Section: Research Paper

PHARMACEUTICAL APPLICATION AND STRUCTURAL INSIGHT INTO THE FUSED DERIVATIVES OF PYRIMIDINE: A REVIEW

Manoj Kumar[1], Sumit Kumar[2*],Dinesh Kumar[3],Suresh Kumar[4] and Ajay Kumar[5]

1. Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar-125001, Haryana, India

2[*].Corresponding Author

Department of Pharmaceutical Sciences, Central University of Haryana, Jant-Pali, Mahendergarh 123031, India

Email-drsumitkumar@cuh.ac.in

3. Atam Institute of Pharmacy, Om Sterling global University, Hisar-125001, Haryana, India

4. Laureate Institute of Pharmacy, VPO-Kathog, Kangra, Himachal Pradesh-177101

5. Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar-125001, Haryana, India

ABSTRACT:

Pyrimidine skeleton, a diverse skeleton with the various applications in medicinal field had beenstudied and reviewed since previous era. This scaffold had given a great revolution in field of pharmaceutical sciences. Many anti-cancer, anti-viral, anti-microbial, anti-inflammatoryagents had been provided by this scaffold utilization. Its fused scaffold had brought a great revolution in the field as a result had become a scaffold with multi target ability. This review basically comprises of various compound synthesized using this scaffold against the various diseases majorly from year 2016-2019.It also gives an insight into the structural moieties'substituent thathelps them to attain the potency of inhibiting the various targets.

KEYWORDS: Pyrimidine, anti-inflammatory activity, antimicrobial activity

HIGHLIGHTS:

- Consists of the various fused pyrimidine derivative that had been synthesized including majority from year 2016-2023.
- Consists of structural insight on those moieties that make them active molecule,
- Focuses especially on the known anti-microbial, anti-inflammatory, anti-cancer derivatives.

INTRODUCTION

Pyrimidine scaffold had been utilized to synthesized compound with various medicinal agents.[1, 2]Various derivatives of pyrimidine had been synthesized by tethering pyrimidine nucleus with other moieties such as pyrazolopyrimidine, pyrrolopyrimidine,Thienopyrimidine, oxidazole, imidazolidene, pyrano, triazine, triazolo,thiouracil, tosyl sulfonamide, tetrazol, etc. Even combination of three moieties with pyrimidine even isknown. Various synthetic approached had been utilized to synthesize pyrimidine derivatives.[3, 4]Polyvinyl had been used to synthesized the pyrimidine derivative.[5, 6]Recently a group reported a one pot synthesis of pyrrolopyrimidine[7, 8] Even now synthesis of it inusing various solvents had been carried out , one of the best and greener synthesis is that creates less harmful effect on the environment,as a result synthesis using water had been carried out by agroup.[9, 10] Catalytic activity in synthesis generally decreased the time for completion of the reaction, Variouscatalyst had been used to synthesize pyrimidine derivatives. [11,12-14]Tutilised e pyrimidine nucleus had been .[15-19]This review generally consist of the various hybridized scaffold of the pyrimidine that had been used to synthesized the effective medicinal agents from year 2016-2019and comprises of structural insight of those active moieties that what make them more active than other in their series.

(A) Anti inflammatory and anti- bacterial and anti- fungal:

Hafez, et al. synthesized compound (1) using pyranomoiety using one pot condensation technique and inaugurated it active against *E. faecalis,E. coliand P. aeruginosa* and suggested that the reimbursement of ind-3-one moiety with pyrolyl,morpholinyl and piperazinylwould bestow compound with potent anti- bacterial effect.[20]Bahashawan, et al. also reported compound (2) using Triazinopyrazolothieno moiety and observed that compound was active against the inflammation, microbes and proliferation and divulged that on reinstating of the Methoxy group with hydroxyl group, compound with same potency would be acquired.[21]Moty, et al. also synthesized compound using thiazolopyrimidine and observed most of them active against inflammation, microbial , and analgesia[22].Prajapat, et al. synthesized compound(3) using hydroxylamine and endowed it as active anti-inflammatory agentandmanifested the importance of the hydrazone and carbonyl function associated with it in bestowing potent activity.[23]Abbas, et al. synthesized compound(4) using tetrazolewith sulfonamide linkage and found it active as anti-bacterial agent and rendered the importance of the sulfonamide moiety and azide group.[24]Shubhalaxmi, et al. synthesized compounds usingtosyl moiety and inaugurated it active against the microbes and articulated that the replacement of the benzyl proton at 2 and 4 position with other halogens and methyl resulted in compound with not amended activity[25].Abdelgawadet.al,synthesized compound (5) against cox2 enzyme and inflammation and observed in docking studies that compound owing methyl group delineated better interaction with cox enzyme and propounded the role of functional group in lashing with enzyme.[26]Aldelghani, et al. synthesized compound(6) using condensed pyrimidine and endowed compoundpossessing halogen substituted phenyl group as active agent and accentuate the importance of the propagyl moiety in bestowing anti-microbial activity[27].Abdelghani,et al. synthesized(7) compound using thiouracil and observed compound owing para substituted

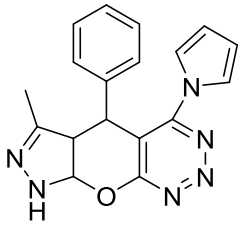
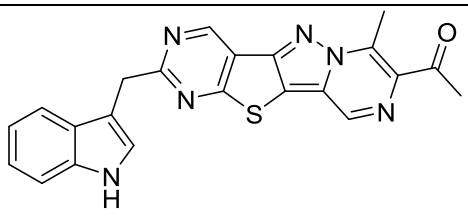
chlorogroup as active agent and displayed the importance of carboxylic group and the amine linkage in anti-microbial activity[28].Razik, et al. synthesized compound(8) using pyrazolopyrimidine moiety and observed it active against cox 2 enzyme at low dose and cytotoxic at high doseandunveiled the importance of chloro substituted phenyl group trussed with piperazine nucleus in rendering potent activity.[29]Chen, et al. synthesized compound(9) using imidazopyrimidine against lipoprotein based phospholipase and endowed reimbursement of oxygen with Sulphur would gave compound with less potent activity and also accentuated the role of the methyl linker and phenyl nucleus in the pie-pie stacking with receptor.[30]Varano, et al. synthesized compound (10)using thiazolo[4-5d]pyrimidine andobservedcompoundpossessing Methoxy at 4position of phenyl ring as active inhibitor of the H2A receptor that get activated in pain and divulged that redeeming position of the Methoxyto 3 position would relinquish compound with same potency, however reinstating Methoxy group with hydroxyl and phenyl group with simple alkyl group would bestow compound with less potent activity[31].Ahmed, et al. synthesized compound(11) using coumarin, isoxazole, and pyrazole against the cox2 enzyme and endowed compound containing pyrimidine moiety as active agent against the enzyme and in docking study they inaugurated that, it show quite similar anchoring like other cox2 inhibitors.[32, 33]Aly, et al. synthesized derivatives of pyrazole and pyrimidine and observed compound(12) possessing pyrimidine as active agent against the microbes and showed the reimbursement of the amide with the methyl group would gave compound with same potency.[34]Bakr, et al. synthesized compound(13) using pyrazole pyrimidine and endowed compound owing pyrrole moiety with the ethyl acetate as substituent unvieled potent activity and displayed replacement of the pyrrolewith the phenyl moiety would accord less potent compound[35].Bekhit, et al.synthesized compound(14) using the thienotriazolopyrimidine and inaugurated compound possessing methyl group as substituent on the triazolo ring as active agent against inflammation and ulcer and delineated that compound possessing phenyl and phenylsubstituted group as less active agents.[36]Bhatt, et al. synthesized compound (15)using triazolo[1,5-a]pyrimidine against wild strain of M. tuberculosis and observed that compound possessing flouro substituted phenyl, and bromo group substituted triazolopyrimidine as potent agent and manifested that the reimbursement of the isopropyl with methyl group would bestow compound with the small docking score and energy.[37]Chandramouli, et al. synthesized compound(16) using pyrano[2,3dpyrimidines and inaugurated it as active agent againstthe selected strain of fungi through ergosterol synthesis and articulatedthe importance of Methoxy substituted phenyl in showing potent activity.[38]Cai, et al. synthesized compound(17) using thiazolo[3,2a] pyrimidine group against the tuberculosis and gram negative bacteria and observed compound possessing chloro substituted phenyl ring showed potent activity against the *M. segmentis* and also inaugurated that substitution of this chloro group with nitro group would gave the compound active against the gram negative bacteriaandpropounded that the sulfonic aciddid not play active role in displaying the anti -bacterial activity.[39]Solanki, et al. synthesized compounds using triazine nucleus and observed that the compound owing the Methoxy group on the phenyl moiety lashed with the amino pyrimidine as activeagentagainst*M. tuberculosis* and as

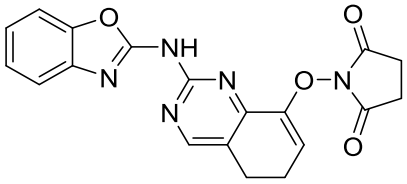
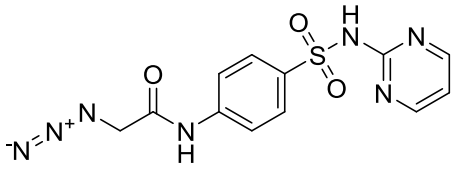
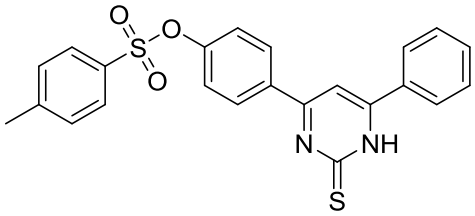
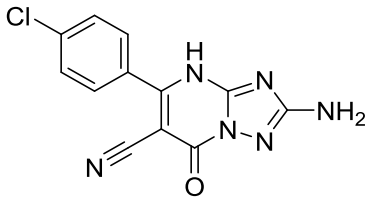
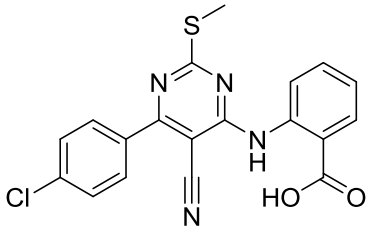
anti- bacterial agent and concluded that the replacement of this Methoxy group with the chloro and nitro relinquish would relinquishanotheractive compound.[40]Chikkula, at al. had also investigated the synthesis of pyrimidine possessing Benzimidazole nucleus and endowed it as ineffectivein acting against bacterial, fungal and inflammatory conditions.[41]Dave, et al. synthesized compound (19) bearing quinolone moiety and inaugurated compound possessing electron withdrawing group to be active against the bacterial strains and observed that, on reimbursement of these group with the Methoxy and amino another compound having activity against S. aureus would be obtained..[42]Dofa,et al. synthesized compound(20) owing anti-microbial action using the triazolo nucleus and observed substitution at Para position with methyl group on phenyl moiety gave active compound and articulated that the replacement of meta and ortho hydrogen with the chloro and methyl group could gave active compound.[43]El-Sayed, et al. synthesized compound(21) using thieno[2,3d]pyrimidine and endowed that compound bearing Methoxygroup on the phenyl group as substituent delineated the potent activity and evinced that the replacement of this with other group would diminish the potency of compound.[44,45]Ganta, et al. synthesized compounds using spiropyrazole and inaugurated it effective against bacterial infection and unveiled the importance of Sulphur group and electron withdrawing group in delineating the activity[46].Hela et al, synthesized compound(22) using thiophene nucleus and observed it as an effective agent against the inflammation and manifested the vital role of morpholine moiety in rendering the activity and also articulated that the reimbursement of this with chromene, pyridnone moiety would gave less active compound.[47]Prabhakar,et al. synthesized compound using thieno [2,3-d] pyrimidine and observed compound (23) owing furan ring asan active compound and manifested that, the replacement of the thiophene ring with furan ring and substitution of Methoxy group with methyl would accord another compound which could act against bacterial and fungal strains selected by them.[48]Imran, et al. synthesized compound(24), which they observed as an active agent against bacterial strain and endowed that compound with chloro at 2 or 4 position would gave active product in disubstituted analogue[49].Kalita, et al. synthesized compound(25) using adamantane and endowed that compound owing phenyl group and chlorosubstituted phenyl group chloro group delineated the potent activity.[50]Kamal, et al. synthesized compound(26) using hydrazone and observed it active against fungal and bacterial strains and accentuated the importance of the nitro group in manifesting the activity.[51]Kaping, et al. synthesized compound (27)using pyrazolopyrimidine by using ultrasonic technique and inaugurated that thecompound possessing pyrimidine moietywith amino group and the Methoxy substituted phenyl group rendered good activity in every selected activity as compared to other compounds.[52]Kethireddy, et al. synthesized compound(28) using5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-2-carbohydrazide and endowed that compound possessing tri flouro methane as potent compound against the bacterial strains and also emphasized that on changing the position of this trifluoro methane and increasing the distance with ethereal linkage the compound with same potency would be obtained.[53]Khalifa , et al. synthesized compound(29) using the Thiazolo[3,2-a]pyrimidine-5H-indeno[1,2-d]pyrimidine fusion and observed that compound containing

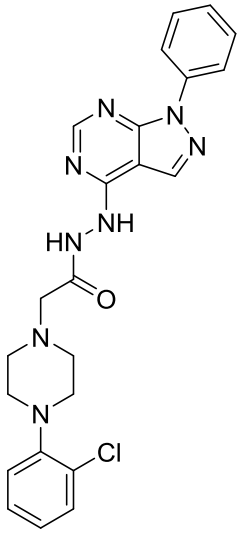
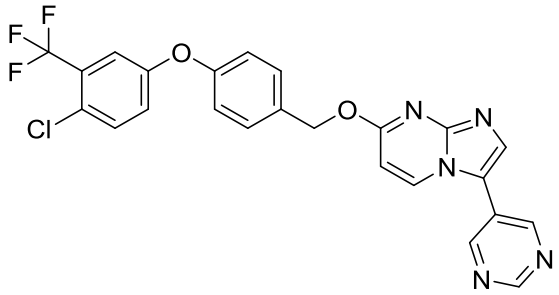
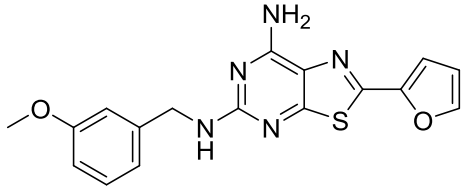
unsubstituted phenyl ring showed the potent activity and found that substituting the phenyl group with various other electron donating and withdrawing group would diminish the compound activity against the selected bacterial and fungal strains.[54]Ziarani, et al. synthesized compound(30) using the tetrahydropyrimidine nucleus against some bacterial (*E.coli, P. aeruginosa,B.subtilus, S. aureus*)and fungal strains (*C.albicans*) endowed that the compound owing phenyl moiety as substituentdelineatedpotent activity and articulated that reimbursement of this moiety with the electron withdrawing group(chloro, fluoro,) and methyl group would gave active compound whereas reinstating it with other electron donating group would give compound with diminished activity.[55]Park, et al. synthesized compound(31) using thepyrimidine2,4 Dione moiety and observed that compound withchloro substituted benzyl group gave the potent activity against$P2X_7$ receptor.[56]Pontiki,et al. synthesized compound (32)using petridine2,4 diamine moiety and endowed compound containing amine substituted with the thiophene ring showed potent activity against inflammation and propounded that reinstatement of this thiophene nucleus with the other morpholine or Ncontainingheterocycles would relinquish less potent compound.[57]Elgemie, et al. synthesized compound (33) using one pot synthesis against the bacterial and fungal strain and articulated that reimbursement of the thiophene nucleus with morpholine gave less potent compound.[58]Ragab, et al. synthesized compound(34) bearing thiadiazole moiety against COX2 enzyme and inaugurated that compound bearing pyridine ring as substituent unveiled potent activity and deduced that replacement of this moiety with other nitrogen heterocycles would afford less potent compound.[59]Tageldin, et al. synthesized compound(35) against COX-1 using the pyrazolo[3,4d]pyrimidine and observed that compound possessing the cyano group on pyrazolo ring relinquished potent activity against chronic inflammation whereas reimbursement of this group with phenyl and its bromosubstituted phenyl group would relinquish another compound with potent activity against the acute inflammation.[60]Tageldin, et al. synthesized compound (36)using pyrazolo[3,4-d] pyrimidine group and endowed that compound bearing thiazolidenone group as an active agent against inflammation and delineated that replacement of the Sulphur with oxygen linkage Methoxy bearing phenyl group gave compound with same potency[61]. Tolba, et al. synthesized compound using thienopyrimidines and endowed compound(36) as an active against inflammation andunveiled the role of nitrile and amide group and phenyl moieties tetheredwiththieno pyrimidine nucleus in displaying activity.[62]Undare, et al. synthesized compound(37) using indenopyrimidine and inaugurated that compound bearing amino on one phenyl moiety and nitro on other phenyl moiety showed potent activity against inflammation, ulcer and COX2 enzyme and propounded that reimbursement of the amino group with phenyl and nitro group and with other electron withdrawing , donating group would decrease the activity of the compound.[63]undare, et al. synthesized compound(38) using one pot synthesis through various aldehyde and endowed compound possessing nitro group at para position of benzaldehyde moiety renderedpotent activity and recommended that replacement of this group with bromo and amine group would bestow compound with less potent activity against COX2 enzyme.[64]Viveka,et al. synthesized compounds using the pyrazole moiety anchored to

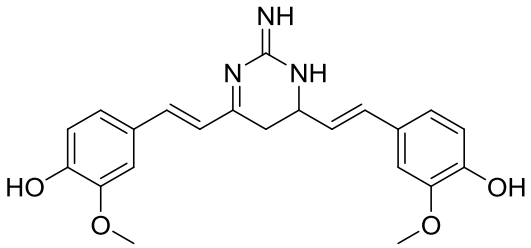
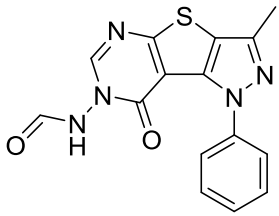
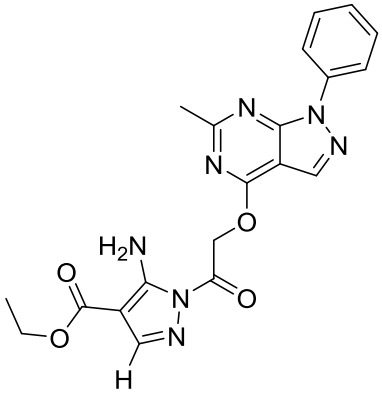
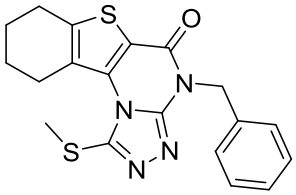
thiazolopyrimidine and observed that compound (39) bearing two chloro group on the phenyl moiety anchored to pyrazole and methyl and flouro group on the other phenyl group trussed with thiazolopyrimidine gave the potent activity against the inflammation and microbial infection and evinced that the reimbursement of chloro group with flouro gave compound with same potency however when it is replaced with electron donating group, a compound with less potent activity would be obtained .[65, 66]Zhang, et al. synthesized compound(40) using pyrazole-pyrimidine and observed that the compound possessing phenol moiety delineated potent activity against fungi andpropounded that substitution of phenol moiety with other halogen group would accord less active compound.[67]Elkamhawy, et al. synthesized compound(41) using pyrimidinamide and endowed compound possessing CF_3 group and flouro group displayed the potent activity against inflammation through reduction of generation of interleukins and nitric oxide and articulated that reinstating of this group withother electron donating and withdrawing group would decreases the activity.[68]Abdellal, et al. synthesized compound (42)using pyrazolopyrimidine moiety and inaugurated that compound possessing unsubstituted phenyl ring hitched with triazolo ring bestowed potent compound and articulated that the substitution of the phenyl group with chloro group would relinquish another active compound against COX 1 and COX2 enzyme.[69]Shoukrof, et al. synthesized(43) compound using thienopyrimidines and inaugurated that compound possessing the amino group on the pyrazole ring relinquished potent activity against cox2 enzyme and deduced that reimbursement of this amine group with the hydroxyl group would retain the activity whereas replacement of this amino group would be with other group then compound would not retain the activity and in docking study it renderedthe significant role thienopyrimidines moiety in binding with receptor[70].Tageldin, et al. synthesized compound (44)using pyrazolopyrimidine and endowed that compound owing nitrile group manifested potent activity whereas ester possessing group were inactive and in docking study against COX2 they found that compound attached with receptor through pie-pie stacking and hydrogen bond interaction resulting from various groups associated with it.[71]Somakala, et al. synthesized compound(45) possessing pyrazolopyrimidine against theinflammation, ulcer and MAPkinase and observed that replacement of chloro group of phenyl moiety with other electron withdrawing and electron donating group would decreased the activity of compound because of high and low electronegativity and electro positivityeffect of those group and observed this compound displayed excellent docking score.[72]Bakr synthesized compound(46) using thiazolo[4,5-d]pyrimidine and inauguratedcompound possessing ketone group and nitro substituted phenyl unveiled potent activity and deduced that replacement of this group with the flouro group would bestow compound with inhibiting activity against the inflammation, cox2 and ulcer but less than the nitro bearing compound.[73]Wang, et al. synthesized compound(47)against Janus kinase responsible in mediating inflammation through using furan nucleus and endowed that compound owing acetonitrile and the phenyl, morpholine moieties as potent compound through the docking study and rendered that reimbursement of these group with various substituted phenyl group would wane the activity.[74]Shi, et al. synthesized compound(48) using Pyrazolo[4,3-d]pyrimidine and observed that compound bearing stryl group

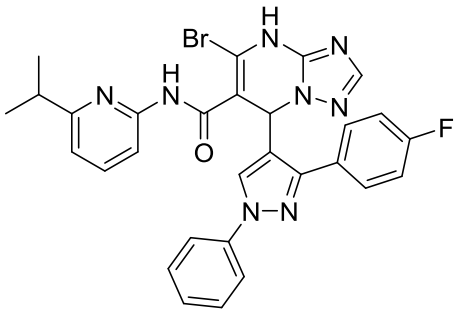
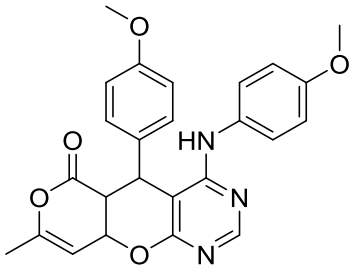
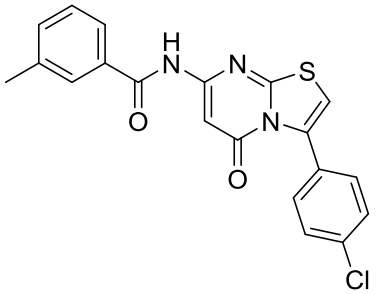
as linker and propyl amine moiety as the substituent on pyrimidine manifested potent activity in reducing nitric oxide generation responsible for inflammation.[75]Abdelgawad,et al. synthesized azo nucleus possessing compound (49)and found it effective against various strains of bacteria and manifested that reimbursement of chloro with Methoxy group on phenyl group would relinquish compound with same potency.[76]Lavanya, et al. synthesized compound(50) with pridopyrimidine moiety and inaugurated compound with Methoxy and hydroxyl group as substituent unveiled effective result as antioxidant as well as against inflammation and delineated that changing hydroxyl group with the amine andMethoxy group would proffer compound with diminished activity.[77]Shiva Raju, et al. synthesized compound using triazolo nucleus and manifested triazolo nucleus as important part in binding to *M. tuberculosis*(51) active domains and observed that substitution of N oftriazolo with heteroalkyl group would relinquish potent activity in which if hetero moiety would be substituted with flouro containing phenyl group then it would bestow most potent activity due to electronegativity of this group and in docking study they studied, compound interacted to bacterial protein through hydrogen bond interaction and hydrophobic interaction.[78]Tolba, et al. synthesized compound (52)using the thienopyrimidines and observed that compound possessing the para chloro substituted phenyl group manifested the effective activity and showed replacement of hydrogen of alkene group with methyl even in the Para chloro substituted compoundwould display effective activity against bacterial strains and inflammation.[79]

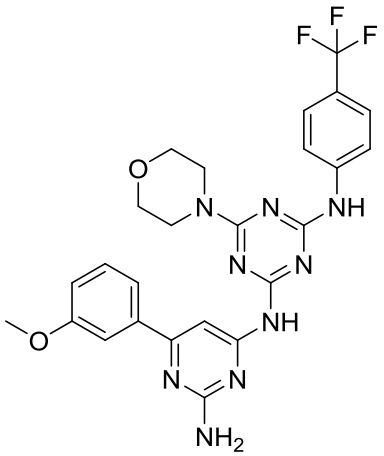
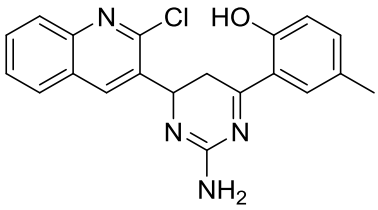
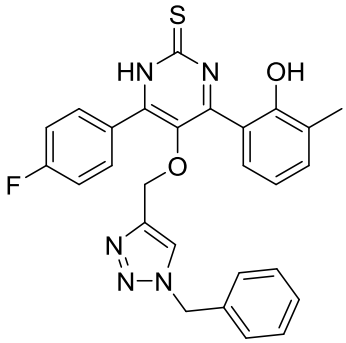
S.no.	Compound
1	 6-methyl-5-phenyl-5,5a,8,8a-tetrahydropyrazolo[4',3':5,6]pyrano[2,3-d][1,2,3]triazine
2	 1-(2-((1H-indol-3-yl)methyl)-7-methylpyrazino[1",2":1',5']pyrazolo[3',4':4,5]thieno[2,3-d]pyrimidin-8-yl)ethan-1-one

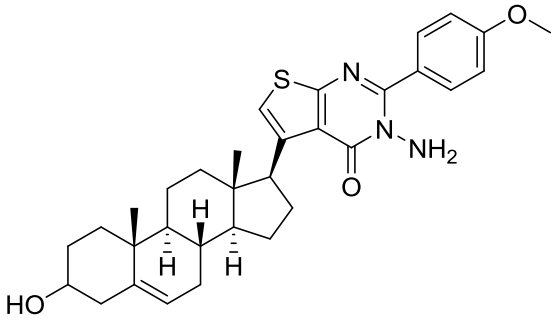
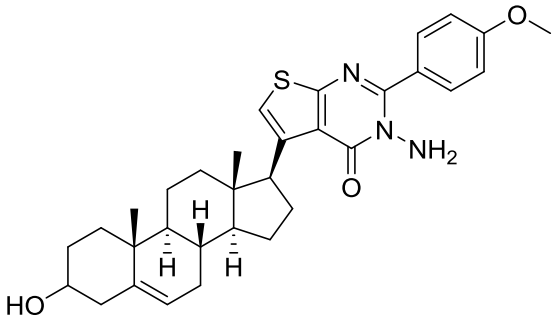
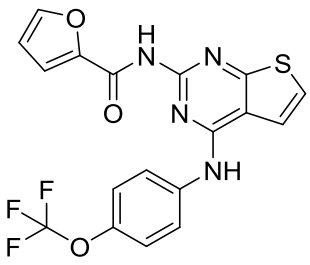
3	 1-((2-(benzo[d]oxazol-2-ylamino)-5,6-dihydroquinazolin-8-yl)oxy)pyrrolidine-2,5-dione
4	 2-azido-N-(4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)acetamide
5	 4-(6-phenyl-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl 4-methylbenzenesulfonate
6	 2-amino-5-(4-chlorophenyl)-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile
7	 2-((6-(4-chlorophenyl)-5-cyano-2-(methylthio)pyrimidin-4-yl)amino)benzoic acid

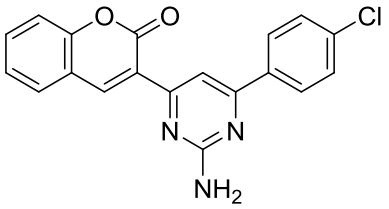
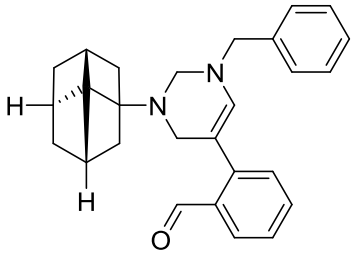
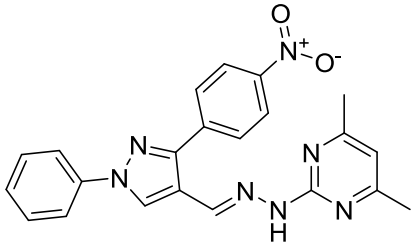
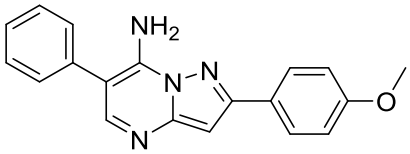
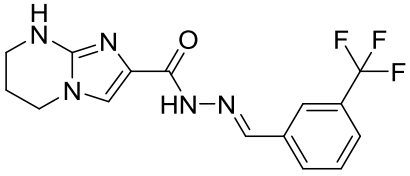
8	 2-(4-(2-chlorophenyl)piperazin-1-yl)-N'-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)acetohydrazide
9	 7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine
10	 2-(furan-2-yl)-N5-(3-methoxybenzyl)thiazolo[5,4-d]pyrimidine-5,7-diamine

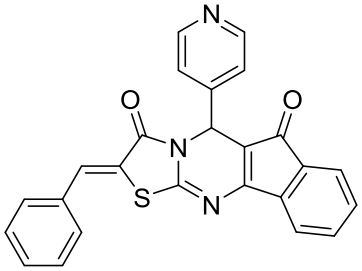
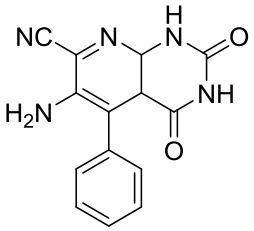
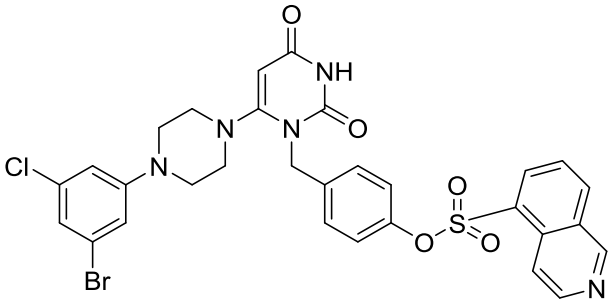
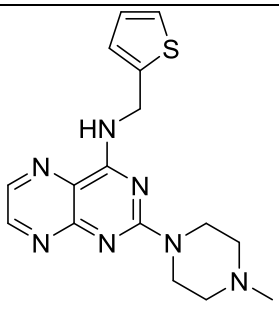
11	 4,4'-((1E,1'E)-(2-imino-1,2,5,6-tetrahydropyrimidine-4,6-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)
12	 N-(3-methyl-8-oxo-1-phenyl-1H-pyrazolo[3',4':4,5]thieno[2,3-d]pyrimidin-7(8H)-yl)formamide
13	 Ethyl 5-amino-1-(2-((6-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)oxy)acetyl)-1H-pyrazole-4-carboxylate
14	 4-benzyl-1-(methylthio)-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-e][1,2,4]triazolo[4,3-a]pyrimidin-5(4H)-one

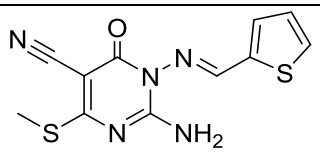
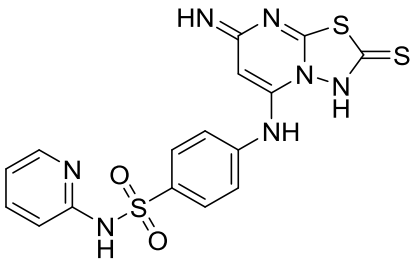
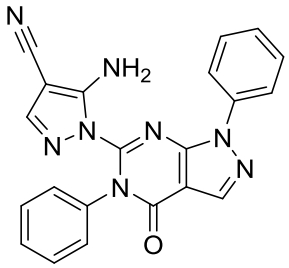
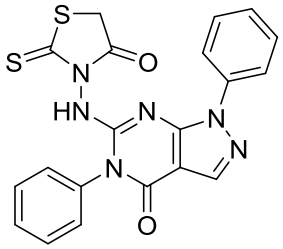
15	 5-bromo-7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-N-(6-isopropylpyridin-2-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide
16.	 5-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-8-methyl-5a,9a-dihydro-5H,6H-pyrano[3',4':5,6]pyrano[2,3-d]pyrimidin-6-one
17.	 N-(3-(4-chlorophenyl)-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)-3-methylbenzamide

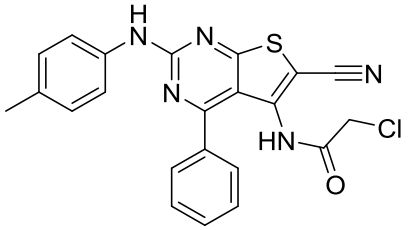
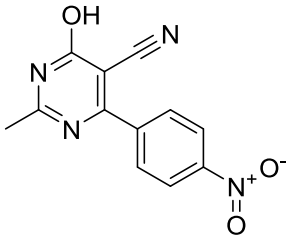
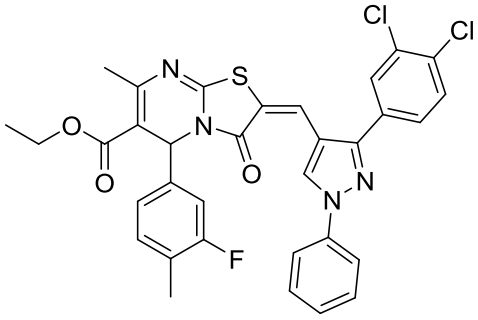
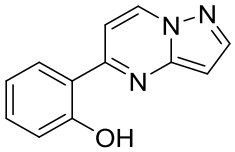
18.	 N2-(2-amino-6-(3-methoxyphenyl)pyrimidin-4-yl)-6-morpholino-N4-(4-(trifluoromethyl)phenyl)-1,3,5-triazine-2,4-diamine
19.	 2-(2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl)-4-methylphenol (19)
20.	 5-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-6-(4-fluorophenyl)-4-(2-hydroxy-3-methylphenyl)pyrimidine-2(1H)-thione

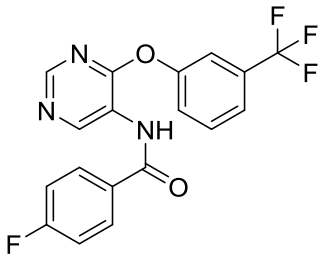
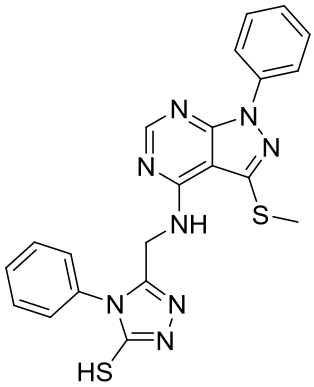
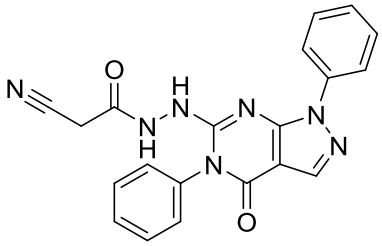
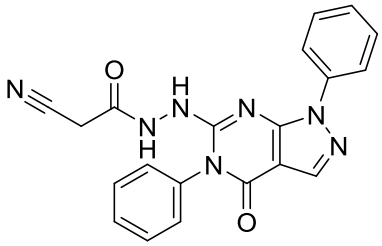
21.	 3-amino-5-((8S,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(4-methoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one
22.	 3-amino-5-((8S,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(4-methoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one
23.	 N-(4-((4-(trifluoromethoxy)phenyl)amino)thieno[2,3-d]pyrimidin-2-yl)furan-2-carboxamide
24.	

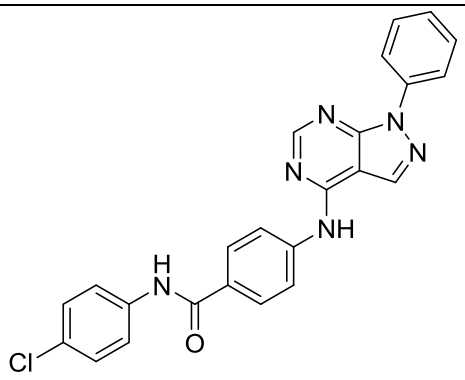
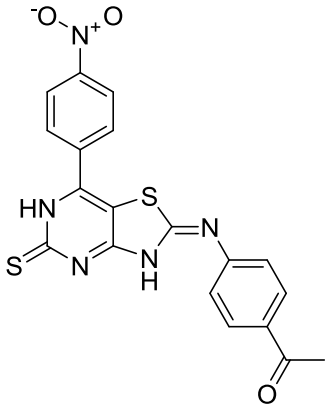
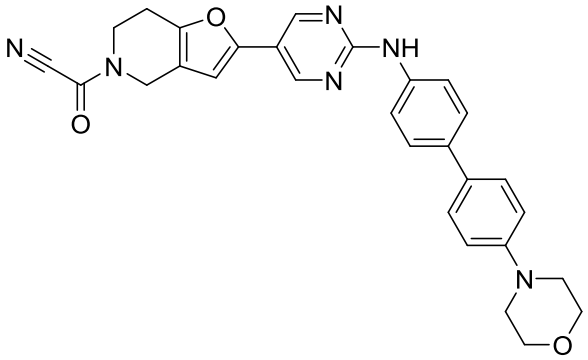
	 3-(2-amino-6-(4-chlorophenyl)pyrimidin-4-yl)-2H-chromen-2-one
25.	 2-(1-benzyl-3-((3R,5s,7S,8r)-tetracyclo[5.1.1.03,8.05,8]nonan-1-yl)-1,2,3,4-tetrahydropyrimidin-5-yl)benzaldehyde
26.	 (E)-4,6-dimethyl-2-(2-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazinyl)pyrimidine
27.	 2-(4-methoxyphenyl)-6-phenylpyrazolo[1,5-a]pyrimidin-7-amine
28.	 (E)-N'-(3-(trifluoromethyl)benzylidene)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-2-carbohydrazide

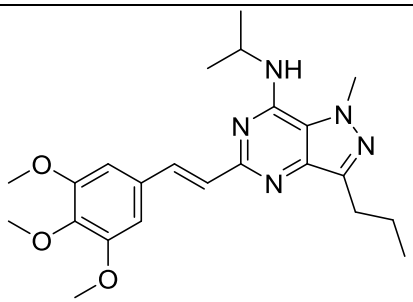
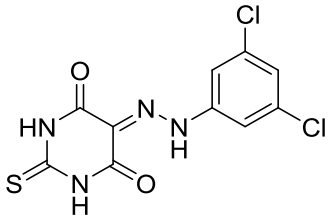
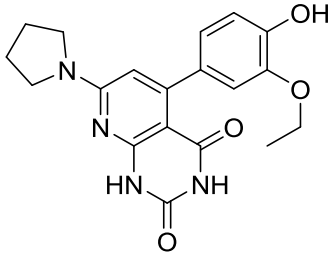
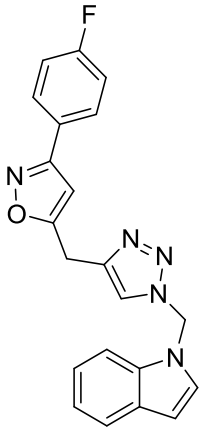
29.	 (Z)-2-benzylidene-5-(pyridin-4-yl)indeno[1,2-d]thiazolo[3,2-a]pyrimidine-3,6(2H,5H)-dione
30.	 6-amino-2,4-dioxo-5-phenyl-1,2,3,4,4a,8a-hexahydropyrido[2,3-d]pyrimidine-7-carbonitrile
31.	 4-((6-(4-(3-bromo-5-chlorophenyl)piperazin-1-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)phenyl isoquinoline-5-sulfonate
32.	 2-(4-methylpiperazin-1-yl)-N-(thiophen-2-ylmethyl)pteridin-4-amine

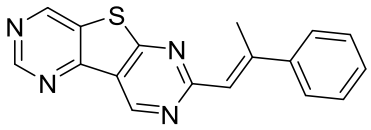
33.	 (E)-2-amino-4-(methylthio)-6-oxo-1-((thiophen-2-ylmethylene)amino)-1,6-dihydropyrimidine-5-carbonitrile
34	 4-((7-imino-2-thioxo-2,3-dihydro-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-yl)amino)-N-(pyridin-2-yl)benzenesulfonamide
35.	 5-amino-1-(4-oxo-1,5-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-1H-pyrazole-4-carbonitrile
36.	 3-((4-oxo-1,5-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)amino)-2-thioxothiazolidin-4-one

37.	 2-chloro-N-(6-cyano-4-phenyl-2-(p-tolylamino)thieno[2,3-d]pyrimidin-5-yl)acetamide
38.	 4-hydroxy-2-methyl-6-(4-nitrophenyl)pyrimidine-5-carbonitrile
39.	 Ethyl (E)-2-((3-(3,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-5-(3-fluoro-4-methylphenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate
40.	 2-(pyrazolo[1,5-a]pyrimidin-5-yl)phenol

41.	 4-fluoro-N-(4-(3-(trifluoromethyl)phenoxy)pyrimidin-5-yl)benzamide
42.	 5-(((3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol
43.	 2-cyano-N'-(4-oxo-1,5-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetohydrazide
44.	 2-cyano-N'-(4-oxo-1,5-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetohydrazide

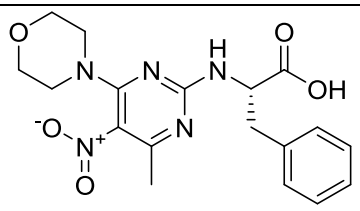
45.	 N-(4-chlorophenyl)-4-((1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)benzamide
46.	 (E)-1-(4-((7-(4-nitrophenyl)-5-thioxo-5,6-dihydrothiazolo[4,5-d]pyrimidin-2(3H)-ylidene)amino)phenyl)ethan-1-one
47.	 2-(2-((4'-morpholino-[1,1'-biphenyl]-4-yl)amino)pyrimidin-5-yl)-6,7-dihydrofuro[3,2-c]pyridine-5(4H)-carbonyl cyanide

48.	 (E)-N-isopropyl-1-methyl-3-propyl-5-(3,4,5-trimethoxystyryl)-1H-pyrazolo[4,3-d]pyrimidin-7-amine
49.	 5-(2-(3,5-dichlorophenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione
50.	 5-(3-ethoxy-4-hydroxyphenyl)-7-(pyrrolidin-1-yl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione
51.	 5-((1-((1H-indol-1-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(4-

	fluorophenyl)isoxazole
52	 (E)-7-(2-phenylprop-1-en-1-yl)thieno[2,3-d:4,5-d']dipyrimidine

‘

Anti viral: Danesh, et al. checked activity of compound (53) against viral infection through plaque reduction assay and found compound phenyl as substituent to be potent in reducing the plaque.[80]

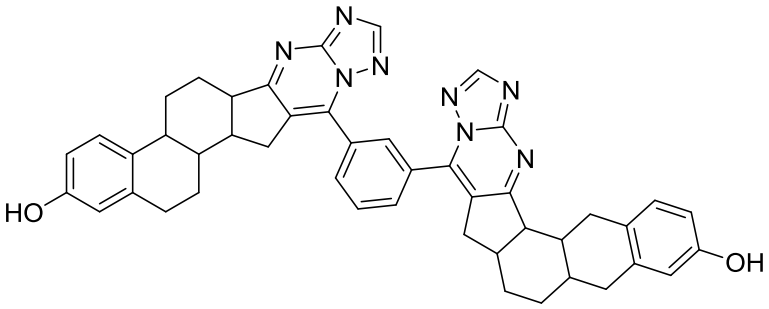
S.no.	Compound
53.	

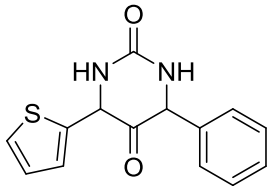
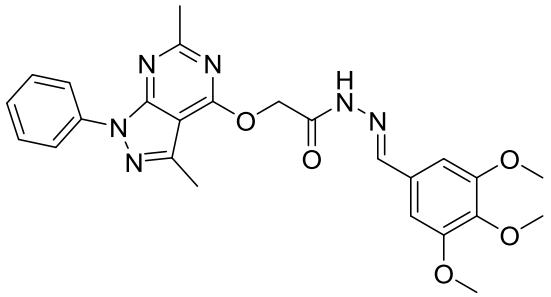
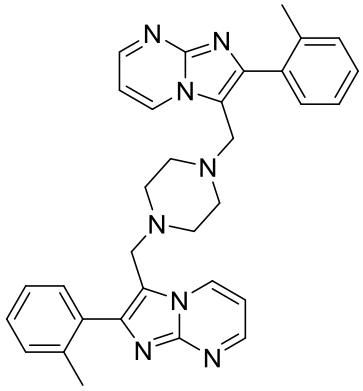
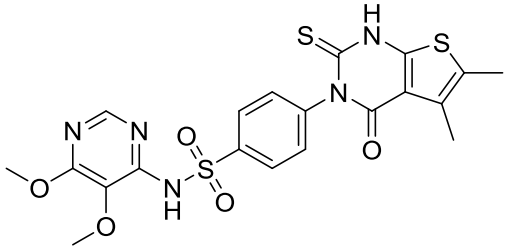
Anti-cancer:

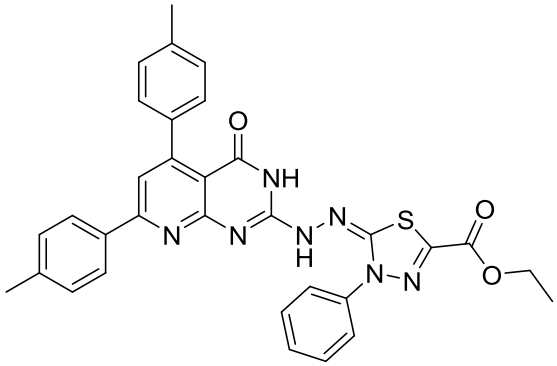
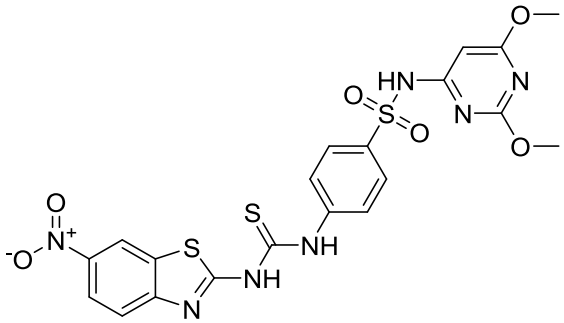
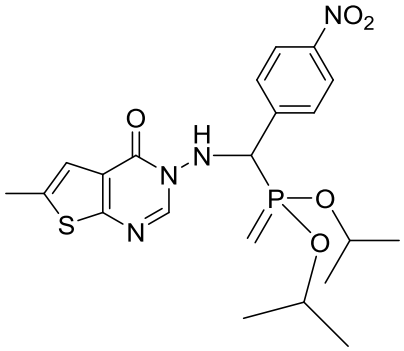
Gonzalez, et.al. reported the synthesis of pyrimidine compound (54) fused with the steroid nucleus through cyclo addition and claisenSchmidt process using unsaturated ketone and established it active against proliferation and deduced the importance of 3 OH group in displaying the activity.[81]Yousif, et al. synthesized compound (55)using thiophene group and observed it active against HCT16 cell line and inaugurated that the substitution of the ring with the phenyl group bestowed potent activity and substituting phenyl with dimethoxy group diminished the activity.[82]Abdelgawad, et al. synthesized compound against EGFR-TK and found compound (56) possessing the tri Methoxy substituted phenyl ring as active compound and also concluded that the redeeming of any of Methoxy with the nitro , hydrogen diminished the activity.[83]Aleuri, et al. synthesized compound(57) using imidazopyrimidine and inaugurated that the compound with Mannich base of piperazine displayed the potent activity as anti-proliferative against various cell lines and reinstating it with the5 member heterocycle and the mono substituted piperazinerelinquished compound with same activity and also delineated the role of methyl substituted phenyl moiety in the activity[84]. Ghorab et al. synthesized compound (58)against breast cancer cell line using thieno[2,3d]pyrimidine moiety and endowed that

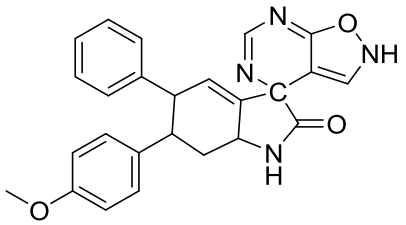
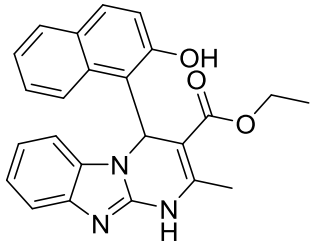
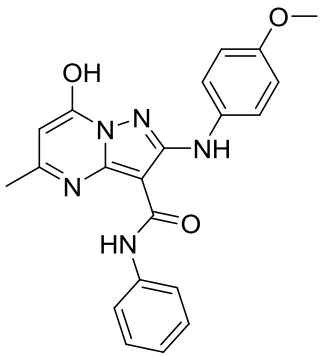
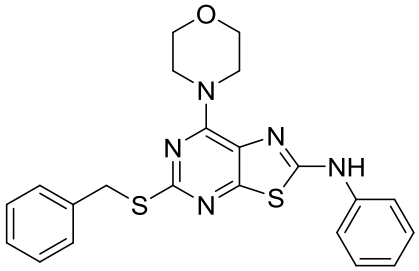
compound bearing Methoxy as substituent as active agent and concluded that reinstating the Methoxy group position and substitution of Methoxy with methyl group proffered did not amended the activity[85]. Gomha et al. synthesized compound(59) using pyridopyrimidinone and thiazolo against breast cancer and inaugurated that compound possessing ethyl acetate group at 5 position of the ring rendered potent activity.[86]Ghorab et al. synthesized compound (60)using thiouriedobenzene sulfonamide and inaugurated it active against the cancer cell and in docking they unveiled that compound interacted with various amino acids through pie-pie interaction and hydrogen bond interaction and also deduced that the replacement of that benzothiazole group with pyrimidine conferd compound active against the bacterial infection.[87]Guo et al. synthesized compound (61) using amino phosphate and thieno pyrimidine and observed that compound owing nitro group as substituentdelineated most potent activity against the hepato, gastric and lung carcinoma cell.[88]Hamama et al. synthesized compound (62) using isoxazole and observed that compound possessing Spiro-pyrimidine Isatin moiety rendered the potent activityagainst the tumor cell lines and manifested that reimbursement of this moiety with isoxazole accorded subordinate potent compound.[89, 90]Kaur, et al. synthesized compound(63) against the lung, prostate, colon cancer cell line using dihydropyrimidine and endowed that compound bearing napthyl moiety with dihydropyrimidinesunveiled the potent intercalation and evinced the role of hydroxyl group in delineating the activity.[91] Hassan et al. synthesized compound (64) using pyrazolo[1,5-a]pyrimidines and observed compound possessing the phenyl moiety manifested potent activity against liver HepG2, lung A549, breast MCF-7cell line and deduced that the reimbursement of this moiety with chloro substituted phenylmoiety elinquished less potent compound.[92]Li et al. synthesizedcompound(65) using repurposing strategy against the MGC-803 cells using thiazolo[5,4-a]pyrimidine moiety and endowed that the compound possesing piperazine moiety didn't manifest good activity and displayed reinstating phenyl group with napthyl bestowed less potent compound.[93]Liu, et al. synthesized (66)compound against the angiogenesis using the oxazole moiety and observed it effective in controlling angiogenesis.[94]Manaliet al. synthesized compound (67)using tetrahydropyrimidine and observed that the compound with unsubstituted aromatic ring rendered potent active as anti-proliferative agent and displayed that substitution of the respective positionsof phenyl ring with chloro group a compound possessing antimicrobial nature would obtained[95]. Naresh et al. synthesized compound(68)using tetrazole moiety andinaugurated compound owing ethyl moiety on pyrimidine ring and aliphatic chain on the triazolo ring delineated potent activity against PANC-1 and A549 and manifested that the reimbursement of the ethyl with phenyl and other substituentaccorded less potent compound.[96]Prajapati et al. synthesized compound (69)using indole moiety andobserved that compound possessing phenyl moiety substituted with chloro group relinquished most potent activity against U87-MG,PA-1,LnCaP,MCF-7 cell lines and deduced that replacement of this with other group like nitrogen heterocycles and phenyl substituted with other electron withdrawing group bestowed less active compound[97].Rahmouni et al. synthesized (70)two compound using the pyrazolopyrimidine and observed that compound (a) possessing longer alkyl and hydroxyl group at para position showed potent activity against

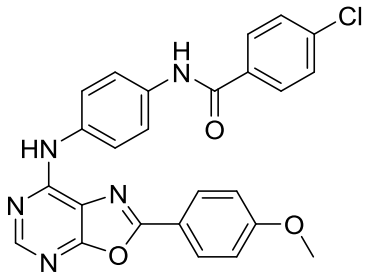
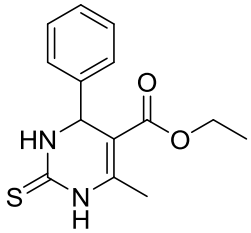
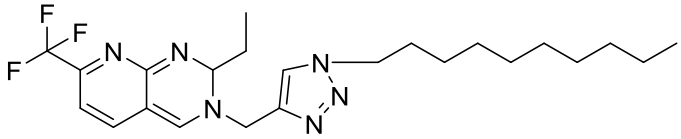
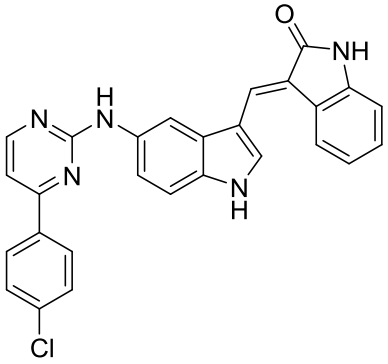
the lipoxygenase and compound(b) possessing the chloro substituted aromatic ring attached to the tetrazole ring accorded potent activity against the MCF-7 cell lines ,In this derivative they accentuated the role of the tetrazole ring and its substituents in delineating the activity.[98] Tiwari et al. synthesized compound (71)using thiadiazole moiety and endowed compound possessing the hydroxyl group at 3 and Methoxy group at 4 position rendered the potent activity againstK562,MCF-7,HeLaandPC-3 and when they substituted hydroxyl group with Methoxy group and halogens like chloro and flouro they found that the compound unveiled less potent activity and in docking study they evinced the role of hydrophobic interaction and hydrogen bond interaction in binding of compound with Thymidylate Synthase enzyme[99]. Zhang et al. synthesized compound(72) using thieno moiety and inaugurated that compound possessing chloro substitution on the pyrimidine moiety unveiled potent activity against inflammation through various pathways and observed that on substitution of this group with other group like pyrimidine and various substituted phenyl derivatives , compounds with diminished activity would be obtained.[100] Ahmed et al. synthesized compound(73) using anthracene and pyrazole moiety against hepatocellular cancer cell lines and observed that compound with the pyrazoline substituted with flouro group rendered potent activity and displayed that reinstating this moiety with Methoxy, indole proffered less potent compound.[101]wang et al.synthesized compound(74) using pyrazolo[3,4] pyrimidine and endowed compound possessing morpholine ring substituted on the pyrazolo ring delineated potent activity against lung cancer through inhibition of various factor involved in it.[102]Salem, et al. synthesized two derivatives(75, 76)possessing antioxidant and anticancer activity and confirmed their potency through pharmacophoricstudy and evinced the importance of 4th position of pyrimidine moiety in sdisplaying potent activity[103].

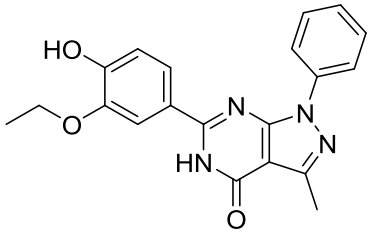
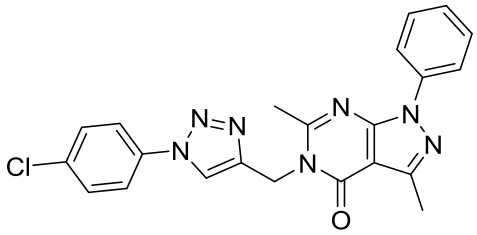
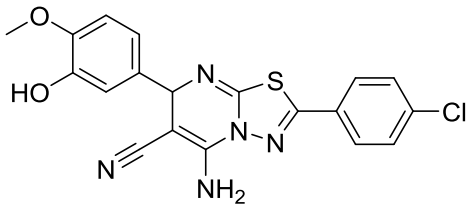
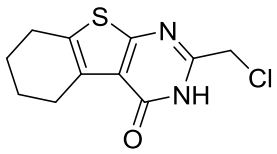
S. NO.	Compound
54.	 14-(3-(3-hydroxy-5,5a,6,7a,8,14b,14c,15-octahydro-7H-naphtho[2',3':6,7]indeno[1,2-d][1,2,4]triazolo[1,5-a]pyrimidin-9-yl)phenyl)-1,6b,7,8,8a,15,15a,15b-octahydro-2H-naphtho[2',1':4,5]indeno[1,2-d][1,2,4]triazolo[1,5-a]pyrimidin-4-ol

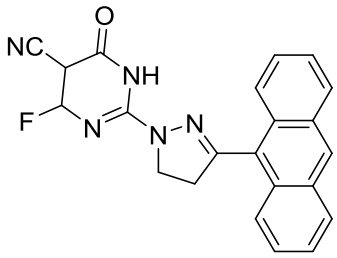
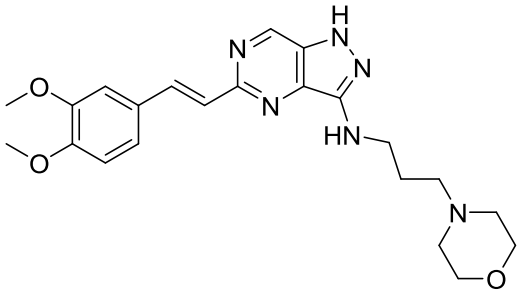
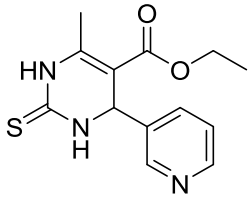
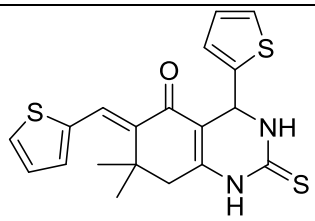
55.	 4-phenyl-6-(thiophen-2-yl)tetrahydropyrimidine-2,5-dione
56.	 (E)-2-((3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)oxy)-N'-(3,4,5-trimethoxybenzylidene)acetohydrazide
57.	 1,4-bis((2-(o-tolyl)imidazo[1,2-a]pyrimidin-3-yl)methyl)piperazine
58.	 N-(5,6-dimethoxypyrimidin-4-yl)-4-(5,6-dimethyl-4-oxo-2-thioxo-1,4-dihydrothieno[2,3-d]pyrimidin-3(2H)-yl)benzenesulfonamide

59.	 ethyl (E)-5-(2-(4-oxo-5,7-di-p-tolyl-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate
60.	 N-(2,6-dimethoxypyrimidin-4-yl)-4-(3-(6-nitrobenzo[d]thiazol-2-yl)thioureido)benzenesulfonamide
61.	 3-(((diisopropoxy(methylene)-l5-phosphanyl)(4-nitrophenyl)methyl)amino)-6-methylthieno[2,3-d]pyrimidin-4(3H)-one

62.	 6-(4-methoxyphenyl)-5-phenyl-5,6,7,7a-tetrahydro-2'H-spiro[indole-3,4'-isoxazolo[5,4-d]pyrimidin]-2(1H)-one
63.	 ethyl 4-(2-hydroxynaphthalen-1-yl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate
64.	 7-hydroxy-2-((4-methoxyphenyl)amino)-5-methyl-N-phenylpyrazolo[1,5-a]pyrimidine-3-carboxamide
65.	 5-(benzylthio)-7-morpholino-N-phenylthiazolo[5,4-d]pyrimidin-2-amine

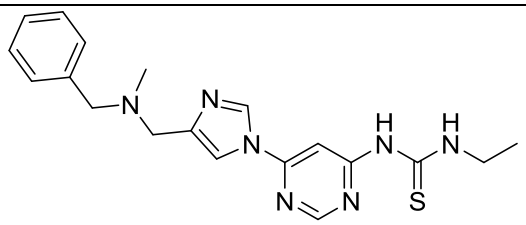
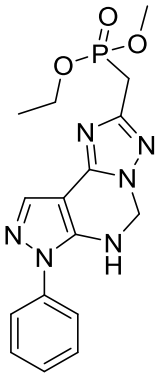
66.	 4-chloro-N-(4-((2-(4-methoxyphenyl)oxazolo[5,4-d]pyrimidin-7-yl)amino)phenyl)benzamide
67	 ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
68	 3-((1-decyl-1H-1,2,3-triazol-4-yl)methyl)-2-ethyl-7-(trifluoromethyl)-2,3-dihydropyrido[2,3-d]pyrimidine
69.	 (E)-3-((5-((4-(4-chlorophenyl)pyrimidin-2-yl)amino)-1H-indol-3-yl)methylene)indolin-2-one

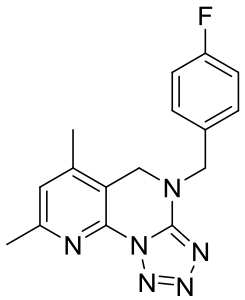
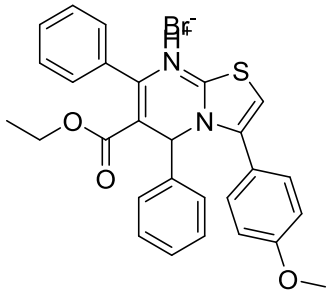
70.	 6-(3-ethoxy-4-hydroxyphenyl)-3-methyl-1-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (a)  5-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3,6-dimethyl-1-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (b)
71.	 5-amino-2-(4-chlorophenyl)-7-(3-hydroxy-4-methoxyphenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile
72.	 2-(chloromethyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one

73.	 2-(3-(anthracen-9-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-fluoro-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carbonitrile
74.	 (E)-5-(3,4-dimethoxystyryl)-N-(3-morpholinopropyl)-1H-pyrazolo[4,3-d]pyrimidin-3-amine
75.	 ethyl 6-methyl-4-(pyridin-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
76.	 (E)-7,7-dimethyl-4-(thiophen-2-yl)-6-(thiophen-2-ylmethylene)-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one

Against alzhiemer:

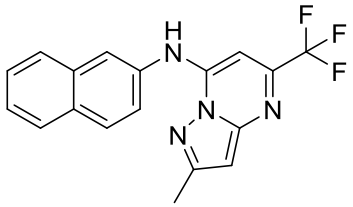
Li, et Al. synthesized compound(77) using thiourea and endowed it as capable to inhibit Ache and as metalc helator with antioxidant activity and deduced that presence of di-propyl aminomethyl moiety as important part of the compound for crossing the blood brain barrier.[97]Romdhane, et al. synthesized compound(78) using tetrazole and pyrazole moiety and inaugurated that compound owing hydrogen as substituent on pyrazole ring at 3 position and methyl at one of the oxygen of the phosphonate group delineated potent activity and concluded that the reimbursement of this methyl group with ethyl group diminishes the activity.[104]Zhang, et al. synthesized compound (79) using thepyrido[2,3-d]pyrimidine and observed compound possessing Para flouro group on phenyl ring as active compound in case of both rings i.e. tetrazole and triazole against depression.[105]Maghoub, et al. synthesized compound (80) using thiazolo[2,3-d]pyrimidine andendowed that compound bearing methoxy group unveiled potent activity against acetylcholinesterase and in docking study confirmed the binding of compounds to the peripheral site of the enzyme.[106]

S.NO.	Compound
77.	 1-(6-(4-((benzyl(methyl)amino)methyl)-1H-imidazol-1-yl)pyrimidin-4-yl)-3-ethylthiourea
78.	 ethyl methyl ((7-phenyl-6,7-dihydro-5H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)methyl)phosphonate

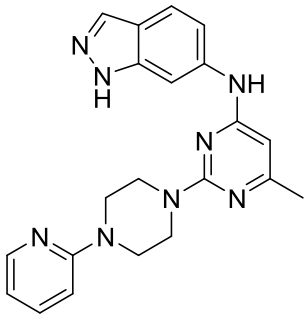
79.	 4-(4-fluorobenzyl)-6,8-dimethyl-4,5-dihydropyrido[3,2-e]tetrazolo[1,5-a]pyrimidine
80.	 6-(ethoxycarbonyl)-3-(4-methoxyphenyl)-5,7-diphenyl-5H-thiazolo[3,2-a]pyrimidin-8-ium bromide

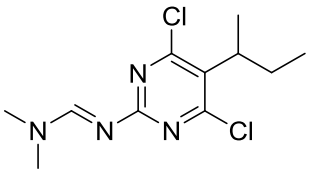
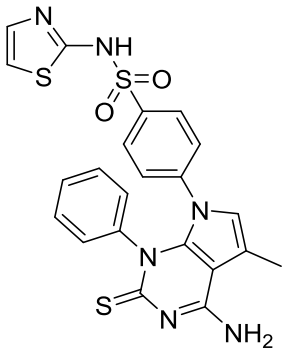
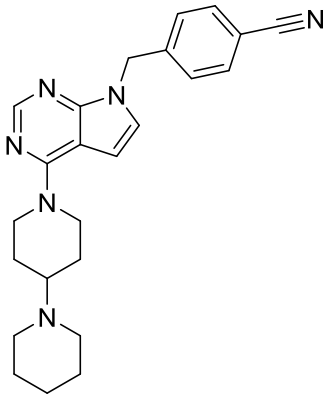
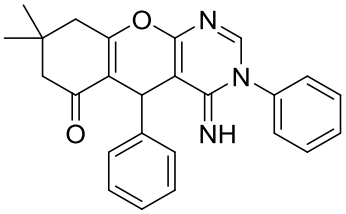
Anti malarial:

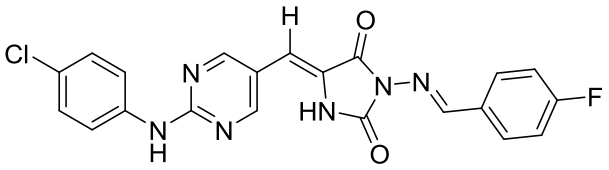
Azeredo, et al. synthesized compound (81) using triazolopyrimidine against Dihydro-Orotate enzyme and they inaugurated that compound bearing triflouromethyl group delineated the potent activity.[107]Bhalla, et al. had also investigated the synthesis of pyrazolylmethylene hybrids and evinced that its derivative could give potential new agent in future.[108, 109]

S.NO.	Compound
81.	 2-methyl-N-(naphthalen-2-yl)-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-7-amine

Others : Ihn,et al. reported the synthesis of the pyrimidine derivative active against theosteoclastogenesis induced by RANKL through JNK and NF-κB pathway inhibition.[110, 111]Jansa, et al. synthesized compound (82)able to inhibit nitric oxide production and inaugurated that the presence of chloro at 4,6 position and amino group as vital part for the activity.[112, 113]Sharma, et al. synthesizedcompound(83) using triazolopyrimidine and observed that the compound possessing Methoxy group as substituent on quinolone ring delineated potent activity in opening DNA and displayed that reimbursement of this group with methyl group would relinquish compound with potent activity and in docking study endowed the role of triazolo and pyrimidine ring in strong binding to the DNA through hydrogen bond interactions.[114]Katuoha, et al. synthesized compound(84) using pyrrole-pyrimidine moiety and evinced the role of sulfonamide group as essential part for blocking the kinase receptor which is responsible for hypertension and in docking study they manifested the role of hydrogen bond and Vander wall interaction that results due tothiazolo moiety, thimino group of pyrimidine and amino group in binding to the receptor.[115]Frank, et al. synthesized compound(85) using pyrrolo pyrimidine and observed that compound bearing bipiperidine moiety trussed with the acetonitrile substituted phenyl group delineated the potent activity and evinced substitution of phenyl moiety with di chloro group gave compound with same potency and in docking study they accentuated the role of the bipiperidine moiety in the activity.[116]Debbabi, et al. synthesized pyranopyrimidine and pyranotriazolepyrimidine derivative and endowed pyranopyrimidine(86) derivative as potent compound in inhibiting tyrosine and against coagulation and suggested potent compound could develop through this moiety modification.[117]Alneyadi, et al. synthesized compound (87) using oxidazole and imidazolidene and observed that thecompound owing imidazolidene ring with substitution of flouro possessing phenyl group renderd potent activity against PPARy receptor with vital feature of not increasing basal insulin secretion and articulated =-that it could act as novel compound for development of various other derivatives[118].

S.No.	Compound
82.	 N-(6-methyl-2-(4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-4-yl)-1H-indazol-6-amine

83.	 (E)-N'-(5-(sec-butyl)-4,6-dichloropyrimidin-2-yl)-N,N-dimethylformimidamide
84.	 4-(4-amino-5-methyl-1-phenyl-2-thioxo-1,2-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(thiazol-2-yl)benzenesulfonamide
85.	 4-((4-([1,4'-bipiperidin]-1'-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)benzonitrile
86.	 4-imino-8,8-dimethyl-3,5-diphenyl-3,4,5,7,8,9-hexahydro-6H-chromeno[2,3-d]pyrimidin-6-

	one
87.	 (Z)-5-((2-((4-chlorophenyl)amino)pyrimidin-5-yl)methylene)-3-(((E)-4-fluorobenzylidene)amino)imidazolidine-2,4-dione

Conclusion: This review basically focuses on the various pyrimidines derivatives that have been synthesized against the various diseases and study of their active substituents which make them such an important part in giving activity. As the fusion of this heterocycle had created many derivatives that can be used to target various receptors and enzymes. This can beinferred that this heterocycle fusion with various analogs can make this scaffold as an active agent in targeting multiple disease. Secondly pyrimidine moiety is present in many molecules involved in our various metabolic and biochemical process as a result it would provide very less side effects and if so occurred could be overcome through structural modification .So this scaffold in future could act as legend moiety in targeting multiple diseases at a time.

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