PYRIMIDINE: IT'S DIVERSE BIOLOGICAL ACTIVITIES AND METHODS OF SYNTHESIS

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Summary

Six membered aromatic systems having two heteroatoms at symmetrical positions such as 1, 3 i.e. Pyrimidine have been studied extensively owing to their interesting pharmacological activities. This review article covers the most active pyrimidine derivatives that have shown considerable biological actions such as antimicrobial, anti-inflammatory, anticancer, antilipidemic, antiviral, antihypertensive, and antitubercular. This review also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing pyrimidine moiety that could be better agents in terms of efficacy and safety.

Key words: Antiviral activity,Biological activities, Pyrimidine,SAR ,Total synthesis.

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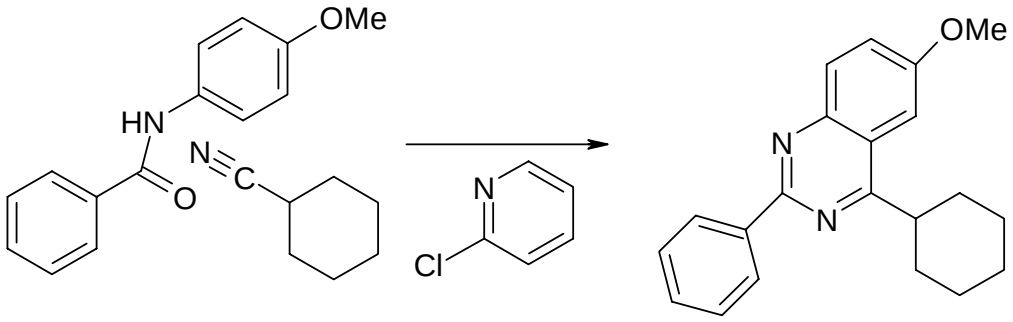
Introduction

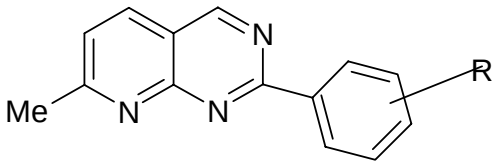
Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring.[1] It is isomeric with two other forms of diazine. A pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier. An example of the last reaction type is the displacement of the amino group in 2-aminopyrimidine by chlorine[2] and its reverse.[3] Reduction in resonance stabilization of pyrimidines may lead to addition and ring cleavage reactions rather than substitutions. Pyrimidines can also be prepared within the laboratory by organic synthesis. One method is the classic Biginelli reaction.

Many other methods rely on condensation of carbonyls with amines for instance the synthesis of 2-Thio-6-methyluracil from thiourea and ethyl acetoacetate [5] or the synthesis of 4-methylpyrimidine with 4,4-dimethoxy-2-butanone and formamide [6].A novel method is by reaction of certain amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluoromethanesulfonic anhydride.



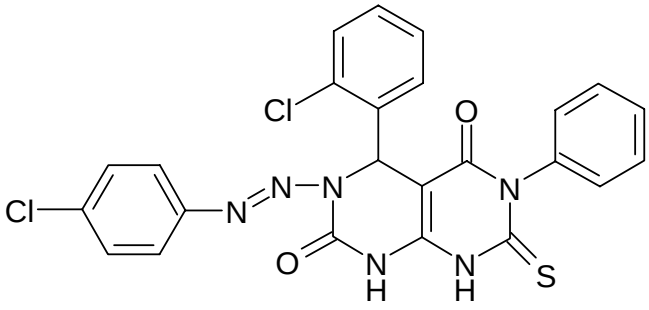
m Glu5 receptor antagonists [7]

A series of readily accessible 2-aryl pyrido[2,3-d]pyrimidines were synthesized that possessed potent mGlu5 receptor antagonist activity of the 2arylpyrido[2,3d]pyrimidines studied, it appears that appropriate substitution at the aryl ring and further substitution at the 3,5-positions of the aryl ring are preferred for mGlu5 receptor antagonist activity. In particular non-polar moieties appear to provide optimal antagonist activity. Additional substitution of 7-methyl onto the pyrido[2,3-d]pyrimidine ring yielded more potent analogs than the corresponding 7-desmethyl analogs. In vivo activity (po) of compound 18 was comparable in activity to the reference standard (COX-2 inhibitor, rofecoxib) in the rat MIA model. These results validate that the 2-aryl pyrido[2,3-d]pyrimidine is a promising new class of mGlu5 receptor antagonists and provides an additional tool beyond MPEP to investigate the important area of glutamate research.

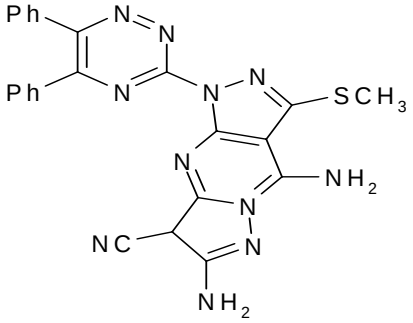


Antimicrobial activity

1. A synthesis of a series, namely 4-(2-chlorophenyl)-3-(4-chlorophenylazo)-6-aryl-7-thioxo-4,6,7,8-tetrahydro-1H 3H-pyrimido[4,5-d]pyrimidine-2,5-dione, incorporating first time biginelli compound as the precursor followed by their in vitro antibacterial and antifungal screening studies. [8]

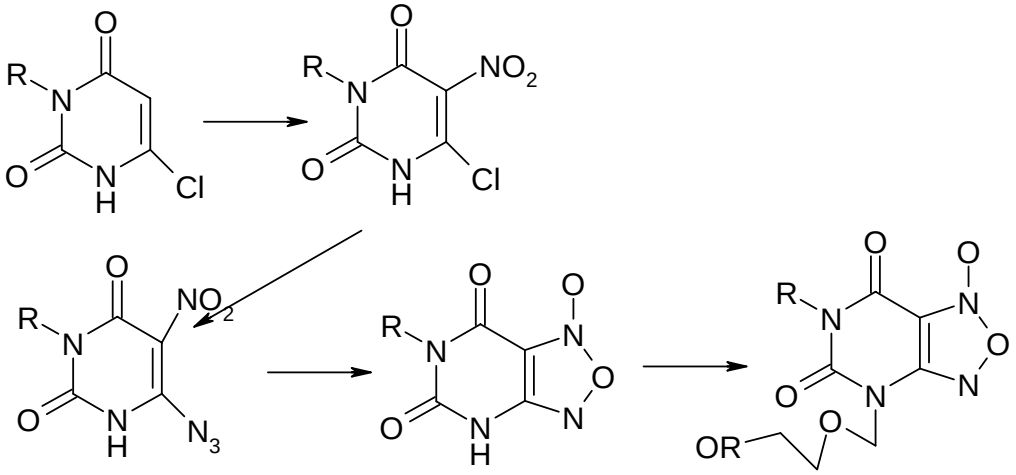


2. A series of novel pyrazolo [3,4-b]pyridines and pyrazolo[3,4-d]pyrimidines fused with nitrogen heterocycles and bearing 5,6-diphenyl-1,2,4-triazine moiety. The antimicrobial activity data of the prepared compounds showed that some fused heteropolycyclic rings showed good antimicrobial activity with lower toxicity. In our study, we have replaced the 1H-atom of the pyrazole of pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine by 5,6-diphenyl-1,2,4-triazine moiety as bioactive moiety. These structural changes made Increasing activity against the tested organisms.[9]

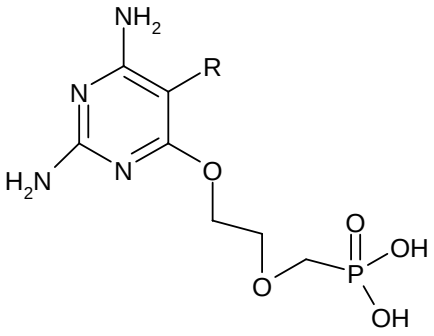


Antiviral activity

1. A series of 4H-[1,2,5]oxadiazolo[3,4-d]pyrimidine-5,7-dione 1-oxide nucleosides was designed, synthesized and evaluated against vesicular stomatitis virus (VSV) inWish cell. The antiviral activities of all compounds were stronger than those of acyclovir, while their toxicities were similar to those of acyclovir.[10]

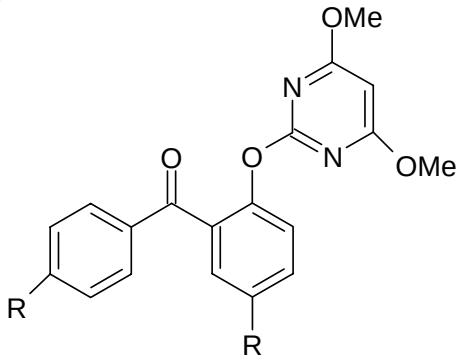


2. Synthesis of 2, 4 amino5cyano6{[(diisopropoxyphosphoryl)methoxy]ethoxy}pyrimidine was based on the formation of the pyrimidine ring by cyclization followed by modification of the side chain by alkylation. The 5-cyano group was also transformed to a 5-formyl and 5-hydroxymethyl group by reduction. As a side product an unexpected dimer was formed. Resulting compounds were converted to the free phosphonic acids by treatment with bromotrimethylsilane followed by hydrolysis. The 5-cyano and 5-formyl derivatives showed pronounced antiretroviral activity, comparable to that of the reference drugs adefovir and tenofovir. [11]

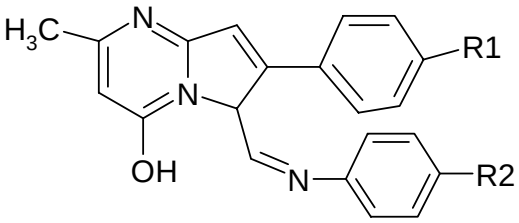


Anti-inflammatory activity

1. The newly synthesized heterocycles of pyrimidine were characterized by IR, 1H NMR, and mass spectral data. Compounds were screened for their anti-inflammatory activity and were compared with standard drugs of the compounds studied; the compound showed more potent activity than the standard drugs at all doses tested. [12]

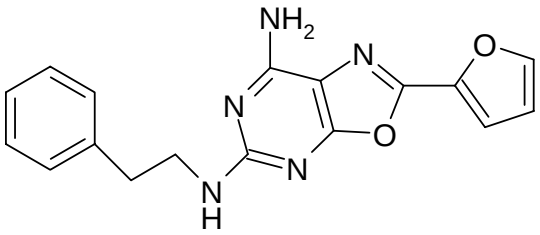


2. A series of imidazo[1,2-a]pyrimidine derivatives substituted adjacently with two aryls at positions 2 and 3 were designed and synthesized in order to improve their anti-inflammatory activities. Biological tests suggested that these compounds have anti-inflammatory activities with COX-2 selectivity to some extent.[13]



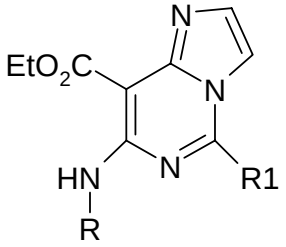
Adenosine receptor antagonists

The brain A2A adenosine receptor (A2AAR) participates with the dopamine D2 receptor in the control of movement and also might influence behavior. Because PET is an important tool for studying the roles of receptors in disease, a ligand for imaging the brain A2AAR is desirable. This report describes the synthesis and A2AAR antagonist activities of a panel of phenyl-substituted 7-amino-2-(2-furyl)-5-phenylethylamino-oxazolo [5,4-d]pyrimidines, 11aa–af, and their 3-furyl congeners, 11ba–bd. In competitive binding studies all compounds displaced [3H]CGS21680 from the A2AAR with Ki values of 14–33 nM with selectivity for the A2AAR over the A1AR of 5- to 94-fold. Autoradiography of brain sections showed a high level of unspecific binding that obscured specific binding. Thus, these compounds are not promising PET ligands. [14]



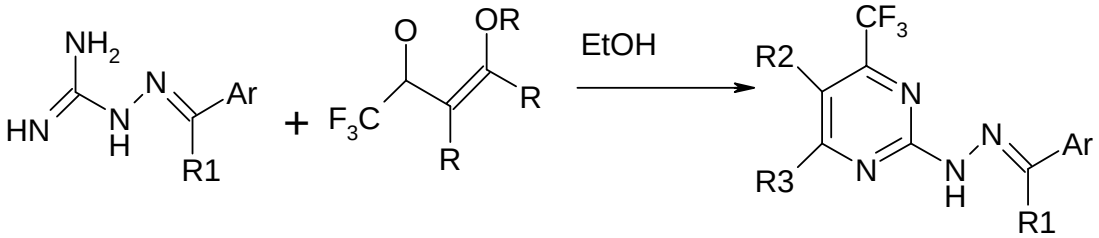
Antimycobacterial activity

Tuberculosis, due to its relentless nature, is now a major public health threat. The concomitant resurgence of TB with the MDR- or XDR-TB and HIV/AIDS pandemic has exposed the frailties of the current drug armatorium. Based on isosteric replacement and good 3D structural similarity between PA-824, a novel antimycobacterial agent undergoing clinical trials, and imidazo[1,2-c]pyrimidines, we have designed novel imidazo[1,2-c]pyrimidines. The designed molecules were synthesized by nucleophilic displacement of chloro group of various substituted 4-chloropyrimidines by ethanolamine followed by cyclisation of these 4-(2-hydroxyethyl)aminopyrimidines to imidazo[1,2-c]pyrimidines in good yield. All the compounds were screened for their antimycobacterial activity on Mycobacterium tuberculosis H37Rv strain by 1% proportion method. Some of the synthesized compounds exhibited potent antimycobacterial activity with MIC values in the range of 2–20 mg/mL.[15]



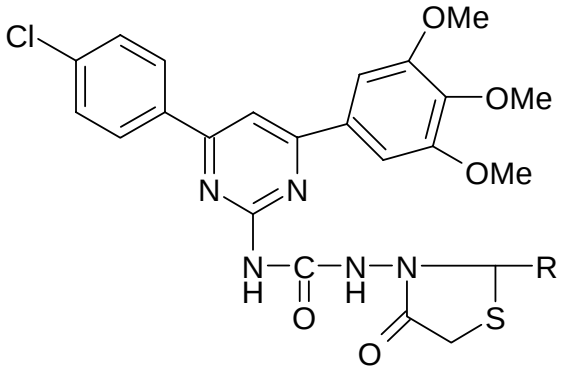
Cruzain inhibitory activity

To search for new cruzain inhibitors, the synthesis of a series of novel 2-(N0-benzylidenehydrazino)-4-trifluoromethyl- pyrimidines in a convergent manner is presented. The cruzain inhibitory activity of some of these compounds was evaluated and a binding model was proposed.[16]



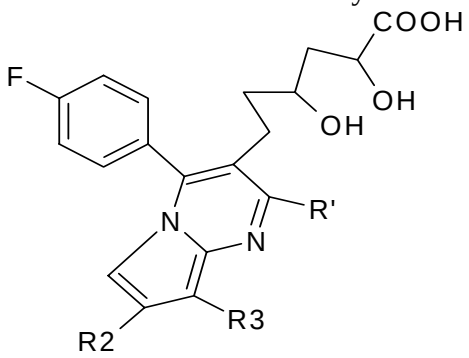
Antitubercular activity

Several 2-aryl-3-[4-(4-chlorophenyl)-6-(3,4,5-trimethoxy- phenyl)pyrimidin-2-yl-ureido]-4-thiazolidinones and 1-[4-(4- chlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl-ureido 3-chloro-4-aryl-2-azetidinones have been synthesized and tested for their antibacterial, antifungal and antituberculosis activities against different microorganisms.[17]



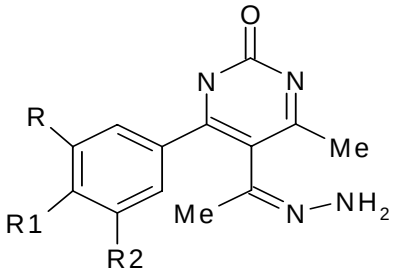
HMG CoA reductase inhibitors

QSAR has been established on a series of compounds of condensed pyrimidine analogues showing promising HMG CoA Reductase inhibitor activity.[18]



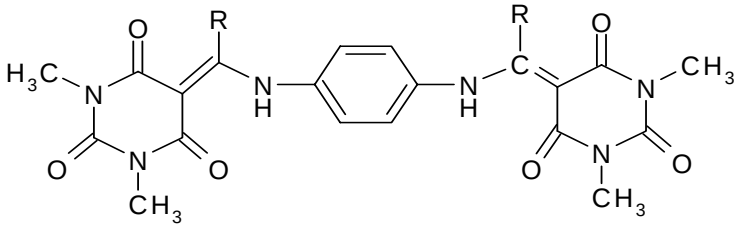
Antihypertensive activity

4-aryl-pyrazolo[3,4-d]-pyrimidin-6-0ne derivatives have received significant attention owing to their structural relationship with clinically active DHP Ca channel blockers and showing prominent antihypertensive activity.[19]



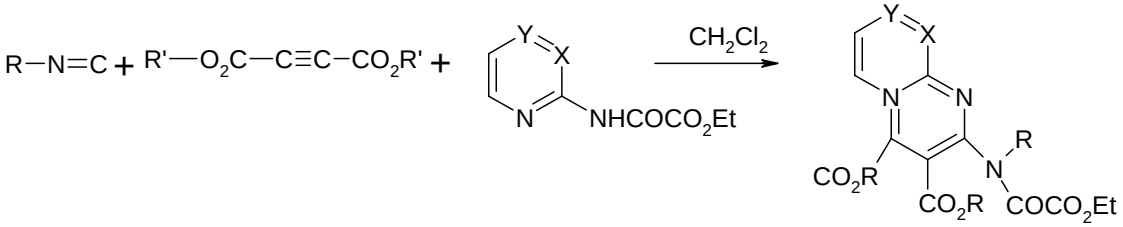
Anticancer activity

Reaction of 5-benzoyl-/5-carbolide-5(3-phenyl-acryloyl)-6-hydroxy-1H-pyrimidine-2,4-diones with amines results in the formation of corresponding enamines showing appreciable anticancer activity.[20]

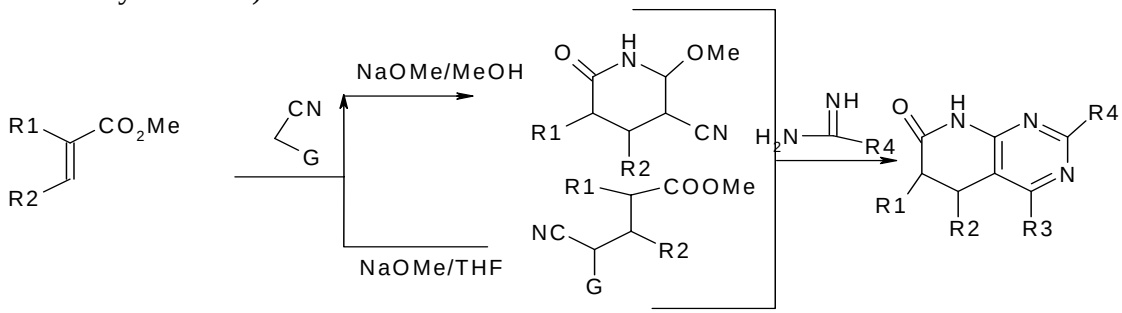


Method of synthesis

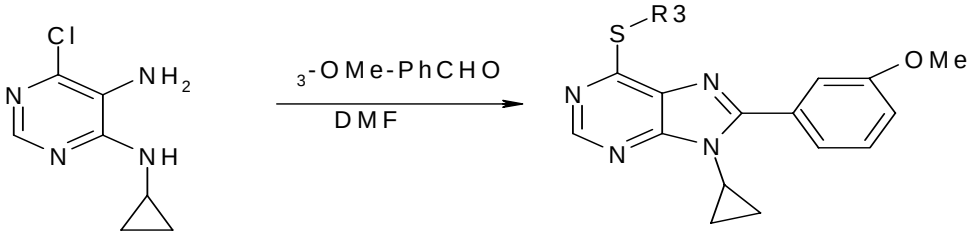
1. A new, one-pot and three-component synthesis of 4H-pyrido[1,2-a]pyrimidines, 4H-pyrimido[1,2-a]pyrimidines, and 4H-pyrazino[1,2-a]pyrimidines is described.[21]



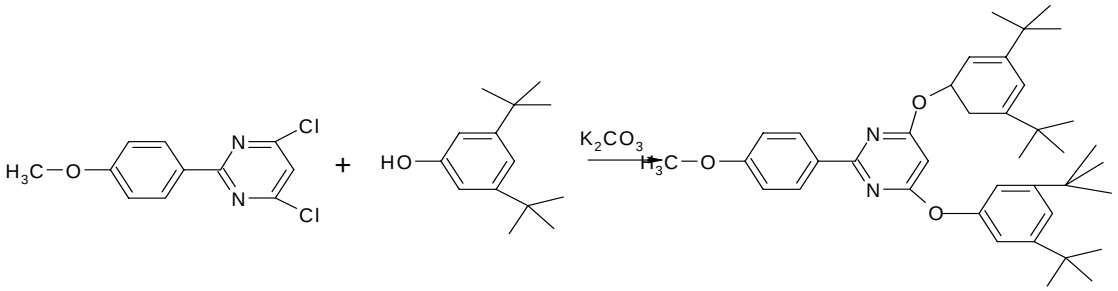
2. A new, high yield multicomponent reaction providing multifunctionalized pyrido [2,3-*d*]pyrimidines in a microwaveassisted one-pot cyclocondensation of _,_-unsaturated esters, amidine systems and malononitrile (or ethyl cyanoacetate) is described (the 'Victory' reaction).[22]



3. A one-pot synthesis of 6-mercaptopurines from 4, 5-diamino-6-chloro-pyrimidine, an aldehyde and elemental sulfur is presented. The key advantage of this procedure is that it utilizes the in situ generated H2S to convert the chloro to a mercapto group.[23]



4. A novel convergent approach to dendritic macromolecules is described in which 4,6-dichloro-2-(4-methoxyphenyl)-pyrimidine is used as the building block. The nucleophilic aromatic substitution reaction at this AB2-monomer was used as the key step in the propagation of the dendrons. Different core reagents were used to form the dendrimers, including a 5,15-bis(pyrimidyl)porphyrin core. Fourth-generation dendrons and third-generation dendrimers could be synthesized.[24]



Conclusions

The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by pyrimidine derivatives. The biological profiles of these new generations of pyrimidines would represent a fruitful matrix for further development of better medicinal agents.

References

1. Heterocyclic Chemistry (3rd Edition) Thomas. L. Gilchrist .
2. Organic Syntheses, Coll. Vol. 4, p.182 (1963); Vol. 35, p.34 (1955)
3. Organic Syntheses, Coll. Vol. 4, p.336 (1963); Vol. 35, p.58 (1955)
4. Nuevo M, Milam SN, Sandford SA, Elsila JE, Dworkin JP (2009). "Formation of uracil from the ultraviolet photo-irradiation of pyrimidine in pure H2O ices.". *Astrobiology* **9** (7): 683-95.
5. Organic Syntheses, Coll. Vol. 4, p.638 (1963); Vol. 35, p.80 (1955).
6. Organic Syntheses, Coll. Vol. 5, p.794 (1973); Vol. 43, p.77 (1963).
7. John A. Wendt,a, Susan D. Deeter, Susan E. Bove, Christopher S. Knauer, Rache M. Brooker,Corinne E. Augelli-Szafran, Roy D. Schwarz, Bioorganic & Medicinal Chemistry Letters 17 (2007) 5396–5399.
8. Jack J. Kinsorac and Kenneth S. Kilgorec Bioorganic & Medicinal Chemistry Letters 17 (2007) 5396–5399.
9. Pratibha Sharma, Nilesh Rane and V. K. Gurram Bioorganic & Medicinal Chemistry Letters 14 (2004) 4185–4190.
10. Tarik El-Sayed Ali European Journal of Medicinal Chemistry 44 (2009) 4385–43.
11. Jing Bo Shi , Jing Gao , Ya Ping Wang , Qi Zheng Yao , Chinese Chemical Letters 20 (2009) 404–406.
12. Dana Hockov,Anton_ın Hol, Milena Maso, raciela Andrei, Robert Snoeck, Erik De Clercq and Jan Balzarinib Bioorganic & Medicinal Chemistry 12 (2004) 3197–3202.
13. T. D. Venu , S. A. Khanum , Aiysha Firdouse , B. K. Manuprasad , Sheena Shashikanth, Riyaz Mohamed , Bannikuppe Sannanaik Vishwanth, Bioorganic & Medicinal Chemistry Letters 18 (2008) 4409–4412.
14. Jin Pei Zhou, Yi Wei Ding , Hui Bin Zhang , Lian Xu , Yue Dai ,Chinese Chemical Letters 19 (2008) 669–672.
15. Marcus H. Holschbach , Dirk Bier, Stefan Stüsgen, Walter Wutz, Wiebke Sihver, Heinz H. Coenen, Ray A. Olsson 6. European Journal of Medicinal Chemistry 41 (2006) 7–15.
16. Nilo Zanatta , Simone S. Amaral, Convergent synthesis and cruzain inhibitory activity of novel 2-(N0-benzylidenehydrazino)-4-trifluoromethyl- pyrimidines, Bioorganic & Medicinal Chemistry 16 (2008) 10236–10243.
17. R B Patel, P S Desai, K R Desai, Synthesis of pyrimidine based thiazolidinones and azetidinones: Antimicrobial and antitubercular agents, Indian Journal of Chemistry, Vol. 45B, Marc h 2006, pp. 773-778.
18. M.Saxena, L.K Soni, Indian J of Biochem. And Biophysics, vol.43,Feb-2006,32-36.
19. W.S.Hamouly,Indian J of Chem.,45B,2006,2091-98.
20. Mehdi Adib, A new, one-pot, three-component synthesis of 4H-pyrido[1,2-a]- pyrimidines, 4H-pyrimido[1,2-a]pyrimidines, and 4H-pyrazino[1,2-a]pyrimidines, Tetrahedron 63 (2007) 11135–11140.
21. Mehdi Adib, A novel, one-pot, three-component synthesis of 4H-pyrido[1,2-a]pyrimidines, Tetrahedron Letters 48 (2007) 4195–4198.
22. Nu´ ria Mont, A three-component synthesis of pyrido[2,3-*d*]pyrimidines, Tetrahedron Letters 44 (2003) 5385–5387.
23. Sagun Tandel, One-pot syntheses of 6-mercaptopurines (6MP) from 4,5-diamino- 6-chloro-pyrimidines, Tetrahedron Letters 45 (2004) 2321–2322.
24. Wouter Maes, Synthesis of novel dendrimers containing pyrimidine units, Tetrahedron 59 (2003) 3937–3943.