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Evolution in Medicinal Chemistry of Prazolopyrimidine Derivatives as Anticancer Agents

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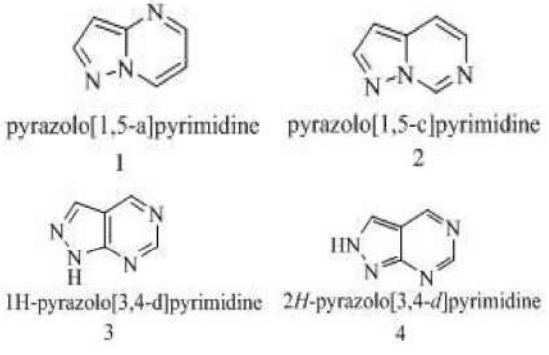
Abstract

Pyrazolopyrimidines are the fused heterocyclic ring systems which structurally resemble with purines, and exhibit important biological actions. Pyrazolopyrimidines derivatives have great importance in the field of chemical synthesis, agriculture and pharmaceutical industries due to their wide range of applications. Over the past few decades, researchers have focused their research on the synthesis of novel pyrazolopyrimidine derivatives. The pyrazolopyrimidines heterocyclic ring is an integral part of various synthetic compounds with wide range of therapeutic and pharmacological potentials like anti-inflammatory, antibacterial, anticancer, antifungal, antiviral, anticonvulsant, anti-tubercular, etc Many marketed drugs are pyrazolopyrimidine derivatives like antiviral drugs which include acyclovir, ganciclovir, didanosine, abacavir and adefovir. Due to the wide scope of pharmacological potentials of pyrazolopyrimidine derivatives, research community has shown great interest to discover new pyrazolopyrimidines having potent bioactivities with no or lesser side effects. This review summarizes the recent developments on the synthetic approaches, mechanism of action and anticancer activity of pyrazolopyrimidines.

Keywords: Pyrazolopyrimidines, Anticancer

Introduction

There are several systems of pyrazolopyrimidine; two (1,2) do not display tautomerism, four NH-tautomers (3-6) present in [3,4-d]-system,and CH-tautomers (7). The [4,3-d]-system possesses two uncharged(8,9) and three zwitterionic NH- (10) and CH-forms (11) [1].



pyrazolo[1,5-a]pyrimidine 1

pyrazolo[1,5-c]pyrimidine 2

1H-pyrazolo[3,4-d]pyrimidine 3

2*H*-pyrazolo[3,4-*d*]pyrimidine 4

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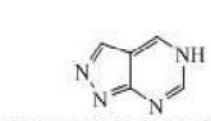
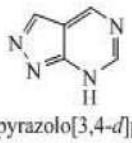
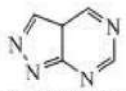


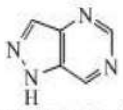
5*H*-pyrazolo[3,4-*d*]pyrimidine
5



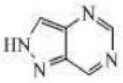
7*H*-pyrazolo[3,4-*d*]pyrimidine
6



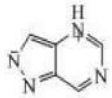
3a*H*-pyrazolo[3,4-*d*]pyrimidine
7



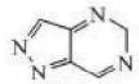
1*H*-pyrazolo[4,3-*d*]pyrimidine
8



2*H*-pyrazolo[4,3-*d*]pyrimidine
9



pyrazolo[4,3-*d*]pyrimidin-4-ium-2-ide
10



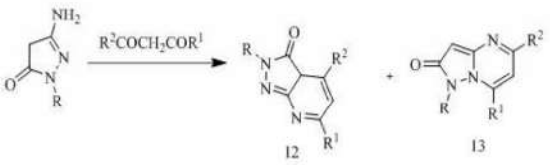
5*H*-pyrazolo[4,3-*d*]pyrimidine
11

Chemistry

Preparation ofpyrazolopyrimidines

A number of methods of synthesis of pyrazolopyrimidines are reported in the literature.

Cyclocondensation of 3-amino-2-pyrazolin-5-ones with P-diketones produces either pyrazolo [3,4-d] pyridines or pyrazolo [1 *S*-a] pyrimidines. In acid **13** is produced, whereas under alkaline conditions **12** is the major product [1].

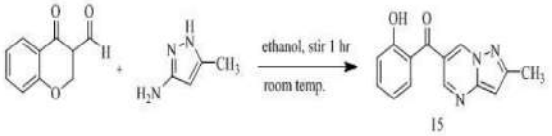


12 13

By reaction of the perchlorate with semi- and thiosemicarbazides, Pyrazolo [1,5-c] pyrimidine derivatives were obtained [1].

14

4-oxochromane-3-carbaldehyde stir in ethanol for 1 hour with aminopyrazoleto produce (2-hydroxyphenyl)(2-methylpyrazolo[1,5-a] pyrimidin-6-yl) methanone (95% yield) [2].



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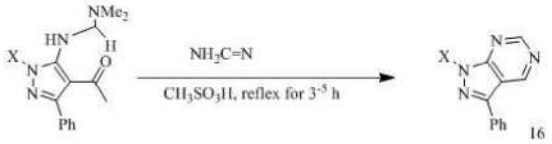
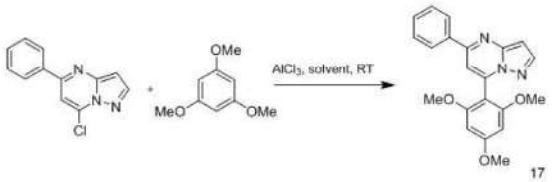
Pyrazolo [3,4-d] pyrimidine products 2aej were obtained from the reaction of 1H-pyrazol-5-yl-N, N-dimethylformamidines with cyanamide ($NH_2C{=}N$).[3]



16

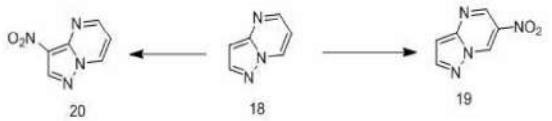
7-Chloro-5-phenylpyrazolo[1,5-a]pyrimidine (1.0 equiv), 1,3,5-trimethoxybenzene (1.0 equiv) in the presence of $AlCl_3$ (1.2 equiv) in dichloroethane (5 ml) was stirred at room temperature to obtain 5-phenyl-7- (2,4,6-trimethoxy-phenyl)-pyrazolo[1,5-a] pyrimidine [4].



17

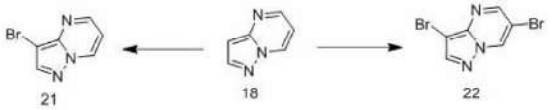
Reactions with Electrophiles

Nitration of pyrazolo[1,5-a]-pyrimidine in the presence of nitric acid and sulphuric acids gives 3-nitropyrazolo [1,5-a]-pyrimidine **19**, whereas in the presence of nitric acid in acetic anhydride gives the 6-nitro compound **20**. [5]



20 18 19

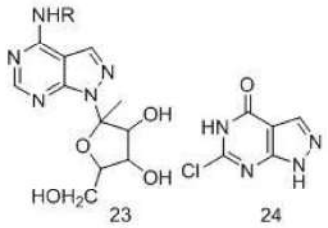
Bromination of pyrazolo [1,5-a]-pyrimidine gives either the 3-bromo derivative or the C-3, C-6 dibromo derivative. C-6 bromination didn't occur in any case [6].



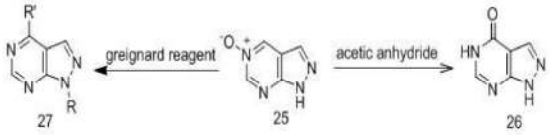
21 18 22

Reactions with Nucleophiles

Allopurinol gives the nucleoside upon trimethylsilylation and ribosylation with tetra-0-acetylribofuranose, chlorination at C-4, and amination [7].

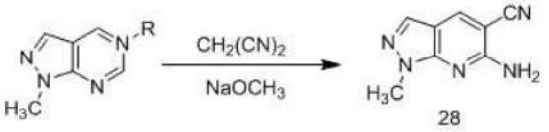


The compound **25** reacts with acetic anhydride to yield allopurinol **26**, and with Grignard reagents furnishes compound **27**.[8]



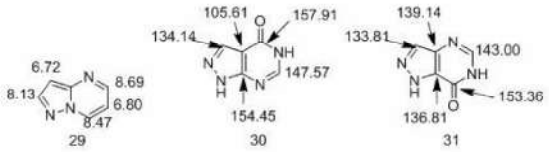
Rearrangements and Ring Cleavage

N-methyl ammonium saltis converted into upon treatment with active methylene reagents in the presence of sodium methoxide [9].



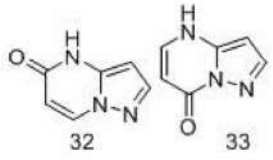
Spectral Properties

'H-NMR shifts of pyrazolo[1,5-a] pyrimidine are shown in **29**. [13] C-NMR data of pyrazolo-[3,4-d] pyrimidine-6-one and of pyrazolo[3,4-d]pyrimidin-7-one are shownin **30** and **31**.[10-12]



IR and UV spectra of pyrazolo [1,5-a]pyrimidin-5-one and the isomeric 7-one are shown in **32** and **33**. A difference of 20 cm^{-1} is observed between theCO absorption in the two isomers.

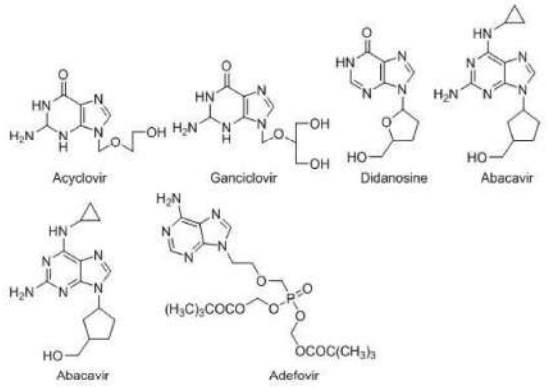
Several other pairs of isomeric pyrazolo[1,5-a] pyrimidines were prepared. Since differences in CO absorption are used to distinguish between the two isomers, structures that are assigned on these bases should be rechecked [14-16].



UV: λ_{max},(MeOH), 230 nm UV: λ_{max} (MeOH), 21 1 nm;

IR: (KBr) 1738, 1672,1578 cm^{-1} IR: (KBr), 1682, 1624, 1583 cm^{-1}

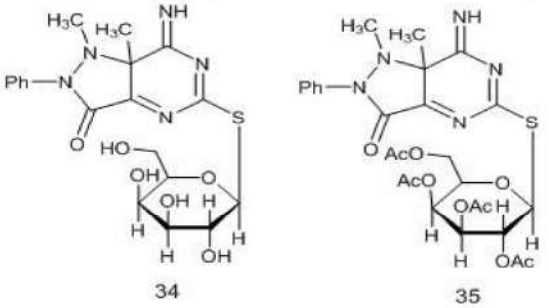
Several currently available drugs containing pyrazolopyrimidine nucleus are used for different clinical conditions [17].



Biological activity of Pyrazolopyrimidines

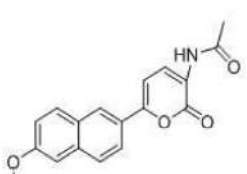
Anticancer activity

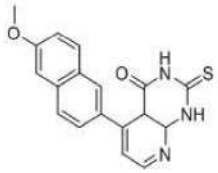
Galal *et al. [18]* synthesized a novel series of 4-aminoantipyrines and their corresponding pyrazolopyrimidine thioglycosides and pyrazolopyridine thioglycosides. All the synthesized compounds were analysed by spectral data. The compounds were evaluated for antitumor activity against human cancer cell lines; liver (HEPG2), breast (MCF-7) and colon (HCT116). Out of all, compound **34** was the most cytotoxic drug, inhibiting replication of human liver cancer cells in vitro, while compound **35** was effective ontwo human cancer cells (liver cancer and colon cancer).



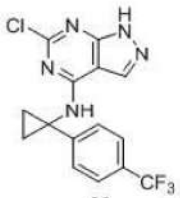
Mardia *et al. [19]* have been reported the novel Pyrazolo[1,5-a]pyrimidines and Pyrido [2,3-d] pyrimidines that can inhibit tyrosine kinase in cancer cells. Compound **36** reported as most active against MCF-7 with GI% 62.5 whereas compound **37** proved

to be the most active one among the synthesized series with GI% 81.72 at 25 nM concentrations and IC_{50} 8.4 nM which is very close to the reference drug Sorafenib. in vitro cytotoxicity activity was also performed using the MCF-7 breast cell line.

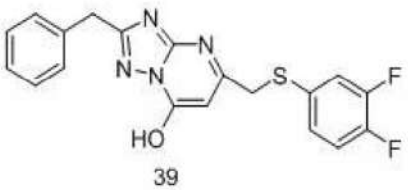

36


37

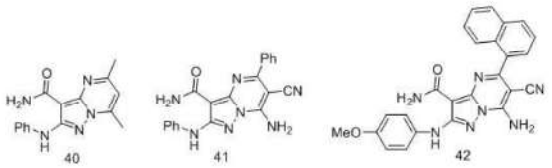
Ashley *et al. [20]* have identified a novel PDE2 inhibitor series using fragment-based screening. By the use of molecular modeling and X-ray crystallography, this fragment was developed into a series of potent PDE2 inhibitors with good physicochemical properties. Compound **38**, a PDE2 selective inhibitor, was identified that exhibited favourable rat pharmacokinetic properties.


38

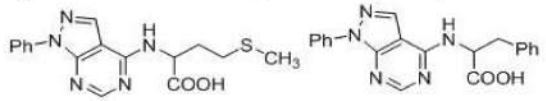
David *et al. [21]* were synthesized and evaluated, pyrazolopyrimidine 2-methyl-5-((phenylthio) methyl) pyrazolo [1,5-a] pyrimidin-7-ol, resulting in the discovery of CXCR2 receptor antagonist 2-benzyl-5-(((2,3-difluorophenyl)thio) methyl)-[1,2,4]triazolo[1,5-a] pyrimidin-7-ol **39**. Favourable biological and pharmacokinetic properties were reported when pyrazolopyrimidine core was replaced by atriazolo alternative.


39

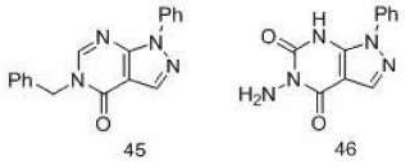
Taghrid *et al. [22]* synthesized many series of compounds. The newly synthesized compounds were characterized by analytical and spectroscopic data. All the compound were screened for their *in vitro* antitumor activities against different human cancer cell lines and found that 4a, 7e, and 7f were most active among all.


40 41 42

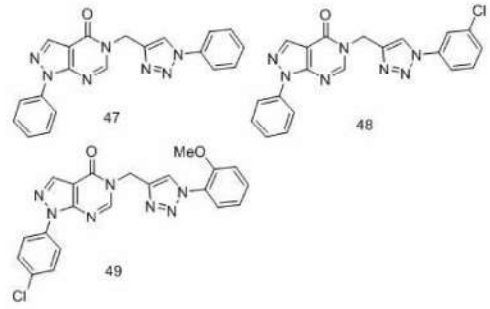
Mostafa *et al [23]* have been synthesized numerous purine analogues possessing the pyrazolo [3,4-d] pyrimidine ringcontaining amino acid residue. All the structures of the synthesized analogue were evaluated by spectral data. All the compounds were tested for anticancer activity, out of all compound **43** and **44** were the most active compounds. Moreover, compounds 3e exhibited significant in vivo radioprotective activity.


43 44

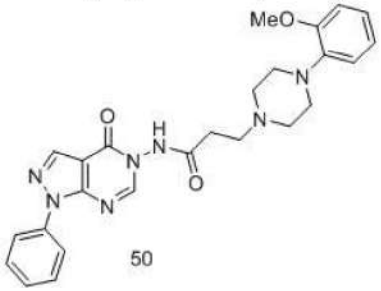
Mostafa *et al. [24]* were synthesized a new hybrids of pyrazolo [3,4-d] pyrimidine derivatives and evaluated for in-vitro anticancer activity against Ehrlich Ascites Carcinoma (EAC) cell line. All the synthesized compounds were confirmed by microanalyses, IR, NMR, and mass spectral data. Intermediate anticancer activity exhibited by compounds **45** and **46** compared to doxorubicin with IC_{50} values of 90 and 100 mg/ml, respectively.


45 46

Muralidhar *et al. [25]* were synthesized a series of hybrid azaheterocycles containing pyrazolo [3,4-*d*]pyrimidin-4(5*H*)-ones and evaluated for their anticancer efficacy *in vitro* against C6 rat and U87 human glioma cell lines. *In silico* docking studies reveal that the compounds **47, 48** and **49** were more effective in binding with TGFBR2 than other compounds.

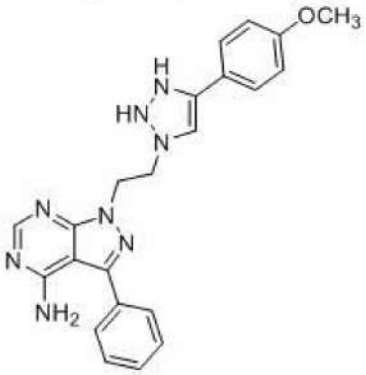

47 48 49

Heba *et al. [26]* were synthesized and reported new purine bioisosteres comprising a pyrazolo [3,4-d] pyrimidine scaffold linked to piperazine moiety through different amide linkages. The newly synthesized compounds were evaluated for anticancer activity against four cell lines (MDA-MB-231, MCF-7, SF-268, B16F-10), and cyclooxygenase (COX-2) protein expression inhibition in lipopolysaccharide (LPS)-activated rat monocytes. Out of all, the compound **50** exhibited relatively high inhibitory activity.



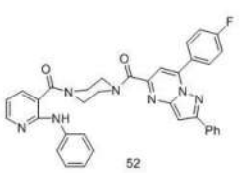
50

Anil *et al. [27]* were synthesized 3-phenylpyrazolopyrimidine-1,2,3-triazole hybrids using click chemistry approach. All compounds were tested for inhibition of Src kinase and breast carcinoma (MDA-MB-361), human ovarian adenocarcinoma (SK-Ov-3) and colon adenocarcinoma (HT-29). Compound **51** at a concentration of 50 µMinhibited the cell proliferation of HT-29 and SK-Ov-3 by 73% and 58%, respectively.

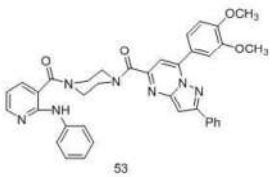


51

Ahmed *et al. [28]* were synthesized a series of anilinonicotinyl linked pyrazolo [1,5-a] pyrimidine conjugates and evaluated for their antiproliferative activity. Among all, **52** and **53** exhibited significant effects, apart from G2/M cell cycle arrest. Interestingly they showed profound effects on cyclin D1, Bcl-2 and survivin proteins that regulate breast cancer cell proliferation.

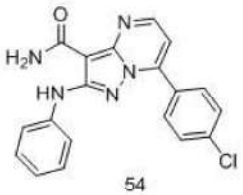


52

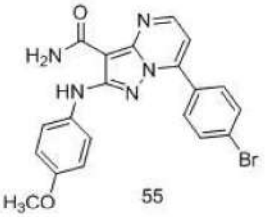


53

Ashraf *et al. [29]* were synthesized and reported a novel series of pyrazolo [1,5-*a*] pyrimidines and pyrazolo [1,5-*a*] quinazolines. Structures of the synthesized compounds were confirmed by their spectral data. These compounds were evaluated for their *in vitro* antiproliferetive activities against human cancer cell lines (MCF-7 and HepG-2) using MTT assay. The compounds **54** and **55** were found to be the most potent in comparison with doxorubicin.

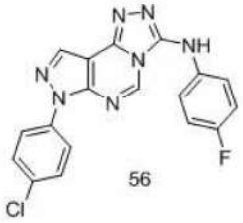


54



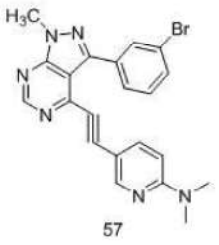
55

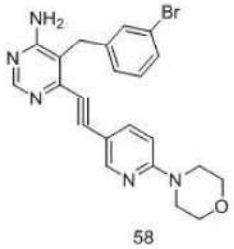
Heba *et al. [30]* were synthesized of some novel pyrazolopyrimidines and fused pyrazolopyrimidines and evaluated for their anticancer on three human cancer cell lines: cervical carcinoma HelaS3, hepatocellular carcinoma HepG2 and colon carcinoma CaCo. and antimicrobial activity. Out of all, the compound **56** found to be the most active. All the newly synthesized compounds were evaluated for in vitro antibacterial and antifungal activity and found that all the compound possess variable degrees of antimicrobial activities.



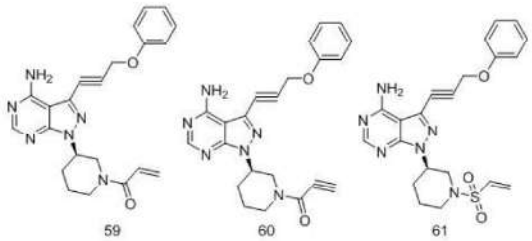
56

Arthur *et al. [31]* synthesized a novel compound and evaluated for their anticancer activity approaches have been tested to modify existing pyridopyrimidine and alkynyl pyrimidine classes of non nucleoside adenosine kinase inhibitors 2 and 3. 4-Amino-substituted pteridines 8a–e were generally less active than corresponding 5- and 6-substituted pyridopyrimidines 2. Pyrazolopyrimidine **57** with IC_{50}=7.5nM was superior to its open chain alkynyl pyrimidine analog **58** (IC_{50}=22 nM).

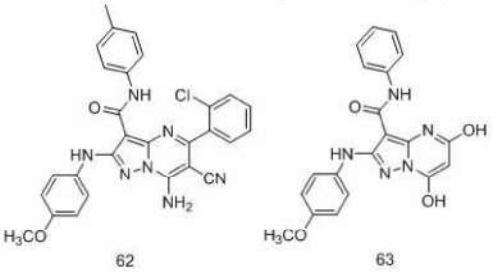

57


58

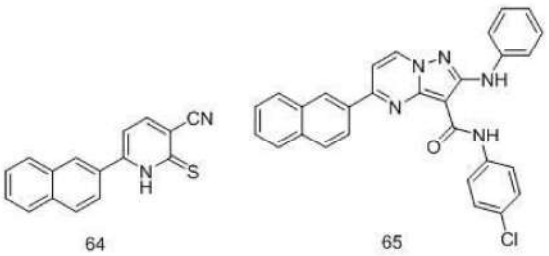
Nan *et al. [32]* were synthesized 1-substituted pyrazolopyrimidine derivatives as potent BTK inhibitors and compounds weretested by enzyme-based assay and *in vitro*cytotoxic against multiple B-cell lymphoma cell lines. Among all, compound **61** exhibited the highest potency against enzyme BTK, with IC_{50} value of 4.2 nM. The compound **59** and **60** foundto be most potent which act against the proliferation of B lymphoma cell lines DOHH2 and WSU-DLCL2 compare with ibrutinb.


59 60 61

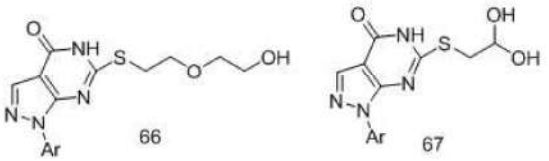
Ashraf *et al. [33]* were synthesized and reported a novel series of pyrazolo [1,5-a] pyrimidine derivatives and evaluated for their in vitro anticancer activity against three human cancer cell lines, namely prostate adenocarcinoma (PC-3), colorectal carcinoma (HCT116), and liver carcinoma (HepG-2) using MTT assay. Among these compounds, **62** and **63** showed better antitumor activity against reported cell lines. structures of the newly synthesized compounds were confirmed by different spectral data and elemental analysis and discussed structure-activity relationship (SAR).


62 63

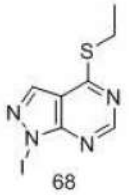
Osama *et al. [34]* were synthesized pyridin-2(1H)-thione, pyrazolo [1,5-a] pyrimidine and pyridin-2-one, derivatives. Allthe compounds were evaluated for their antitumor activity. Among alltested compound, 5b and 9f showed potent cytotoxic activity in vitro using different human cancer cell lines.


64 65

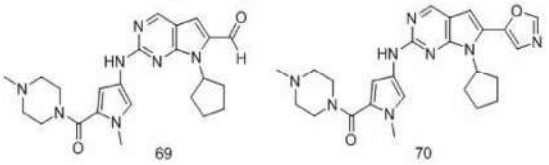
Aymn *et al. [35]* were synthesized 6-Mercapto-1-(9-Methyl-5,6-dihydronaphtho[1′,2′:4,5] thieno[2,3-d]pyrimidin-11-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-one and evaluated for cytotoxicity against breast MCF-7 cancer and liver HepG2 cancer cell lines The results stated that, compounds **66** and **67** revealed promising anticancer activity compared to the activity of the commonly used anticancer drug, doxorubicin with inhibiting the expression of uPA.


66 67

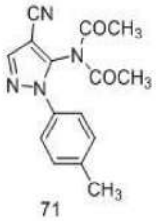
Aymn *et al. [36]* were synthesized a series of novel substituted pyrazolo [3,4-d] pyrimidines derivatives and evaluated in vitro cytotoxicity against human breast adenocarcinoma (MCF-7) cell lines. Compound **68** revealed the highest anticancer activity among the other tested compounds against MCF-7 cell line.


68

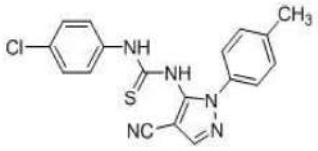
Jean-Yves *et al. [37]*introduced the optimization a series of pyrrolopyrimidine as dual inhibitors of Aurora A/B kinases. Pyrazolopyrimidine series inhibits both of aurora kinases and CDKs. The intermediates **69** and **70** which led to analogues with bothaccessible activity against CDK1 and maintained cell potency


69 70

Ahmed *et al. [38]* were synthesized a novel pyrazolo [3,4-d] pyrimidines and pyrazoles andall the compounds were evaluated for in vitro anticancer activities against the HepG2 liver cancer, A549 lung carcinoma, and MCF-7 breast cancer cell lines. Out of all, compounds **71** and **72** were potent anticanceractivity compared to doxorubicin, by inhibiting the expression of uPA.

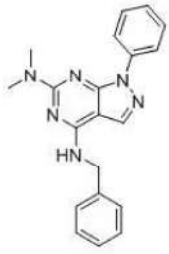


71

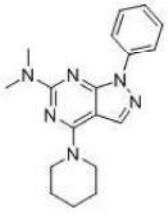


72

Jose *et al. [39]* have been synthesized a series of 1H-pyrazolo [3,4-d] pyrimidines and their effect on the release of histamine from rat peritoneal mast cells measured. After chemical stimulation, (polymer 48/80), several compounds produce inhibition two to three times higher (40–60%) than DSCG. Compounds **73** and **74** showed cytotoxic activity (IC_{50}=1 µg/mL) to HT-29 human colon cancer cells.

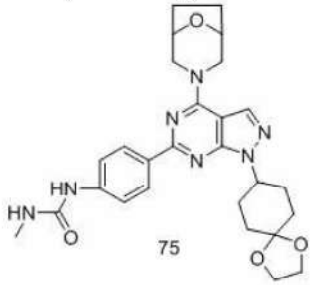


73



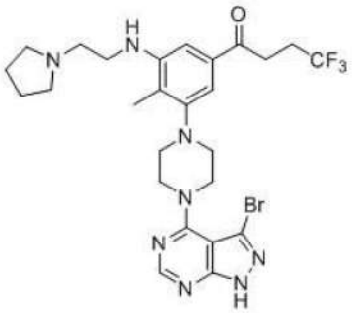
74

Kevin *et al. [40]* have been synthesized a new series of pyrazolopyrimidine derivatives acts as (mTOR) inhibitors. There are various substituents at the 1-position which results the compounds with excellent potency, microsomal stability and selectivity. Among all, compound **75** selectively suppressed key mTOR biomarkers in vivo and revealed excellent oral activity in a xenograft tumor model.



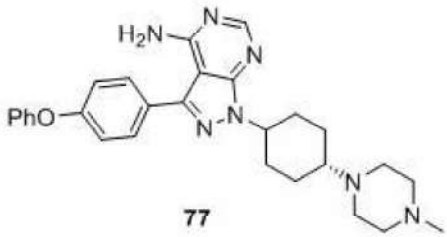
75

Kenneth *et al. [41]* were reported the PI3K/ Akt/mTO Ractivation kinase pathway which is associated with human cancer. In the PI3K pathway targeting multiple sites might be advantageous for optimal activity. Compound **76** act as lead which was eventually advanced into clinical development.



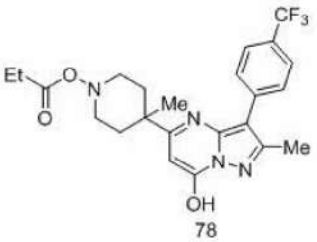
76

Andrew *et al. [42]* have been synthesized a series of para-substituted 3-phenyl pyrazolopyrimidines and evaluated as inhibitors of lck. The nature of the substitution affected enzyme selectivity and potency for lck, src, kdr, and tie-2. Among all, the compound **77** is an orally active lck inhibitor with a bioavailability of 69% and exhibits an extended duration of action in animal models of T cell inhibition.



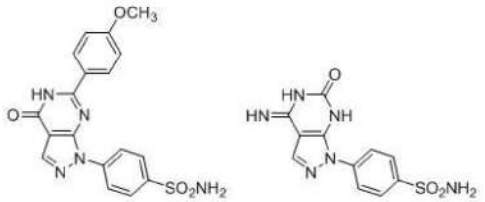
77

Mingmin *et al. [43]* have been synthesized and reported compound **78** and its analogues had very weak agonistic activity at TRPC6 expressed in HEK293 cells but showed strong inhibition on both **4o**-mediated and receptor-operated activation of TRPC6 with an IC_{50} of about 1 µM. Compound **78** suppressed proliferation of AGS and MKN45 cells with IC_{50} values of 17.1 ± 0.3 and 18.5 ± 1.0 µM, respectively.

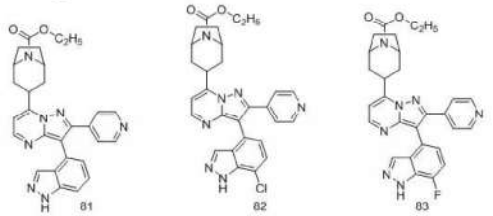


78

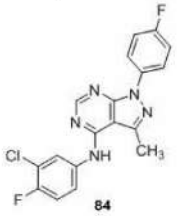
Ghaneya *et al. [44]* were synthesized a series of novel pyrazolo [3,4-d] pyrimidines bearing benzenesulfonamide moiety. Cytotoxic activity was evaluated against MCF-7 and HepG2. The compound **79** and **80** were found to be potent cytotoxic activity with IC_{50} 1.4 mM (MCF-7) and 0.4 µM (HepG2), respectively compared to that of doxorubicin, (IC_{50} = 1.02 µM and 0.9 µM, respectively). Compounds **79** and **80** were subjected to cell cycle analysis and apoptosis assay after 24 h and 48 h treatment. Compound **79** arrested cell at G1 phase, while **80** arrested cell at S and G2/M phases, respectively.



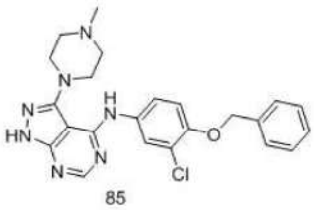
Martin *et al. [45]* have been reporteded series of pyrazolo [1,5-a] pyrimidines as potent B-Raf inhibitors. Compounds **81**, **82**, and **83** strongly inhibited cell proliferation at very low concentrations in the A375 and WM266 cell lines, and these compounds also showed better therapeutic indices.



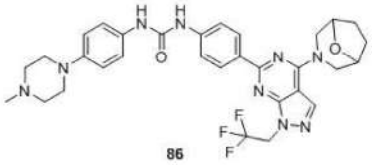
Maher *et al. [46]* were synthesised a series of novel pyrazolo [3,4-d] pyrimidines and revealed for their anticancer activity against 60 human tumour cell lines by NCI (USA). Among all, the compound **84** proved to be most prominent anticancer activity. It showed 1.6-fold more potent anti-proliferative activity against OVCAR-4cell line with IC_{50}= 1.74 µM. andIC_{50} value 5.53 µM against ACHN cell line, representing 2.2-fold more potent than Erlotinib. It showed accumulation of cells in pre-G1 phase and cell cycle arrest at G2/M phase.



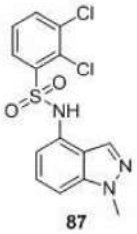
Richard *et al. [47]* have been synthesized a Novel 4-anilino-1H-pyrazolo [3,4-d] pyrimidines and evaluated in vitro for erbB2 and EGFR kinase inhibition. Compound **85** potential of this series to provideorally active erbB2 inhibitors.



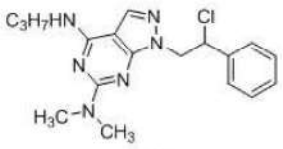
David *et al [48]* were synthesized and reported a new series of potent and selective pyrazolopyrimidinem TOR inhibitors. Compound **86 (**IC_{50} = 0.6 nM) showed elevated cellular potency and notably improved stability towards human microsomes.



Afjal *et al. [49]* have been synthesized novel hybrid of 4-aminoindazole sulphonamide. Out of all, compound **87** was recognised as human CCR4 antagonists. Introduction of a methoxy group adjacent to the sulfonamide substituent and replacement the indazole core with a pyrazolopyrimidine, and resulted in the identification of pyrazolopyrimidine, which exhibited good binding affinity in the high solubility (CLND solubility 581 µM, low lipophilicity (clogP = 2.2, GTPcS assay (pIC_{50} = 7.2), chromlog$D_{7.4}$ = 2.4) and high LE (0.41).

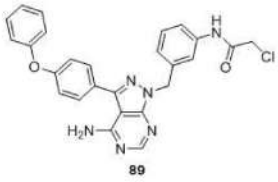


Stefano *et al. [50]* have been reported that antiproliferative pyrazolopyrimidines also exert anti-inflammatory effects comparable to known COX inhibitors. Even through the anti-inflammatory potency of these compounds was not as high as the known COX-2-selective inhibitor DuP 697, compound **88** discovered an interesting COX-2 activity and selectivity compared with the other three reference drugs.



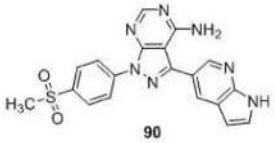
88

Fansheng *et al. [51]* have been synthesized a novel series of pyrazolopyrimidine derivatives capable of potent inhibition of BTK. Compound **89** showed higher selectivity against BTK and exhibited robust antiproliferative effects in both mantle cell lymphoma cell lines and primary patient tumor cells. Low micromolar doses of **89** induced strong cell apoptosis in Jeko-1 and Z138 cells.



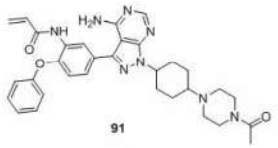
89

Sreekanth *et al. [52]* have been reported compound **90**, a pyrazolopyrimidine-containing ATR inhibitor targeting PI3K. In divergent proliferating cancer cells, it can help to maintain adequate genomic integrity for the progression of cancer cell.

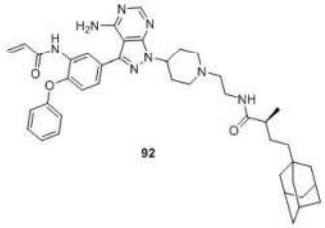


90

Sang *et al. [53]* Her3 have been reported on the development of the first selective irreversible Her3 ligand **91** that forms a covalent bond with cysteine 721 which is unique to Her3 among all kinases and a bi-functional compound **92** containing a hydrophobic moiety and the same warhead of **91** that is capable of inhibiting Her3-dependent signalling and growth.

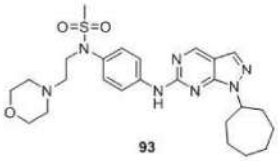


91



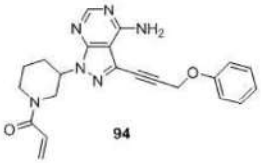
92

Lin *et al. [54]* have been synthesized and reported a novel class of pyrazolopyrimidine-sulfonamides. These compounds act as selective inhibitors of aurora kinase A (AKA) and cyclin-dependent kinase 1 (CDK1). The compound **93** has been reported for good efficacy in HCT116 colon cancer xenograft model.



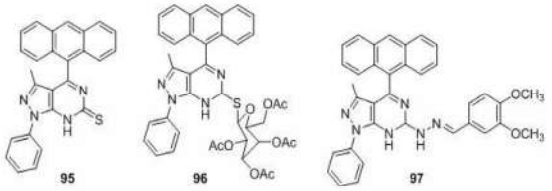
93

Nan *et al. [55]* were designed and synthesized a novel series of 3-substituted pyrazolopyrimidine derivatives by structure based drug design. All the compounds were evaluated for anti-proliferation against Ramos and Raji cells. Among all, compound **94** exhibited excellent potency (IC_{50} = 7.95 nM against BTK enzyme, 8.91 µM against Ramos cells and 1.80 µM against Raji cells), with a better hydrophilicity (ClogP = 3.33). Synthesis of 3-substituted pyrazolopyrimidine derivatives provided new clues to discover as novel and potent antitumor agents.



94

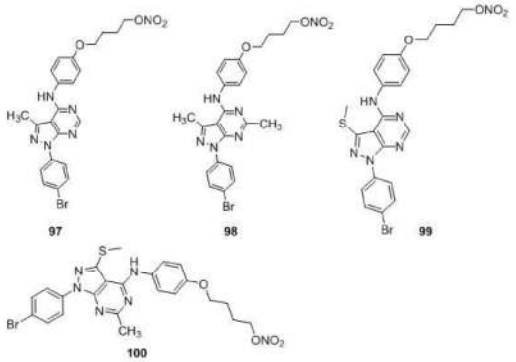
Ibrahim *et al. [56]* have been synthesized a number of *S*- and *N*-glycosides. All the synthesized compounds were evaluated for their antitumor activity against three different tumor cell lines HEPG2 (liver), HCT116 (colon) and MCF-7 (breast) with a docking study against CDK2. Compounds **95**, **96**, and **97** are the most potent against HEPG-2, HCT116, MCF-7 cell lines.



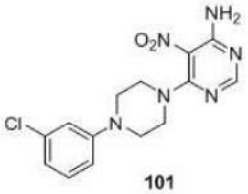
95 96 97

Yaseen *et al. [57]* have been designed and synthesized a new hybrid of pyrazolo [3,4-d] pyrimidines tethered with nitric oxide (NO). All the compounds were evaluated for Anti-proliferative activity against HepG2 cell line and identified that compounds **97**, **98**, **99** and **100** as the most cytotoxic compounds in the series of IC_{50}=3, 5, 3 and 5µM, respectively, compared to erlotinib as a reference

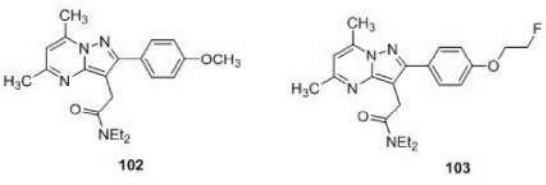
drug (IC_{50} = 25 µM). Compound **97** arrested the cells cycle in G0/G1 phase while **98** arrested the cell cycle in S phase. Docking study also support the synthesized compounds, which have done on EGFR (PDB code: 1M17.



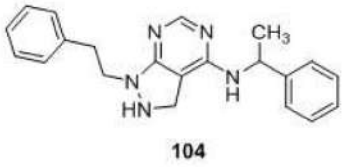
Joerg *et al. [58]* have been reported the 70-kDa ribosomal protein S6 kinase (p70S6K) which is present in PI3K/AKT/mTOR pathway. Screening results in the identification of aminopyrimidine **101** as potent inhibitor. Lead optimization of **101** resulted in highly potent, selective, and orally bioavailable pyrazolopyrimidines. Compound **101** act as lead which was eventually advanced into clinical development.



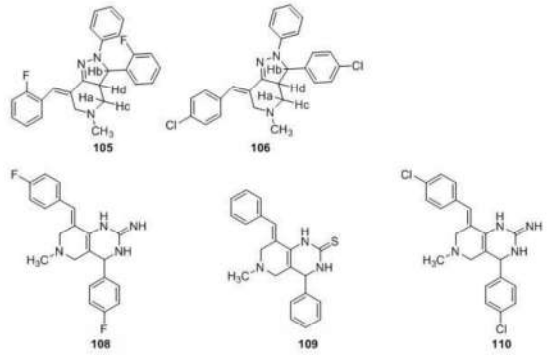
Eryn *et al. [59]* reported the potential anti-glioblastoma activity of **102** and **103** analogues, and explored the effect of alkyl ether chain on TSPO affinity and its potential. Out of all,the synthesized compounds were showed diverse functional activity. The compound **102** and **103** did not affect the proliferation of human T98G glioblastoma cells, while the decreased proliferation of T98G cells in hexyl ether and benzyl ether derivatives.



Guido *et al. [60]* have been reported the strong effect on antiproliferative and pro-apoptotic activity of CLM3 on endothelial and cancer cells. After CLM3 treatments in activated endothelial Phospho-VEGFR-2, phospho-EGFR and phospho-RET levels significantly decreased. The expression of the cyclin D1 gene was mostly inhibited by CLM3 treatment in endothelial and cancer cells.



Ashraf *et al. [61]* were synthesized a series of pyrazolopyridine and pyridopyrimidine derivatives. All the compounds were evaluated using 59 different human tumor cell lines, representing cancers of CNS, ovary, renal, breast, colon, lung, leukemia, and melanoma, prostate as well as kidney. Compound **105, 106, 107, 108, 109** and **110** were the most active derivatives against all tested cell lines.



Conclusion

Cancer is a devastating disease that causes hundreds of thousands of mortality across the world each year. It is one of the major health problems that inflict a heavy socio-economic burden. Anti-cancer drugs are the main weapon to tackle this disease but emergence of resistance to current therapy, limited availability of alternatives warrants discovery and development of new, affordable, safer and effective anti-cancer drug candidates. Pyrazolopyrimidine derivatives offer vast opportunity to develop lead chemotherapeutic molecules for cancer. To accomplish this task, an integrated approach should be adopted which focus on the synthesis of the novel heterocyclic compounds having pyrazolopyrimidine core that are capable of acting at multiple targets during various stages of cancer development.

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