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Anticancer and antimicrobial prospective of Pyrimidine derivatives: A review

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Abstract
Pyrimidine is the parent heterocycle of a very important group of compounds that have been extensively studied due to their occurrence in living systems. Pyrimidine and its derivatives demonstrate a diverse array of biological and pharmacological activities. During the last two decades several pyrimidine derivatives have been developed which are found to have wide clinical and pharmacological applications.The aim of this paper is to review the anticancer and antimicrobial potentials of pyrimidine derivatives.

Keywords: Anticancer, antimicrobial, pyrimidine derivatives

Introduction
Cancer is a devastating disease characterized by malignant growth of cells that could be clearly distinguished from normal cells by their out-of-limit growth. Approximately 50% of patients will ultimately die of locally advanced or metastatic disease. The term *metastatic cancer* indicates that the cancer has spread or metastasized to lymph nodes or other parts of the body especially to bones [1, 2]. Antiproliferative and cytotoxic drugs play a major role in cancer therapy, whether used alone or in combination with other treatments such as surgery, radiation, and biological therapy. In the past 50 years, mass screening of both synthetic derivatives and natural products has led to the discovery of a number of the currently utilized anticancer drugs. In the field of chemotherapeutic drugs, search for new, more active, selective and less toxic compounds is still in progress, and promising new anticancer approaches are being pursued [3].
Infectious diseases are responsible for a great number of deaths in the world population. The reduction of sensibility to antimicrobial agents in current use has been increasing for a great variety of pathogens and the resistance to multiple drugs is common for several microorganisms, especially for Gram positive bacteria. Infection by methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE) presents a difficult problem for medicine. Given the evidence for the rapid global spread of resistance, the need for discovery or optimization of antimicrobial agents active against these resistant strains is of paramount importance [4].
Pyrimidines are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1st and 3rd position of the six membered rings (Fig-1) Pyrimidines are biologically very important heterocycles and represent by far the most ubiquitous members of the diazine family with uracil and thymine being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities and clinical applications [5].

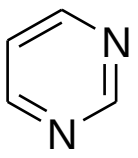
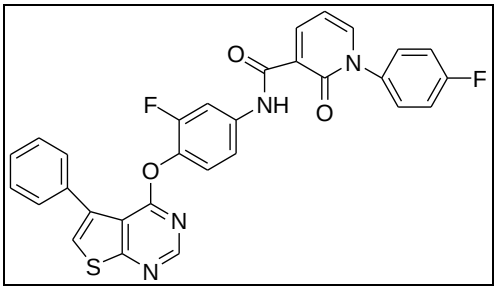


Fig 1: Pyrimidine

In the light of above facts, in the present review article, we hereby report antimicrobial and anticancer potential of pyrimidine derivatives.

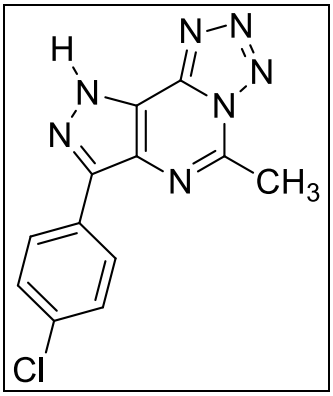
Anticancer activity

Zhao *et al.* synthesized a novel derivatives of thieno [2, 3-*d*] pyrimidine or furo [2, 3-*d*] pyrimidine and evaluated their anticancer activity by inhibition of c-Met kinase enzyme. Among the synthesized compounds, derivative 1 was found to be most active compound (IC_{50} = 35.7 nM) [6].



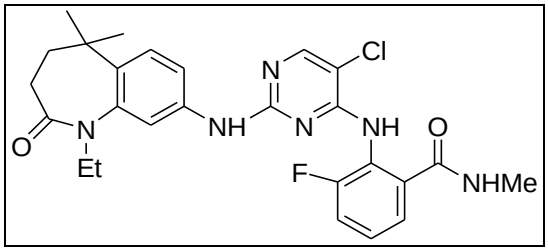
1

Hafez *et al.* synthesized novel derivatives of pyrazole and screened its *in vitro* anticancer activity against human colon (HT29), liver (HepG2) and breast adenocarcinoma (MCF-7) tumor cell lines. Compound 2 (7-(4-chlorophenyl)-5-methyl-9*H*-pyrazolo [3, 4-*e*] tetrazolo [1, 5-*c*] pyrimidine) showed the good anticancer activity as compared to standard drug doxorubicin [7].



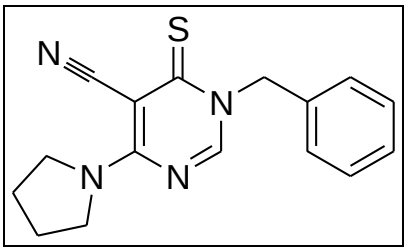
2

Weinberg *et al* synthesized a series of 2, 4-diaminopyrimidine as c-Met kinase inhibitors. Anticancer activity results indicated that compound 3, 2- (5-chloro-2- (1-ethyl-5, 5-dimethyl-5,5-dimethyl-2-methylene-2,3,4,5-tetrahydro-1*H*-benzo [*b*] azepin-8-ylamino) pyrimidin-4-ylamino)-3-fluoro-*N*-methyl benzamide, was found to possess maximum inhibition against c-met kinase (IC_{50} = 35.7 nM) [8].



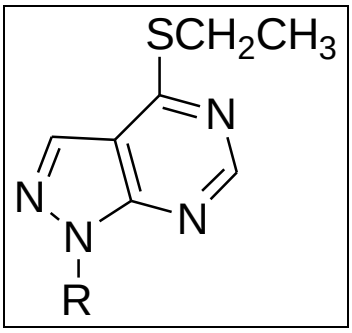
3

Cocco *et al.* synthesized novel derivatives of 6-thioxopyrimidines and evaluated its *in vitro* anticancer activity. Among the synthesized derivatives compound 4 (1-benzyl-4-(pyrrolidin-1-yl)-6-thioxo-1, 6-dihydro pyrimidine-5-carbonitrile) showed the best cytotoxicity against CNS cancer lines [9].



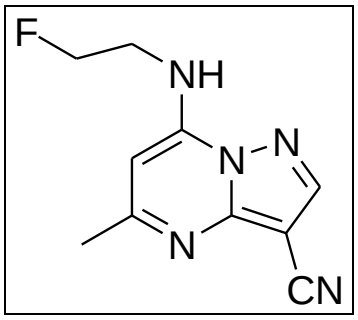
4

A series of novel pyrazolo [3, 4-*d*] pyrimidine derivatives was synthesized by Rashad *et al.* and performed their cytotoxicity against human breast adenocarcinoma (MCF-7) cell lines. Compound 5 showed significant activity on MCF-7 cells [10].



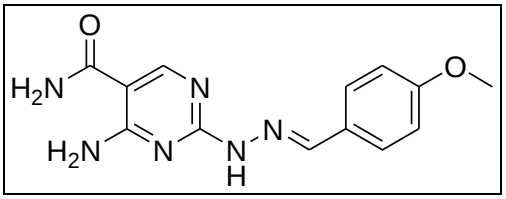
5

Xu *et al.* synthesized novel derivatives of pyrazolo [1, 5-*a*] pyrimidine derivatives and screened their anticancer activity. The anticancer results revealed that compound 6 (7-(2-[18F] fluoroethylamino)-5-methylpyrazolo [1, 5-*a*] pyrimidine-3-carbonitrile), exhibited good activity [11].



6

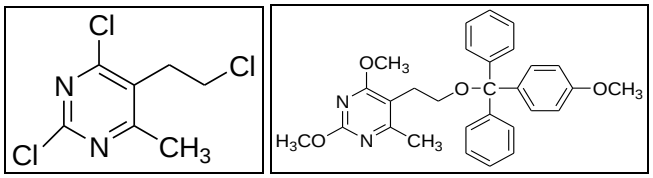
A new series of pyrimidines and fused pyrimidines derivatives as triazolo [4, 3-a] pyrimidine, pyrido [2, 3-d] pyrimidine and pyramido [4, 5-d] pyrimidine systems was synthesized by Shaaban *et al.* All the synthesized derivatives were evaluated for their anticancer and antimicrobial activities. Among the tested derivatives, compound 7 exhibited the best activity against different cancer cell lines [12].



7

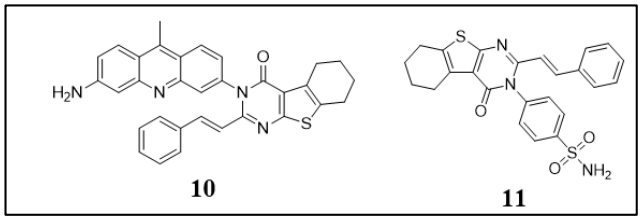
A series of 5, 6–disubstituted pyrimidines was synthesized by kreljevic *et al.* and screened their antitumor activity against

human malignant cell lines. Among all the tested compounds, derivatives 8 (IC_{50} = 4 µM) and 9 (IC_{50} = 0.4 µM) showed the most prominent inhibitory effects [13].



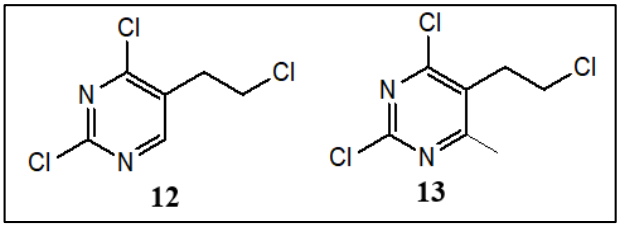
8 9

Abbas *et al.* synthesized a novel series of tetrahydrobenzo [4, 5] thieno [2, 3-*d*] pyrimidine derivatives. All the synthesized derivatives were screened for its anticancer activity against breast MCF-7 and liver HEPG-2 cancer cell lines. Compounds 10 ((*E*)-3-(6-amino-9-methylacridin-3-yl)-2-styryl-5, 6, 7, 8 -tetrahydrobenzo [4, 5] thieno [2, 3-*d*] pyrimidin-4 (3*H*)-one) and 11 ((*E*)- 4- (4-oxo-2-styryl-5,6,7,8-tetrahydrobenzo [4, 5] thieno [2,3-*d*] pyrimidin-3 (4*H*)-yl) benzene sulfonamide) showed excellent activity [14].



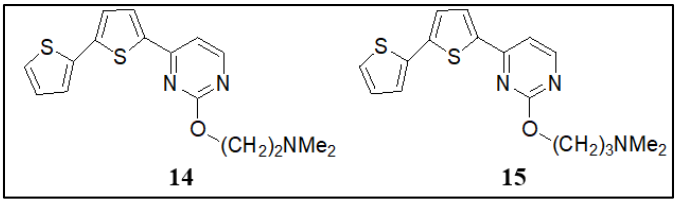
10 11

Kraljevic *et al.* synthesized C-5 substituted and *N*-acyclic pyrimidine derivatives and evaluated their cytotoxic activity. Among the synthesized derivatives, compound 12 and 13 were found to be most potent against colon carcinoma (HCT116) cells [15].



12 13

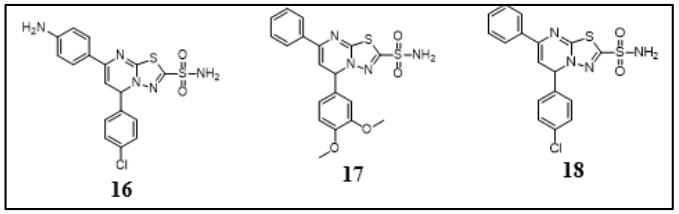
Chou *et al.* synthesized bithienyl-pyrimidines with electrostatic binding side chains and performed their anticancer activity. Among the synthesized derivatives, the compounds 14 and 15 showed significant activity against the tested cell lines [16].



14 15

Comp.	IC50 (µM)			
	Hep2	Hela	Colon205	KB
14	16	15	12	17
15	11	7	7	5

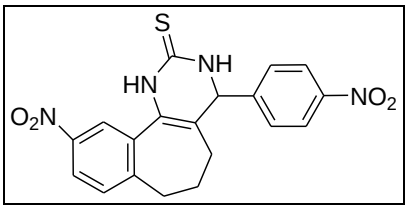
El-Sayed *et al.* designed and synthesized novel derivatives of pyrimidine and evaluated its antitumor potentials. Preliminary biological studies revealed that compounds, 16 (4- (5- (4-



16 17 18

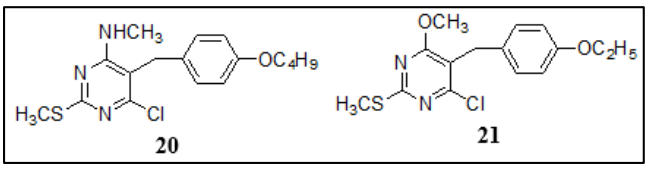
chlorophenyl) - 2- sulfamoyl-5*H*- [1, 3, 4] thiadiazolo [3, 2-*a*] pyrimidin-7-yl) benzenamine), 17 (5-(3,4-dimethoxyphenyl)-7-phenyl-5*H*- [1, 3, 4] thiadiazolo [3, 2-*a*] pyrimidine) and 18 (5- (3, 4- dimethoxy phenyl) -7-phenyl-5*H* [1, 3, 4] thiadiazolo [3, 2-*a*] pyrimidine-2-sulfonamide) showed the good affinity to DNA and highest percentage increase in lifespan of mice inoculated with Ehrlich ascites cells over 5-flurouracil [17].

With the aim to develop the new anticancer drug, Amr *et al.* synthesized pyridine, pyrane and pyrimidine derivatives. Among all the derivatives, compound 19 exhibited most potent anticancer activity [18].



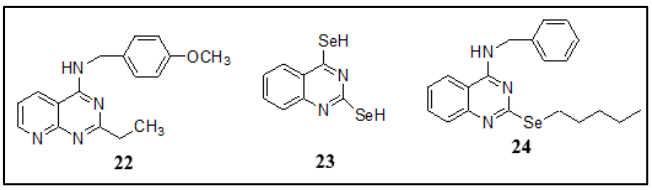
19

Grigoryan *et al.* synthesized novel 5-(4-alkoxybenzyl) pyrimidine derivatives and studied their antitumor activity and found that compounds 20 and 21 were the most potent ones [19].



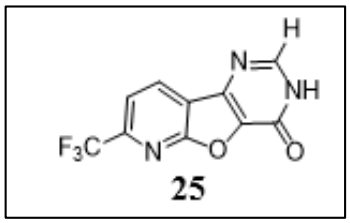
20 21

Moreno *et al.* synthesized novel derivatives of quinazoline and pyrido [2, 3-*d*]pyrimidine and their *in vitro* cytotoxic activity was performed. Anticancer results revealed that the compounds 22, 23 and 24 showed very high potency against MCF-7 cancer cell lines [20].



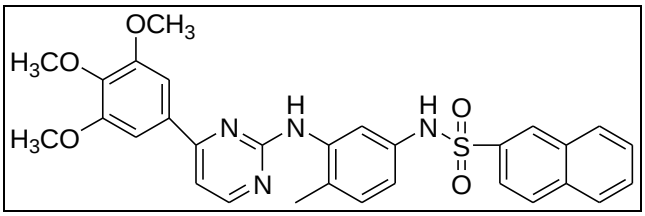
22 23 24

A new series of trifluoromethyl substituted furo[2,3-*b*]pyridine and pyrido [3′,2′:4,5] furo[3,2-*d*]pyrimidine derivatives was synthesized and evaluated for its anticancer activity against four human cancer cell lines by Kumar *et al.* All the compounds showed good anticancer activity against all the tested cell lines at <25 µM concentration except few derivatives. Compound 25 (7- (trifluoromethyl) pyrido [3', 2': 4, 5] furo [3, 2-*d*] pyrimidin-4(3*H*)-one) were found highly potent one and exhibited promising cytotoxicity comparable to standard drug 5-fluorouracil [21].



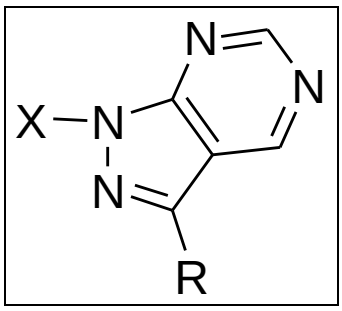
25

In order to synthesize new anticancer agents, Kamal *et al.* developed new anilino substituted pyrimidine sulphonamides as anticancer agents against K562 cell lines. Among the synthesized derivatives, compound 26, *N*- (4-methyl-3- (4-(3, 4, 5-trimethoxyphenyl) pyrimidin-2-ylamino) phenyl) aphthalene-2-sulfonamide, was found to be most potent with IC_{50} values 5.60, 9.33 and 6.93 (μM) against K562, MCF-7 and MDA-MB 231 cell lines respectively [22].



26

Huang *et al.* synthesized a new class of parasol [3, 4-*d*] pyrimidine derivatives and evaluated for its ant proliferative activity against NCI-H226 (human lung carcinoma) and NPC-TW01 (human nasopharyngeal carcinoma) cancer cells by MTT assay. Among them, compounds (27-30) possessed better potency against NCI-H226 and NPC-TW01 cancer cells (Table 1) [23].



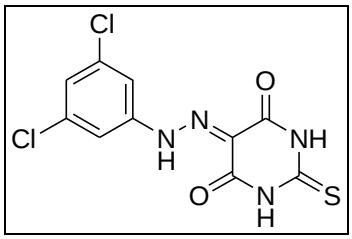
27 X= Ph; R= *p*-Cl-Ph; 28 X=2-Quinolinyl; R= *p*-Me-Ph
29 X= 2-Quinolinyl; R= *p*-Cl-Ph; 30 X= 2-Quinolinyl; R= *p*-e-Ph

Table 1: Antiproliferative results of active compounds

Compounds	Cancer cell lines (GI_{50} = μM)	
	NCI-H226	NPC-TW01
27	18	23
28	29	30
29	39	35
30	37	36

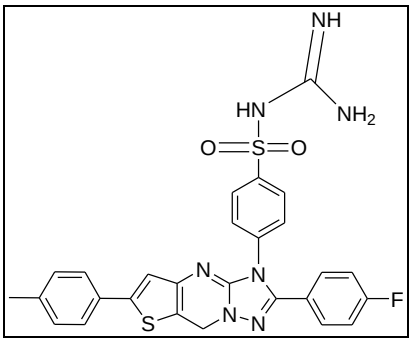
Antimicrobial activity

Abdelgawad, synthesized new azo-pyrimidine derivatives. The minimum inhibitory concentration of new azo-compounds was evaluated for their antibacterial activity against Gram-positive microorganisms; *Sarcina lutea*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Enterococcus faecalis*; and Gram-negative microorganisms; *Pseudomonas aeruginosa*. Among the synthesized derivative, compound 31, 5-[(3,5-Dichloro-phenyl)-hydrazone]-2-thioxo-dihydro-yrimidine-4,6-dione found to be most active one against the bacterial strains [24].



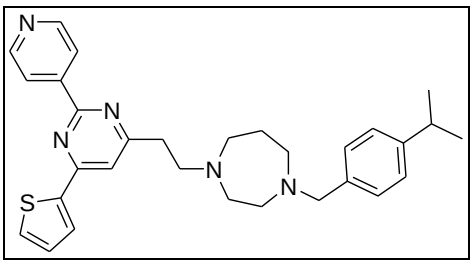
31

A novel series of carbamothioylamino-benzene-sulfonamidethiophene -carboxylates and thieno [3, 2-*d*] pyrimidin-2-yl-amino-benzene-sulfonamides were synthesized. All the synthesized compounds were evaluated for their *in vitro* activity against three human tumor cell lines, namely, liver cancer (HepG-2), colon cancer (HT-29) and lung cancer (NCI-H460), using doxorubicin as standard. Compound 32 exhibited high activity against Gram-positive and Gram-negative bacteria [25].



32

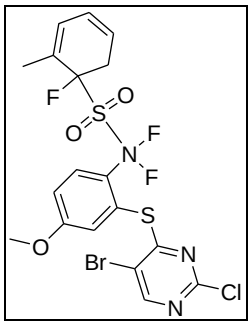
A series of novel 2, 4-disubstituted-6-thiophenyl-pyrimidine derivatives was synthesized by Fang *et al.* and their antibacterial activities against clinically related pathogens were investigated. Compounds show strong antibacterial activities against MRSA and VREs. The antibacterial activity of compound 33 against MRSA and VREs (MIC values: 2 mg/mL) is stronger than that of methicillin and vancomycin. From the *in vitro* and *in vivo* results, Compound 33 was found to inhibit ATPase activity and Fts Z polymerization. The compound is able to inhibit bacterial cell division through interacting with GTP binding site of Fts Z and thus causing cell death. In addition, S. aureus was found to develop resistance to methicillin but not for 33, which was proved in our resistance generation experiments [26].



33

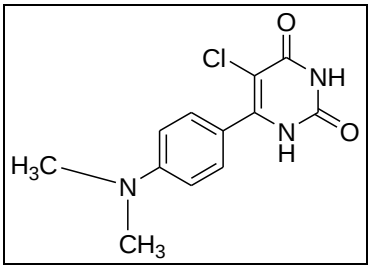
Mallikarjunaswamy *et al.*, synthesized a series of novel 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives by the reaction of 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine with

various sulfonyl chlorides, and *in vitro* antimicrobial activity was evaluated. Among the synthesized derivatives compound 34 exhibited an elevated antibacterial activity against Gram positive (zone of inhibition 29–33 mm) and Gram negative (zone of inhibition 32–33 mm) bacteria. Compound 34 also showed good antifungal activity with 96.9% inhibition when compared with other compounds in the series against F. oxysporum [27].



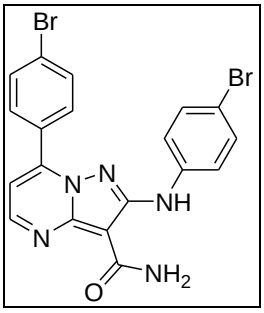
34

Sebastin *et al.*, synthesized novel derivatives of 1,3-dihydro pyrimidine from different substituted aldehydes. All the synthesized derivatives were screened for antibacterial activity using gram positive (*Bacillussubtilis*, *Staphylococcus aureus*) and gram negative (*Pseudomona aeruginosa*, *Escherichia coli*) organisms at concentrations of 400µg/disc and 200µg/disc. Among the synthesized derivatives, compound 35 (p-dimethyl aminophenysl derivative) was found to be sensitive in all strains [28].



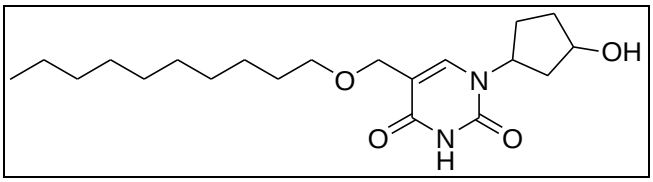
35

Abdallah *et al.*, synthesized novel derivatives of Pyrazolo [1, 5-*a*] pyrimidine and screened for its antibacterial and antifungal activities. Among the synthesis of derivatives, compound 36 with two moieties of 4-Br-C_6H^4 revealed increased reactivity compared with ampicillin as standard reference [29].



36

Khandazhinskaya *et al.*, synthesized a series of novel 5'-norcarbocyclic derivatives of 5-alkoxymethyl or 5-alkyltriazolyl-methyl uracil were synthesized and the activity of the compounds evaluated against both Gram-positive and Gram-negative bacteria. Most of the bacteria were not sensitive to the tested compounds. The only exception was against M. smegmatis, whose growth was completely inhibited by compound 37. The growth of Mycobacterium smegmatis was completely inhibited by the most active compound 37 at a MIC99 of 67 µg/mL (mc^2155) and a MIC99 of 6.7–67 µg/mL (VKPM Ac 1339). Several compounds also showed the ability to inhibit the growth of attenuated strains of Mycobacterium tuberculosis ATCC 25177 (MIC99 28–61 µg/mL) and Mycobacterium bovis ATCC 35737 (MIC99 50–60 µg/mL), as well as two virulent strains of M. tuberculosis; a laboratory strain H37Rv (MIC99 20–50 µg/mL) and a clinical strain with multiple drug resistance MS-115 (MIC99 20–50 µg/mL) [30].



37

Conclusion

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine base in thymine, cytosine and uracil, which are the essential binding blocks of nucleic acids, DNA and RNA is one possible reason for their activity. The review article has outlined the anticancer and antimicrobial activities of the pyrimidine scaffold. The scientific information of this manuscript may be worthwhile in encouraging the prospective researchers working on this heterocyclic scaffold.

References

1. Malhotra M, Dhingra R, Sharma T, Deep A, Narasimhan B, Phogat P *et al.* Cabazitaxel: A Novel Drug for Hormone-Refractory Prostate Cancer. Mini Rev Med Chem. 2013; 13:915-920.
2. Gopalakrishnan S, Vadivel E, Pon P, Kumar S, Praba MS. Synthesis, molecular docking and ADME prediction of some pyridine and pyrimidine derivatives as anti-colorectal cancer drugs. J Chem. Pharm. Res. 2010; 2(5):60-66.
3. Deep A, Kumar P, Narasimhan B, Ramasamy K, Mani V, Mishra RK *et al.* Synthesis, antimicrobial, anticancer evaluation of 2-(aryl)-4-thiazolidinone derivatives and their QSAR studies. Curr. Topic Med Chem. 2015; 15:990-1002.
4. Deep A, Narasimhan B, Mishra RK, Mani V, Mani V, Ramasamy K *et al.* 4-Thiazolidinone derivatives: synthesis, antimicrobial, anticancer evaluation and QSAR studies. RSC Adv. 2016; 6:109485-109494.
5. Sharma V, Chitranshi N, Agarwal AK. Significance and Biological Importance of Pyrimidine in the Microbial World. Int. J Med Chem, 2014, 1-31.
6. Zhao A, Gao X, Wang Y, Ali J, Wang Y, Chen Y *et al.* Discovery of novel c-Met kinase inhibitors bearing a thieno [2,3-*d*] pyrimidine or Furo [2,3-*d*] pyrimidine scaffold. Bioorgan Med Chem. 2011; 19:3906-3918.
7. Hafez HN, Abdel-Rhman BA, El-Gazzar ARBA, Al-Hussain SA. Novel pyrazole derivatives with oxa/thiadiazolyl, pyrazolyl moieties and pyrazolo [4, 3-*d*]-pyrimidine derivatives as potential antimicrobial and anticancer agents. Bioorg. Med. Chem. Lett. 2016; 26:2428–2433.

8. Weinberg LR, Albom MS, Angeles TS, Husten J, Lisko JG, McHugh RJ *et al.* Fused bicyclic derivatives of 2,4-diaminopyrimidine as c-Met inhibitors. Bioorg Med Chem Lett. 2011; 21:164-167.
9. Cocco MT, Congiu C, Onnis V, Piras R. Synthesis and antitumor evaluation of 6-thioxo-, 6-oxo- and 2,4-dioxopyrimidine derivatives. Farmaco. 2001; 56:741–748.
10. Rashad AE, Mahmood AE, Ali MM. Synthesis and anticancer effects of some novel pyrazolo [3, 4-*d*] pyrimidine derivatives by generating reactive oxygen species in human breast adenocarcinoma cells. Eur J Med Chem. 2010; 46:1019-1026.
11. Xu J, Liu H, Li G, He Y, Ding R, Wang X *et al.* Synthesis and biological evaluation of novel F-18 labeled pyrazolo [1,5-*a*] pyrimidine derivatives: Potential PET imaging agents for tumor detection. Bioorg Med Chem Lett. 2011; 21:4736-4741.
12. Shaaban MA, Mohamed KO, Hegazi ME, Montaser A. Shaykoon3, Yaseen AMM Elshaier. Synthesis of Some Pyrimidine and Fused Pyrimidine Derivatives with Antimicrobial and Anticancer Activities. Der Pharma Chemica, 2018; 10(7):180-200.
13. Kraljevic TG, Klika M, Kralj M, Kleiner IM, Jurmanovic S, Milic A *et al.* Synthesis, cytostatic activity and ADME properties of C-5 substituted and *N*-acyclic pyrimidine derivatives. Bioorg Med Chem Lett. 2012; 22(1):308-12.
14. Abbas SE, Gawad NMA, George RF, Akar YA. Synthesis, antitumor and antibacterial activities of some novel tetrahydrobenzo [4,5] thieno [2,3-*d*] pyrimidine derivatives. Eur. J Med. Chem. 2013; 65:195-204.
15. Kreljevic TG, Kristafor S, Suman L, Kralj M, Ametamey SM, Cetina M *et al.* Synthesis, X-ray crystal structure study and antitumoral evaluations of 5,6-disubstituted pyrimidine derivatives. Bioorgan Med Chem. 2010; 18:2704-2712.
16. Chou Y, Lai MC, Hwang T, Ong CW. Synthesis and antitumor activity of bithienyl-pyrimidine derivatives with electrostatic binding side chains. Bioorg Med Chem Lett. 1999; 9:2643-2646.
17. El-Sayed NS, El-Bendary ER, Saadia M, El-Ashry SM, El-Kerdawy MM. Synthesis and antitumor activity of new sulfonamide derivatives of thiadiazolo [3,2-*a*] pyrimidines. Eur. J Med. Chem. 2011; 46:3714-3720.
18. Amr AE, Mohamed AM, Mohamed SF, Hafej N, Hammam A. Anticancer activities of some newly synthesized pyridine, pyrane and pyrimidine derivatives. Bioorgan Med Chem. 2006; 14:5481-5488.
19. Grigoryan LA, Kaldrikyan MA, Ogandzhanyan RG. Synthesis and antitumor activity of new 5-(4-alkoxybenzyl) pyrimidines. Pharm Chem J. 2008; 42:13-15
20. Moreno E, Plano D, Lamberto I, Font M, Encio I, Palop JA *et al.* Sulfur and selenium derivatives of quinazoline and pyrido [2,3-*d*] pyrimidine: Synthesis and study of their potential cytotoxic activity *in vitro*. Eur J Med Chem. 2012; 47:283-298.
21. Kumar RN, Poornachandra Y, Nagender P, Mallareddy G, Kumar NR, Ranjithreddy P *et al.* Synthesis of novel trifluoromethyl substituted furo [2,3-*b*] pyridine and pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine derivatives as potential anticancer agents. Eur. J Med. Chem. 2016; 108:68-78.
22. Kamal A, Dastagiri D, Ramaiah MJ, Reddy JS, Bharathi EV, Reddy MK *et al.* Synthesis and apoptosis inducing ability of new anilino substituted pyrimidine sulfonamides as potential anticancer agents. Eur J Med Chem. 2011; 46:5817-5824.
23. Huang YY, Wang LY, Chang CH, Kuo YH, Kaneko K, Takayama H *et al.* One-pot synthesis and antiproliferative evaluation of pyrazolo [3,4-*d*] pyrimidine derivatives. Tetrahedron. 2012; 68:9658-9664.
24. Abdelgawad MA. Synthesis and antibacterial evaluation of new azo-pyrimidine derivatives. J Appl Pharm Sci. 2019; 9(1):9-16
25. Hafez HN, Alsalamah SA, Rhman A, El-Gazzar A. Synthesis of thiophene and *N*-substituted thieno [3, 2-*d*] pyrimidine derivatives as potent antitumor and antibacterial agents. Acta Pharm. 2017; 67:275-292.
26. Fang Z, Zheng S, Chan KF, Yuan W, Guo Q, Wu W *et al.* Design, synthesis and antibacterial evaluation of 2,4-disubstituted-6-thiophenyl-pyrimidines. Eur J Med Chem. 2019; 161:141-153.
27. Mallikarjunaswamy C. Mallesha L, Bhadregowda DG, Pinto O. Studies on synthesis of pyrimidine derivatives and their antimicrobial activity. Arab J Chem. 2017; 10:484–490.
28. Sebastin V, Sarath PS, Ramachandran A, Sumayya CH. Synthesis and Antibacterial Activity of Pyrimidine Derivatives of 1,3-Dihydropyrimidine Am. J Pharm Tech Res. 2017; 7(5):24-29
29. Abdallah AEM, Galal HE. Design, synthesis, docking, and antimicrobial evaluation of some novel pyrazolo [1,5-*a*] pyrimidines and their corresponding cycloalkane ring-fused derivatives as purine analogs. Drug Des Devel Ther. 2018; 12:1785-1798.
30. Khandazhinskaya AL, Alexandrova LA, Matyugina ES, Solyev PN, Efremenkova OV, Buckheit KW *et al.* Norcarbocyclic Pyrimidine Derivatives as Antibacterial Agents. Molecules. 2018; 23:23-12.