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PHARMACOLOGICAL POTENTIAL AND MEDICINAL SIGNIFICANCE OF VERSATILE PYRIMIDINE NUCLEUS

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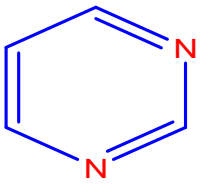
ABSTRACT

Pyrimidine nucleus has been long targeted by the researchers due to its versatile biological and pharmacological applications such as antifungal, antibacterial, antimicrobial, anti-inflammatory, antiviral, anticancer, antioxidant, antitubercular, antiparkinsonian, analgesic, antimalarial and anti-HIV activities. It is the constituent of nucleic acid including uracil, thymine, cytosine, adenine, and guanine which are the fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It also play an important role in many biological processes, such as it is found in nucleoside antibiotics, antibacterials and cardiovascular. In this review the recent development of pyrmidinre, fused pyrimidine derivatives and their potential medical importance is discussed which can be used as a guide for researchers and will be helpful for further development in this area.

KEYWORDS: Pyrimidine derivatives, biological activities

1. INTRODUCTION

Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring. It is isomeric with two other forms of diazine [Figure-1].

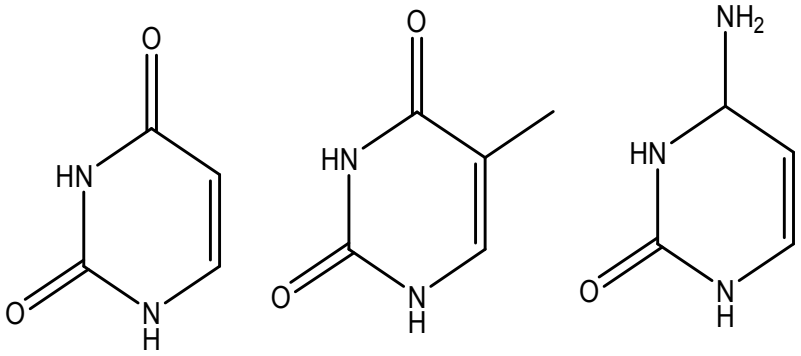


Pyrimidine

Figure-1

Pyrimidine and fused pyrimidine derivatives are one of the most prominent structures found in nucleic acid including uracil, thymine, cytosine, adenine, and guanine are fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Among the various heterocyclic compounds, pyrimidine and fused pyrimidine plays an important role in the medicinal chemistry because they play an essential role in several biological processes, found in nucleoside antibiotics, anti-bacterials, and cardiovascular. Condensed pyrimidine derivatives have been reported as antifungal [1-4,anti-bacterial [5-11], Antimicrobial [12] Analgesic [13], anti-viral [14-17], anti-inflammatory, [18] anti-HIV,[19] anti-tubercular,[20] anti-tumor, [21] anti-neoplastic, [22] anti-malaria, [23] diuretic, [24] cardiovascular [25] agents and hypnotic drugs for the nervous system. [26] They are found calcium-sensing receptor antagonists [11] and also antagonists for the human A2A adenosine receptor. [27] Many of pyrimidines derivatives are reported to possess potential central nervous system (CNS) depressant properties [28, 29] and also act as calcium channel blockers. [30]

Pyrimidines and its derivatives are integral part of DNA and RNA shown in [Figure-2].



Uracil **Thymine** **Cytosine**

Figure-2

Pyrimidine nucleus is also found in a number of biologically active nucleus some of them are shown in [Figure-3].

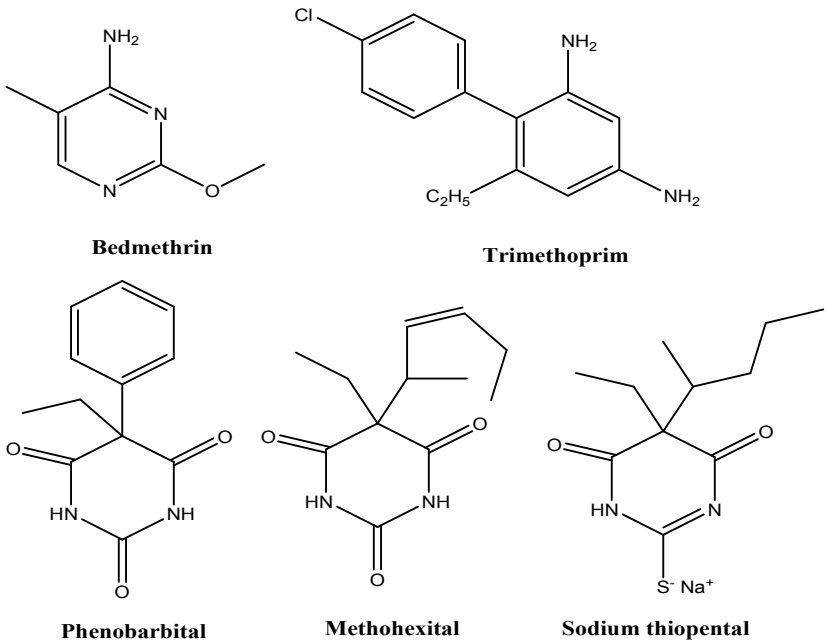


Figure-3

2. Review of literature

Humaira P. et al. [31] reported the synthesis of 6-ferrocenyl-4-aryl-2-substituted pyrimidine derivatives and subjected them for antiamoebic evaluation against HM1: IMSS strain of Entamoeba histolytica and for cytotoxicity studies of these compounds on human kidney epithelial cell. The results revealed tha out of sixteen, ten compounds were found to possess promising inhibitory activity and also non toxic nature. One compound, 4-(4-Chlorophenyl)-6-ferrocenyl-2-piperidin-1-yl-pyrimidine was found most active and least toxic among all the compounds [Figure-4].

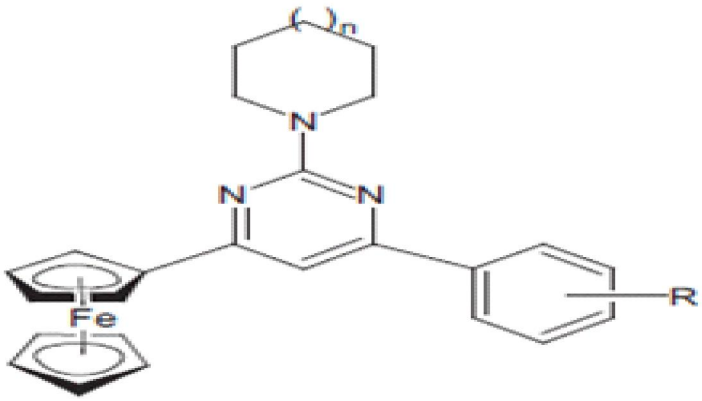


Figure-4

Derivatives of thiazolo[3,2-a]pyrimidine and thiazolo[2,3-b]quinazoline analogues were designed, and synthesized by Fatmah A.M. Al-O. et al [32]. The compounds were evaluated for their in-vitro antitumor activity using the NCI's disease-oriented human cell lines assay. On the other hand pyrrole derivatives, pyrrolo[2,3-d]pyrimidine derivatives, pyrrolotriazolopyrimidines and pyrrolotetrazolopyrimidines were synthesized by Khalid Mohammed H H. [33]. The screening of all the synthesized compounds was done against Staphylococcus aureus, Escherichia coli, and Candida albicans. The results exhibited that pyrrolo[2,3-d]pyrimidines, possessed excellent activity against C. albicans with MIC 0.31-0.62 mg/mL. These compounds displayed better antifungal activity than that of standard drug (fluconazole with MIC 1.5 mg/ mL) [Figure-5].

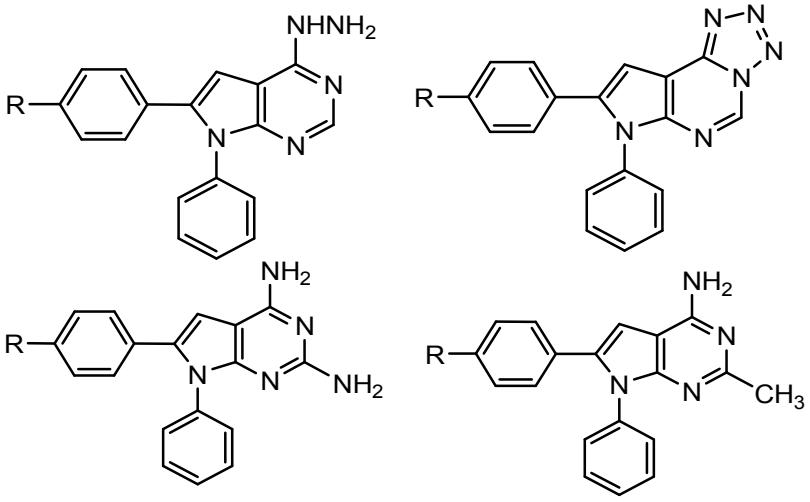


Figure-5

Nadia S. El-S. et al. [34] reported that a new series of sulfonamide derivatives of [1,3,4]thiadiazolo[3,2-a]pyrimidine were synthesized and investigated as antitumor agents. The prepared compounds were tested for their in vitro and in vivo antitumor activities preliminary biological studies revealed that compounds some compounds exhibited the highest affinity to DNA, while some compounds exhibited moderate activity. Results also revealed that some compounds showed the highest percentage increase in lifespan of mice inoculated with Ehrlich ascites cells over 5-flurouracil (positive control) [Figure-6].

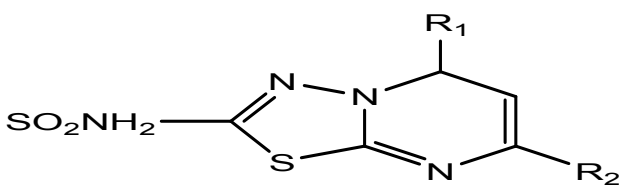


Figure-6

Aymn E. R. et al. [35] synthesized a series of novel substituted pyrazolo[3,4-d]pyrimidines starting with pyrimidinone derivative. The in vitro cytotoxicity against human breast adenocarcinoma (MCF-7) cell lines has been investigated and most of the tested compounds exploited potent cytotoxic activity against MCF-7 cell lines comparable to the activity of the commonly used anticancer drug cisplatin. The author observed that acyclic nucleoside derivative revealed the highest anticancer activity among the other tested compounds [Figure-7].

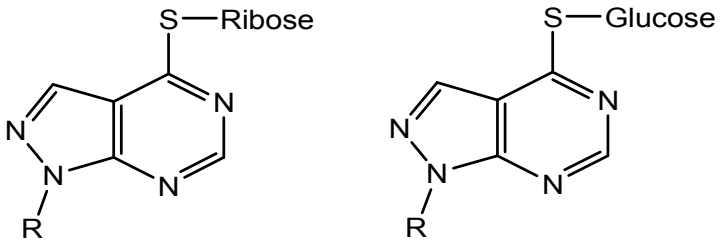


Figure-7

In search for novel agrochemicals with higher antifungal activity, a series of new 1,2,4-triazolo[1,5-a]pyrimidine derivatives bearing 1,3,4-oxadiazole moieties were designed and synthesized by Qiong C. et al. [36]. The antifungal activity of these compounds was screened against Rhizoctonia solani and the results revealed that some of the compounds found to possess promising antifungal activity. To further explore the comprehensive structure activity relationships, a 3DQSAR analysis using the method of comparative molecular field analysis (CoMFA) was performed and a statistically reliable model with good predictive power (r2 ¼ 0.929, q2 ¼ 0.588) on the basis of the common substructure-based alignment. According to the CoMFA model, the structureeantifungal activity relationship was explained reasonably [Figure-8].

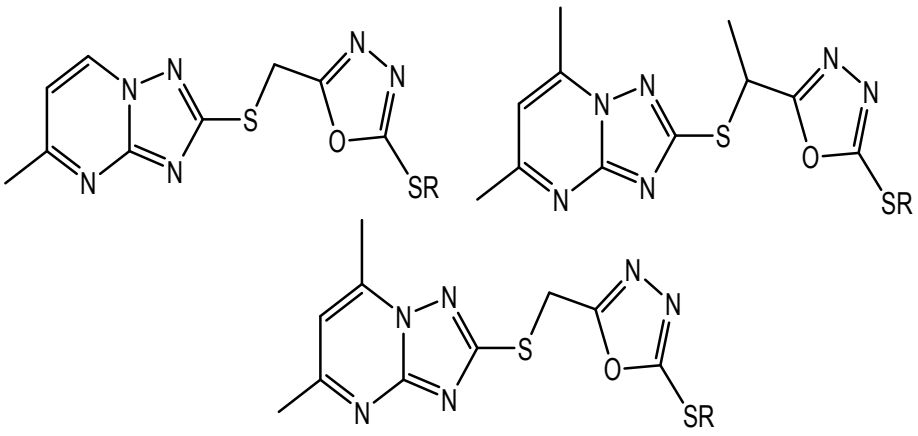


Figure-8

Salwa F. M. et al. [37] designed and synthesized some new substituted pyrimidine, thiopyrimidine and thiazolopyrimidine derivatives and evaluated them for Anti-HSV-1 activity. The antiviral screening showed that many of these compounds have good antiviral activities comparable to Acyclovir as standard. Two compounds from the series were found to exhibit over 90% inhibition and considered to be highly promising and on confirming their activity and comparing them to antiviral activity of Acyclovir [**Figure-9**].

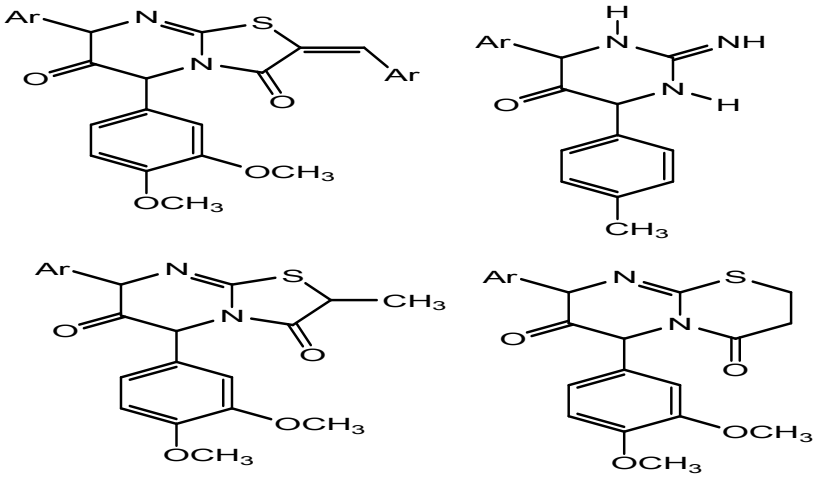


Figure-9

Mohammed K. Abd El H. et al. [38] reported that a series of new 1-aryl-4-benzylidenehydrazinyl-3- methylsulphanyl-pyrazolo[3,4-d]pyrimidines was synthesized. The cytotoxic activity of the newly synthesized compounds against human breast cancer cell line (MCF7) was investigated. The compounds possessing 1-phenyl substitution exhibited better antitumor activity than containing 1-(4-methoxyphenyl) substitution. Most of the test compounds showed potent antitumor activity comparable to that of doxorubicin. Further studies were also carried out to determine the exact mechanism of the antitumor action as well as to explore the SAR of other positions of the nucleus [Figure-10].

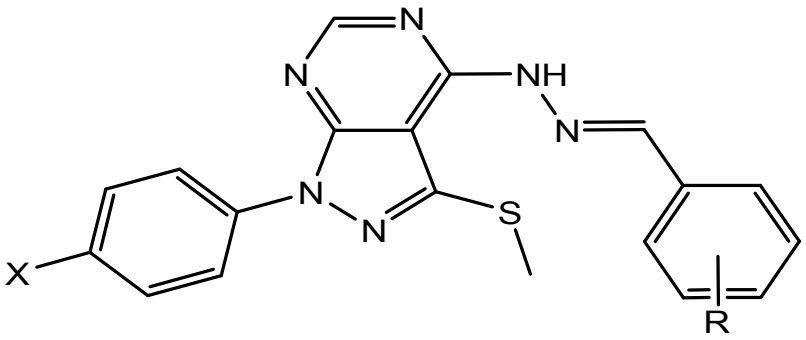


Figure-10

The chemometric protocol VLAK was applied to predict improvement of the biological activity of pyrrolo-pyrimidine derivatives as anticancer agents by Antonino L. et al. [39] using the NCI ACAM Database as depository of antitumor drugs with a known mechanism of action. Among the selected compounds two of these showed a good increase in the antitumor activity. These new pyrrolo-pyrimidine compounds were demonstrated effective against the full panels of NCI DTP tumour human cell lines. The derivative 8-[3- (piperidino)propyl]-4,10-dimethyl-9-phenyl-6-(methylsulfanyl)-3,4-dihydropyrimido[1,2-c]pyrrolo[3,2-e]pyrimidin-2(8H)-one found more efficacious against the leukemia subpanel, in particular the RPMI cell line resulted the most sensitive (pGI50 ¼ 6.68). Moreover the derivative 7-(3-Chloropropyl)-9-methyl-5-(methylsulfanyl)-8-phenyl-3H-imidazo[1,2-c]pyrrolo[3,2-e]pyrimidin-2(7H)-one showed a good antitumor activity against the leukemia subpanel with a low cytotoxic activity [Figure-11].

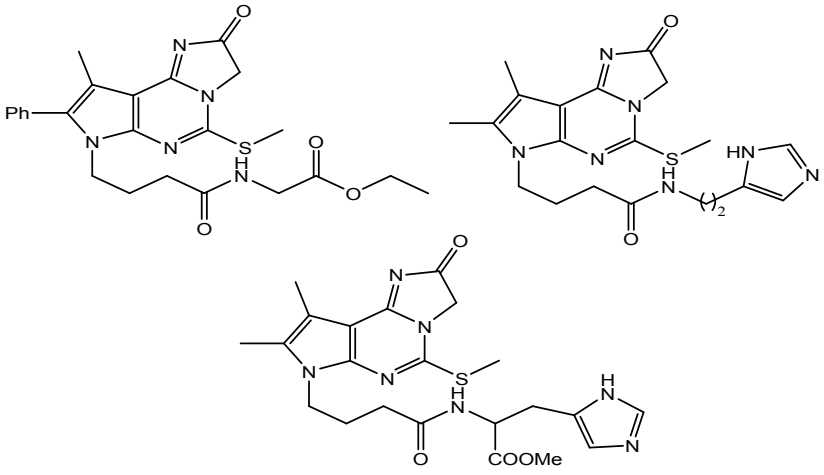


Figure-11

Shrikant B. K. et el. [40] reported a new class of substituted thieno[2,3-*d*]pyrimidine derivatives and their antibacterial and antifungal assessmenet. Results revealed that most of the compounds showed promising antibacterial and antifungal activity [Figure-12].

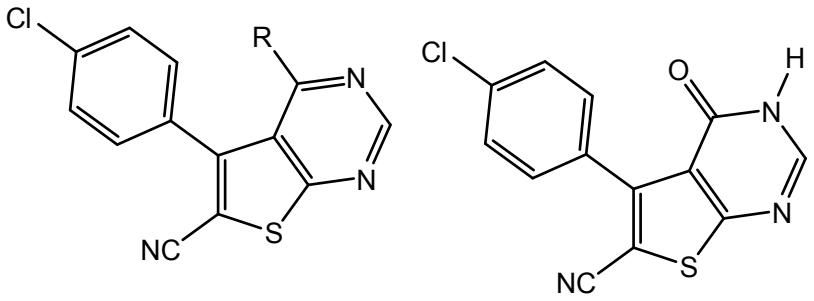


Figure-12

A series of novel pyrido[2,3-d]pyrimidine derivatives were prepared by Kurumurthy C. et al. [41] using an efficient route and subjected to alkylation to obtain two regioisomers in definite proportion. The synthesized derivatives were screened for anticancer activity and promising compounds were found to possess good anticancer activity [Figure-13].

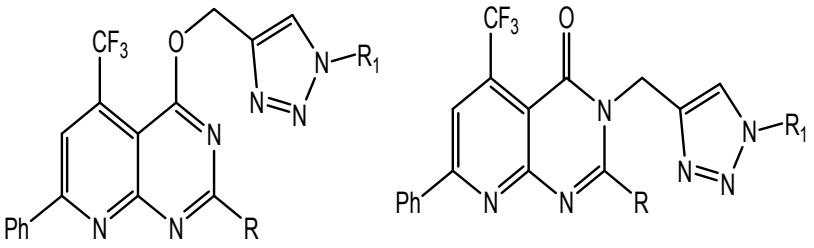


Figure-13

Haider B. et al. [42] reported the synthesis of a new class of pyrido[1,2-a]thieno[3,2-e]pyrimidine, quinoline and pyridin-2-one derivatives. Most of the synthesized compounds in this investigation were tested and evaluated as antimicrobial agents. The results of biological evaluations demonstrate that members from these compounds have promising antimicrobial activities against Gram negative bacteria, Gram positive bacteria and Yeast [Figure-14].

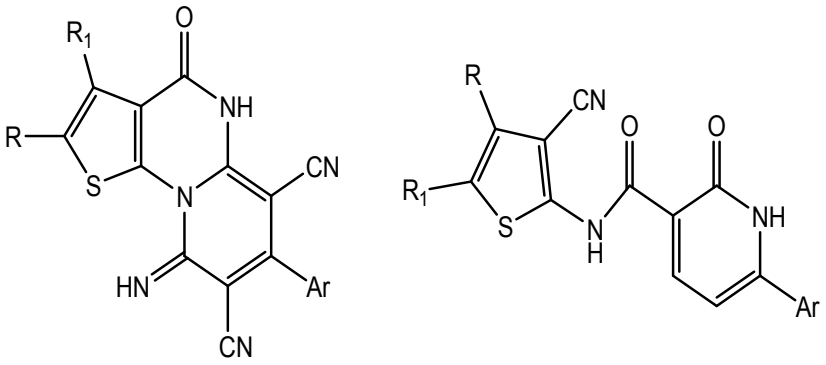


Figure-14

Humaira P. et al. [43] synthesized a new series of 2,4,6-trisubstituted bis-pyrimidines and evaluated for in vitro antiamoebic activity against HM1:IMSS strain of Entamoeba histolytica. Some compound of the series exhibited higher antiamoebic activity than the reference drug metronidazole (IC50¼1.9 mM). The toxicological studies of active compounds on PC12-rat pheochoromocytoma cell line showed that all compounds were non-toxic at a concentration of 100 mM. One compound named as Benzene-1,3-diylbis[6-(4-

methylphenyl-2-(piperidin-1-yl)pyrimidine] was found most active (IC50 ¼ 0.10 mM) and least toxic among all the compounds [Figure-15].

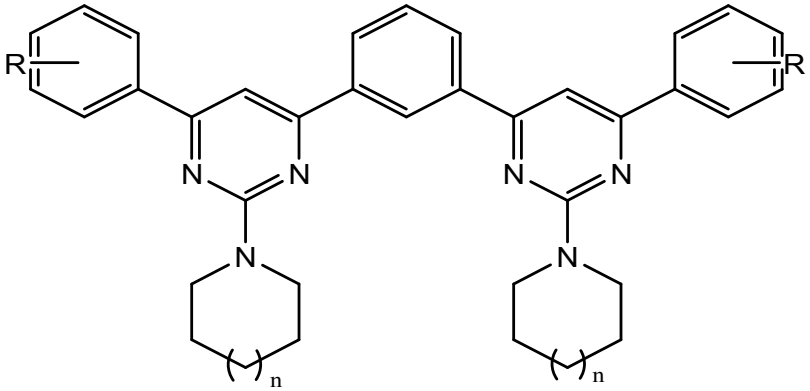


Figure-15

A series of new arylpiperazines, ligands of the 5-HT1A receptor that contain a 4-aryl-2H-pyrido[1,2-c]pyrimidine moiety in the molecule, was synthesized by Franciszek H. et al [44]. The new derivatives revealed high affinity for the 5-HT1A receptor in vitro studies, while a few of these derivatives may be regarded as ligands with a mixed (type 5-HT1A/5-HT2A) profile of receptor affinity. One compound from the series (Ki = 1.3 nM), 10 (Ki = 2.2 nM), and 6 (Ki = 7.0 nM) exhibited the highest values of affinity for 5-HT1A receptor [Figure-16].

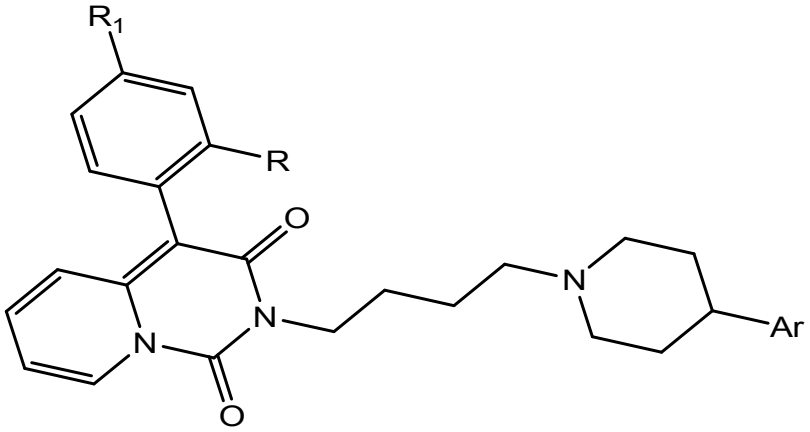


Figure-16

Some novel chromeno[2,3-d]pyrimidinone, pyrano[2,3-d]pyrimidine, dihydropyrimidine, pyridopyranopyrimidine and pyrimidopyranopyrimidine have been synthesized by Hala M. A. et al. [45] The structures elucidation was done by elemental analyses and spectral data. The antimicrobial activity of all the target synthesized compounds were tested against various microorganisms such as Pseudomonas aeruginosa; Staphylococcus aureus (Bacteria),

Aspergillus flavus (Fungus) and Candida albicans (Yeast fungus) by the disc diffusion method. In general, the novel synthesized compounds showed a good antimicrobial activity against the previously mentioned microorganisms [Figure-17].

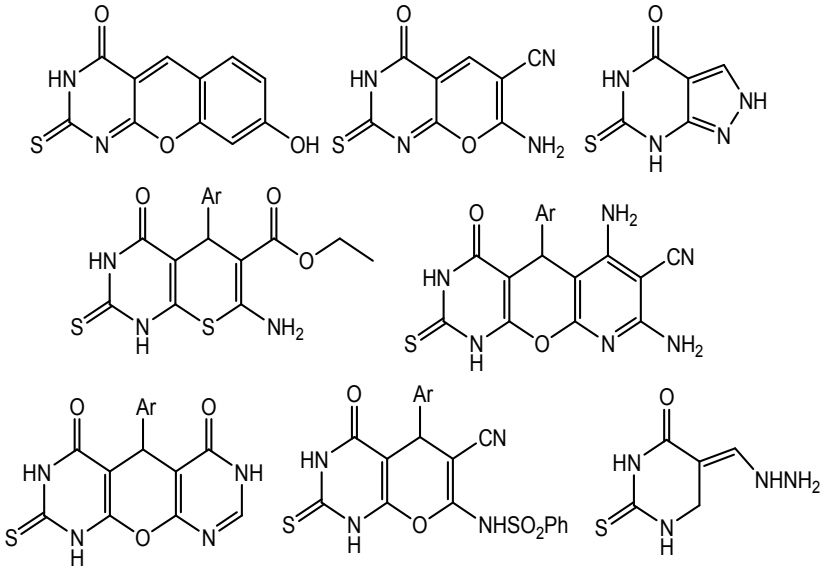


Figure-17

Mohamed R. S. et al. [46] reported a simple, facile, efficient and one pot three-component procedure for the synthesis of pyrazolo[1,5-a]pyrimidines, triazolo[1,5-a]pyrimidines and pyrimido[1,2-a]benzimidazoles ring systems incorporating phenylsulfonyl moiety was developed via the reaction of 1-aryl-2-(phenylsulfonyl)ethanone derivatives 1aed with the appropriate heterocyclic amine and triethyl orthoformate 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 (4b) and its p-methoxy analogue 4c were found to be equipotent to Doxorubicin as a reference drug. Molecular modeling study was carried out in order to rationalize the in vitro anti-tumor results [Figure-18].

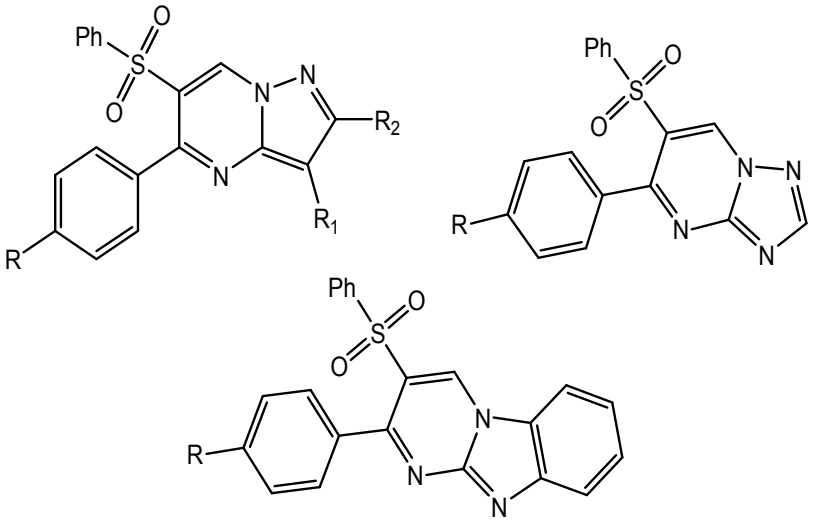
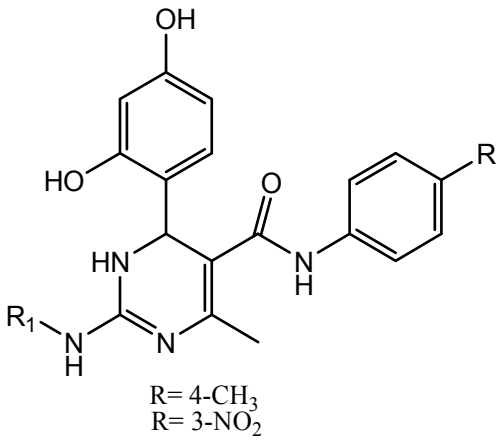


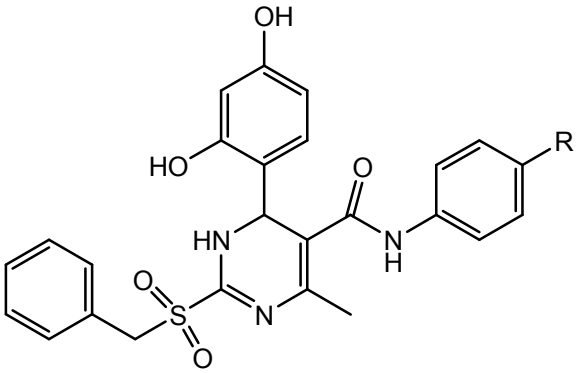
Figure-18

Novel derivatives of 2,4,5,6-tetrasubstituted pyrimidine cyclin-dependent kinase (CDK2) inhibitors was designed and synthesized by Diaa A. I. et al. [47] the results exhibited that the newly synthesized compounds showed potent and selective CDK2 inhibitory activities and inhibited in-vitro cellular proliferation in cultured human tumor cells [Figure-19 (a) & (b)].



R= 4-CH_3
R= 3-NO_2

Figure-19 (a)



R= CH_3
R= NO_2

Figure-19 (b)

Kotaiah Y. et al. [48] reported the synthesis and antioxidant activity of 1,3,4-oxadiazole tagged thieno[2,3-d]pyrimidine derivatives [Figure-20]. All the novel compounds were screened for their *in vitro* antioxidant activity by employing DPPH, hydrogen peroxide, and nitric oxide radical scavenging assays. From the series a number of compounds showed significant radical scavenging activity due to the presence of electron donating substituent on both sides of the thienopyrimidine ring. It was observed that there is an enhancement in the activity in

presence of electron donating group while in presence of electron withdrawing groups like nitro group the activity decreases.

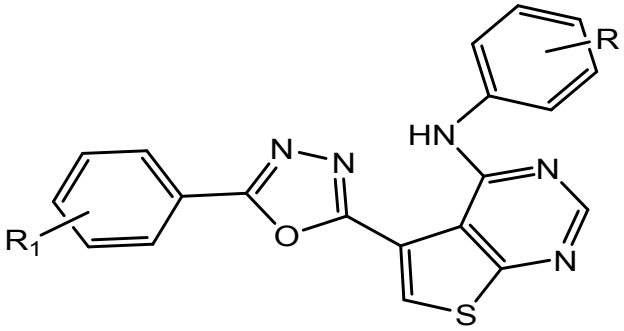


Figure-20

Giles D. et al. [49] synthesized a new group of pyrimidine derivatives of indane-1,3-dione [Figure-21] aiming at the analgesic, anti-inflammatory and antimicrobial activity in a single component. The title compounds were synthesized from chalcone derivatives of indane-1,3-dione through cyclization reaction with urea and evaluated for anti-inflammatory, analgesic, antibacterial and antifungal activities.

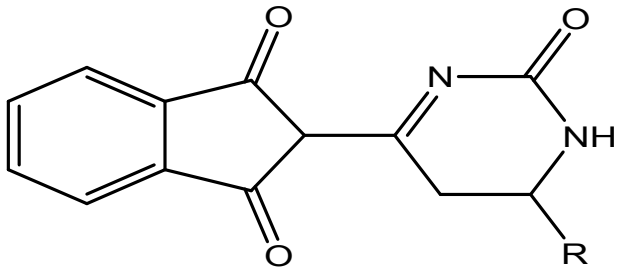


Figure-21

Schenone S. et al. [50] reported the antiproliferative activity of new1-aryl-4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives [Figure-22] towards the human epidermoid carcinoma A431 cell line.

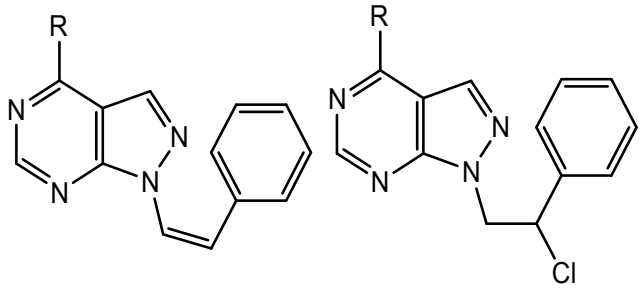


Figure-22

Keri R S. et al. [51] synthesized some novel pyrimidine derivatives of coumarin moiety [Figure-23] and evaluated their analgesic, anti-pyretic and DNA cleavage activities. All the synthesized compounds were screened for *in vivo* analgesic and anti-pyretic activities at a dose of 25 and 100 mg/kg body weight (b.w) respectively. Among them many compounds exhibited significant analgesic activity comparable with standard drug analgin using Tail-flick model. Rai U S. et al. [52] reported the synthesis of some novel chromeno-[2,3-b]-pyrimidine derivatives [Figure-24] and tested for anti-microbial activity.

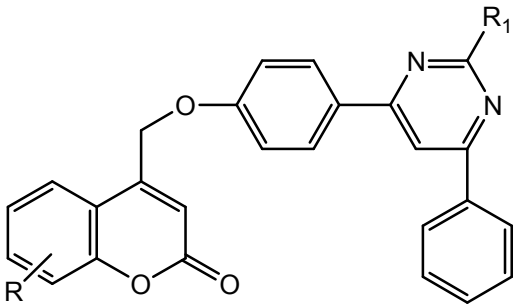


Figure-23

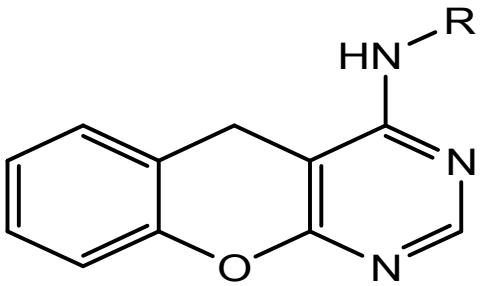


Figure-24

Mehdi B. et al. [53] reported the molecular iodine promoted synthesis of new pyrazolo[3,4-d]pyrimidine derivatives as potential antibacterial agents. The *in vitro* antibacterial activity of the newly synthesized compounds were screened for the antibacterial activity against several pathogenic representative Gram-positive bacteria (*Staphylococcus aureus* PTCC 1074 and Bacillus subtilis PTCC 1365), Gram-negative bacteria (*Escherichia coli* HB101 BA 7601C and *Pseudomonas aeruginosa* PTCC 1431) using disc diffusion sensitivity test [Figure-25].

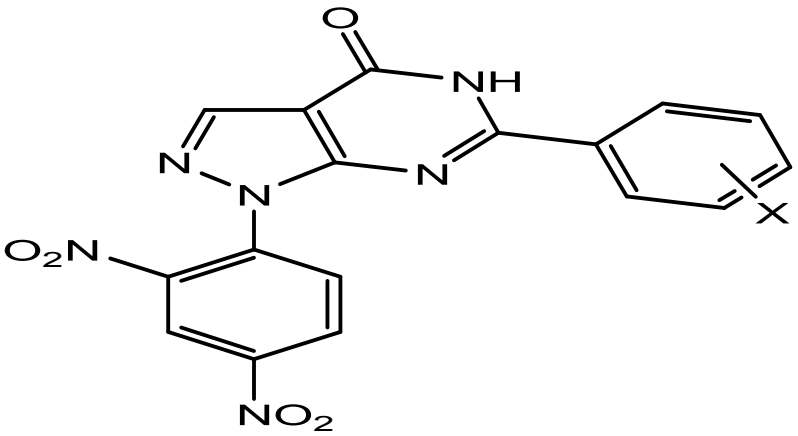


Figure-25

Singh K. et al. [54] synthesized a series of pyrimidine derivatives bearing amine substituents at C-2 position were obtained from Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones shown in

[Figure-26]. The author also evaluated the effect of structural variation on anti-TB activity against *Mycobacterium tuberculosis* H37Rv strain and antiviral activity in a series of cell cultures. Some compounds were found to possess structure dependent cytostatic activity. While some compounds were not found to be efficient inhibitors of *M. tuberculosis* and they did not inhibit variety of DNA or RNA viruses in cell culture.

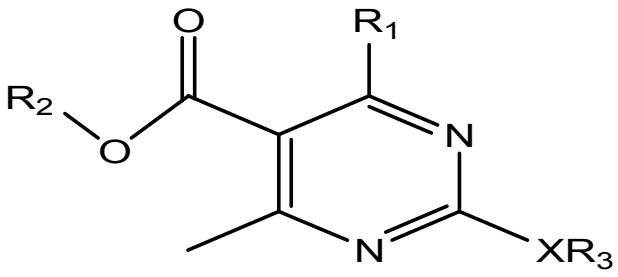


Figure-26

Keeping in mind the versatile biological application of pyrimidine nucleus containing compounds many more scientists contributed their efforts in the development of new pyrimidine derivatives with potential pharmacology some of them are described in the Table-1.

Table -1: Representing the variety of pyrimidine derivatives and their medical importance.

S.No.	Name of compound	Medical importance	Reference
1	Pyrrole and pyrrolo[2,3-d]pyrimidine derivatives	Antifungal	El-Gaby M.S.A. et al. [55]
2	Pyrimidines and their thioethers	Antifungal	Chetan M. B. et al. [56]
3	2H-4-arylaminopyrimidines	Antifungal	Kishor S. J. et al. [57]
4	Thienopyrimidin-4(3H)-thiones	Antifungal	Sanjay B. B. et al. [58]
5	Benzothiazole pyrimidine derivatives	Antibacterial and antifungal	Suresh M. et al. [59]
6	Pyrazolo[3,4-d]pyrimidine	Antimicrobial	Bantwal Shivarama H. et al. [60]
7	Methyl-7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylates	Antibacterial and antifungal	Ajmal R. B. et al. [61]
8	7-Trifluoromethylpyrazolo[1,5-a]pyrimidines	Anti-inflammatory and antimicrobial	Ranjana A. et al. [62]
9	2,4-Bis(substituted phenoxy)-6-(phenylthio)	Antimicrobial	Goudgaon N.M. et al. [63]

	pyrimidine		
10	Polyfunctional imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrimidine	Antimicrobial	Taleb H. Al-T. et al. [64]
11	Pyrimidine and thioxopyrimidine	Antimicrobial and antioxidant	Padmaja A. et al. [65]
12	2,4-Diaminoquinazoline, 2,4-diaminopyrido[2,3-d]pyrimidine and 2,4-diaminopyrimidine	Anti-tumor	María F. et al. [66]
13	Imidazo[1,2-a]pyrimidine	Antifungal	Rival Y. et al. [67]
14	5-(o-hydroxyaroyl)pyrimidines	Antimicrobial	Tilak R et al. [68]
15	Imidazo[4,5-b]pyridine and 4-heteroarylpyrimidine	Anti-cancer	Lukasik P M. et al. [69]
16	Pyrimido [3,2-*b*]-1,2,4,5-tetrazine, pyrimido [3,2-*b*]-1,2,4-triazine, pyrimido [3,2-*b*]-1,2,4-triazole and pyrimidine	Anticancer	Al-Issa S.A. et al. [70]
17	Thiazolo[3,2-a]pyrimidine	Biological activities	Samia G. A. M. et al. [71]
18	Pyrimidine containing piperazine nucleus	Anti-histaminic	Rahaman Sk. A. et. al. [72]
19	1H-pyrazolyl-thiazolo[4,5-d]pyrimidines	Anti-inflammatory and antimicrobial	Adnan A. B. et al. [73]
20	4-Aryl-pyrido[1,2-c]pyrimidines	SSRI and 5-HT1A activity	Franciszek H. et [74]
21	Quinazolinoneepyrimidine	Anti-inflammatory, and ulcerogenicity	Safinaz E. A. et al. [75]
22	[1,2,4]triazino[5,6-b]indol-3-ylthio-1,3,5-triazines and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines	Leishmaniasis,	Leena G. et al. [76]
23	Pyrazolo[3,4-d]pyrimidines	Anti-proliferative	Elena D. et al. [77]
24	4-Aryl-pyrido[1,2-c]pyrimidines	SSRI and 5-HT1A	Franciszek H. [78]
25	Thieno[2,3-d]pyrimidine-2,4-dithiones and their S-glycoside analogues	Antiviral and antibacterial	Hend N. H. et al. [79]
26	4-amino-2-aryl-5-cyano-6-{3- and 4-(N-phthalimido phenyl)} pyrimidines	Antiinflammatory activity	EmersonPeter da S. F. et al. [80]
27	Bi-, tri- and tetracyclic condensed pyrimidines	Analgesic and anti-inflammatory	Kamilia M. A. et al. [81]
28	Pyrimido[5,4-e]pyrrolo[1,2-c]pyrimidine	Anti-inflammatory, analgesic and ulcerogenicity	Mona M. H. et al. [82]
29	Pyrido[2,3-d]pyrimidine	Anti-proliferative	Diaa A. I. et al. [83]

		CDK2 inhibitor	
30	Pyrimidin-2(1H)-ones	Antitubor cular and cytostatic	Kamaljit S. et al. [84]
31	3-(4-Chlorophenyl)-2-hydrazino-5,6,7,8-tetrahydrobenzo(b)thieno[2,3-d]pyrimidine-4(3H)-ones	CNS depressant, muscle relaxant and anticonvulsant	Sunil V. G. et al. [85]
32	4-Aryl-pyrido[1,2-c]pyrimidines	SSRI and 5-HT1A activity	Franciszek H. et al. [86]

3. CONCLUSION

The pharmacological potential of pyrimidine nucleus is cleared from the literature and clinically used drugs. The literature reveals that pyrimidine nucleus possess diverse biological potential, easy synthetic routes and attracted researchers for development of new therapeutic agents with this nucleus. Though it can be concluded that pyrimidine nucleus are widely investigated as antimicrobial, antifungal, anti-inflammatory and anti cancer agents. From these observations the importance of the nucleus is highlighted. The article possesses high impact developments performed with this nucleus which will help researchers for further development.

4. CONFLICT OF INTERESTS

The authors have no conflict of interest

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