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A REVIEW ON BIOLOGICAL ACTIVITIES OF DIHYDRO PYRIMIDINONES / THIONES

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ABSTRACT

Dihydropyrimidones/ thiones are an important class of heterocyclic compounds reported in 1893 for the first time by P. Biginelli**.** It possess wide spectrum of biological activities like including anti-tubercular, Anti-malarial, anticancer, anti-HIV activity, analgesic, antiepileptic, CNS activity, anti-inflammatory, antitumor activity. The present review gives brief information about the biginelli reaction and biological activities of dihydropyrimidones.

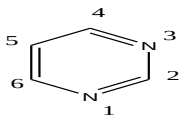
Keywords: Dihydropyrimidones, Biginelli, Biological activities, Anti-tumor, Anti HIV.

INTRODUCTION

The chemistry of pyrimidines has become increasingly important as a result of recent developments in medicinal chemistry.. Various individuals belonging to the general class of pyrimidines had been known for fifty years before Pinner in 1885 called attention to the fact that all such substances could be regarded as derivatives of a ring structure closely analogous to pyrimidine [1].

Pyrimidines are the most important six membered heterocyclic compounds containing two nitrogen atoms at 1 and 3 positions. They are present among the three isomeric diazines. Pyrimidine is a colourless compound having melting point (225°C) and boiling point (124°C)**.** Pyrimidine is a much weaker base than pyridine and soluble in water [2].The pyrimidines have been isolated from the nucleic acid hydrolyses. The nucleic acid are essential constituent of all cell and thus of all living matter cytosine is found to be present in both types of nucleic acid i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) while uracil present only in RNA and thymine only in DNA[3].

STRUCTURE



The prebiotic relevance of pyrimidine synthesis is from urea and cyanoacetaldehyde. The main concerns are the availability and instability of the reactants. In the case of cyanoacetaldehyde, it could react with amino acids, undergo hydrolysis to generate formate and acetonitrile, form a dimer. Consequently, any cyanoacetaldehyde is unlikely to survive long enough to be available in quantity to produce the necessary concentration for cytosine synthesis [4]. Urea sufficiently decomposes to ammonia and carbon dioxide at pH<5 and hydrolyses at pH>5 with a gradual decrease in concentration [5].

Pharmacologically Active Pyrimidines

Pyrimidines and their derivatives are considered to be important for drugs and agriculture chemicals. The use of pyrimidines is critical for successful treatment of various diseases. Uracil and Thymine may be considered to contain neutral urea unit or acidic imide moiety. Thymine is also referred as 5-methyluracil.The metabolism of these pyrimidines are unique and important to understand both biochemical utilization of these compounds and drug metabolism of pyrimidine derivatives[6]. Pyrimidine and its derivatives have gained prominence because of their potential pharmaceutical values. Many pyrimidine derivatives play vital role in many physiological actions[7].

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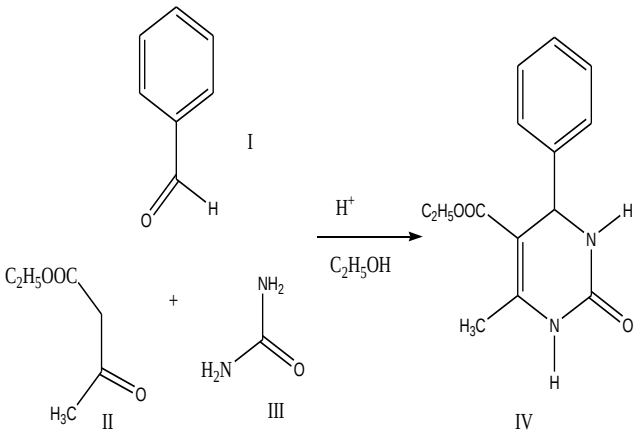
Pyrimidine derivatives possess several interesting biological activities such as antimicrobial, antitumour, and antifungal activities. Many pyrimidine derivatives are used for thyroid drugs and leukaemia [8] Anti hyper lipidemic activity[9] Antifungal activity[10] Anti-HIV agents[11] Immunosuppressants.

Dihydropyrimidones

In 1893, the synthesis of functionalize 3,4-dihydropyrmidine2-(1 H) ones (DHPMs) by three compound condensation reaction of an aromatic aldehyde, urea and ethyl aceto acetate, was reported for first time by P. Biginelli[12]. In post decade, such Biginelli type dihydropyrimidines have received a considerable amount of attention, due to interesting pharmacological property associated with calcium channel blocker activity, antihypertensive activity, antibacterial and antimicrobial activity.

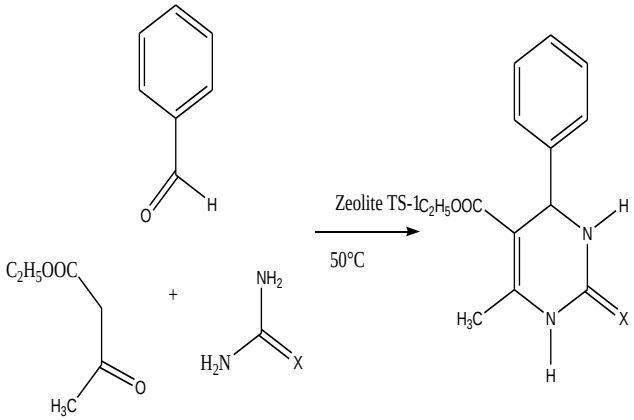
Biginelli Reaction

The Biginelli reaction which is an one example of the multicomponent reactions used industrially can be used to prepare 3,4-dihydropyrimidinones in a one-pot procedure. Examples of 3,4-dihydropyrimidinones useful in a clinical setting include the antihypertensive drug, the mitotic inhibitor monastrol, among many others classic Biginelli reaction involves the reaction between an aldehyde I, a 1,3- dicarbonyl II, and urea III under acidic conditions, which proceeds through a sequence of reactions [13]



The product of this novel one-pot, three-component synthesis is that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1H)-one IV. The solid state structure of dihydropyrimidine analogues shows that they can adopt a conformation which is similar to reported conformation of dihydropyridine calcium channel blockers [14]

Mukund G Kulkarni et al., reported [15] a zeolite-catalyzed, simple, one-pot, solvent-free, cost effective, and environmentally benign process for the synthesis of dihydropyrimidones



X = O,S

Improved Reaction Conditions

With a deeper mechanistic understanding of the Biginelli reaction, several advancements were made to address the poor and variable yields (20-70%) and limited substrate scope often associated with this reaction. Conditions that support the formation and reaction of N-acyliminium ion **provide** one route to improving the Biginelli reaction. Hu and

Coworkers report consistently high yields when the reaction proceeds in the presence of BF_3•OEt_2 and CuCl in a mixture of acetic acid and THF [16].

Ionic Liquids

Ionic liquids are considered as the green solvent of present century which obey the twelve principles of the green chemistry and are extensively used as catalysts or solvent or both in the organic synthesis[17]. In the synthesis of DHPMs a variety of Ionic liquids like task-specific[18] Polymer-supported [19] chiral ionic liquid [20] have been used.

Biocatalysts

Reports on an elegant use of fermenting yeast,[21] and enzyme,[22] for Biginelli reaction is described. Evidently more work is needed in the use of biocatalysts in this reaction.

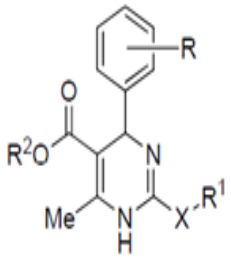
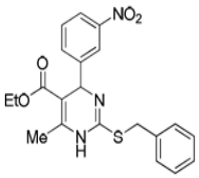
BIOLOGICAL ACTIVITES

The dihydro pyrimidones shows the biological activities as follows:

Antihypertensive Agents

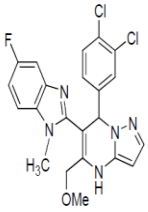
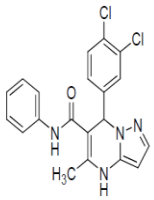
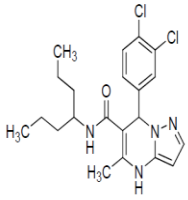
As a usual temptation biologists saw Biginelli products resemblance to Hantzsch 1,4-dihydropyridine , as being aza-analogues of nifedipine and other related molecules which are well-known calcium channel modulators and Biginelli compounds viz (effective orally active antihypertensive agents) are promising targets for bringing them to actual use. Hetero-substituted DHPMs

compound with a branched ester (e.g. isopropyl, sec-butyl) and an alkylthio group[23].

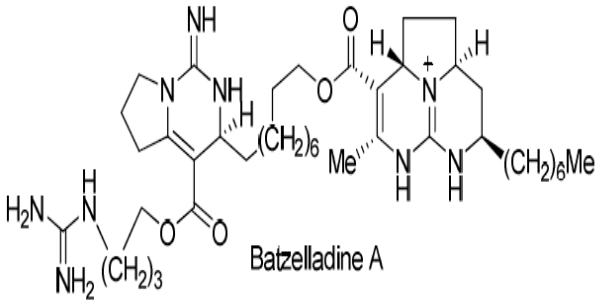
Potassium Channel Antagonists

Annulation of benzimidazole ring with this Biginelli showed potassium channel antagonists activity and these are at preclinical developments[24].

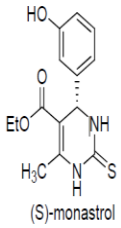
Anti-HIV Agents

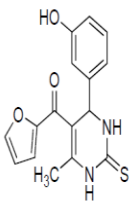
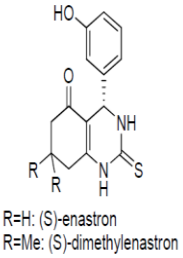
Batzelladine derivatives of DHPMs obtained from marine natural source have promising anti HIV activity. These low molecular weight derivatives inhibit the binding of HIVgp-120 to CD4 cells[25].



Antitumor Activity

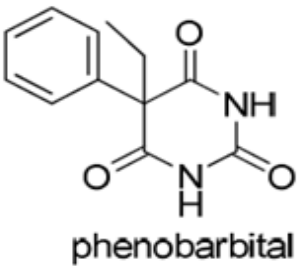
The first Biginelli compound which has excellent anticancer activity, further a series of compounds for their ability to inhibit , activity has been investigated using two *invitro* steady-state ATPase assays (basal and microtubule-stimulated) as well as a cell-based assay. In an attempt, another dihydropyrimidine i.e. furyl derivative appeared more potent, than monastrol by a fivefold factor. Reported compounds enastron, mondimethylenastron, and fluorastrol, potency of these new inhibitors, have been compared with the monastrol which are better fit of the ligand to the allosteric binding site and the addition of fluorine atoms [26].



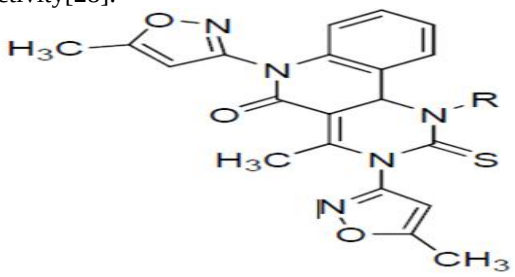
Anti-Epileptics

Phenobarbital is well known drug for epilepsy when one sees Biginelli compounds it has similar structural framework and as a natural tendency when compounds of the type were examined for epilepsy they have shown promising anti-epilepsy activity [27].



Anti-Microbials

Biginelli compounds multi-functionalized with isoxazole amines i.e. 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6,10b-tetrahydro-1H-pyrimido[5,4-c]quinolin-5-ones showed anti-microbial also apart from antibacterial, antifungal, and antimalarial activity[28].

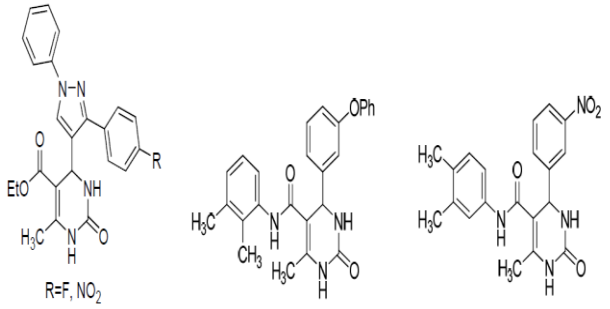


R=C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-BrC_6H_4, $C_6H_5CH_2$, 4-ClC_6H_4, 3-$CH_3OC_6H_5$, 2-ClC_6H_4.

Anti-Tubercular Activity

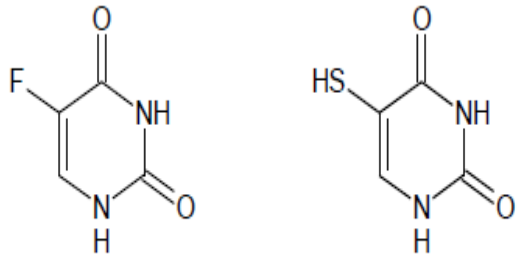
Dihydro pyrimidines also were evaluated for their antitubercular activity against Mycobacterium tuberculosis H37Rv.This study was *invitro* only. Only two compounds,ethyl4-[3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidin -5carboxylate and ethyl 4-[3-(4-nitrophenyl)-1-phenyl-1H-

pyrazol-4-yl] -6-methyl- 2-oxo-1,2,3,4- tetrahy dropyrimidine -5-carboxylate were shown to be the most active compounds and foundto be more potent than isoniazid. Compounds with 2,3-dimethylphenyl and 3,4-dimethyl carbamoyl side chain, respectively, showed 65% and 63% inhibition against Mycobacterium tuberculosis H37Rv[29].



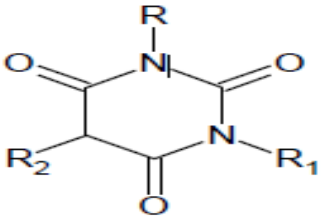
Anticancer Activity

The pyrimidine moiety with some substitution shows promising antitumor activity as there are large numbers of pyrimidine based antimetabolites. The structural modification may be on the pyrimidine ring or on the pendant sugar groups. Early metabolite prepared was 5-fluorouracil, a pyrimidine derivative followed by 5-Thiouracil which also exhibits some useful antineoplastic activities [30].



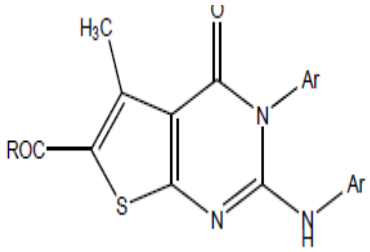
CNS Activity

Agents involved in this category include sedatives, hypnotic, anticonvulsants, anxiolytic agents, pyrimidine anaesthetics etc. Large variety of barbiturates are used as CNS active agents and are classified as short, intermediate and long acting depending upon duration of action[31].



Analgesic Activity

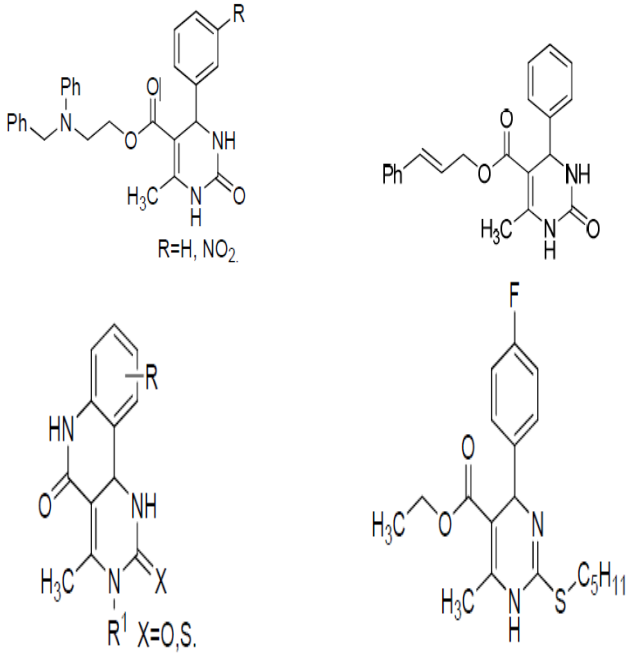
Rathod synthesized 2- aryl amino- 3- aryl- 5-methyl- 6- (substituted) thione [2, 3- d] pyrimidin- 4 (3H)-ones. All the synthesized compounds were screened for the analgesic activity by tail flick method an albino rats and by writing method on albino mice[32].



Miscellaneous activities

Since our major objective in this account is to keep present description brief following structure are presented and given below them is given their activities [33].

(a) Anti-oxidants and Anti-filarial agents.
(b) Adrenergic receptor antagonists
(c) Anti-HBV (hepatitis B virus) agents



CONCLUSION

Nowadays the practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. Out of the various drugs Pyrimidines has gained a lot of importance because it is an essential constituent of all cells and thus of all living matter. So several new approaches are carried out to in order to improve the synthetic applicability and biological activities of Pyrimidines.

REFERENCES

1. Johnson TB and Hahn DA. Pyrimidines: Their amino and amino oxy derivatives. 1933, 193.
2. Katzung, Bertram G. Basic and Clinical Pharmacology, 10th ed, 406-407.
3. Agarwal OP. Organic chemistry, Reactions and Reagent, 2006, 735
4. Shapiro R. *Proc. Natl. Acad. Sci. USA*, 96, 1999, 4396 –4401.
5. Warner RC. *Journal of. Biological Chemistry,* 1941, 137, 705 –723.
6. Bansal RK. Herocylic Chemistry, New Age international (P) Limited, 3rd edition, 2001, 452-453.
7. Tominago Y & Matsuoka KA. *Heterocycles,* 26(3), 1987, 613-616.
8. Shishoo CJ, Pathak US, Jain KS, Devani IT, Chhabria MT. *Chem Inform*, 25(38), 1994, 436-440.
9. Singh JS, Khan MH, Tiwari N, Nizamuddin. *Indian journal of Chemistry*, 33(B), 1994, 350-354.
10. DK Olaf, GB Richard, D Monica, KM Courtney, M Ester, P Silvia, R Michael, S Vincenzo, Tetrahedron letters, 2008, 49(46), 2008, 6556-6558.
11. Mi-Yeon J, Steven DJ, Kenneth S, Jozef A, Piet H. *Bioorganic and Medicinal Chemistry*, 19(1), 2011, 702- 714.
12. Kappe OC. *Tetrahedron*, 49, 1993, 6937.
13. Biginelli, P. Gazz. Chim. Italian chemistry. 1893, 23, 360
14. Institute of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria
15. Mukund GK. *Beilstein Journal of Organic Chemistry*, 5(4), 2009, 1294-1298.
16. Atwal KS, Rovnyak GC, Schwartz J, Moreland S, Hedberg A, Gougoutas JZ, Malley MF, Floyd DMJ. *Med. Chem,* 33, 1990, 1510.
17. Anastas PT, Warner JC. Green Chemistry: Theory and Practice; Oxford University Press: New York, 1998, 30.
18. Ma JJ, Zang XH, Zhou X, Wang C, Li JC, Li Q. *Indian J. Chem*, 46B, 2007, 2045.
19. Ma JJ, Zang XH, Zhou X, Wang C, Li JC, Li Q. *Indian J. Chem*, 46B, 2007, 2996.
20. Yadav LDS, Rai A, Rai VK, Awasthi C. *Tetrahedron,* 64, 2008, 1420.
21. Jiang C, You QD. *Chin. Chem. Lett.* 18, 2007, 647.
22. Prasad AK, Arya P, Bhatia S, Sharma RK, Singh R, Singh BK, Eycken EV, Singh R, Olsen CE, Parmar VS. *Indian J. Chem*, 48B, 2009, 1738.
23. Lloyd J, Finlay HJ, Atwal K, Kover A, Prol J, Yan L, Bhandaru R, Vaccaro W, Huynh T, Huang CS, Conder M, Jenkins-West T, Sun H, Li D, Levesque P. *Bio org. Med. Chem. Lett*, 19, 2009, 5469.
24. Carte B, Breen AL, Hertzbery RP, Johnson RK, Westley JW, Potts BCM. *J. Org. Chem*, 1995, 60, 1182.
25. Klein E, DeBonis S, Thiede B, Skoufias DA, Kozielskib F, Lebeaua L. *Bio org. Med. Chem*, 2007, 15, 6474.
26. Lewis RW, Mabry J, Polisar JG, Eagen KP, Ganem B, Hess GP. *Biochemistry*, 2010, 49, 4841.
27. Trivedi AR, Bhuva VR, Dholariya BH, Dodiya DK, Kataria VB, Shah V. H. *Bio org. Med. Chem. Lett*, 2010, 20, 6100.
28. Deshmukh MB, Salunkhe SM, Patil DR, Anbhule PV. *Eur. J. Med. Chem*, 44, 2009, 2651.
29. Ismaili L, Nadaradjane A, Nicod L, Guyon C, Xicluna A, Robert J-F, Refouvelet B. *Eur. J. Med. Chem*, 43, 2008, 1270.
30. Al Safarjalani ON, Zhou XJ, Ras RH, Shi J, Schinazi RF, Naguib FN and El Kouni MH. *Cancer Chemotherapy Pharmacology*, 55, 2005, 541-551.
31. Daniels TC and Jorgensen EC; Central nervous system depressants-In Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry(ed. Doerge RF), Lippincott JB, Philadelphia, 1982; 33.
32. Shah PR, Shah GK and Pandya PS. *Indian Journal of Pharmaceutical sciences,* 48, 1986, 75.
33. Singh BK, Mishra M, Sahoo MK, Gaur RL, Murthy PK, Tripathi RP. *European. Journal of Medicinal Chemistry,* 43, 2008, 2717.