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A Study of Pyrimidines and Related Heterocycles' Biological and Therapeutic Relevance

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Abstract – Fusion of the pyrimidine moiety with heterocycle scaffolds creates a novel class of hybrid heterocycles that are more active than their predecessors. Pharmacological and biological activity is seen in heterocycles with sulphur and nitrogen in the core structure. In the last decade, numerous fused pyrimidines such purines, pteridines and quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyrrolopyrimidines have been examined and discovered to have exceptional pharmacological effects. Compounds with a fused Pyrimidine nucleus exhibit a wide range of biological and therapeutic effects, as discussed in this article.

Key Words – Heterocycles, Fused Pyrimidines, Biological, Pharmacological Significance.

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INTRODUCTION

As with aliphatic and aromatic molecules, heterocyclic chemistry follows the same rules. The theoretical and practical aspects of their research are of tremendous interest. Heterocyclic ring systems may be found in a wide variety of chemicals, including alkaloids, vital amino acids, vitamins, haemoglobin, hormones, and a huge number of synthetic medications and colours. A vast variety of synthetic heterocyclic compounds including pyrrolidine, furan, thiophene and piperidine have major applications and many of these chemicals are key intermediates in synthesis. As a result of their vast range of biological actions, fused pyrimidines have gained a lot of interest in the scientific community over the years. Regularly published reviews on chemistry related to systems where pyrimidine ring is fused to heterocycles such as purines, pteridines and quinazolines as well as various heterocycles such as pyridopyrimidines, triazolo-pyrimidines, pyrazolopyrimidines and pyrimidoazepines are a clear indication of this.

In addition to being a vital component of DNA and RNA, the pyrimidine pharmacophore has significant chemical and pharmacological applications as antimicrobial, antibacterial, cardiovascular, and agrochemical and veterinary products. Anti-inflammatory and analgesic, antibacterial, anti-avian influenza virus (H5N1) anti-herpes simplex virus type-1 (HSV-1) and hepatitis-A virus (HAV) serotonin 5-HT6 receptor antagonist, anti-arrhythmic drugs, etc. were discovered to be among the various activity of these derivatives. Platelet aggregation inhibitors, antagonists, anti-conceptives, and anti-parkinsonism medicines have all been established for pyrimidine analogues.

In chemical and medicinal chemistry, pyrimidines have an important place because of their strong biological activity. Biomolecules like DNA and crucially essential medications like Fluorouracil, Etravirine, Risperidone, Avanafil, and Rosuvastatin all contain pyrimidine cores.

Scheele's discovery of uric acid in 1776 ushered in the era of fused pyrimidine chemistry. Yet it wasn't until the efforts of renowned chemists such as Bischler, Riedel, Niementowksi and Bogert that considerable advance in this subject was made roughly a century later. Since the discovery of certain purine and pyrimidine bases in double-stranded nucleic acids, several studies have been written on the chemistry of pyrimidines and purines. Purines and pteridines, for example, are simple fused pyrimidines that are physiologically active on their own or are necessary building blocks for a wide range of crucial naturally occurring chemicals (i.e., nucleic acids). In addition to being utilised as anti-leukemic medicines, several pteridine derivatives are also employed as potassium-conserving diuretics. As a bonus, quinazoline alkaloids have hypnotic, bronchodilatory, and anti-malarial properties. As an anti-allergy medication, several thieno[3, 2-d]pyrimidines are employed. Folic acid, as well as many antibiotics and diuretics, have a physiologically active pteridine system (fused pyrazino[2,3-d]pyrimidine). In addition, pteridine was identified in the vitamin B2 riboflavin (6,7-dimethyl-9-

(D-1-ribityl) isoalloxazine, vitamin B2). Prazosin, quinethazone (Fig. 1), trimethotrexate, folic acid, and riboflavin are examples of physiologically active pyrimidine derivatives.

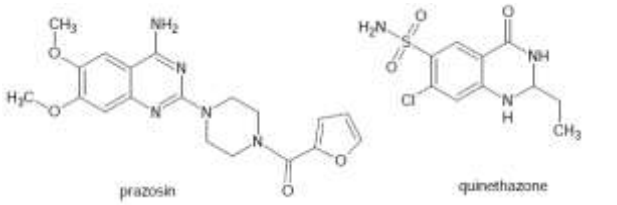


Fig.1

Myocardial infarction (MI), unstable angina (UA), and acute stroke linked with deep vein thrombosis (DVT) are among the leading causes of death globally due to atherothrombotic coronary artery disease. Clinical trials have proven the efficacy and safety of fused pyrimidines as antiplatelet and antithrombotic medications. As a result, it appears that additional research into pyrimidine chemistry is desirable. [1].

Medicinal Properties of Pyrimidines

The presence of pyrimidine bases in the nucleic acids DNA and RNA is a possible explanation for their widespread usage as therapeutic agents. The pyrimidines' wide spectrum of biological actions include in vitro activity against unrelated DNA and RNA, viruses like polioherpes, diuretic, antitumour, anti-HIV, and cardiovascular characteristics. Compounds containing pyrimidine nucleus show a wide range of pharmacological properties, according to a literature review. As a result, various pyrimidine analogues have been found to have a wide range of therapeutic properties, including antibacterial and antifungal, antileishmanial, antiinflammatory, antihypertensive, antipyretic, and antiviral properties. Many pyrimidine derivatives have also been shown to behave as calcium channel blockers and to have possible CNS depressive characteristics.

Antibacterial activity:

Using Michael addition, El-Hossini MS et al.[2] synthesised a -enaminoester from ethyl cyanoacetate and -cyano chalcone. The pyranopyrimidines were produced by reacting this with ethyl cyanoacetate, phenyl isothiocyanate, and trichloroacetonitrile (Fig. 2). Antibacterial properties have been demonstrated.

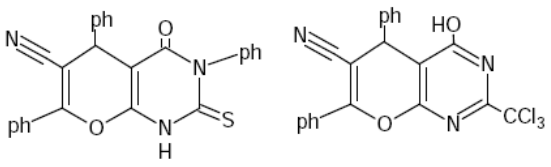


Fig. 2

Barbituric acids, aromatic aldehydes, and 6-amino-uracils or 1H pyrazol-5-amines were used in a simple, clean and three-component one-pot cyclocondensation procedure to produce pyrido[2,3-d:6,5-d]dipyrimidines and pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidines (Fig. 3a) (Fig. 3b). They were tested for their antibacterial properties in a laboratory setting. Antimicrobial activity of most of the substances ranges from a limited to a good spectrum.

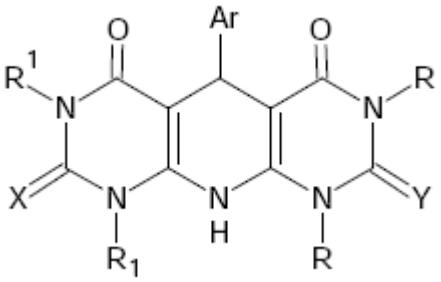


Fig. 3(a)

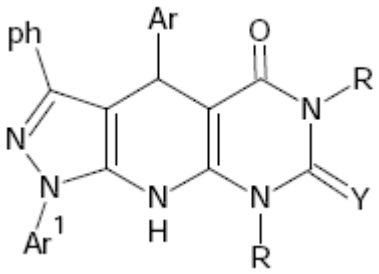


Fig. 3(b)

Antihyperlipidemic activity:

In the presence of dry hydrogen chloride gas, Shishoo CJ and his colleagues[4] have synthesised certain 2-substituted 6-phenyl and 7-phenyl thieno[3,2-d] pyrimidin-4-one thiopheno aminoesters. Some thieno pyrimidines have been found to have antihyperlipidemic properties (Fig. 4).

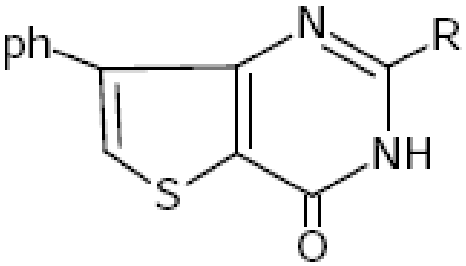


Fig. 4

Antifungal activity:

A number of 3,10-diaryl-2-thiothiazo[4,5-d]pyrimidines and 3,6,9 triaryl-2-thiothiazo(4,5-d)pyrimidines were synthesised by Singh JS et al.[5]. These [1,3,4]thiadiazolo[2,3-b]pyrimidines were formed via the reaction of arylidenorhodanines

with 2-aminopyridine and 5-aryl-1,3,4-thiadiazoles. It has been determined that thiazolo-thiadiazolo-pyrimidines have better antifungal activity than the thiazolo-pyrido-pyrimidines (Fig. 5), which has a comparable activity to the commercial fungicide Carbendazim.

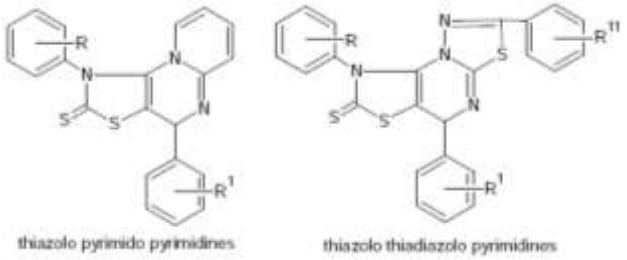


Fig. 5

Regioisomers of indazole, such as 3-amino-6-(trifluoromethyl)-1H-indazole-7-carbonitrile and 3-amino-6-(trifluoromethyl)-1H-indazole-7-carbonitrile, were reacted with formaldehyde, followed by unsymmetrical, symmetrical, and cyclic electron-rich olefins in the presence of GdCl3 as a catalyst, and pyrimidine fused indazole derivatives were obtained. [6] Compounds containing ethenyl benzene moeity (Fig. 6) and cyclohexa-1,3-diene moeity (Fig. 6) exhibited substantial action against all species of Gram-positive and Gram-negative bacteria, respectively.

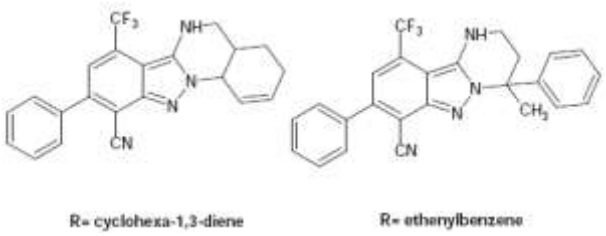


Fig. 6a

Using sodium ethoxide and formamide, Desai JM et al.[7] reacted 2-amino-3 carboxamido/cyano-5-styryl-7,7-dimethyl-6,7-dihydrobenzo[b]thiopheno[2,3-d]pyrimidines were formed (Fig. 6). Various strains of bacteria and fungi have been tested for antibacterial properties. Against A.awamori, the compounds demonstrated moderate to excellent antifungal efficacy.

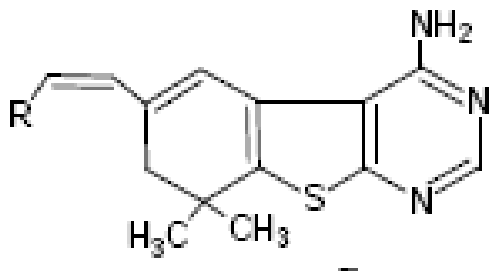


Fig. 6

Blood related disorders:

A number of 3-(dialkylamino)-IH-pyrimido[1,2-a]quinolin- 1-ones and 2-(dialkylamino)4H-pyrimido[2,1-a]isoquinolin-4ones were synthesised by treating the chloro derivatives with an excess of dialkylamines. Dialkylamino substituents with 1-piperazinyl compounds had the strongest in vitro antiplatelet action (Fig. 7a and Fig. 7b). A similar technique was utilised to create the new 2-(l-piperazinyl)-4H-pyrido[1,2-pyrimidin-4-one], which yielded the chemical with the highest activity against all of the platelet aggregation inducers tested (ADP. collagen. A 23187).[8]

Analgesic and anti-inflammatory activities:

Olga BA et al.[9] synthesised a series of N-methyl-N-pyrimidin-2-yl glycines, each of which had the pyrimidine ring fused with a cyclohexane, cyclohexene, 1,2,3,4-tetrahydronaph - thalene, and benzopyrane. They tested each for anti-inflammatory activity in a rat model of inflammatory disease.

To make sixteen novel 2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6- carboxylic acid methyl esters (Figure 9), Birsen T et al.[10] used chloroacetic acid and suitable benzaldehydes to react 1,2,3,4,tetrahydro pyrimidine-2-thiones with each other. Anti-inflammatory properties of the substances were examined. A modest amount of anti-inflammatory action was found in compounds with the R1=4-Br CH_3/OCH_3 and R1=2-F H/4-OCH_3, when compared to Indomethacin..

There are several amides of 7-methyl-3-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3–d]pyrimidine-5-carboxylic acid and their 1-[2-hydroxy-3(4-phenyl-1-piperazinyl)propanoic acid] derivatives that have been reported. Analgesic action was evident in several of them.[11]

Anti-cancer agents:

For the first time, a quaternary-substituted dihydrofuropyrimidine was used to create inhibitors of the mammalian target of Rapomycin (mTOR) enzyme. 4-Acetamido pyrazole moiety chemical was shown to be the most powerful.[12]

The pyrimidinone derivative was the starting point for a series of new substituted pyrazolo[3,4-d]pyrimidines produced by Aymn ER et al.[13]. To see if they have any anticancer potential, researchers tested them in vitro against human breast adenocarcinoma (MCF-7) cell lines, and they found that the majority of the tested compounds had substantial cytotoxic activity when compared to Cisplatin, a regularly used anticancer treatment.

There were several studies done by Ailing Z and his colleagues employing thieno[2,3-d]pyrimidines and furo[2,3-d]pyrimidines as starting materials and

testing them for their ability to inhibit cMET. Thieno[2,3-d]pyrimidine inhibited cell growth in BaF3-TPR-MET cells with a high degree of potency and selectivity for members of the c-MET family, according to the study. A c-MET dependent U-8TMG human glioblastoma model failed to show any benefit from the treatment.[14]

Dual thymidylate synthase and dihydrofolate reductase (DHFR) inhibitors have been produced by oxidative aromatization of 2-amino-4-methyl-4,5,6,7-tetrahydro-1- benzothiophene-3-carboxylate, a tricyclic benzothieno[2,3-d] pyrimidine scaffold. Human Ts were inhibited, but not human DHFR, by 2-CH_3 moiety compounds. Dual hTS/hDFHR inhibitors were created by substituting 2-NH_2 for the original 2-NH_2 compound.[15]

To test for Aurora-A inhibitory activity, Mohamed RS et al.[16] synthesised pyrazolo[1,5-a]pyrimidines, triazolazolo[1,5-a]pyrimidines, and pyrimido[1,2-a]benzimidazoles using phenyl sulfonyl moiety. Anti-HST116 colon cancer cell line cytotoxic efficacy of newly synthesised chemicals was tested. Equivalent Doxorubicin activity was observed for 2,7-Diphen-6-(Phenylsulfonyl)pyrazolo[1,5-a]pyrimidine and its p-methoxy analogue.

Pyrolo[2,3-d]pyrimidines may be synthesised quickly and easily using Sekhar N.M. et al.[17] condensation of aldehydes with 2,4-diamino-6-hydroxy pyrimidine under moderate basic conditions. A unique multi-targeted antifolate was synthesised using this methodology, which was proven in the production of pemetrexed disodium metabolites.

The solubility of pyrazolo[3,4-d]pyrimidines was increased in order to block Src and Abl tyrosine kinase phosphorylation and to drastically lower the proliferation of leukemic and osteosarcoma cell lines, as demonstrated by Elena D et al.[18]. In comparison to non-complexed substances, tests showed a significant increase in biological response.

For the first time, pyrazolo [3, 4-d] pyrimidines and their triazole derivatives were synthesised from p-toluene sulfonyl hydrazide by F Ibrahim and colleagues[19] using electrophilic and nucleophilic reagents. It has been shown that a number of newly synthesised chemicals have strong cytotoxicity against MCF7 breast cancer cells.

Anti-HIV agents:

An effective and reliable method for the synthesis of methyl-3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was published by Olaf DK et al.,[20]. The scope of the synthesis regarding the introduction of substitutes on the pyrido ring was examined in this study. Consequently, they came up with a novel framework for HIV-1 integrase inhibitors.

CNS related agents:

Among all 3-(3- chlorophenyl sulfonyl)-5,7-dimethyl-pyrazolo derivative, the most powerful antagonist is 3-phenyl sulfonyl-5-methoxy methyl-7-methyl pyrazolo derivative, which was produced by Alexandre VI et al.[21] and examined for 5-HT6 receptor antagonistic activity.

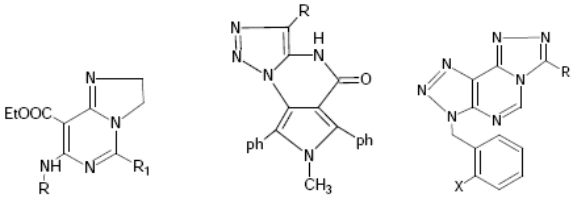
Immunosuppressants:

For the first time, thiazolo[5,4-d] pyrimidines have been characterised as an immunosuppressive drug that can be used to prevent graft rejection following organ transplantation. As a starting point, diethyl amino malonate hydrochloride was employed. There is no difference in effectiveness between them and Cyclosporin A. Because of this, new immunosuppressive medications can be developed on the basis of these discoveries.[22]

Miscellaneous activities:

It was shown that the type II inhibitors of vascular endothelial growth factor receptor 2 (VEGFR2) were able to block the kinase activity of pyrrolo[3,2-d]pyrimidines, which were synthesised by Yuga O and colleagues[23]. These inhibitors were made by incorporating the diphenylurea moiety into the pyrrolo[3,2-d] pyrimidine core through an oxygen.

TC Mahesh[24] and his colleagues developed new imidazo[1,2-c]pyrimidines. After the chloro group was nucleophilically replaced by ethanolamine in different substituted 4-chloro pyrimidines, the resulting 4-(2-hydroxy ethyl) amino pyrimidines were successfully cyclized to imidazo[1,2-c]pyrimidines in a high degree of yield. Antimycobacterial activity was tested on all of them. Some of the produced substances have a high degree of efficacy.

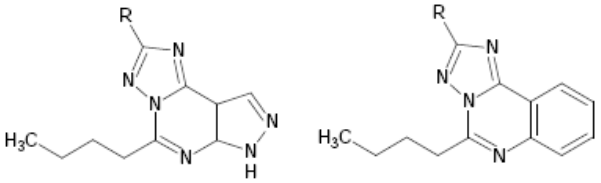


By reacting 3-azido pyrrole with substituted acetonitriles, Antonino L et al.[25] produced in high yields derivatives of the novel ring system pyrrolo[3,4-e][1,2,3]triazolo [1,5-a]pyrimidine. When heated in DMSO with water to form pyrrolo[3,4-d][1,2,3]triazolo-[1,5-a]pyrimidine, the newly synthesised chemical exhibited intercalating activity equivalent to that of well-known intercalating drugs like Amasacrine or Doxorubicin.

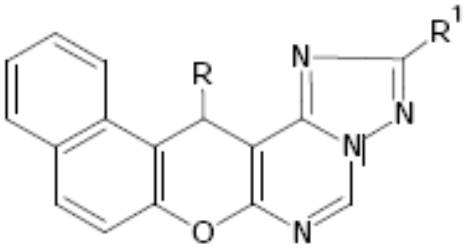
Tricyclic 7-substituted 3-(2-chlorobenzyl) and 3-(2-fluorobenzyl)-1,2,3-triazoloids were synthesised by replacing 7-chloro-3-(2-chlorobenzyl) and 7-chloro-3-(2-fluorobenzyl)-1,2,3-triazoloids with hydrazides, which underwent intramolecular cyclization to form

the new tricyclic 7-substituted tricyclic 7-substituted triazolo[4,5-d]pyrimidines.[26]

1,2,4-triazolo[4,3-c]pyrimidines. For adenosine A1 and A2 receptor affinity, they were shown to be ineffective.



Fusion triazolopyrimidine derivatives with a high affinity and selectivity to human A3 adenosine receptors were synthesised by Takashi O et al.[27]. With the aid of acyl hydrazines and imidate produced in situ, the fused triazolopyrimidine compounds could be conveniently made in a one-pot procedure. As a result of this procedure, novel tricyclic A3 receptor antagonists were discovered as well as a variety of substitutes were added to the fused triazolopyrimidine ring. In the end, they discovered novel pyrazolo[4,3-e] scaffolds. -1,2,4-triazolo[1,5-c]pyrimidines and 1,2,4-triazolo[1,5-c]quinazolines as powerful and selective hA3 receptor agonists.



CONCLUSION

Pyrimidines have a wide range of biological action, as indicated by the huge number of compounds that have been found. Medicinal chemists will be able to design, organise, and apply new methods to the development of novel medications thanks to the versatility and biological activity of these heterocycles.

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