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PYRIMIDINE DERIVATIVES AS POTENTIAL PHARMACOLOGICAL AGENTS: A REVIEW

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ABSTRACT

Various pyrimidine derivatives have been synthesized and evaluated for the past several decades, as they possess a number of pharmacological activities. Of all the pyrimidine derivatives; 2- hydroxypyrimidines, 2-mercaptopyrimidines and 2-aminopyrimidines exhibit greater similarity with pyrimidine nucleobases. This is one reason why they hold broad-spectrum of biological activities. Substitutions on these pyrimidine ring systems results in compounds with numerous biological activities like antioxidant, anti-inflammatory, antimicrobial, analgesics, antitubercular and so on. Chalcones on condensation with urea derivatives in the presence of a base and an alcohol produces pyrimidines. Chalcones are prepared by Claisen-Schmidt Condensation reaction. This review is intended to study the synthetic routes, chemistry and biological activities of various substituted pyrimidines.

KEYWORDS

Pyrimidine, Antimicrobial, Cytotoxicity and Antitubercular.

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INTRODUCTION

Heterocyclic compounds are cyclic compounds which possess at least one heteroatom within the ring system. The heteroatom may be nitrogen, oxygen, sulphur, phosphorous and boron. These compounds are used as pharmaceuticals, veterinary products, sanitizers, developers, copolymers, dye stuff, and agrochemicals. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use. The interesting fact about heterocyclic compounds is

that, they are essential for sustaining life on earth, as they constitute the major compounds which are involved in the mechanism of life. Genetic material, the basis of each life, is also composed of heterocyclic bases like pyrimidines and purines[1].

Pyrimidines are six membered heterocyclic aromatic organic compounds containing two nitrogens within the ring system, at 1 and 3 positions. It is present in nucleic acids and vitamins[2]. The pyrimidine bases that are present in living cells are thymine, cytosine and uracil. The nucleic acids RNA (ribonucleic acid) and DNA (deoxyribonucleic acid) have cytosine moiety, whereas thymine is present only in DNA and uracil in RNA[3]. The base pair analogs of pyrimidine nucleotides play a vital role in drug development.

The pyrimidine nucleus possess a wide array of pharmacological activities like antimalarial, antimicrobial[4,5], antioxidant, anti- inflammatory, cytotoxic[3] and antitubercular activity[6-8]. The diverse pharmacological activities of pyrimidines have created interest in designing promising novel molecules. Numerous marketed drugs having pyrimidine and fused pyrimidine are proof of their pharmacological potential. A few drugs among this category are Methotrexate, Flurouracil, Floxuridine, Tegafur, Trimethoprim, Flucytosine and Idoxuridine[9].

SYNTHESIS OF PYRIMIDINE DERIVATIVES

Classic method for the synthesis of pyrimidine is Biginelli reaction. Falsone F S *et al*, reported on the one-pot synthesis of dihydropyrimidines. They used an aldehyde, acetoacetate, urea and tetrahydrofuran (THF) containing polyphosphate ester (PPE) to produce dihydropyrimidine derivativee[10].

Electrophilic activation of N-vinyl or N-aryl amides with carbonitriles using 2-chloropyridine and trifluromethanesulphonic anhydride yields pyrimidine derivatives[9].

Another synthetic procedure is a two-step process. First step involves the claisen-schimdt condensation of an aldehyde with aromatic ketone to produce chalcones. These chalcones on reaction with urea derivatives in the presence of a base and alcohol yield pyrimidine derivatives[11-13]. As in Figure No.1.

Thiophene-2-carbaldehyde on reaction with substituted aromatic ketones yield corresponding chalcones, which up on reaction with urea in the presence of sodium hydroxide and ethanol forms various 2-hydroxy pyrimidine derivatives[14].

A mixture of substituted chalcones produced by the reaction of 4- nitrobenzaldehyde and substituted acetophenone; in presence of ethanol/glacial acetic acid and sodium hydroxide yields 2-mercaptopyrimidine derivatives[15].

Prasad Y R *et al*, synthesized a series of 2-aminopyrimidines using chalcones of 4'-piperizino acetophenone and substituted aldehyde, with guanidine hydrochloride in ethanol and potassium hydroxide[16]. Studies also show that chalcones on reaction with guanidine hydrochloride in the presence of potassium tert-butoxide in butanol gives 2-aminopyrimidine derivatives.

Sahoo B M *et al*, reported the green chemistry approach by microwave irradiated synthesis of 2-hydroxypyrimidine derivatives. The study was carried out, using microwave at 210 W for 7-10 min for a reaction mixture containing Chalcone and urea dissolved in ethanol and 40% potassium hydroxide solution[17].

PHARMACOLOGICAL ACTIVITY OF PYRIMIDINES

Antimicrobial Activity

Monica Kachroo *et al*, reported that 2-aminopyrimidine derivatives (3a-3e) showed more antibacterial activity than the corresponding 2-mercaptopyrimidine derivatives and 2-hydroxypyrimidine derivatives. Compounds 4-Pyridin-4-yl-6-p-tolylpyrimidin-2- ylamine (3b) and 4-(4-methoxyphenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine(3c) showed good antibacterial activities against gram positive and gram negative bacteriae[11].

M. Mumtaz Mohammed Hussain *et al*, reported that 2- Hydroxypyrimidines (4a-4l) showed significant activity against gram positive and gram negative bacteria. 2-hydroxypyrimidines with substitutions 4-methyl, 4- bromo and 3-nitro groups showed significant activity against gram positive bacteria like *E.fecalis* and *S.aureus*,; whereas all compounds displayed moderate activity against gram negative

bacteria *K.pneumoniae*. Compounds 4-(4-nitrophenyl)-6-(thiophen-2-yl) pyrimidin-2-ol and 4-(3-nitrophenyl)-6-(thiophen-2-yl) pyrimidin-2-ol showed good activity against *E.coli*. 4- (substituted phenyl)-6-(thiophen-2-yl) pyrimidin-2-ol showed good antifungal activity against *C.albicans* and *A.fumigatus*[14].

Studies also revealed that 2-mercaptopyrimidine derivatives (RPY 1-RPY 8) showed moderate antifungal activity when compared with the standard drug fluconazole. Compound 6-(substituted phenyl)-4-(nitrophenyl) pyrimidin-2-ol with substitutions 4-fluro, 4-amino and 4-methoxy groups showed good antibacterial activity against gram positive and gram negative bacteria[15].

Anti-tubercular Activity

It has been reported that the compound 4-(4-fluorophenyl)-6- pyridin-4-yl-pyrimidin-2-ylamine Figure No2 showed excellent antitubercular activity at a concentration of 3.12µg/ml as compared to other compounds[11]. Studies showed that 2-hydroxypyrimidines possess significant antitubercular activity with Minimum Inhibitory Concentration ranging at 12.5µg. Compound 4-(substituted phenyl)-6-(thiophen- 2-yl) pyrimidin-2-ol with substitutions 4-nitro, 4-amino, 4-fluro and 3-nitro showed potent antitubercular activity when compared with the standard drug INH[14]. Bhat K I *et al*, reported that compounds 6-(4-methylphenyl)-4-(nitrophenyl) pyrimidin-2-ol [RPY 5] and 6-(2-methylphenyl)-4- (nitrophenyl) pyrimidin-2-ol [RPY 7] showed significant antitubercular activity at a concentration of 6.25µg/ml compared to the standard drugs streptomycin and pyrazinamide[15].

Antioxidant Activity

Monica Kachroo *et al* reported that most of the 2-hydroxy, 2- amino and 2-mercaptopyrimidine derivatives showed moderate antioxidant activity as compared to the standard ascorbic acid. Compounds like 4-(4-fluorophenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (3d) and 6-(4-flurophenyl)-4-pyridin-4-yl-1, 6- dihydropyrimidin-2-thiol (2d) exhibited excellent activity at 10µg/ml[11].

Cytotoxic Activity

Studies revealed that the *in vitro* cytotoxicity against Ehrlich Ascites Carcinoma (EAC) cells reported that compounds 6-(4- flurophenyl)-4-(nitrophenyl) pyrimidin-2-ol [RPY 2] and 6-(2- methoxyphenyl)-4-(nitrophenyl) pyrimidin-2-ol [RPY 8] possess potent activity. These compounds induces an activity more than 60% at a concentration of 200µg/ml on EAC cells[15].

Anti-inflammatory Activity

Derivatives of 2-mercaptopyrimidine exhibited excellent anti- inflammatory activity when compared to the corresponding derivatives of 2-hydroxy and 2-amino pyrimidine [Figure No.3]. Compounds 2e, 2d and 3d showed potent activity as compared to standard indomethacin at 200µg/ml. Also 2b, 3c and 4c exhibited good *in vitro* anti-inflammatory activity[11].

Vishal D Joshi *et al* reported that 4-chlorophenyl and 4- flurophenyl derivative of 2-hydroxy pyrimidine (D1, E1), 2- mercaptopyrimidine (D2, E2) and 2-aminopyrimidine causes significant inhibition of paw edema at the dose 100µg/ml. As compred to the standard drug diclofenac sodium, 4-flurophenyl derivatives showed maximum inhibition at the 4th hour[16].

Analgesic Activity

Vishal D Joshi *et al* reported that 4-chlorophenyl and 4- flurophenyl derivative of 2-hydroxy pyrimidine (D1, E1) and 2- mercaptopyrimidine (D2, E2) showed significant analgesic activity when compared to the standard drug pentazocine. The study also points that the activity decreases after 90 minute of administration, which points its shorter duration of activity[16].

Antihistaminic Activity

Prasad Y R *et al* reported that 2-aminopyrimidine derivatives showed significant antihistamine activity as compared with standard drug mepiramine. The study points out that the percentage histamine inhibition increases with increase in concentration of compounds (RCP 1-5) from 0.1µg/ml to 0.8µg/ml. Fluorine substituted compound, RCP 1 [Figure No.4] showed greater antagonistic activity, whereas chlorine substituted ones exhibited moderate activity[17].

Rahman S A *et al*, also studied on pyrimidines derived from chalcones of 4'-piperazine acetophenone and reported that bromine-substituted

and 2-hydroxyphenyl-substituted pyrimidines showed greater anti-histaminic activity[18].

Anthelmintic Activity

Sahoo *et al*, reported that derivatives of 2-hydroxypyrimidines showed excellent anthelmintic activity as compared to the standard drug albendazole. Compound 4-(4-hydroxyphenyl)-6-phenylpyrimidin-2(1H)-one [4e] [Figure No.5] exhibited potential anthelmintic activity 25 ± 0.36 and 35 ±0.72 min for paralysis and death respectively. All other compounds showed significant anthelmintic activity[19].

Antihypertensive Activity

Rana K *et al*, reported that dihydropyrimidine derivatives possess potent antihypertensive activity. Various 6-methyl-4- substitutedphenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5- carboxylic acid ethyl esters and 6-methyl-4-substituted phenyl-2-S-alkyl(benzyl)-1, 4-dihydropyrimidine-5-carboxylic acid ethyl esters were synthesized and evaluated for their calcium channel blocking activity, by comparing with the standard drug nifedipine. S-Ethyl derivative possess potent antihypertensive activity with least IC50 value[20].

Kumar B *et al* reported a similar study on antihypertensive activity on 6-methyl-4-substitutedphenyl-2-oxo-I, 2, 3, 4 tetrahydropyrimidin-5-carboxylic acid ethylesters, 6methyl-4-substitutedphenyl-2-thioxo-I, 2, 3, 4 tetrahydropyrimidin5-carboxylic acid ethyl esters and 6-methyl- 4substitutedphenyl-2-S-alkyl-1, 4-dihydropyrimidin-5-carboxylic acid ethyl esters. The S-benzyl moiety in the S-derivatives possess maximum activity due to the increased lipophilic character[21].

Anticonvulsant Activity

Shaquiquzzaman M *et al* studied 14 derivatives of 2-(2-{1- phenyl-ethylidene}hydrazinyl) 4-(4-methoxy-phenyl)-6-oxo-1, 6- dihydro-pyrimidine-5-carbonitrile for their anticonvulsant activity by measuring their ability to reduce seizure spread and by evaluating seizure threshold. It has been found that p-substituted bromo and m-substituted nitro groups possess greater activity, with lesser CNS depressant effect[22].

Anticancer Activity

Xie F *et al* synthesized 2, 4, 5-substituted pyrimidine derivatives and evaluated their inhibition on human hepatocellular carcinoma BEL-7402 cancer cell line. The results suggest that most compounds exhibited excellent activity with lesser IC50 value. The study also reveals that an electron donating group in the 2nd position of pyrimidine, determines the anticancer activity[23].

Hypoglycemic and Hypolipidemic Activity

Lee H W *et al* studied on various substituted pyrimidine derivatives having Thiazolidinedione (TZD) moiety for their hypoglycemic and hypolipidemic activity as compared to pioglitazone and rosiglitazone. Results showed that compounds 5-(4-{2-[methyl-(6-phenoxypyrimidin-4-yl) amino] ethoxy} benzyl) thiazolidine-2, 4-dione and 5-(4-{2-[6-(4-methoxyphenoxy) pyrimidin-4-yl] methylamino ethoxy}benzyl) thiazolidine-2, 4dione are having excellent hypoglycemic and hypolipidemic activity[24].

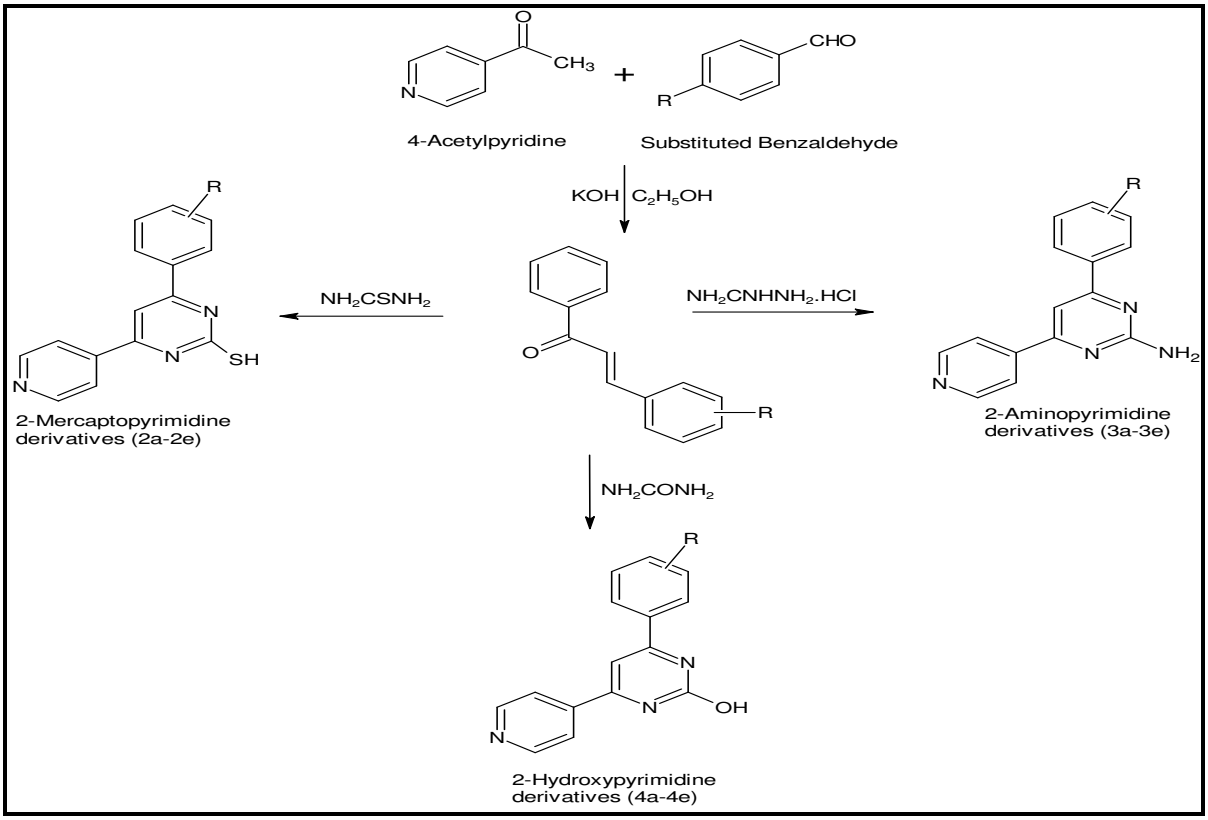
Antiviral Activity

Holy *et al* studied the antiviral activity of 6-[2-(Phosphonomethoxy) alkoxy] pyrimidine derivatives and concluded that 6-[2-(phosphonomethoxy) ethoxy] and 6-[2-(phosphonomethoxy) propoxy] pyrimidines are the most active antiviral agents among the series. Their activity is comparable to 9-[2-(phosphonomethoxy) ethyl] adenine (PMEA) and 9-(R)-[2-(phosphonomethoxy) propyl] adenine (PMPA). These compounds are active against a series of viruses like herpes viruses [herpes simplex type 1 (HSV-1) and type 2 (HSV-2)] and retroviruses [human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2)[25].

Ramiz M M M *et al*, reported that N-substituted pyrimidine glycosides possess antiviral activity against Hepatitis B Virus (HBV), and was evaluated using the HepG2.2.2.15-cell line[26].

Danesh A *et al* synthesized four pyrimidine derivatives and evaluated their antiviral activity using plaque reduction assay. Compound2-(4-methyl-6-morpholino-5-nitropyrimidin-2- ylamino)-3-phenylpropanoic acid and 2-(4-methyl-5-nitro-6-(pyrrolidin-1-yle)-pyrimidin-2-ylamino)-3-

phenylpropanoic acid shows significant activity. The study also points out that the 5- nitropyrimidine derivatives possess potential antiviral activity[27].



2a, 3a, 4a:- R = Cl; 2b, 3b, 4b:- R = CH_3

2c, 3c, 4c:- R = OCH_3, 2d, 3d, 4d:- R = F

2e, 3e, 4e:- R = 3, 4-$(OCH_3)_2$

Figure No.1: Scheme for synthesis of various 2-substituted pyrimidine derivatives[11]

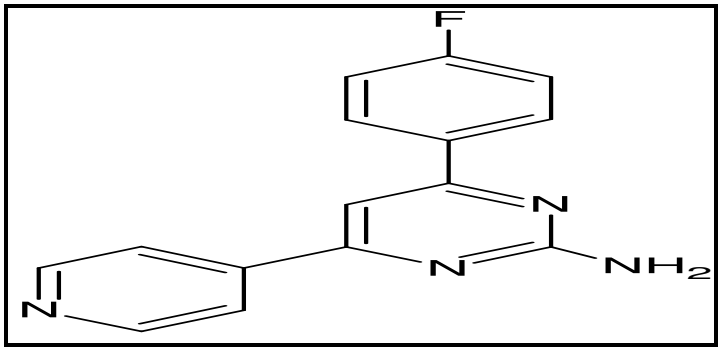
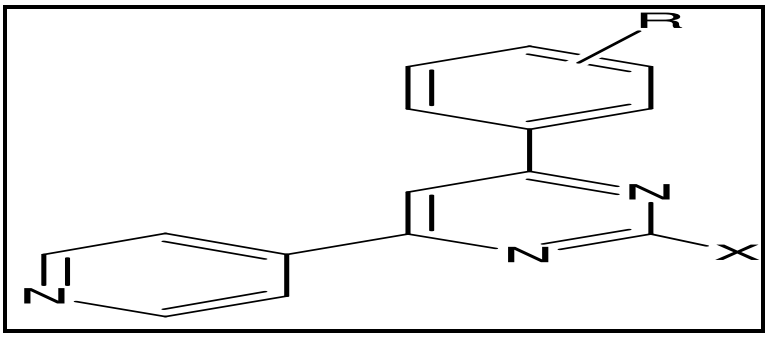


Figure No.2: 4-(4-fluorophenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine



2e:- X=SH, R=-3, 4-$(OCH_3)_2$
2d:- X=SH, R=4-F
3d:- X=NH_2, R=4-F

Figure No.3: General structure for 2-substituted pyrimidine derivatives

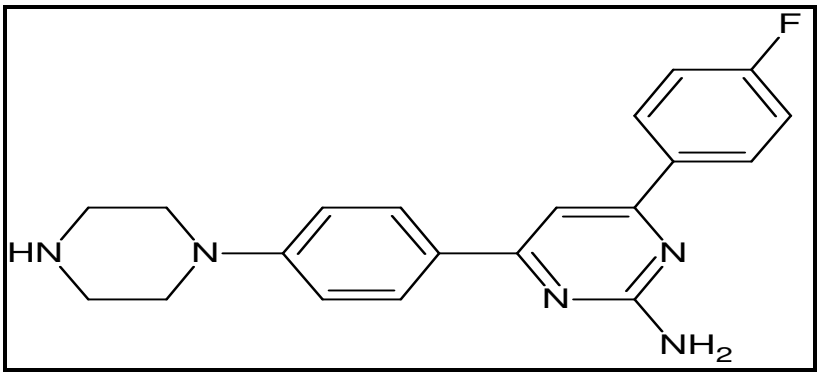


Figure No.4: Structure of RCP 1

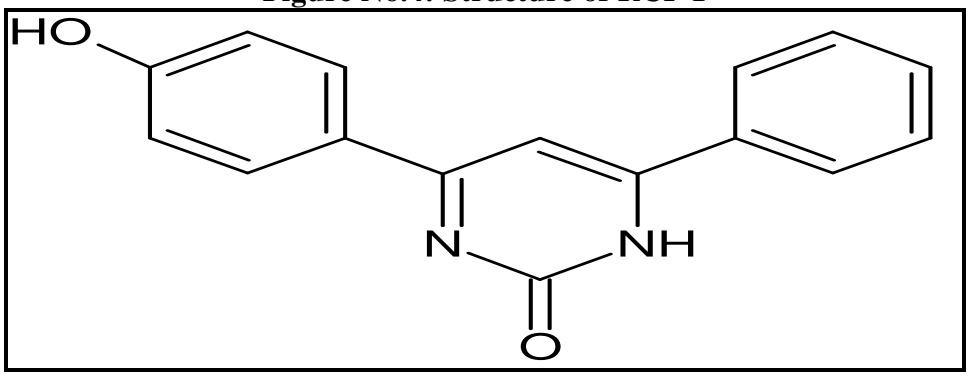


Figure No.5: Structure of 4-(4-hydroxyphenyl)-6-phenylpyrimidin- 2(1H)-one [4e]

CONCLUSION

Pyrimidine derivatives showed a variety of biological activities. Derivatives of 2-hydroxypyrimidine, 2-mercaptopyrimidine and 2-aminopyrimidine showed significant antimicrobial, anticancer and antitubercular activity, depending on the substitution of electron withdrawing and electron donating groups on the pyrimidine nucleus. 2-Substituted pyrimidines possessing 4-flurophenyl group or 4-chlorophenyl group shows potent antioxidant, anti- inflammatory, antihistaminic activity and analgesic activity. Cytotoxic activity is shown by 2-mercaptopyrimidines with fluorine at 4^{th} position. 2-hydroxypyrimidines exhibits excellent anthelmintic activity. Dihydropyrimidine derivatives shown anticonvulsant and antihypertensive activity. Depending on the substitutions, pyrimidine moeity possess antiviral, hypoglycemic and hypolipidemic

activity. This review has been done with the sole objective of understanding the various pharmacological activities of pyrimidine nucleus and it seems to have enormous potential to be explored further.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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