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An Investigation into the Biological Effects of Dihydropyrimidines

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Abstract – A class of heterocyclic compounds known as dihydropyrimidones/thiones was initially discovered in 1893 by P. Biginelli. It has a wide range of biological actions, including anti tubercular, anti-malarial, anticancer, anti-HIV activity, analgesic, antiepileptic, cns activity, anti-inflammatory, and antitumor activity. According to this review, dihydropyrimidones' biginelli reaction and biological properties are briefly discussed.

Key Words – Dihydropyrimidones, Biginelli, Biological Activities, Anti-tumor, Anti HIV.

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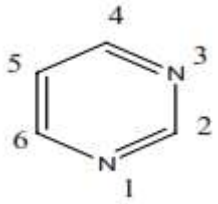
INTRODUCTION

Recent advances in medicinal chemistry have elevated the profile of pyrimidine chemistry. Before Pinner in 1885 brought attention to the fact that all such chemicals may be regarded as derivatives of a ring structure nearly analogous to pyrimidine, several members of the general class of pyrimidines had been recognised for fifty years[1]. Six-membered heterocyclic molecules with two nitrogen atoms in positions 1 and 3 are known as pyrimidines. The three isomeric diazines all include them. It has a melting point of 225°C, while its boiling point is 124°C, making pyrimidine a colourless molecule. In comparison to pyridine, pyrrimidine is a weaker basic that is water soluble[2]. The nucleic acid hydrolyses have yielded the pyrimidines. Cytosine can be found in both ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), whereas uracil and thymine are exclusively found in RNA and DNA, respectively, in the nucleic acid family[3].

STRUCTURE:



The urea and cyanoacetaldehyde synthesis of pyrimidines has a prebiotic significance. Concerns are around reactant availability and stability. It is possible that amino acids might react with cyanoacetaldehyde, which would produce formate and acetonitrile, and then form a dimer. In order to achieve the concentration of cytosine required for DNA synthesis, cyanoacetaldehyde is unlikely to be accessible long enough.[4] At a pH of 5, urea decomposes to ammonia and carbon dioxide in a controlled manner[5].

PHARMACOLOGICALLY ACTIVE PYRIMIDINES:

Pharmaceutical and agricultural compounds may benefit from the use of pyrimidines and their derivates. The successful treatment of many diseases relies on the usage of pyrimidines. In terms of urea and imide moiety, Uracil and Thymine might be regarded neutral. 5-methyluracil is another name for thymine. It is vital to understand the metabolism of these pyrimidines in order to understand both the biological usage of these chemicals and the pharmacological metabolism of pyrimidine derivatives. The potential therapeutic efficacy of pyrimidine and its derivatives has propelled pyrimidine and its derivatives into the limelight. In several bodily functions, pyrimidine derivatives play an important role.[7] Some of the noteworthy biological actions of pyrimidine derivatives include antibacterial, antitumor, and antifungal properties. Thyroid and leukaemia medications make extensive use of pyrimidine derivatives. [8] It has anti-lipidemic properties. Activity against fungi[10] Anti-HIV medications[11] Immunosuppressants.

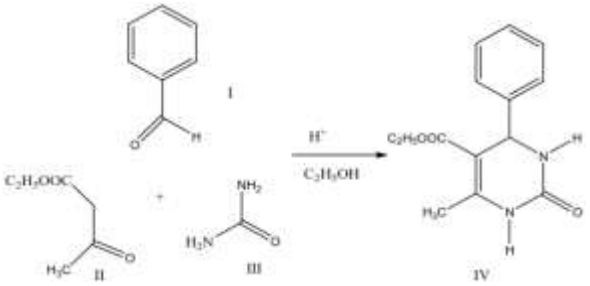
DIHYDROPYRIMIDONES:

In 1893, a three-component condensation reaction of an aromatic aldehyde, urea, and ethyl aceto acetate (DHPMs) was described for the first time by P. Biginelli[12]. Due to their intriguing pharmacological properties related with calcium channel blocker action, antihypertensive activity,

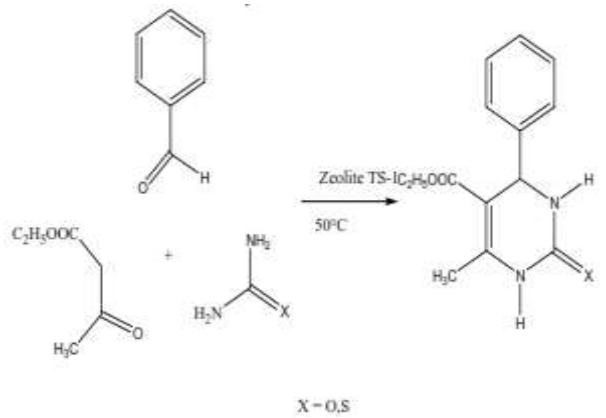
antibacterial and antimicrobial activity, such Biginelli type dihydropyrimidines have drawn substantial attention in the post-decade.

BIGINELLI REACTION:

Biginelli reaction, a multicomponent reaction utilised in industry, can be applied to the one-pot preparation of 3,4-dihydropyrimidinone. Monastrol, an antihypertensive medication, is an example of a 3,4-dihydropyrimidinone that is beneficial in a clinical setting. classic Aldehyde I and 1,3-dicarbonyl II and urea III react under acidic circumstances to form the Biginelli reaction, which consists of a series of reactions [13]



After cooling the reaction mixture, Biginelli correctly recognised the precipitate as 3,4-dihydropyrimidin-2(1H)-one IV, the product of this innovative one-pot, 3-component synthesis. The solid state structure of dihydropyrimidine analogues reveals that they can adopt a configuration comparable to that of dihydropyridine calcium channel blockers. [14] A zeolite-catalyzed, simple, one-pot, solvent-free, cost-effective, and environmentally friendly approach for the synthesis of dihydropyrimidones has been reported by Mukund G Kulkarni et al. [15].



IMPROVED REACTION CONDITIONS:

A better knowledge of the Biginelli reaction's molecular underpinnings has led to a number of improvements in the reaction's yields and substrate scope. One way to improve the Biginelli reaction is to create conditions that encourage the creation and reaction of N-acyliminium ion. In the presence of BF3 •OEt 2 and CuCl in a combination of acetic acid and THF, Hu and coworkers report consistently high yields.

IONIC LIQUIDS:

According to the Green Chemistry principles, Ionic liquids, which are widely utilised in organic synthesis as catalysts or solvents, are regarded the green solvent of the 21st century. Ionic liquids such as task-specific Polymer-supported and chiral ionic liquid have been employed in the manufacture of DHPMs.

BIOCATALYSTS:

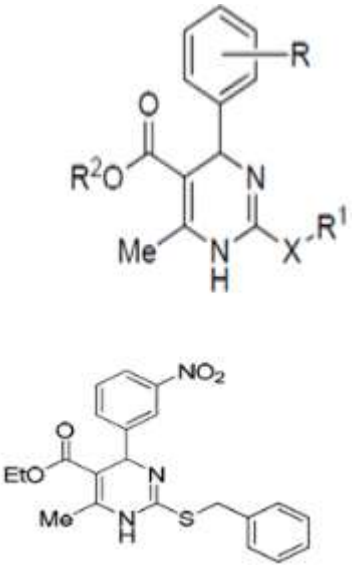
The Biginelli reaction is explained using reports on an elegant utilisation of fermenting yeast and enzyme. Biocatalysts in this process clearly need additional work.

BIOLOGICAL ACTIVITES:

The dihydro pyrimidones shows the biological activities as follows:

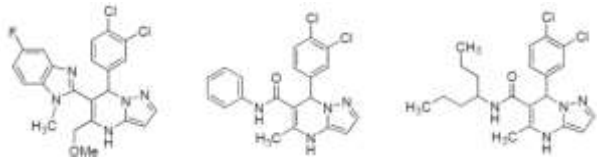
ANTIHYPERTENSIVE AGENTS:

Biologists were drawn to Biginelli products because of their similarities to Hantzsch 1,4-dihydropyridine, a well-known calcium channel modulator, and because Biginelli compounds viz (effective orally active antihypertensive medicines) are interesting targets for bringing them to real usage. DHPMs hetero-substituted by an ester (e.g., isopropyl, sec-butyl) and an alkylthio group.



POTASSIUM CHANNEL ANTAGONISTS:

Potassium channel antagonists were discovered when the benzimidazole ring was annulated using this Biginelli method. These are still in preclinical stages of development.

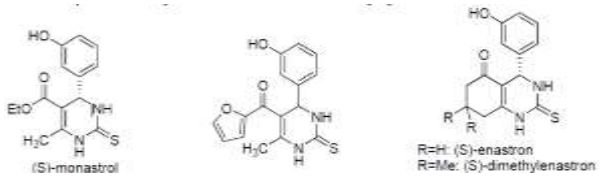


ANTI-HIV AGENTS:

The anti-HIV activity of marine natural source batzelladine DHPM derivatives is promising. Inhibition of HIVgp-120 binding to CD4 cells is achieved using these low molecular weight derivatives.

ANTITUMOR ACTIVITY:

Biginelli's first anticancer drug has been studied utilising two invitro steady-state ATPase assays (basal and microtubule-stimulated) as well as a cell-based assay for its capacity to inhibit activity. Another dihydropyrimidine, furyl derivative, was tested and found to be five times as effective than monastrol. Monastrol has been tested against the newly discovered and reported compounds such as enastron, mondimethylenastron, and fluorastrol, all of which have higher inhibitory potencies due to the fluorine atoms added.

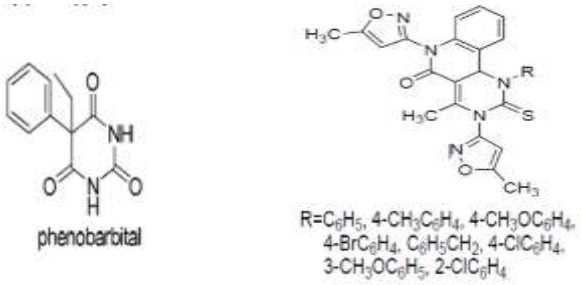


ANTI-EPILEPTICS:

Phenobarbital is a well-known epilepsy medicine with a chemical framework similar to Biginelli compounds, and when compounds of this class were studied for epilepsy, they showed potential antiepileptic activity.

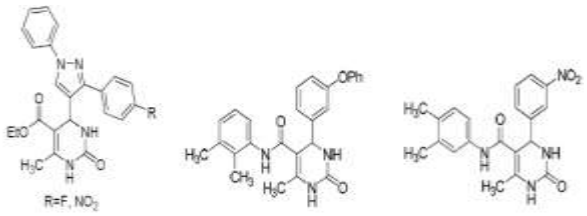
ANTI-MICROBIALS:

One example of Biginelli compounds with isoxazole amines is 1-aryl-4-methyl-3,6–bis–isomerone (5-methylisoxazol-3- yl) -2-thioxo-2,3,6,10b-tetrahydro-1Hpyrimido[5,4-c] In addition to antibacterial, antifungal, and antimalarial activity, quinolin-5-ones displayed antimicrobial activity.



ANTI-TUBERCULAR ACTIVITY:

Additionally, the antitubercular activity of dihydropyrimidines against Mycobacterium TB H37Rv was tested. Experiments were done only in vitro. Only two compounds, ethyl4-[3-(4-fluorophenyl)-1- phenyl-1H-pyrazol-4-yl] and ethyl4-[3-(4-fluorophenyl)-1- phenyl-1H-pyrazol-4-yl]. In this case, -6-methyl-2oxo1,2,3,4-tetrahydropyrimidine-5carboxylate and ethyl ethoxy 4-[3 nitrophenyl) 1-phenyl-1-Hpyrazol-4-yl] More powerful than isoniazid, the most active molecule was discovered to be 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. For example, compounds containing 2,3-dimethylphenyl and 3,4-dimethyl carbamoyl side chains inhibited Mycobacterium tuberculosis H37Rv 65 percent and 63 percent, respectively.

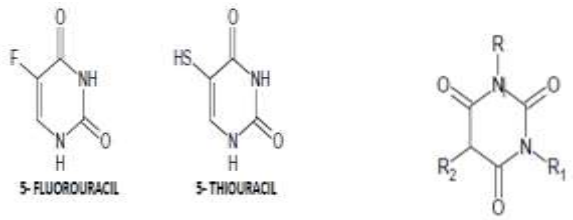


Anticancer Activity:

Some substitutions have led to promising anticancer activity for the moiety of the pyrimidine antimetabolite. The pyrimidine ring or the sugar groups attached to it may be modified. 5-Fluorouracil, a pyrimidine derivative, was the first metabolite to be synthesised, followed by 5-Thiouracil, which also has anticancer properties.

CNS Activity:

Sedatives, hypnotics, anticonvulsants, anxiolytic agents, pyrimidine anaesthetics, etc. fall within this area. Short, intermediate, and long-acting barbiturates are the most commonly utilised CNS active agents and come in a wide variety of forms.

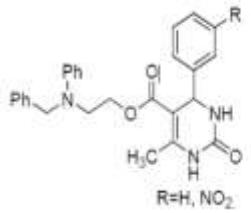


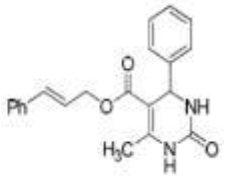
Analgesic Activity:

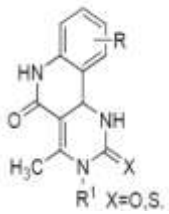
This is a pyrimidin-4 (3H) compound that Rathod created by synthesising 2-aryl amino3-aryl- 5-methyl-6- (substituted) thiones. A tail flick method on albino rats and a writing method on albino mice were used to test the analgesic activity of all the produced compounds.

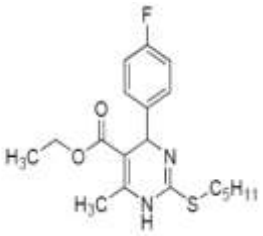
Miscellaneous activities:

In order to keep this report as concise as possible, the following structure is offered, followed by a brief description of each of the following activities: The anti-oxidants and anti-filarial agents. Agonists for the adrenergic system Agents that fight the hepatitis B virus









CONCLUSION:

Medicinal chemistry today is focused on discovering and developing new treatments for disease. Because Pyrimidines is a vital component of all cells and thus all living things, it has attracted a lot of attention among the many medications. There are numerous novel techniques to improve Pyrimidines' synthetic and biological applications.

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