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Fused pyrimidines: The heterocycle of diverse biological and pharmacological significance

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ABSTRACT

Fusion of pyrimidine moiety with different heterocycle scaffolds gives rise to a new class of hybrid heterocycles possessing improved activity. Heterocycles containing sulphur and nitrogen atoms in the core structure, shows number of pharmacologically and biologically active compounds. So, various fused pyrimidines like purines, pteridines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyrrolopyrimidines were studied in the past decade and were found to possess remarkable pharmacological properties. The present review provides a broad view of the biological and medicinal properties expressed by compounds having fused Pyrimidine nucleus.

Key words: Heterocycles, Fused Pyrimidines, Biological, Pharmacological Significance.

INTRODUCTION

The chemistry of heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. Their study is of great interest both from the theoretical as well as practical importance. Various compounds such as alkaloids, essential amino acids, vitamins, haemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are large number of synthetic heterocyclic compounds, like pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridine and thiazole having important application and many are important intermediates in synthesis[1]. Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily due to very wide spectrum of biological activities. This is evident in particular from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles such as purines, pteridines, quinazolines, pyridopyrimidines, triazolo pyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyralopyrimidines.

Fused pyrimidine chemistry began in 1776, when Scheele isolated uric acid. However, more systematic investigations were undertaken around 100 years later, when the works of well-known chemists such as Bischler, Riedel, Niementowski, Gabriel, and Bogert established significant progress in this field[2]. Particularly, numerous papers on chemistry of pyrimidines

and purines have been published since the discovery of the presence of some purine and pyrimidine bases in double stranded nucleic acids. Many simple fused pyrimidines such as purines and pteridines are biologically active by themselves[3, 4], or are essential components of very important naturally occurring substances (*i.e.*, nucleic acids). Some pteridine derivatives are also used as anti-leukemic drugs[5], or potassium-conserving diuretics[6]. In addition, several quinazoline alkaloids exhibit hypnotic[7,8], bronchodilatory[9], and antimalarial[10,11] activity. Some fused thieno[3, 2-*d*]pyrimidines serve as anti-allergy drugs, some act as fungicides. A very important biologically active pteridine system (fused pyrazino[2,3-*d*]pyrimidine) is present in folic acid, as well as in several antibiotics and diuretics. Pteridine was also found in riboflavin (6,7-dimethyl-9-(D-1-ribityl) isoalloxazine, vitamin B_2), a growth-regulator for microbes and animals. Examples of some biologically active pyrimidine derivatives are prazosin, quinethazone (Fig. 1), trimethotrexate, folic acid, riboflavin[12].

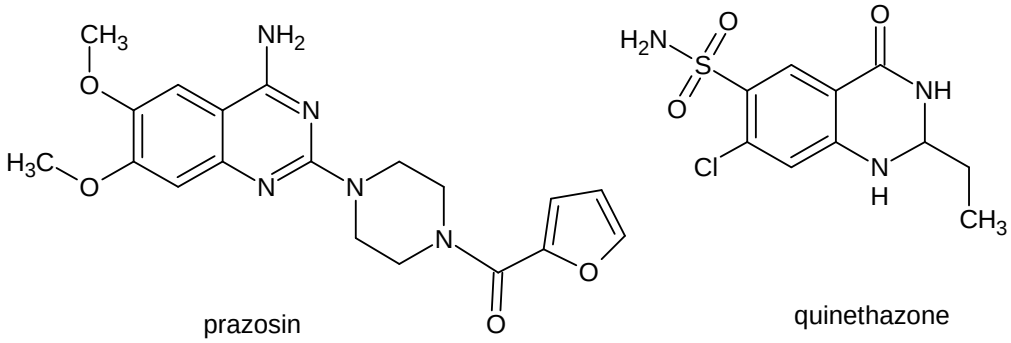


Fig.1

Atherothrombotic coronary artery disease, giving rise to a number of cardio circulatory disorders such as myocardial infarction (MI), unstable angina (UA), or acute stroke associated with deep vein thrombosis (DVT), is one of the most important causes of death worldwide. The relevance of fused pyrimidines as antiplatelet and antithrombotic drugs has been firmly established by clinical trials. Thus, further exploration of pyrimidine chemistry appears to be worthwhile[13].

Antibacterial activity:

El-Hossini MS *et al*.,[14] carried out the reaction of ethyl cyanoacetate with α-cyano chalcone, lead to the formation of a β-enaminoester via Michael addition. This was reacted with ethyl cyanoacetate, phenyl isothiocyanate and trichloroacetonitrile to yield the pyranopyrimidines (Fig. 2). They have shown antibacterial activities.

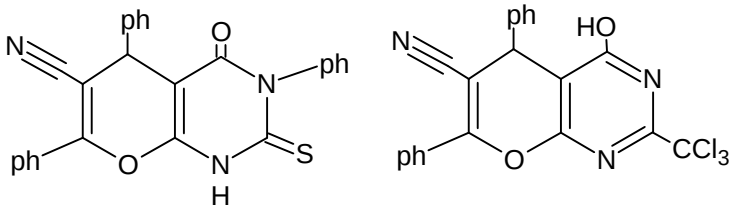


Fig. 2

Ayoob B *et al*.,[15] reported that a simple, clean and three-component one-pot cyclo-condensation reaction of barbituric acids, aromatic aldehydes and 6-amino-uracils or 1*H*-pyrazol-5-amines for the synthesis of pyrido[2,3-*d*:6,5-*d*]dipyrimidines (Fig. 3a) and pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines (Fig. 3b). These products were evaluated *in vitro* for their antibacterial activities. Most of the compounds have a narrow to good spectrum antimicrobial activity.

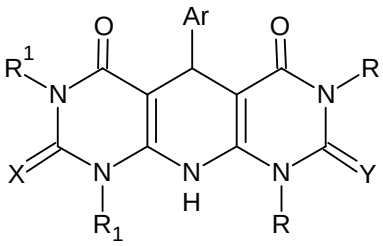


Fig. 3(a)

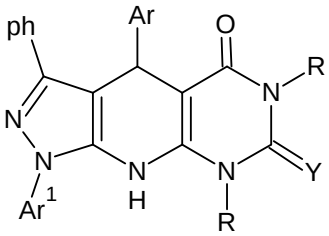


Fig. 3(b)

Antihyperlipidemic activity:

Shishoo CJ *et al*.,[16] have prepared some 2-substituted-6-phenyl and 7-phenyl thieno[3,2-*d*] pyrimidin-4-ones through cyclocondensation of the corresponding thiopheno aminoesters with a variety of nitriles in the presence of dry hydrogenchloride gas. Antihyperlipidemic activity has been reported in a few thieno pyrimidines (Fig. 4).

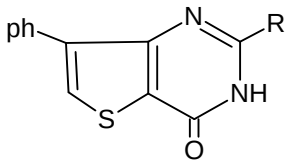
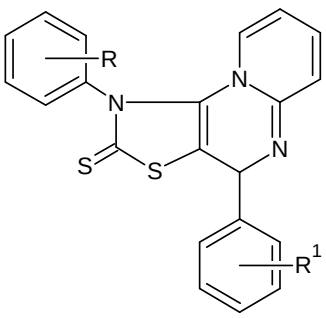


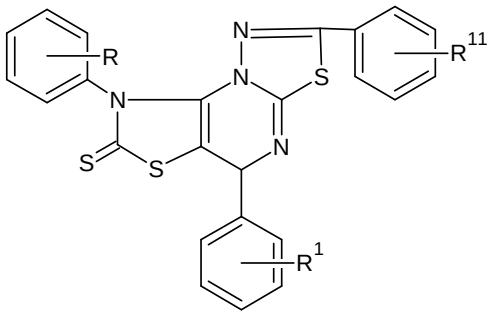
Fig. 4

Antifungal activity:

Singh JS *et al*.,[17] synthesized a number of 3,10-diaryl-2-thiothiazolo[4,5-*d*]pyrido[2,1-*b*] pyrimidines and 3,6,9-triaryl-2-thiothiazolo[4,5-*d*][1,3,4]thiadiazolo[2,3-*b*]pyrimidines from the Michael adducts which in turn have been prepared by the reaction of arylidenorhodanines with 2-aminopyridine and 2-amino-5-aryl-1,3,4-thiadiazoles.The antifungal activity of the title compounds has been screened and it was found that thiazolo-thiadiazolo-pyrimidines showed greater activity than thiazolo-pyrido-pyrimidines (Fig. 5) whose activity is comparible with commercial fungicide Carbendazim.



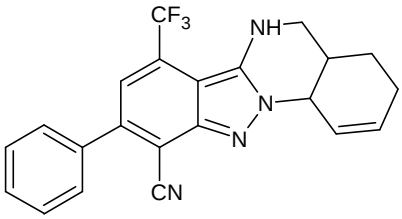
thiazolo pyrimido pyrimidines



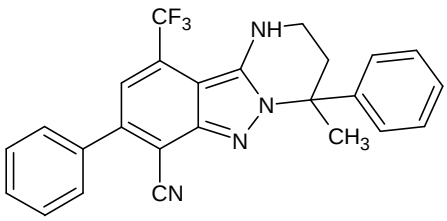
thiazolo thiadiazolo pyrimidines

Fig. 5

Yakaiah T *et al*.,[18] reacted Indazole regioisomers such as 3-amino-4-(trifluoromethyl)-6-phenyl-1*H*-indazole-7-carbonitrile and 3-amino-6-(trifluoromethyl)-4-phenyl- 1*H*-indazole-7-carbonitrile independently with formaldehyde followed by unsymmetrical, symmetrical and cyclic electron rich olefins in presence of $GdCl_3$ as catalyst and obtained pyrimidine fused indazole derivatives. Compound with ethenyl benzene moeity (Fig. 6) showed significant activity against all species of Gram-positive and Gram-negative bacteria, Similarly compound with cyclohexa-1,3-diene (Fig. 6) showed promising activity against yeast and filamentous fungi.



R= cyclohexa-1,3-diene



R= ethenylbenzene

Fig. 6a

Desai JM *et al*.,[19] carried out the reaction of 2-amino-3-carboxoamido/cyano-5-styryl-7,7-dimethyl-6,7-dihydrobenzo[*b*]thiophenes in presence of sodium ethoxide with formamide, yielded benzothieno[2,3-d]pyrimidines (Fig. 6). They have been screened for antimicrobial activity against various strains of bacteria and fungi. Compounds showed moderate to good antifungal activity and comparable activity against *A.awamori.*

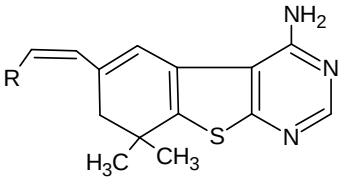


Fig. 6b

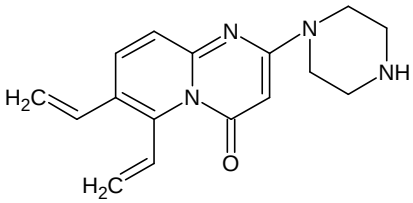


Fig. 7a

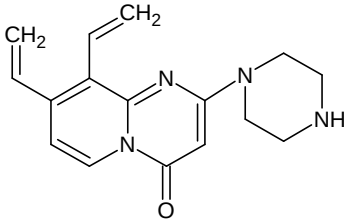


Fig. 7b

Blood related disorders:

Di Braccio M *et al*.,[20] prepared a number of 3-(dialkylamino)-I*H*-pyrimido[1,2-*a*]quinolin- 1-ones and 2-(dialkylamino)4*H*-pyrimido[2,1-*a*]isoquinolin-4-ones by treating the corresponding chloro derivatives with an excess of dialkylamines. The highest *in vitro* antiplatelet activity was obtained when the dialkylamino substituent was 1-piperazinyl compounds (Fig. 7a and Fig. 7b). The novel 2-(l-piperazinyl)-4*H*-pyrido[1,2-pyrimidin-4-one] was also prepared by an analogous procedure, which resulted in the most active compound towards all the platelet aggregation inducers used (ADP. collagen. A 23187).

Analgesic and anti-inflammatory activities:

Olga BA *et al*.,[21] prepared a series of *N*-methyl-*N*-pyrimidin-2-yl glycines, having the pyrimidine ring fused with a cyclohexane [*N*-methyl-*N*-(5,6,7,8-tetrahydroquinazolin-2-yl) glycine],cyclohexene[*N*-methyl-*N*-(5,6-dihydroquinazolin-2-yl)glycine],1,2,3,4-tetrahydronaph - thalene[*N*-methyl-*N*-(5,6-dihydrobenzo[*e*]quinazolin-2-yl)glycine] and benzopyrane[*N*-methyl-*N*-(5-phenyl-5*H*-[1]benzopyrano[4,3-*d*]pyrimidin-2-yl)glycine] and tested for anti-inflammatory activity. All the described products showed an appreciable antiphlogistic activity, particularly Fig. 8a and Fig. 8b.

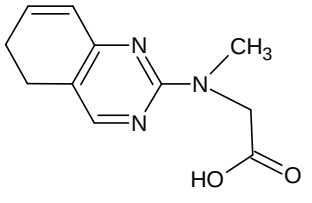


Fig. 8a

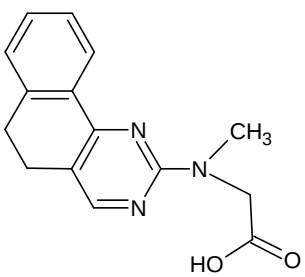


Fig. 8b

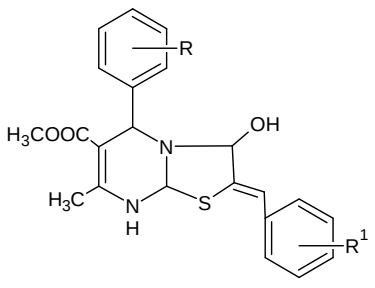


Fig. 9

Birsen T *et al*.,[22] synthesized sixteen new 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid methyl esters (Fig. 9) by reacting 1,2,3,4-tetrahydro pyrimidine-2-thiones with chloroacetic acid and appropriate benzaldehydes in a single step. The compounds were tested for their anti-inflammatory activities. Results revealed that compounds with R=4-Br R^1=4-CH_3/OCH_3 and R=2-F R^1=H/4-OCH_3 exerted moderate anti-inflammatory activity compared with Indomethacin.

Helena SL *et al*.,[23] described the synthesis of 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)propyl] derivatives (Fig. 10). Some of them displayed strong analgesic activity.

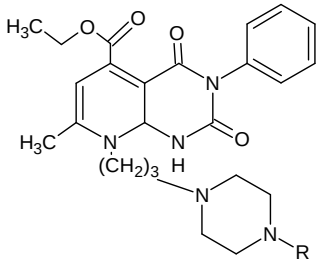


Fig. 10

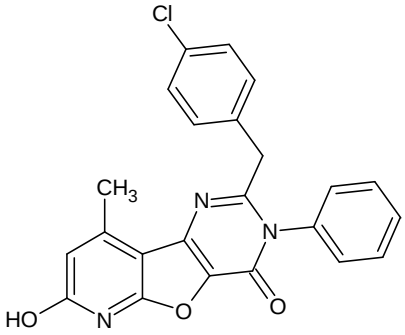


Fig. 11

Vachala SD et al.,[24] synthesized some pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidin-4(3*H*)-ones and evaluated for their antioxidant and anti-inflammatory activities. Compound 2-(4-chlorobenzyl)-7-hydroxy-9-methyl-3-phenyl pyrido furo[3,2-*d*]pyrimidin-4(3*H*)-one (PFP-HM2) (Fig. 11) was found to be a potent antioxidant (IC_{50} value 0.129 µM) and anti-inflammatory agent. It showed 76-98.8% inhibition of inflammation.

Anti-cancer agents:

Frederick C *et al*.,[25] synthesized a series of inhibitors of mammalian target of Rapomycin (mTOR) kinase based on a quaternary-substituted dihydrofuropyrimidine by cyclocondensation of β-keto ester. The compound with 4-acetamido pyrazole moiety (Fig. 12) was found to be most potent.

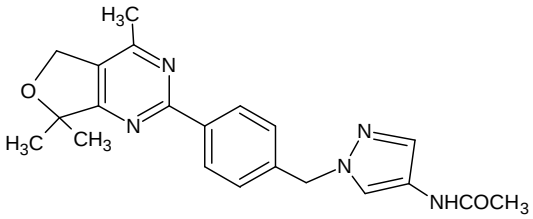


Fig. 12

Aymn ER *et al*.,[26] made a series of novel substituted pyrazolo[3,4-*d*]pyrimidines (Fig. 13) starting with pyrimidinone derivative. Their *in vitro* cytotoxicity against human breast adenocarcinoma (MCF-7) cell lines has been investigated and most of the tested compounds exploited potent cytotoxic activity compared to commonly used anticancer drug Cisplatin, the acyclic nucleoside derivative revealed the highest anticancer activity among the other tested compounds.

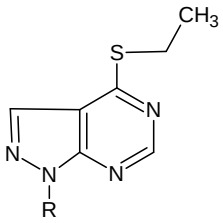


Fig. 13

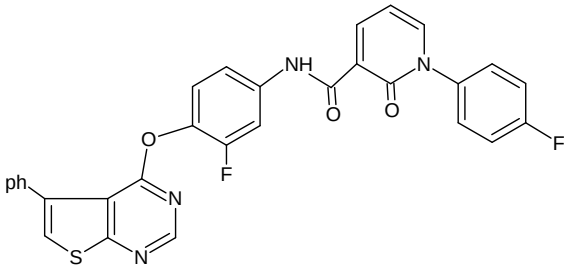


Fig. 14

Ailing Z *et al*.,[27] prepared a series of thieno[2,3-*d*]pyrimidines (Fig. 14) and furo[2,3-*d*]pyrimidines by using thieno[2,3-*d*]pyrimidin-4(3*H*)-one as starting material and evaluated for c-MET inhibition. Thieno[2,3-*d*]pyrimidine displayed high inhibitory effect on cell proliferation in BaF3-TPR-MET cells and showed high selectivity for c-MET family. However it was ineffective in c-MET dependent U-8TMG human glioblastoma xenograft model.

Xin Z *et al*.,[28] synthesized classical antifolates with a tricyclic benzo[4,5]thieno[2,3-*d*] pyrimidine scaffold (Fig. 15) as dual thymidylate synthase and dihydrofolate reductase (DHFR) inhibitors by oxidative aromatisation of ethyl 2-amino-4-methyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate. Compounds with 2-CH_3 moeity inhibited human Ts but not human DHFR. Replacement of it with 2-NH_2 gave increased human Ts inhibition and also human DHFR inhibition affording dual hTS/hDFHR inhibitors.

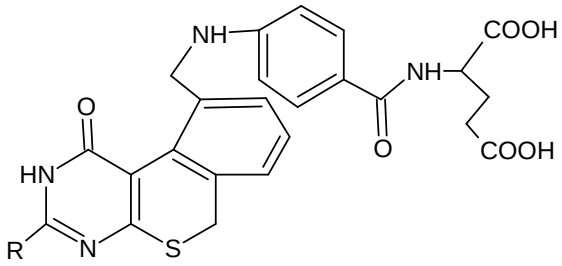


Fig. 15

Mohamed RS *et al*.,[29] reported the synthesis of pyrazolo[1,5-*a*]pyrimidines, triazolo[1,5-*a*]pyrimidines and pyrimido[1,2-*a*]benzimidazoles ring systems incorporating phenyl sulfonyl moiety and evaluated as Aurora-A kinase inhibitors. The cytotoxic activity of the newly synthesized compounds against HST116 colon tumor cell line was investigated. 2,7-Diphenyl-6-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidine (Fig. 16a) and its *p*-methoxy analogue (Fig. 16b) were found to be equipotent to Doxorubicin as a reference drug.

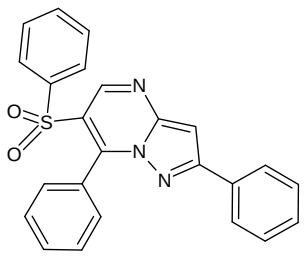


Fig. 16a

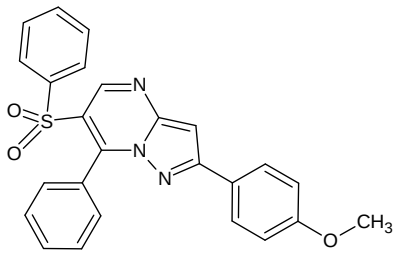


Fig. 16b

Sekhar NM *et al*.,[30] developed a short and efficient synthesis for pyrrolo[2,3-*d*]pyrimidines (Fig. 17) by cyclo condensation of α,α-dibromo aldehydes with 2,4-diamino-6-hydroxy pyrimidine under mild basic conditions in good yields. Application of this protocol has been

demonstrated in the synthesis of a metabolite of pemetrexed disodium, a novel multi targeted antifolate.

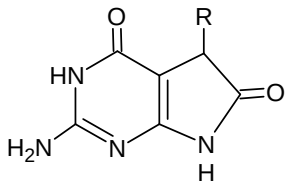


Fig. 17

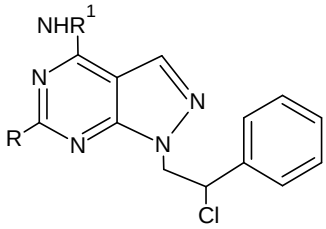


Fig. 18

Elena D *et al*.,[31] carried out studies to enhance the solubility of pyrazolo[3,4-*d*]pyrimidines (Fig. 18) to be able to strongly inhibit Src and Abl tyrosine kinase phosphorylation and to significantly reduce leukemic and osteosarcoma cell lines growth. Tests shown a good enhancement of biological response in comparision with non complexed compounds.

F Ibrahim *et al*.,[32] synthesized some pyrazolo [3, 4- d] pyrimidines (Fig. 19) derivatives and their triazole derivatives from p-toluene sulfonyl hydrazide by reaction with different electrophilic and nucleophilic reagents. Some of the newly synthesized compounds have been evaluated for their potential cytotoxicity against breast cancer cell line (MCF7), which show high activity.

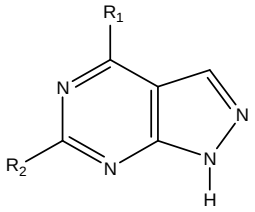


Fig. 19

Anti-HIV agents:

Olaf DK *et al*.,[33] described an efficient and reliable synthesis of the heterocyclic scaffold methyl-3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate (Fig. 20), the scope of the synthesis regarding the introduction of substituents on the pyrido fused ring is explored. Thus they devised a new scaffold for HIV-1 integrase inhibitors.

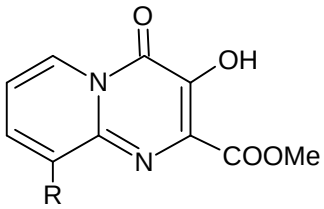


Fig. 20

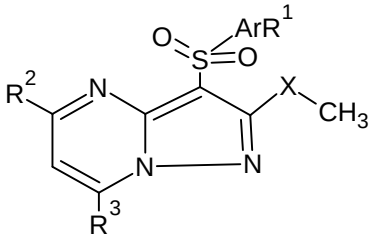


Fig. 21

CNS related agents:

Alexandre VI *et al*.,[34] synthesized a series of novel 3-sulfonyl-pyrazolo[1,5-*a*]pyrimidines (Fig. 21) and their 5-HT_6 receptor antagonistic activities were tested, among all 3-(3-chlorophenyl sulfonyl)-5,7-dimethyl-pyrazolo derivative , 3-phenyl sulfonyl-5-methoxy methyl-7-methyl pyrazolo derivative, 3-phenyl sulfonyl-5-methyl-7-methoxy methyl pyrazolo derivative are the most potent antagonists.

Immunosuppressants:

Mi Yeon J *et al*.,[35] described the synthesis and *in vitro* and *in vivo* activity of thiazolo[5,4-*d*] pyrimidines (Fig. 22) as a novel class of immunosuppressive agents, useful for preventing graft rejection after organ transplantation. Diethyl amino malonate hydrochloride was used as starting

material for its preparation. They are equally active to Cyclosporin A. Therefore these findings are an excellent starting point for the development of new generation immunosuppressive drugs.

Miscellaneous activities:

Yuga O *et al*.,[36] synthesized a series of pyrrolo[3,2-*d*]pyrimidine derivatives and evaluated their application as type-II inhibitors of vascular endothelial growth factor receptor 2 (VEGFR2) kinase. Incorporation of diphenylurea moiety at C_4-position of pyrrolo[3,2-*d*] pyrimidine core via an oxygen linker (Fig. 23) resulted in potent inhibitors.

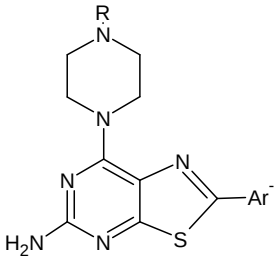


Fig. 22

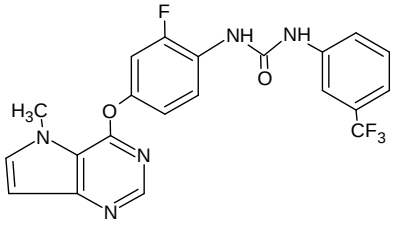


Fig. 23

Mahesh TC *et al*.,[37] designed novel imidazo[1,2-*c*]pyrimidines (Fig. 24). The designed molecules were synthesized by nucleophilic displacement of chloro group of various substituted 4-chloro pyrimidines by ethanolamine followed by cyclization of these 4-(2-hydroxy ethyl) amino pyrimidines to imidazo[1,2-*c*]pyrimidines in good yield. All were screened for antimycobacterial activity. Some of the synthesized compounds exhibited potent activity.

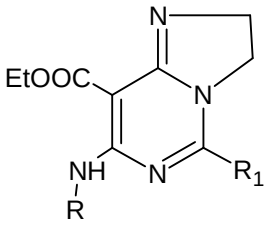


Fig. 24

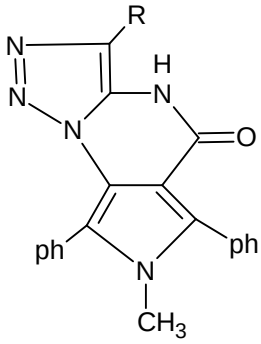


Fig. 25

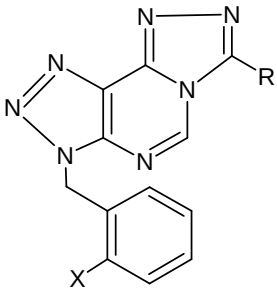


Fig. 26

Antonino L *et al*.,[38] prepared derivatives of new ring system pyrrolo[3,4-*e*][1,2,3]triazolo [1,5-*a*]pyrimidine in high yields in one step by reaction of 3-azido pyrrole and substituted acetonitriles. The obtained compound rearranged, upon heating in DMSO in presence of water to pyrrolo[3,4-*d*][1,2,3]triazolo-[1,5-*a*]pyrimidine (Fig. 25), they have shown comparable intercalating activity with those of well-known intercalating agents such as Amasacrine or Doxorubicin.

Giuliana B *et al*.,[39] carried out nucleophilic replacement of 7-chloro-3-(2-chlorobenzyl) and 7-chloro-3-(2-fluorobenzyl)-1,2,3-triazolo[4,5-*d*]pyrimidines with some hydrazides , gave the corresponding 7-hydrazido derivatives, these by heating underwent an intramolecular cyclization to form the new tricyclic 7-substituted-3-(2-chlorobenzyl) and 3-(2-fluorobenzyl)-1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[4,3-*c*]pyrimidines (Fig. 26). They are evaluated for their affinity towards adenosine A_1 and A_{2a} receptors, resulted lacking in activity.

Takashi O *et al*.,[40] reported a facile synthetic method for fused triazolopyrimidine derivatives having high affinity and selectivity for human adenosine A_3 receptors. The fused

triazolopyrimidine derivatives were easily prepared by one-pot reaction using acyl hydrazines and imidates prepared from amine derivatives bearing cyano group and orthoesters *in situ*. This synthetic method was useful in finding new tricyclic adenosine A_3 receptor antagonists and also in diversifying the substituents at two positions on the fused triazolopyrimidine ring. In conclusion, they found new scaffolds of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines (Fig. 27a) and 1,2,4-triazolo[1,5-*c*]quinazolines (Fig. 27b) as potent and selective hA_3 receptor ligands.

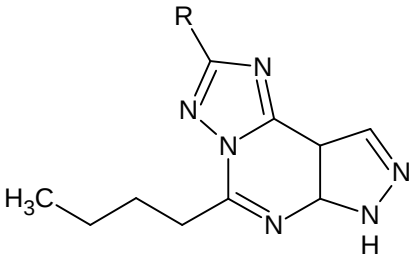


Fig. 27a

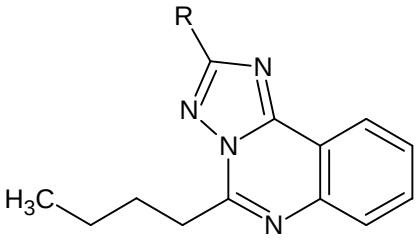


Fig. 27b

Fakher C *et al*.,[41] synthesized some pyrano triazolo pyrimidine derivatives (Fig. 28) by reacting ethoxy methyleneamino derivatives with hydrazides. Antigenotoxic activity of the obtained compounds was tested in *E.coli* PQ37, compounds with R_1 = isopropyl R_2 = Me/ph and R_1= Furyl R_2=ph were found to be more active.

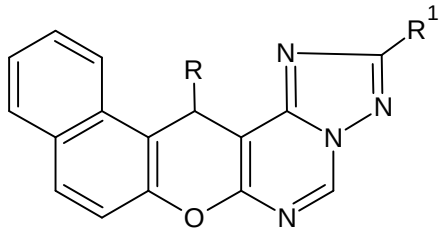


Fig. 28

CONCLUSION

A large number of fused pyrimidines have been discovered and reflected significant biological activities with appreciably wider spectrum. The versatile synthetic applicability and biological activity of these heterocycles will help the medicinal chemists to plan, organize and implement new approaches towards discovery of novel drugs.

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