

PHARMACOLOGICAL POTENTIALS OF PYRIMIDINE DERIVATIVE: A REVIEW

HARSHALATA DANSENA*, DHONGADE HJ, KAVITA CHANDRAKAR

Department of Pharmachemistry, Shri Rawatpura Sarkar Institute of Pharmacy, Kumhari, Durg - 490 042, Chhattisgarh, India.
Email: hemantdhongade@gmail.com

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ABSTRACT

The chemistry of pyrimidine derivatives plays an important role in the field of drugs, agriculture chemicals, and many biological processes. The chemistry of pyrimidine is a provoking field. In recent decades, a large number of pharmacological studies has been done on pyrimidine and their derivative. However, still more research is required in order to necessity the biological compounds. Numerous methods for the synthesis of pyrimidine and also their diverse reaction generate an enormous scope in the field of medicinal chemistry. The utility of pyrimidines as synthon for various biologically active compounds has given impetus to these studies. The pyrimidine derivatives show various biological activities including antitubercular, antioxidant, anti-inflammatory, anticonvulsant, antimicrobial, antibacterial, antiplasmodial, antifungal, anticancer, and analgesic activity. This article aims to review the recent works on pyrimidine derivatives together with the biological potential during the past years.

Keywords: Pyrimidine, Pharmacological studies, Anticancer, Antitubercular.

INTRODUCTION

Chemistry of pyrimidine

Heterocyclic rings have played an important role in medicinal chemistry, serving as key templates central to the development of numerous important therapeutic agents [1]. At very early period in the history of organic chemistry, pyrimidines ("m-Diazine") were known as the breakdown products of uric acid. The first pyrimidine derivative to be isolated was alloxan in 1818 by Brugnatelli, oxidizing uric acid with nitric acid [2]. Pyrimidines (Fig. 1) are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six-membered rings. Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [3,4].

Properties of pyrimidine

Pyrimidine is a colorless compound having 22.5°C melting point and 124°C boiling point. Several (mainly uracil, thymine, and cytosine [Fig. 2]) pyrimidines have been isolated from the nucleic acid hydrolyses. The nucleic acid are essential constituent of all cells and thus all living matter cytosine is found to be present in both types of nucleic acids i.e., ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) while uracil is present only in RNA and thymine only in DNA [5].

In addition to this, pyrimidines skeleton is also present in many natural products such as vitamin B1 (thiamine) and many synthetic compounds, such as barbituric acid (Fig. 3) and veranal (Fig. 4) which are used as hypnotics [6].

The literature indicated that compound having pyrimidine nucleus possesses broad range of biological activity like 5-fluorouracil as anticancer; idoxuridine and trifluridine as antiviral; zidovudine and stavudine as anti-HIV; trimethoprim, sulfamethazine, sulfadiazine as antibacterial; minoxidil and prazosin as antihypertensive; phenobarbitone as sedative-hypnotic and anticonvulsant; propylthiouracil as antithyroid; thiozylamine as H1-antihistaminic and fervernulin as antibiotics [7].

Chalcone derivatives are important starting materials for the synthesis of different classes of heterocyclic compounds such as pyrazolines, thiophenes, and pyrimidines, etc. Most of these compounds are highly bioactive and are widely used as pharmaceuticals [8].

DERIVATIVES: STRUCTURE

Pharmacological Activities

Antitubercular activity

Siddiqui *et al.* [9] had synthesized a series of novel dihydropyrazolo [3,4-d] pyrimidine derivatives (Fig. 5) bearing a phenothiazine nucleus were synthesized in excellent yields via a modified biginelli multicomponent reaction. New synthesized compounds were screened for antitubercular activity. The new compounds were characterized by infrared (IR), ¹H nuclear magnetic resonance (NMR), ¹³C NMR, mass spectra, and elemental analysis followed by antimycobacterial screening. Compound 4-(4-chlorophenyl)-3-methyl-1-(10 H-phenothiazin-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine (4 g) showed most pronounced activity against *Mycobacterium tuberculosis* with minimum inhibitory concentration of 0.02 µg/mL, and compare with first line anti-tubercular drug isoniazid.

Chandrashekaraiah *et al.* [10] reported a series of 1-(3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenyl)-3-chloro-4-(2-mercaptoquinolin-3-yl) azetidin-2-one (Fig.6) (7a-j) have been synthesized. The newly synthesized analogs were examined *in-vitro* for antituberculosis activity against *M. tuberculosis*. The class of newly synthesized analogs 7i and 7j displayed the highest inhibition at a constant concentration level (6.25 µg/mL) against *M. tuberculosis* H37Rv.

Kachroo *et al.* [11] has reported synthesis of chalcones by the reaction of 4-acetylpyridine with various aromatic and heteroaromatic aldehydes and further, chalcones derivatives were cyclized to pyrimidine analogs using thiourea, urea, and guanidine hydrochloride. The newly synthesized compounds (Fig. 7) have been characterized by ultraviolet, IR, ¹H NMR, ¹³C NMR, mass spectra. It was found that 2-amino pyrimidine analog bearing 4-fluoro substitution on phenyl ring (3d) has exhibited excellent antitubercular activity.

Antioxidant activity

Dudhe *et al.* [12] had synthesized, evaluated and validated novel 40 pyrimidine derivatives (Fig. 8). Among them, 3,4-dihydro-1-(tetrahydro-3,4-dihydroxy-5-(hydroxymethyl) furan-2-yl)-6-(4-nitrophenyl)-4-phenylpyrimidin-2(1H)-one [6N] (Fig. 7) exhibited maximum antioxidant activity. It was a yellow crystalline powder with molecular formula is C₂₁H₂₁N₃O₇, and the molecular weight is 427.

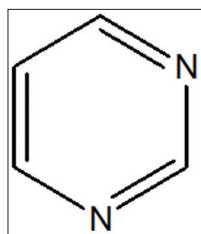


Fig. 1: Pyrimidine

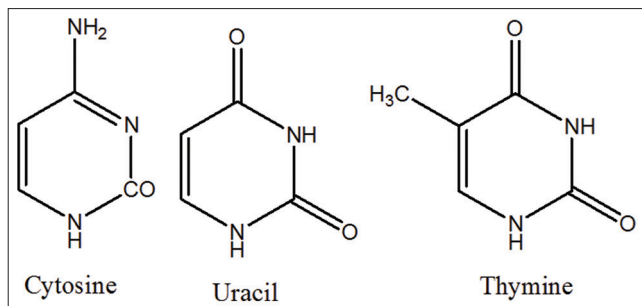


Fig. 2: Derivatives of Pyrimidines

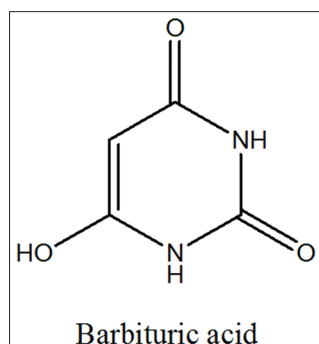


Fig. 3: Barbituric acid

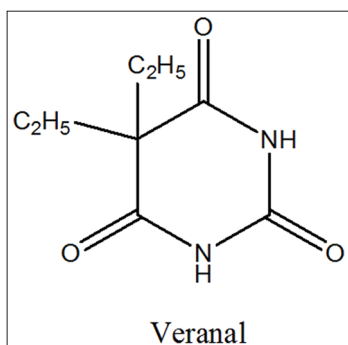


Fig. 4: Vernal

Himaja *et al.* [13], had synthesized pyrimidine analog (Fig. 9). Characterization of the synthesized compounds was done using Fourier transform IR spectroscopy (FTIR), ¹H NMR, and FAB mass. Spectral data of 4,6-Diphenylpyrimidine-2-amine (Fig. 8) showed good antioxidant activity. This activity was measured using 2,2-diphenyl-1-picrylhydrazyl free radical scavenging method.

Bano *et al.* [14] had reported free radical scavenging properties of pyrimidine derivatives (Fig. 10), concentrating on the synthesis and antioxidant activity of the pyrimidine nucleus. Pyrimidine is a unique

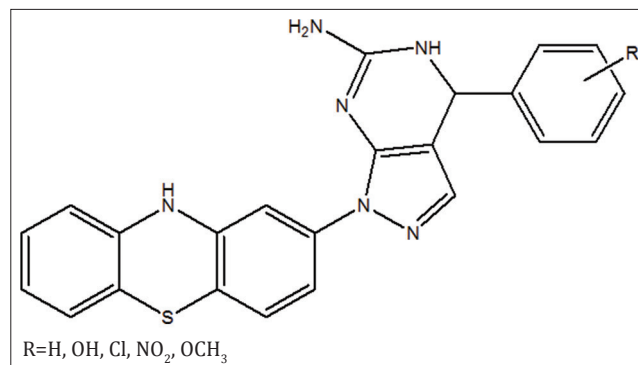


Fig. 5: dihydropyrazolo [3,4-d] pyrimidine derivatives

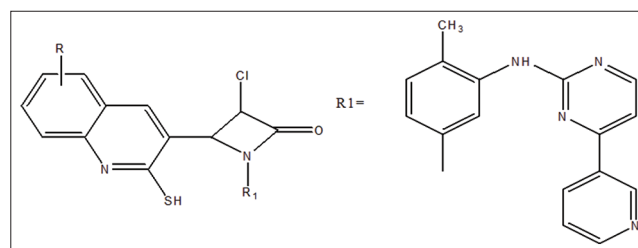


Fig. 6: 1-(3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenyl)-3-chloro-4-(2-mercaptoquinolin-3-yl)azetidin-2-one

Where R = a: Aniline, b: 2-methyl aniline, c: 3-methyl aniline, d: 4-methyl aniline, e: 2-nitro aniline, f: 3-nitro aniline, g: 4-nitro aniline, h: 2-chloroaniline, i: 3-chloroaniline, j: 4-chloroaniline

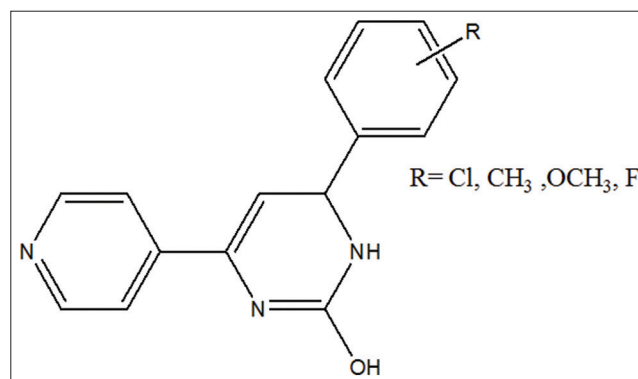


Fig. 7: Nitrogen containing heterocyclic derivative

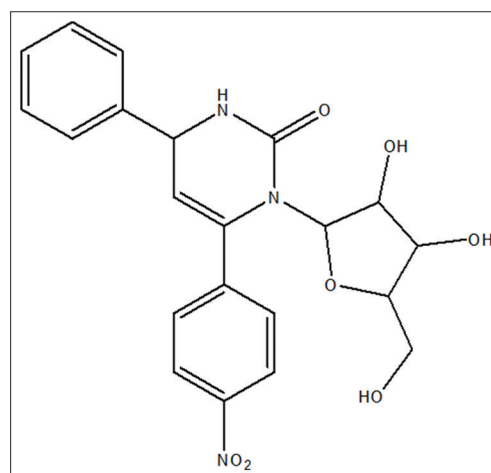


Fig. 8: 3,4-dihydro-1-(tetrahydro-3,4-dihydroxy-5-(hydroxymethyl) furan-2-yl)-6-(4-nitrophenyl)-4-phenylpyrimidin-2(1H)-one

molecule that is associated with several other biological activities. They reported the substitution on pyrimidine nucleus was made by different substitutions of Cl, Br, CF₃, and NO₂, which increased the penetration of molecules into the lipid membrane, so that they increase the antioxidant activity by combining with the reactive oxygen species, which is generated by the different disease conditions.

Anti-inflammatory activity

Goudar *et al.* [15] had synthesized the thienopyrimidines derivatives (Fig. 11) possessing different heterocyclic rings which showed highly potent anti-inflammatory activities. Thienopyrimidines had synthesized by the cyclization of thiophene with formamide to obtain thieno (2, 3-d) pyrimidine. The synthesized compounds were screened for their anti-inflammatory activity using bovine serum albumin denaturation (*in-vitro*) assay model, using ibuprofen as a standard. They studied the thienopyrimidines bearing pyrazole, oxadiazole, and thiadiazole rings shown significant anti-inflammatory activity. Phenyl-(5-(thieno [2, 3-d] pyrimidine-4-yloxymethyl)-(1,3,4) thiadiazol-2-yl)-amine (8a) (Fig. 10) containing thiadiazole was found to be most potent.

Kota *et al.* [16] had synthesized and evaluated some novel pyrazolo [3,4-d] pyrimidines (Fig. 12) and was aimed at creating a new scaffold. Seven new 4-(4-substituted benzoylamino) pyrazolo (3,4-d) pyrimidines have been synthesized by reacting different 4-substituted benzoyl chlorides with 4-amino pyrazolo (3,4-d) pyrimidine in N, N-dimethyl formamide solvent. These compounds were screened for anti-inflammatory activity by carrageenan induced edema model. All these compounds were characterized by physical and spectral data. The electron withdrawing groups such as chloro 6b and fluoro 6d substituted compounds showed appreciable anti-inflammatory activity results at 3 mg/kg when compared with the standard drug indomethacin at 10 mg/kg, respectively.

Kumaresan *et al.* [17] reported the synthesis of some new pyrimidin-2-amines (Fig. 13) and their anti-inflammatory activity against Balb/c mice with locally induced edema. The synthesized compounds were characterized by IR, 1H, 13C NMR, and mass spectroscopic techniques. The synthesized compounds, 4-(9H-Fluoren-2-yl)-6-phenylpyrimidin-2-amine, and 4-(4-[diphenylamino] phenyl) pyrimidine-2-amine are found to have more efficient anti-inflammatory activity than that for 4, 6-Bis-(9H-fluoren-2-yl)pyrimidin-2-amine, and 3-(3-[9H-Fluoren-2-yl]-3-oxoprop-1-en-1-yl)-4H-chromen-4-one.

Anticonvulsant activity

Valarmathy *et al.* [18] had synthesized series of 2-aminopyrimidine derivatives (Fig. 14) (4a-e) and were evaluated for antitubercular, anticonvulsant, and anti-inflammatory activity against Resazurin Microtiter Assay plate method, isoniazid induced convulsion test, and carrageenan-induced paw edema, respectively. Isoniazid, diazepam, and indomethacin were used as the standards in above cited tests respectively. The compounds 4a, 4d, and 4e displayed significant antitubercular activity. 4a and 4b showed excellent anticonvulsant activity, whereas compound 4b, 4d, 4e exhibited moderate activity.

Mohana *et al.* [19] had synthesized pyrimidine analogs, 3, 4, 5, 6 (a-d), 7 (a-d) (Fig. 15) and their anticonvulsant activity was measured. The structures of the compounds were established on the basis of FTIR, 1H NMR, and mass spectral data. Maximal electroshock seizure model was used for the evaluation of the anticonvulsant activity of the compounds on male Wistar rats. Phenytoin (100 mg/kg) was used as a standard drug. The new compounds, 6C and 7C were found to show most potent anticonvulsant activity and showed no neurotoxicity.

Antimicrobial activity

Kaur *et al.* [20] had synthesized a series of pyrimidines (Fig. 16) bearing a pyronyl side chain in the 4-position and screened for antimicrobial activity. A series of compounds (3a-j) were prepared and tested for their antimicrobial activity. Compounds 3b, 3i, 3j showed mild activity

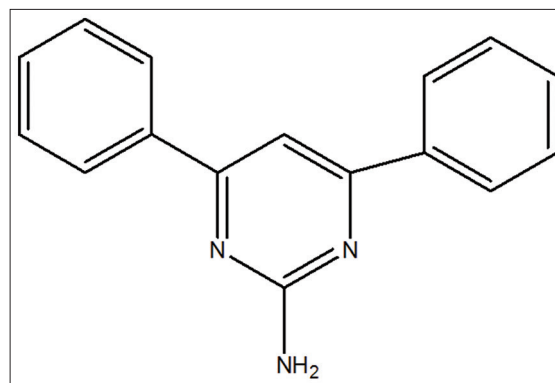


Fig. 9: 6-diphenylpyrimidine-2-amine

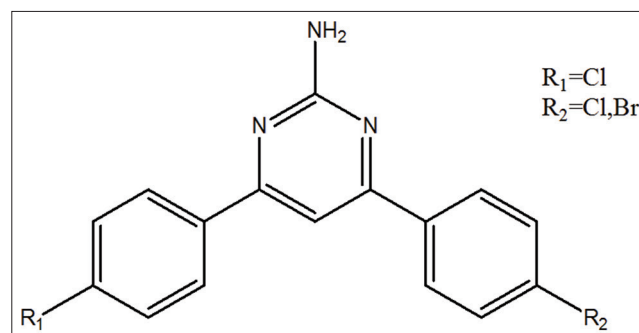


Fig. 10: Pyrimidine derivatives

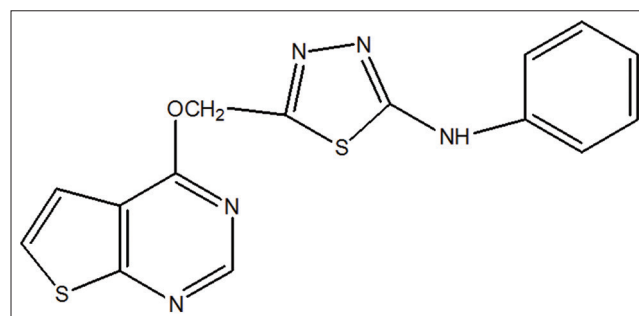


Fig. 11: Thienopyrimidines derivatives

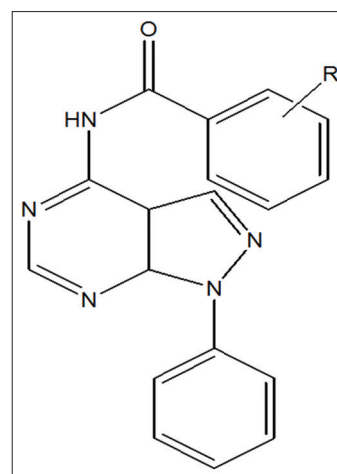


Fig. 12: pyrazolo [3,4-d] pyrimidines

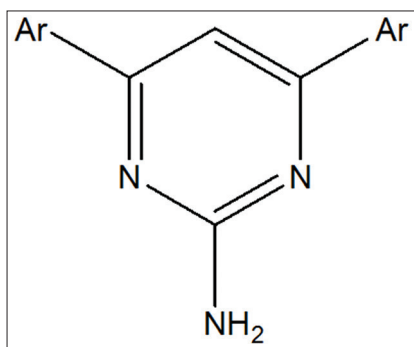


Fig. 13: Pyrimidin-2-amines

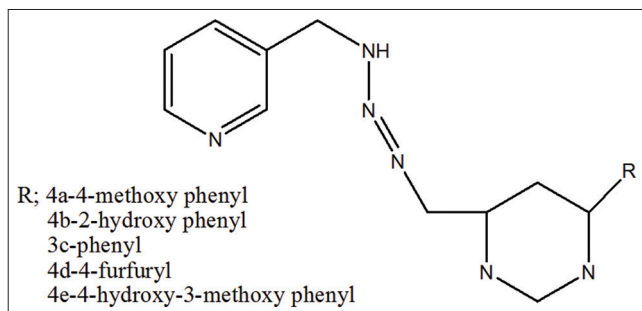


Fig. 14: 2-aminopyrimidine derivatives

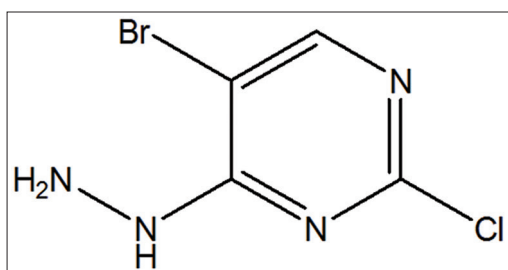


Fig. 15: pyrimidine analoges

against Gram-positive *Bacillus subtilis* bacteria while against Gram-negative *Pseudomonas aeruginosa* compound 3i showed minor activity.

Gupta *et al.* [21] had synthesized, characterized, and screened pyrimidine derivatives for antimicrobial activity. The chalcone was synthesized by an aldol condensation of 4-methoxy acetophenone with m-phenoxy benzaldehydes in the presence of a catalyst that was treated with thiourea to provide pyrimidine. The pyrimidine treated with substituted N-1,3-benzothiazole-2-yl-2-chloro amide gives a compound. Elemental analysis, IR, H NMR, C NMR melting point, thin layer chromatography plates (silica gel G) was used to determine the purity of the compounds. All the synthesized compounds (Fig. 17) were screened against four different strains, viz. two Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative bacteria (*Escherichia coli* and *P. aeruginosa*). From the screening results N-(6-methoxybenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio) acetamide, (4f) possesses excellent activity against Gram-positive, and Gram-negative bacteria compared with ampicilline, chloramphenicol, ciprofloxacin as standard drugs. The antifungal screening results indicated that 2-(4-(4-Methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio)-N-(6-nitrobenzo[d]thiazol-2-yl) acetamide (4g) possessed excellent activity against *Aspergillus niger* analyzed with standard drugs nystatin and griseofulvin.

Sharma *et al.* [22] had synthesized some novel pyrimidine-2,4-diones by condensing various substituted amines with 3-substituted-6-

chlorouracil. They were screened for their antimicrobial profile using kirby bauer disk diffusion method. Pyrimidine-2, 4(1*H*, 3*H*)-diones (Fig. 18) were synthesized by the appropriate urea was reacted with diethyl malonate in the refluxing sodium ethoxide/ethanol to form the substituted barbituric acid. The *N*-alkylbarbituric acid was specifically chlorinated at C6 by refluxing in POCl₃ in the presence of water. The final step employed the resulting substituted 6-chlorouracil and the appropriate aniline heated for 30 minutes. at 150°C on oil bath. The new compounds were analyzed by IR and ¹H-NMR. The antibacterial activity of newly synthesized pyrimidine-2,4-dione derivatives evaluated against gram-positive bacteria viz. *Bacillus subtilis* and Gram-negative bacteria viz. *E. coli*. Ampicillin used as standard drugs. The compounds OBP01 and OBP02 had better activity against tested *B. subtilis* (Gram-positive) whereas OBP03 against *E. coli* (Gram-negative). OBP03 also found to have better anti-fungal activity than rest of the compounds when tested against *A. niger* and *Penicillium marneffeii*.

Antibacterial activity

David *et al.* [23] had synthesized 4,6-disubstituted-2-amino pyrimidines (Fig. 19) and prepared compounds namely 3 (a-g) compounds and were characterized by FT-IR, Mass, and ¹H NMR spectral data. In antibacterial screening, compounds 3a, 3c, 3d, and 3f exhibited significant activity against all the 4 tested organisms and the results were comparable with the standard drug, ciprofloxacin.

Nehad *et al.* [24] had described the synthesized pyridine, pyrimidine, and cyclohexanone derivatives using khellinone methyl ether (1) as a starting material. Compound (1) was allowed to react with different aldehydes namely, benzaldehydes, p-methoxybenzaldehyde, and p-nitro benzaldehyde to give the corresponding chalcones (2a-c). The latter compounds reacted with malononitrile, guanidine, ethyl cyanoacetate, and ethyl acetoacetate to yield cyanopyridine, aminopyrimidine, cyanopyridone, and cyclohexenone derivatives (3a-c), (4a-c), (5a-c), and (6a-c), respectively. When (2a-c) was allowed to react with urea and thiourea, they gave oxypyrimidine and thioxopyrimidine derivatives (7a-c) and (8a-c). On the other hand, compound (8a-c) was condensed with 3-bromopropionic acid or chloroacetic acid to yield thiazinopyrimidine (9a-c) and 3- thiazolo-pyrimidine (10a-c), respectively. Compounds (8a-c) were condensed with chloroacetic acid and aromatic aldehyde to yield the aryl methylene derivatives (11a-c) which could be prepared directly by condensation of the compound (10a-c) with aromatic aldehyde. The characterizations of the resulting products were confirmed by FTIR, ¹HNMR, MS, and elemental analyses. The antibacterial activity of synthesized compounds against, *E. coli*, *Pseudomonas aurignosa*, *Salmonella typhimurium*, *B. subtilis*, and *S. aureus* were measured by measuring the zone of inhibition in disk diffusion method. From the data it was cleared that compounds (4b), (6a), (7b), (9b), (10a), and (11b) possess high activity, while compounds (1), (2c), (3c), (4a), (4c), (5b), (5c), (6b), (7c) (8a), (8b), and (9a) possess moderate activity (Fig. 20).

Gullapelli *et al.* [25] synthesized n-(4-(1*H*-benzo(d) imidazole-2-yl)-2-(4-hydroxy -6-methyl pyrimidine -2-yl thio) acetamide (Fig. 21) from 2-(4-aminophenyl) benzimidazole and 2-mercapto -4-hydroxy-6-methyl pyrimidine, which have been prepared from p-amino benzoic acid and benzene 1,2 diamine with thiourea and was analyzed by the ¹HNMR and IR spectral data. Some prepared compounds (namely 5a-5j) were screened for antibacterial activity. The tested compounds 5h, 5c, 5j, and 5e showed highest antibacterial activities tested at all concentrations against different types of bacterial strains used in the assay.

Antifungal activity

Ishak *et al.* [26] carried out the synthesis of pyrazolo-[1, 5-a] pyrimidine and pyrimidine derivatives and screened them for antifungal activities. New series of pyrazolo-[1, 5-a] pyrimidines (Fig. 22) were also screened for their antifungal activity against (*Candida albicans* [RCMB0005003], *Aspergillus fumigates* [RCMB002006], *Geotrichum candidum* [052008], *Syncephalastrum racemosum* [005004]). The compound 5,7-di(furan-

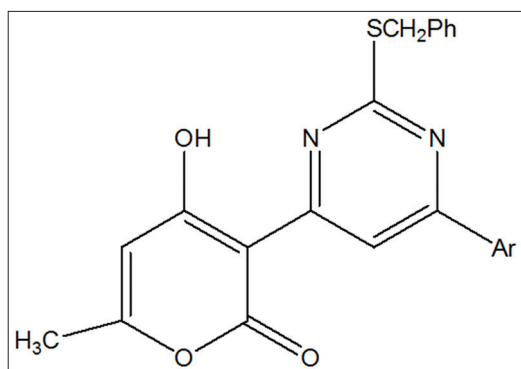


Fig. 16: Pyrimidine derivatives

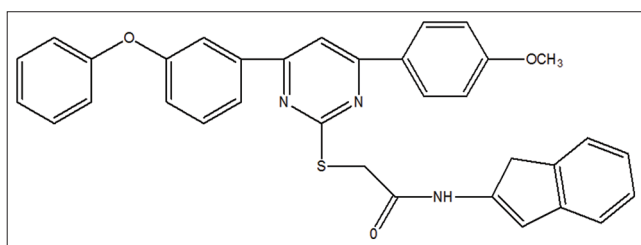


Fig. 17: Pyrimidine derivatives

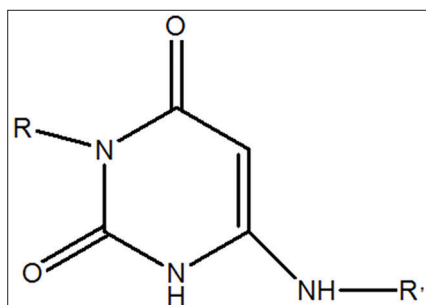


Fig. 18: Pyrimidine-2,4-diones

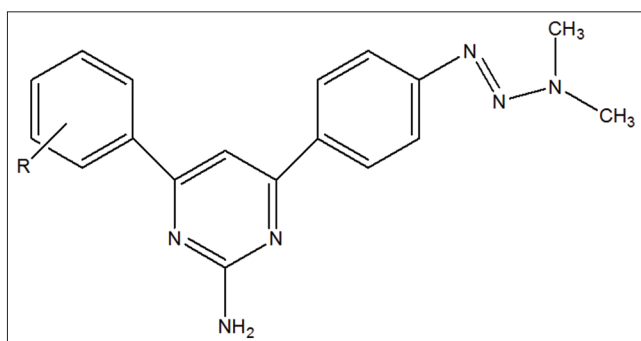


Fig. 19: 4,6-disubstituted-2-amino Pyrimidines

2-yl)-3-(p-tolyldiazanyl)pyrazolo[1,5-a]pyrimidin-2-amine showed better antimicrobial activity than 5-(furan-2-yl)-7-(thiophen-2-yl)-3-(p-tolyldiazanyl) pyrazolo [1,5-a] pyrimidin-2-amin.

Andrews and Mansur [27] had synthesized a series of pyrimidine bearing 1,3,4-oxadiazole derivatives and screened them for antifungal activity. All the structures of the newly synthesized compounds (Fig. 23) have been supported by IR, ¹H-NMR, ¹³C-NMR, GC-MS, and CHN analysis. Newly synthesized pyrimidine derivatives were screened for their antifungal activity *in-vitro* against the species of *C. albicans*,

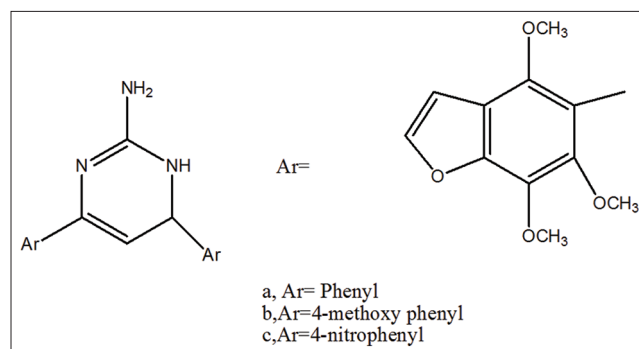


Fig. 20: Pyrimidine derivatives

Penicillium sps., and *A. niger*, using agar well disk diffusion method and using amphotericin-B as the standard drug.

Antiplasmodial activity

Singh *et al.* [28] synthesized 2-Aminopyrimidine based 4-aminoquinolines. Some of the compounds showed *in-vitro* antiplasmodial activity against drug-sensitive CQS (3D7) and drug resistant chloroquine-resistant (CQR) (K1) strains of plasmodium falciparum in the nm range. In particular, 5 - isopropoxy carbonyl-6-methyl-4-(2-nitrophenyl)-2-([7-chloroquinolin-4-ylamino] butylamino) pyrimidine (Fig. 24) depicted the lowest IC₅₀ (3.6 nm) value (56-fold less than CQ) against CQR strain. Structure activity profile and binding with heme, m-oxo-heme has been studied. Binding assays with DNA revealed better binding with target parasite type AT rich pUC18 DNA. Most compounds were somewhat cytotoxic. Molecular docking analysis with pf DHFR allowed identification of stabilizing interactions.

Anticancer activity

Rai *et al.* [29] had synthesized heterocyclic pyrazole chalcones (4a-4e) and diamide (6a-4e) derivatives. Pyrazole chalcones (Fig. 25) were synthesized by the reaction of pyrazole aldehydes and suitable aromatic ketones. Diamide was synthesized by the reaction of phthalic acid and amines. Newly synthesized compounds were characterized by spectral studies and their biological activity was assessed *in-vitro* using MCF-7 and HELA cell lines. Compounds 4c showed the highest inhibition in human MCF-7 and HELA cell lines, which has 4-fluoro-phenyl moieties, which has accounted for the highest activity. This compound has the potential to develop as a new class of anticancer agents.

Verma *et al.* [30] had synthesized a novel N-(sugar pyranosyl) thienopyrimidine 4- amine derivatives with good yield and enhance anticancer activity. These derivatives (Fig. 26) were identified on the basis of melting point range, R_f values, IR, and ¹H NMR. The synthesized derivatives showed very good anticancer activity against previously reported derivative of N-(sugar pyranosyl) thienopyrimidine 4- amine.

Fathalla *et al.* [31] synthesized a series of some new pyrimidine derivatives and screened them for antibacterial and anticancer activity. Some new pyrimidine derivatives (Fig. 27) were synthesized via the reaction of ethyl cyanoacetate with thiourea and the appropriate aldehydes namely 2-methyl-benzaldehyde and 2-methoxy-benzaldehyde to give 1a,b. Compounds 1a,b were chlorinated to give the chloro compounds 2a,b then condensation of 2a,b via different reagents gave compounds 3-5. Compound 4b reacted with acetic anhydride, trimethylorthoformate, p-anisaldehyde, diethyloxalate, and ethylchloroformate to give compounds 6, 7, 8, 9, and 10, respectively. All structures of the new compounds were elucidated by their correct elemental analysis and spectral data. Many thiouracil derivatives have been synthesized in order to evaluate their antitumor activities as a trial to get more effective and less toxic agents. The antitumor activity

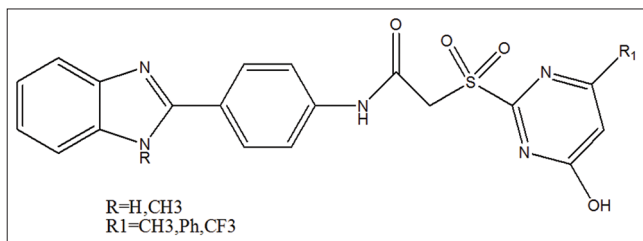


Fig. 21: n-(4-(1h-benzo(d)imidazole-2-yl)-2-(4-hydroxy-6-methyl pyrimidine-2-yl thio) acetamide

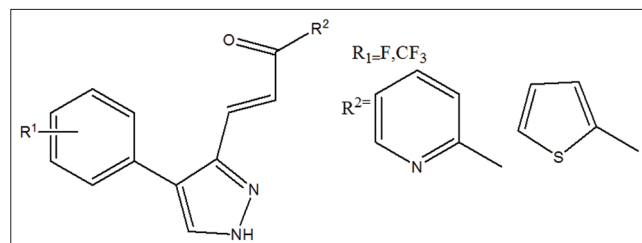


Fig. 25: Heterocyclic pyrazole chalcones & diamide derivatives

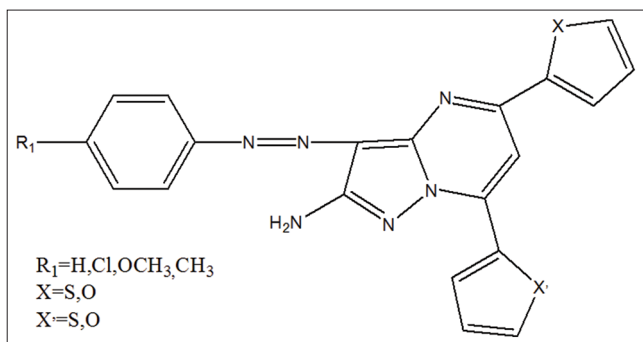


Fig. 22: [1, 5-a] pyrimidine and pyrimidine derivatives

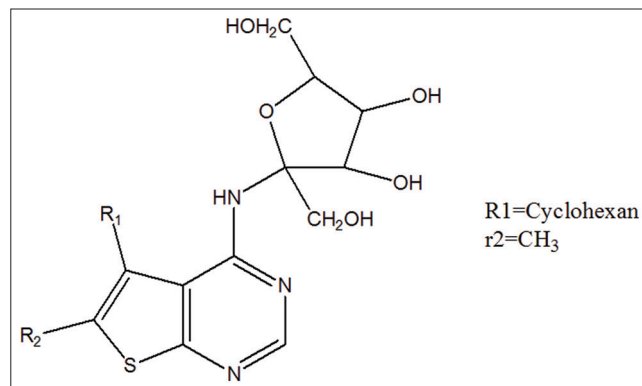


Fig. 26: N-(sugar pyranosyl) thienopyrimidine 4-amine derivatives

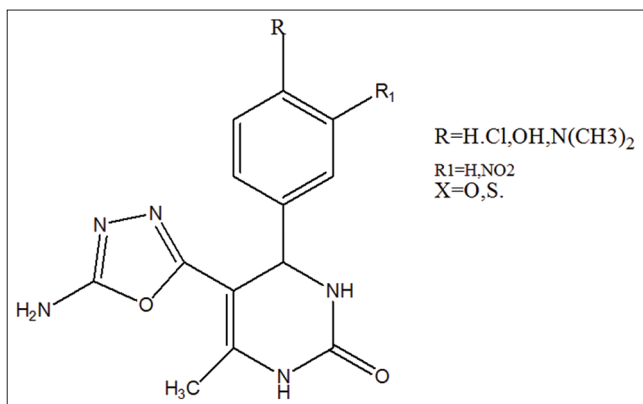


Fig. 23: 1, 3, 4-oxadiazole derivatives

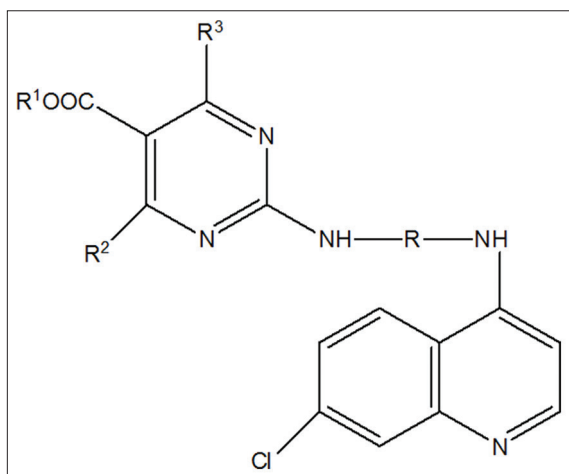


Fig. 24: 2-Aminopyrimidine based 4-aminoquinolines

results indicated that the selected thiouracil derivatives showed antitumor activity against liver cancer (HEPG2) tumor cell line tested, but with varying intensities in comparison to the known anticancer drugs: 5-fluorouracil and doxorubicin.

Kandeel *et al.* [32] had reported structural modification of thieno [2,3-*d*]pyrimidines (Fig. 28) with the purpose of enhancing their anticancer activity. A various series of hexahydrocyclocta [4,5] thieno [2,3-*d*] pyrimidin-4-ones, hexahydrocyclocta [4,5] thieno [3,2-*e*] 1,2,4-triazolo [4,3-*c*] pyrimidine-3 (2H)-thiones and 4-substituted hydrazinyl hexahydrocyclocta [4,5] thieno [2,3-*d*] pyrimidines were synthesized. Most of the synthesized compounds exhibited antitumor activity against human colon carcinoma (HCT 116) cell line *in-vitro*. Compounds 4a, 4b, 3, 12b, and 5c (IC₅₀: 11.90, 12.43, 15.91, 25.80, and 32.11 μM, respectively) exhibited 2.89-1.07 fold more potent antitumor activity than imatinib (IC₅₀: 34.40 μM). A docking study of the newly synthesized compounds with the active site of CDK2 was described to explore their affinity and binding mode to CDK2.

Analgesic activity

Goudgaon and Reddy [33] had reported analgesic and anti-inflammatory activities of 2-(4-fluorobenzylthio)-n-(substituted phenyl) pyrimidine-4-amines (1a-k). The analgesic and anti-inflammatory activities of the synthesized compounds 2-(4-fluorobenzylthio)-N-(substituted phenyl) pyrimidine-4-amines were carried out in albino mice and Sprague Dawley rats respectively. Compounds 1c and 1f showed good analgesic activity when compared to the standard drug pentazocine.

CONCLUSION

Research investigates that pyrimidine derivatives show various important pharmacological activities. Not much of the research is done in screening pyrimidine derivatives for *in-vitro* and *in-vivo* pharmacological activities. Thus, a tremendous scope for research is present in this direction for investigating pyrimidine derivatives as lead molecules.

REFERENCES

- Ghomi AS, Ali M. An efficient route to the synthesis of pyrimidine-2-ones under ultrasound irradiation. Dig J Nanomater Biostruct 2010;5(2):303-6.
- Lagoja IM. Pyrimidine as constituent of natural biologically active compounds. Chem Biodivers 2005;2(1):1-50.
- Brown DJ, Evans RF, Cowden WB. Comprehensive Heterocyclic Chemistry. UK: Pergamon Press Oxford; 1984. p. 15.

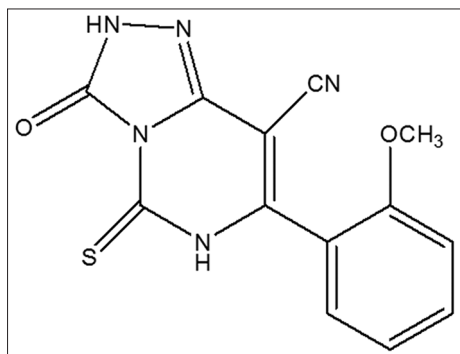


Fig. 27: New pyrimidine derivative

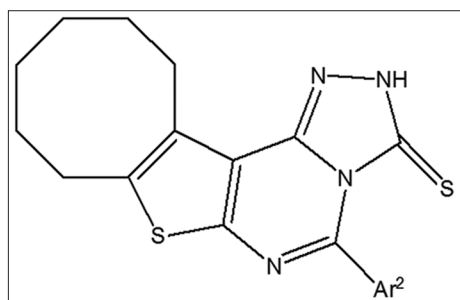


Fig. 28: Thieno [2,3-b]pyrimidines

4. Elderfield RC. Heterocyclic Compounds. USA: John Wiley & Sons New York; 1957. p. 6.
5. Agarwal OP. Organic Chemistry. Reaction and Reagent. New Delhi: Krishna Prakashan Media (P) Ltd.; 2006. p. 735.
6. Porter AE. Diazines and Benzodiazines. Netherlands: Pregamon Press, Elsevier Science BV Amsterdam; 1979. p. 14.
7. Gavilan MD, Gomez-Vidal JA, Serrano FR. Pyrimidine as anticancer agent. Bio Med Chem Lett 2008;18:1457-60.
8. Ali M, Azad M, Siddiquia HL, Nasim FH. Synthesis and antimicrobial studies of some quinolinylpyrimidine derivatives. J Chinese Chem Soc 2008;55:394-400.
9. Siddiqui AB, Trivedi AR, Kataria VB, Shah VH 4,5-Dihydro-1H-pyrazolo[3,4-d]pyrimidine containing phenothiazines as antitubercular agents. Bioorg Med Chem Lett 2014 15;24:1493-5.
10. Chandrashekaraiiah M, Lingappa M, Gowda VD, Bhadregowda DG. Synthesis of some new pyrimidine-azitidinone analogues and their antioxidant, *in vitro* antimicrobial, and antitubercular activities. J Chem 2014;2014:9.
11. Kachroo M, Panda R, Yadav Y. Synthesis and biological activities of some new pyrimidine derivatives from chalcones. Pharm Chem 2014;6(2):352-9.
12. Dudhe R, Sharma PK, Verma PK. Synthesis and biological activities of some new pyrimidine derivatives from chalcones. Int J Res Dev Pharm Life Sci 2015;4:1.
13. Himaja M, Rout PK, Karigar AA, Poppy D, Munirajashakhar D. Synthesis and antioxidant activity of 4,6-diphenylpyrimidine-2-amine & its derivatives. Univ J Pharm 2012;01(01):72-7.
14. Bano T, Kumar N, Dudhe R. Free radical scavenging properties of pyrimidine derivatives. Org Med Chem Lett 2012;2(1):34.
15. Goudar V, Rashmi P, Shantharam U, Hazra K, Nargund LG. synthesis of novel thienopyrimidines and evaluation for their anti-inflammatory activity. J Chem Pharm Res 2012;4(6):3100-6.
16. Kota1 RK, Kompelly KK, Surampudi R, Kulakarni R. Synthesis and antiinflammatory activity of novel pyrazolo [3,4-d] pyrimidines. J Chem Pharm Res 2011;3(4):848-53.
17. Kumaresan S, Chandrasekaran S, Sakthivel KM, Guruvayoorappan C, Israel VM. Synthesis, characterization and anti-inflammatory activity of some novel pyrimidin-2-amines on Carrageenan-induced paw edema in balb/c mice. J Chem Pharm Res 2014;6(10):593.
18. Valarmathy J, Joshua LS, Senthilkumar KL. Synthesis of 2-aminopyrimidine derivatives and evaluation for anti tubercular, anti-convulant and anti-inflammatory activity. Univ Int J Chem 2011;2(2):61-8.
19. Mohana KN, Basavapatna N, Mallesha L. Synthesis and biological activity of some pyrimidine derivatives. Drug Invent 2013;5(3):216-22.
20. Kaur N, Aggarwal AK, Sharma N, Choudhary B. Synthesis and *in-vitro* antimicrobial activity of pyrimidine derivatives. Int J Pharm Sci Drug Res 2012;4(3):199-204.
21. Gupta YK, Gupta V, Singh S. Synthesis, characterization and antimicrobial activity of pyrimidine based derivatives. J Pharm Res 2013;7(6):491-5.
22. Sharma O, Shrivastava B, Singla RK, Bhat V. Synthesis and antimicrobial activity of some novel pyrimidine- 2, 4 (1h,3h)-diones. Indo Glob J Pharm Sci 2011;1(3):252-7.
23. David VB, Babu VH, Reddy VM. Synthesis of novel 4,6-disubstituted-2-amino pyrimidines as antibacterial agents. Int J Pharm Chem Res 2014;3(1):2278-8700.
24. Nehad A, Saeed MM, Ahmed NS, Batran RZ, El-mouhty NA. Synthesis of some pyridine, Pyrimidine and cyclohexenone derivatives as antibacterial agents. Int J Innov Res Sci Eng Technol 2014;3(1):24.
25. Gullapelli K, Thupurani MK, Brahmeshwari Z. Synthesis and anti bacterial activity of 2-(4-aminophenyl) benzimidazole based pyrimidine derivatives. Int J Pharm Bio Sci 2014;5(1):682-90.
26. Ishak CY, Metwally NH, Wahbi HI. *In-vitro* antimicrobial and antifungal activity of pyrimidine and pyrazolo-[1, 5-a] pyrimidine. Int J Pharm Phytopharmacol 2013;2(6):407-11.
27. Andrews B, Mansur A. Synthesis and characterization of pyrimidine bearing 1, 3, 4-oxadiazole derivatives and their potential antifungal action. Int J Chem Stud 2013;1(4):32-9.
28. Singh K, Kaur H, Chibale K, Balzarini J, Little S, Bharatam PV. 2-Aminopyrimidine based 4-aminoquinoline anti-plasmodial agents. Synthesis, biological activity, structure-activity relationship and mode of action studies. Eur J Med Chem 2012;52:82-97.
29. Rai SU, Isloor AM, Shetty P, Pal KS, Fun HK. Synthesis and *in vitro* biological evaluation of new pyrazole chalcones and heterocyclic diamides as potential anticancer agents. Arabian J Chem 2014;8(3):317-21.
30. Verma AK, Kumari R, Sing AK, Sharma BB, Martin A, Kant R. Synthesis characterization and anticancer activity of novel novel N-(sugar pyranosyl)thienopyrimidine 4- amine derivatives. Int Res J Pharm 2014;5(12):922.
31. Fathalla OA, Zeid F, Haiba ME, Soliman M, Abd-Elmoez HI, El-Serwy WS. Synthesis, antibacterial and anticancer evaluation of some pyrimidine derivatives. World J Chem 2009;4(2):127-32.
32. Kandeel MM, Mounir A, Refaat HR, Kassab AE. Synthesis of effective anticancer thieno [2,3-d] pyrimidine-4-ones and thieno [3,2-e] triazolo [4,3-c]pyrimidines. Int J Pharm Pharm Sci 2012;4(3):0975-1491.
33. Goudgaon NM, Reddy RV. Analgesic and anti-inflammatory activities of 2-(4-fluorobenzylthio)-n-(substituted phenyl) Pyrimidine-4-amines. Int J Pharm Chem Biol Sci 2014;4(1):64-8.