at an ambient temperature in the range of 50-80°C to obtain compounds of formula 11(a-e) and optionally converting to acid salts thereof.

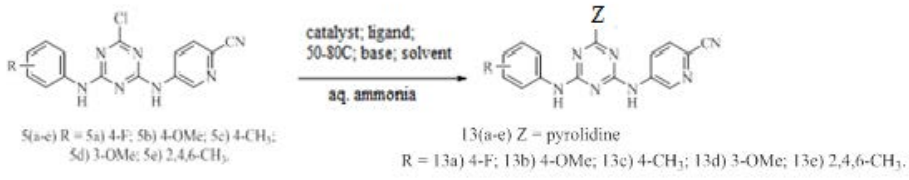


5(a-e) R = 5a) 4-F; 5b) 4-OMe; 5c) 4-CH_3; 5d) 3-OMe; 5e) 2,4,6-CH_3.

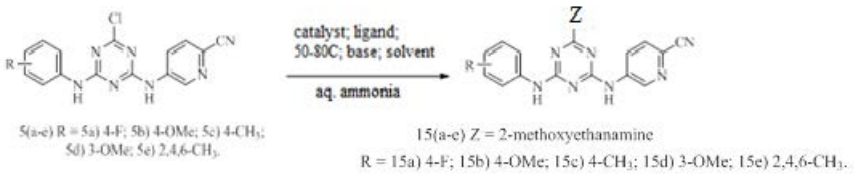
9(a-e) Z = morpholine
R = 9a) 4-F; 9b) 4-OMe; 9c) 4-CH_3; 9d) 3-OMe; 9e) 2,4,6-CH_3.

8. The process according to claim 3, comprising catalytic coupling of 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile of formula-5(a-e) with pyrolidine in presence of a base, ligand as promoter and solvent at an ambient

temperature in the range of 50-80°C to obtain compounds of formula 13(a-e) and optionally converting to acid salts thereof.



9. The process according to claim 3, comprising catalytic coupling of 5-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino) picolinonitrile of formula-5(a-e) with 2-methoxyethanamine in presence of a base, ligand as promoter and solvent at an ambient temperature in the range of 50-80°C to obtain compounds of formula 15(a-e) and optionally converting to acid salts thereof.



10. The process according to any of the preceding claims, wherein, the catalyst is selected from copper catalyst such as Cu(I) chloride, Cu(I) iodide, $CuSO_4.5H_2O$, $[CuBr(PPh_3)_2]$ and the like.

11. The process according to any of the preceding claims, wherein, the ligand is selected from 1,10-phenanthroline, picolinic acid, 4-hydroxy-proline or N,N-dimethylglycine.

12. The process according to any of the preceding claims, wherein, the solvent is selected from polar aprotic solvent such as DMSO, acetonitrile, DMF, DCM and the like.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or its pharmaceutically acceptable addition salts along with pharmaceutically acceptable excipients.

14. The triamino triazine picolinonitrile of formula- I or its pharmaceutically acceptable addition salts according to claim 1 for use in treating or reducing the severity of hyper proliferative diseases by inhibiting metastasis, or for treating or preventing HIV infections with reduced toxicity.

15. A method for treating or reducing the severity of hyper proliferative diseases by inhibiting metastasis, or for treating or preventing HIV infections with reduced toxicity comprising administering therapeutically effective amount of a compound of formula (I) or its pharmaceutically acceptable addition salts to a subject in need thereof.

Dated this 13th day of October, 2015

Dr. Gopakumar G. Nair
(Regn.No.: IN/PA 509)
Agent for the Applicant
Gopakumar Nair Associates