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A Review On Pyrimidine Derivatives As A Potential Anticancer Agents

Ashish Dhanwate[1], Priya Kotkar[2], Abhijit Hon[3], Prof Preetam L. Nikam[4*], Dr Dipti G. Phadtare[5], Shreyash Ahire[6], Hariom Malpani[7], Aniket Tripathi[8]

[1,2]SND College of Pharmacy, Yeola, Nashik
[3,4,5,6,7,8] RG Sapkal Institute of Pharmacy, Anjaneri, Wadholi, Nashik

***Corresponding Author**: Ashish Dhanwate
*Email Id: preetamnikam25@gmail.com.

ABSTRACT
Cancer affects people's quality of life, poses a threat to world health, and has a number of negative side effects when treated. The search for new anticancer agents has been prompted by the resistance of cancer cells to the available medications. A favored scaffold called pyrimidine is found in living things and is essential for many biological processes, including the development of cancer. It is regarded as an important molecule in the therapy of cancer because of its structural similarities to the nucleotide base pair of DNA and RNA.
In the past several years, a large number of brand-new pyrimidine derivatives have been created and studied for their anticancer activities. Focusing on the structure-activity relationship (SAR) of pyrimidine derivatives as an anticancer agent throughout the past ten years is the main goal of the current review.
This review aims to aid in the creation of pyrimidine-based anticancer medications that are stronger and more effective.

Keywords: Pyrimidine, Structure activity relationship, Heterocyclic compounds, Anticancer activity.

INTRODUCTION:

Cancer is a condition that can be fatal wherever [1]. The main problem with current treatment techniques, such as chemotherapy and radiotherapy, is multidrug resistance (MDR). Finding new, diverse structural frameworks may open the door to the creation of powerful new anticancer medications. Due to the wide range of biological and pharmacological actions that pyrimidine exhibits, it is regarded as a crucial heterocyclic moiety. Nucleotides, nucleic acids, vitamins, coenzymes, purines, pterins, and uric acids are examples of naturally occurring molecules that contain this six-membered 1,3-diazine ring with nitrogen at the 1 and 3 positions. The numerous medicinal uses of pyrimidine may be explained by the fact that it is a component of DNA and RNA. The first analogs to be evaluated for biological action were 5-halogenated pyrimidine derivatives. These medications include zidovudine, stavudine, 5-fluorouracil, methotrexate, imatinib, dasatinib, pazopanib, nilotinib, uramustine, tegafur, cytarabine, trimethoprim, sulfamethazine, minoxidil, phenobarbital, primidone, and risperidone [2, 3]. The development of pyrimidine-containing hybrids with in vitro anticancer potential over the past few decades and its relationship to the SAR are highlighted in this review.

Pyrimidine Derivatives as Cancer Prevention Measures

Pyrimidine derivatives as a cancer preventative Pyrimidine is a member of a heterocycle with a lot of electrons and nitrogen. The ability to synthesize pyrimidines in a variety of ways enables the creation of structurally diverse derivatives, such as analogs generated from the substitution of the aryl ring, derivatization of the pyrimidine nitrogen, and substitutions at the carbon at positions 2, 4, 5, and 6 as illustrated in Fig. 1 [4].

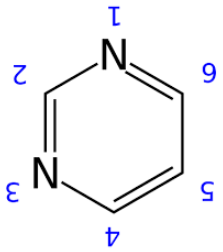

Fig. 1: Structure of Pyrimidine

Disubstituted Pyrimidine Derivatives

2,4-Disubstituted pyrimidine derivative

Utilizing the MTT assay and VX-680 as a positive control, a few new 2,4-disubstituted pyrimidines were created and examined for antiproliferative efficacy. Compound 2 showed effective aurora kinase inhibition against both aurora A and B kinase and was moderate to moderately active against the A549 (IC50 = 12.05 0.45 M), HTC-116 (IC50 = 1.31 0.41

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M), and MCF-7 (IC50 = 20.53 6.13 M) cell lines. Upregulation of Bax and downregulation of Bcl-xl resulted in the induction of apoptosis. According to SAR tests, replacing the benzene ring with a cyclohexyl group improved activity, while replacing the NH in urea with CH2 decreased activity [5].
It was further proven that the buildup of contents in the S phase caused by a decrease in mitochondrial membrane potential blocked the G2-M phase of the cell cycle, making 2,4-diaminopyrimidine derivatives possible anticancer drugs. Due to the different aromatic ring substitutions and terminal aniline on the pyrimidine moiety, compounds 3a and 3b were the most effective against the PC-3, A549, MCF-7, and HCT-116 cancer cell lines [6]. For the cancer cell line K562, novel anilino substituted pyrimidine sulfonamides were shown to induce apoptosis. The MTT and tunnel assays were used to assess cell viability. IC50 values for compounds 4(a-c) ranged from 5.6 to 12.3 M, indicating a promising action [7]. The chemical structure of derivatives of 2,4-disubstituted pyrimidines is shown in Figure 2.

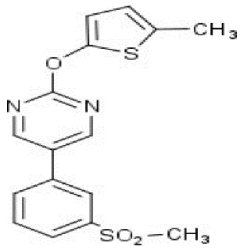

Fig. 2: Structure of 2,4-disubstituted pyrimidine derivatives

2,5-Disubstituted pyrimidine derivatives
Using the MTT cell proliferation assay, Reddy and colleagues revealed in 2015 that 2,5-disubstituted pyrimidines have a moderate anticancer effect against the HeLa cell lines. The best activity is shown in Fig. 3 (IC50 = 82.7 M) [8].

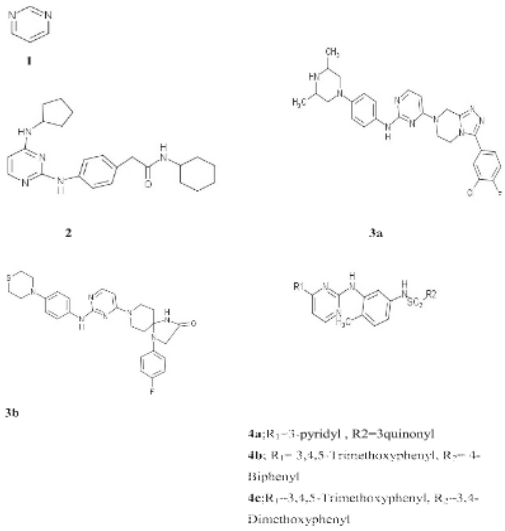

Fig. 3: 2,5-Disubstituted pyrimidine derivatives

4,6-Disubstituted pyrimidine derivatives
Novel 4, 6-disubstituted pyrimidine derivatives were tested in vitro against SIHA, IMR-32, A549, PANC-1, DU145, and MDA-MB-231 cancer cell lines. IMR32 was found to be effectively inhibited by 6a, MDA-MB-231 by 6b, SIHA and DU145 by 6c, and PANC-1 and A549 by 6d, respectively. Figure 4 [9] depicts the SAR.

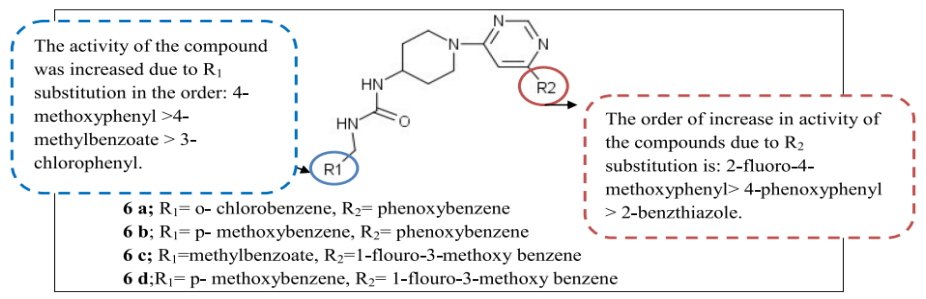

Fig. 4: Structure and SAR of 4,6-Disubstituted pyrimidine derivatives

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Trisubstituted pyrimidines

2, 5, 6-Trisubstituted pyrimidines

There have been reports of a new class of 2,4-diaminopyrimidines acting as potent and specific aurora A kinase inhibitors. By using the VX-680 as a positive control in an MTT assay, the compounds' highest potency against HeLa, A-549, HCT-8, and Hep-G2 cells was determined. With an IC50 range of 0.5 to 4.0 m, compound 7 was the most cytotoxic and caused cell cycle arrest in HeLa cells at the G2/M phase [10].

2, 4, 5-Trisubstituted pyrimidines

Using 5-FU as the positive control, new 5-alkyl pyrimidine derivatives, alkyl N-methoxymethyl pyrimidine derivatives, and 5,6-dihydrofuro[2,3-d] pyrimidines were reported having cytostatic activity. The cancer cell line HCT-116 was cytostatically affected by 5-chloroethyl2,6 dichloro pyrimidine 8 (IC50 = 0.8 to 0.2 M), which resulted in DNA damage and cell cycle arrest at G2/M phase. According to the SAR, the molecule with the highest potential contained two aromatic and one aliphatic chlorine atoms connected to the pyrimidine ring [11]. A powerful inhibitor of c-Met in cellular and enzymatic studies was also developed for the 2-arylaminopyrimidine derivative having a 2- amino-N-methylbenzamide at C4 and chlorine at C5 locations. The best analog of C2 benzazepinone was discovered to have an IC50 value of 10 nM, making it the most effective c-Met inhibitor. Fluorine was added to the aminobenzamide molecule at the C3 position, which resulted in selectivity for c-Met kinase [12].

2, 4, 6-Trisubstituted pyrimidines

Trisubstituted pyrimidines and their N-alkyl derivatives were recently examined for their anticancer activity using ELISA, BRU, and MTT assays, and 10 showed outstanding efficacy. Their IC50 ranged from 2 to 10 m/ml when evaluated against the A549, Hep3B, HT29 FL, MCF-7, and HeLa cell lines [13]. Additionally, the cytotoxic activity of 2,4,6-trisubstituted pyrimidines coupled to an anthranillic acid ester moiety was examined. The substances were tested using the traditional MTT assays against the cancer cell lines U-937, CEM-13, MDAMB-231, DU-145, and BT-474. As CDK9 inhibitors and the most powerful members of the group, 11a and 11b were well known. The (E)-styryl moiety at C-6 position, the methyl group at R2 position, and the presence of methylanthranilate moiety with an EDG at C-4 led to better activity, according to the SAR analyses (Fig. 5) [14].

Pyrimidines and triazolopyrimidines have COX-1/2 inhibitory potential as antiproliferative drugs. Through COX-2 inhibition and in vitro activity against the cancer cell lines HepG-2, MCF-7, CaCo-2, and A549, compound 12 (IC50 range = 8.68 0.2 to 36.56 0.9 g/ml) was demonstrated [15]. Previously, the MTT assay was used to assess the anticancer efficacy of combretastatin bridging pyrimidine derivatives against the MCF-7 and A549 cancer cell lines. The best candidates were determined to be 13a (IC50 = 4.67 M; 3.38 M) and 13b (IC50 = 0.63 M; 3.71 M). By activating the intrinsic apoptotic pathway, 13a produced apoptosis; they were non-toxic to harmful cells and exerted greater inhibitory power than cholcyne in the tunnel assay. The SAR showed that the R2 and R3 substituted rings had an impact on the activity, while EWGs with good activity, such as 2,4-dichlorosubstitution on the rings, and replacement of amine or methyl with hydrogen in the R1 position of the pyrimidine ring, showed little activity. The activity decreased when napthyl was substituted in the rings, while the activity increased when none of the three rings were substituted [16]. Compound 14 (IC50 = 12.2 nM) revealed the greatest activity in the suppression of U937 cell line in a library of N-trisubstituted pyrimidine scaffold. It induced polyploidy (4N, 8N, and 16N) in the cancer cells by causing abnormalities in both chromosomal and spindle formation, which led to the inhibition. Fig. 6 [17] shows a representation of the SAR studies.

A number of pyrimidinebenzimidazole compounds, including compound 15 with an IC50 range of 1.06 to 12.89 M, were investigated for their ability to inhibit the proliferation of the MGC-803, SMMC7721, EC-9706, and MCF-7 cell lines. The active chemical caused MGC-803's cell cycle to stop at the G2/M phase while also increasing apoptotic cell death [18]. Additionally, in the previous year, the primary CLL cells and novel thiazolopyrimidine derivatives were tested against human cancer cell lines. As it inhibited the CDK enzyme, 16 showed good anticancer activity against the cell lines and caused cell death by apoptosis [19].

A review of certain novel 1, 2, 4-triazole-containing pyrimidine derivatives' pharmacological activity was done. Using the MTT assay, 17(a-b) was revealed to have efficient action on HOP-92 [20]. In a previous study, the cytotoxic effects of a series of new pyrimidine derivatives with a 4-chlorophenyl substitution on position 6 of the pyrimidine were assessed using the MTT test (% inhibition at 50 g/mL = 43.62). Fig. 1 2, 4-disubstituted pyrimidine derivatives' chemical composition Mahapatra and others. Future Journal of Pharmaceutical Sciences (2021) 7:123 Page 3 of 38 nucleus and 18b, which has a thiophene ring, demonstrated the greatest effectiveness (% inhibition at 50 g/mL = 39.52). According to the SAR, the majority of the activity was caused by the replacement of mono- or di-chlorine at the R1 position of the phenyl ring [21]. The in vitro anticancer activity of new pyrimidine derivatives was reported, and it was found that 19 of the 60 cancer cell lines tested, particularly lung cancer cell lines, displayed the greatest activity. The SAR analyses showed that the EDG groups like NH2 and EWG groups like Cl and C=O at orthoandparaposition of the ring is significantly influential for the activity (Fig. 7) [22]. The cell lines were evaluated at various concentrations of the compounds.

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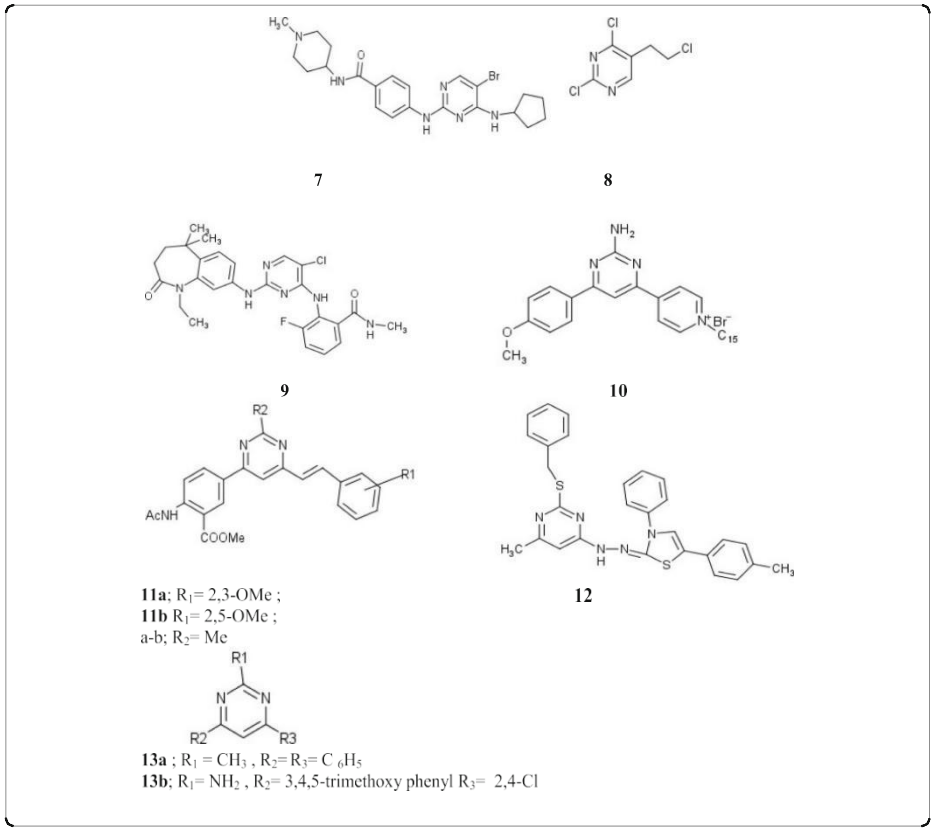

Fig. 5: Structure of trisubstituted pyrimidine derivatives

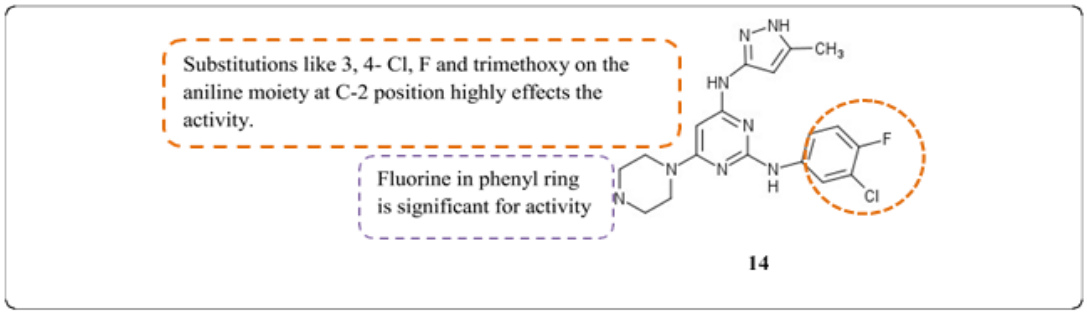

Fig. 6: Chemical structure and SAR studies of trisubstituted pyrimidine

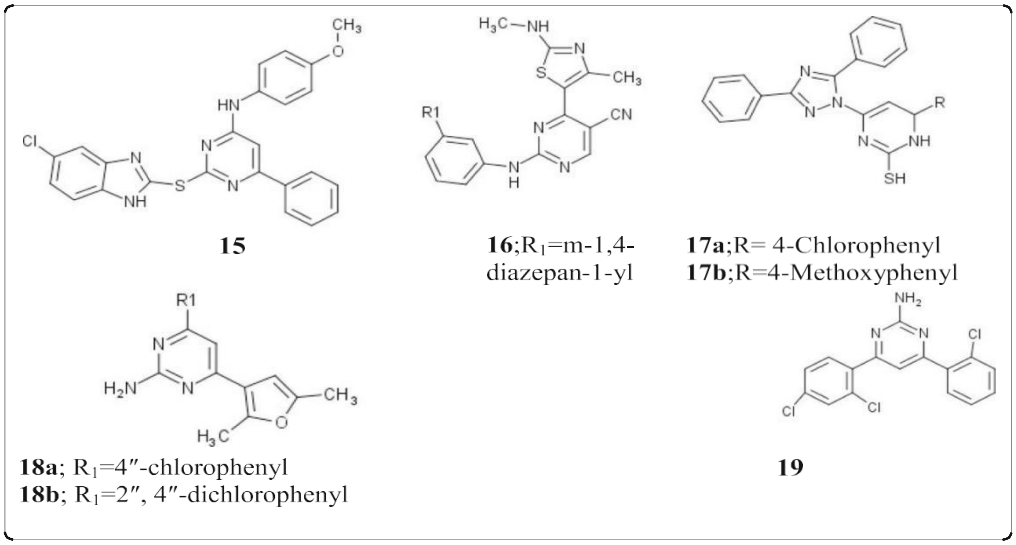

Fig. 7: Structures of some 2,4,6-trisubstituted pyrimidine derivatives

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Tetrasubstituted pyrimidine derivatives

2,4,5,6-Tetrasubstituted pyrimidines

A study revealed 2, 4-disubstituted pyrimidine derivatives as ERα and VEGFR-2 ligands and tested them against the MCF-7 cancer cell lines. 20 exhibited ER binding affinity (IC50 = 1.64 M) as well as VEGFR-2 inhibitory activity (IC50 = 0.085 M). Progesterone inhibition mRNA and in vivo angiogenesis inhibition in the CAM experiment were suppressed as a result of its action. There have also been reports of Raf-1/MAPK/ERK inhibition of cell migration, apoptosis, and transduction resistance in MCF-7 cells. According to SAR analyses, an increase in ER binding affinity is significantly attributed to the hydrogen bonding interaction at the head (Fig. 8).

It has been claimed that a number of pyrimidines, including thioxopyrimidine, iminopyrimidine, bicyclic thiazolopyrimidine, and arylidine derivatives of thiazolopyrimidine, have anticancer properties and have been tested against the cancer cell lines HCT-116, PC-3, and Hep-2. With IC50 values of 66.6±3.6 g/ml, 69.6±2.1 g/ml, and 65.8±2.8 g/ml, respectively, compound 21a, compound 21b, and compound 21d all shown greater activity against PC-3 than compound 21c and compound 21d did against HCT-116.

When used against the HepG2 and UO-31 cancer cell lines, a novel series of 2,4-disubstituted-2-thiopyrimidine derivatives was described as a VEGFR-2 inhibitor. The inhibitors 22a (IC50 = 1.23 M) and 22b (IC50 = 3.78 M) were discovered to have action against HePG2 with IC50 values of 13.06 M and 8.35 M, respectively. According to the SAR investigations, the phenyl group at position 4 and the substitutions at position 2 of the thiouracil molecule interacted hydrophobically to produce the potency [24].

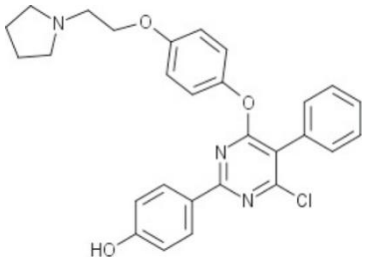

Fig. 8: Structure of tetrasubstituted pyrimidines derivatives

2,3,4,6–Tetra substituted pyrimidine

In a study, the antiproliferative effects of new substituted pyrimidines and triazolopyrimidines against the cancer cell lines PC3, HCT116, MCF-7, and RPE1 were assessed. 28 was shown to have the strongest potential against the RPE1 cell line (IC50 = 66 6 m). Triazolpyrimidine glucosides/xylosides were shown to be less active than substituted pyrimidine glycosides, according to the results of the SAR investigations (Fig. 9) [25].

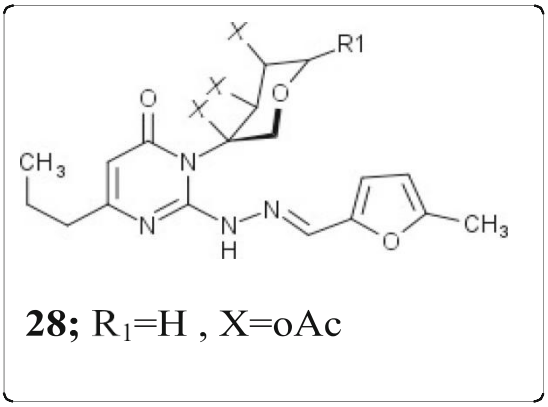

Fig. 9: Structure of 2,3,4,6-tetra substituted pyrimidine derivatives

Pyrimidine fused with heterocyclic rings

Pyrazole-pyrimidine derivatives

Two pharmacophores with strong anticancer properties are the heterocyclic molecules pyrazole and pyrimidines. Various isomeric forms of pyrazolopyrimidine, such as pyrazolo[1,5-a]pyrimidines, pyrazolo[3,4-d]pyrimidines, and pyrazolo[4,3-d]pyrimidines, are known to have high anticancer activity.

Pyrazolo [1, 5-a] pyrimidines

New fused pyrazolopyrimidine derivatives were examined for anticancer efficacy and COX-2 inhibition against a panel of 60 cancer cell lines in recent research. In both studies, compound 29 proved effective. Due to the presence of the 5-amino-1-oxo-substituted pyrazole-4-arbonitrile moiety, it was selective for COX [26]. The pyrazolo [1,5-a] pyrimidine

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derivatives 30a (IC50 = 67.27±3.8 M/mL) and 30b (IC50 = 58.44±3.8 M/mL) showed the greatest activity against HCT116 and PC-3 cell lines in the MTT experiment against cancer cell lines PC-3, HCT116, and HepG-2.
According to SAR analyses, the anticancer activity against cell lines was in the following order: 4 methyl phenyl, 4 chloro phenyl, and phenyl derivative [27]. The chlorine atom at position 2 was more active than the ones at positions 3 and 4. The same group also used the MTT assay to screen the anticancer effects of pyrazolo [1, 5-a] pyrimidines against HepG-2 and MCF-7. According to reports, 31a (IC50 = 63.2±5.9 g/mL) and 31b (IC50 = 70.3±4.1 g/mL) have the best potential against MCF-7 cancer cells and HepG2 carcinoma cells, respectively. According to SAR, methoxy and bromo alterations provided considerable anticancer action (Fig. 10) [28]. There have been reported on a new group of diamide substituted pyrazolo [1, 5-a] pyrimidine derivatives. 32(a-c) was more effective than the commercially available medication cisplatin at killing HeLa cell lines, with an IC50 value of each less than 10 M. To assess the cytotoxicity of the compounds, the MTT test was carried out. Fig. 11 discussion on SAR [29].

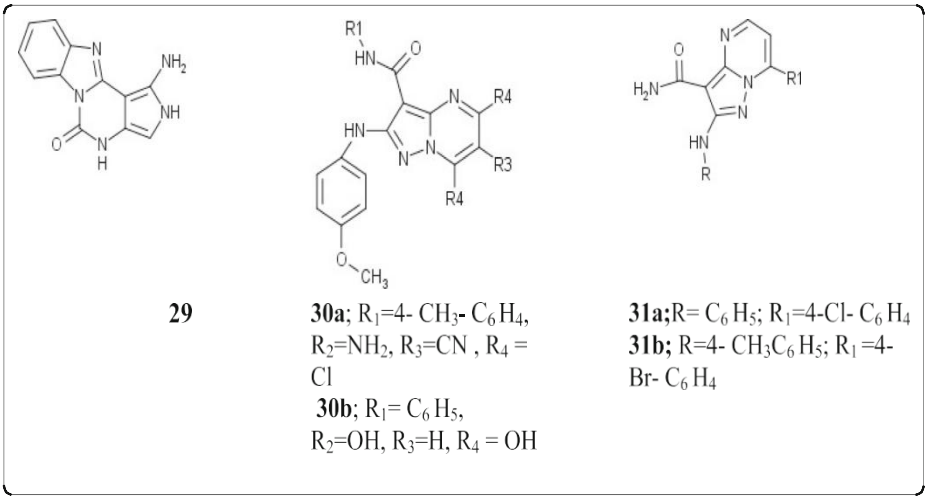

Fig. 10: Structure of Pyrazolo [1, 5-a] pyrimidines

Pyrazole coupled to a chalcone [1, 5-a] It has been suggested that pyrimidines have anticancer properties. MTT assay screening revealed that 33 (IC50 = 2.6 M) was most effective against the MDA-MB231 cancer cell line. The substance increased the expression of proteins that trigger apoptosis, such as p53, p21, and Bax, and lowered the expression of proteins that promote apoptosis, such as Bcl-2 and procaspase-9, while halting the cell cycle in the sub G1 phase. The C5 substitution phenylprop-2-en-1-one and C-7 phenyl ring were mostly responsible for the activity [30].

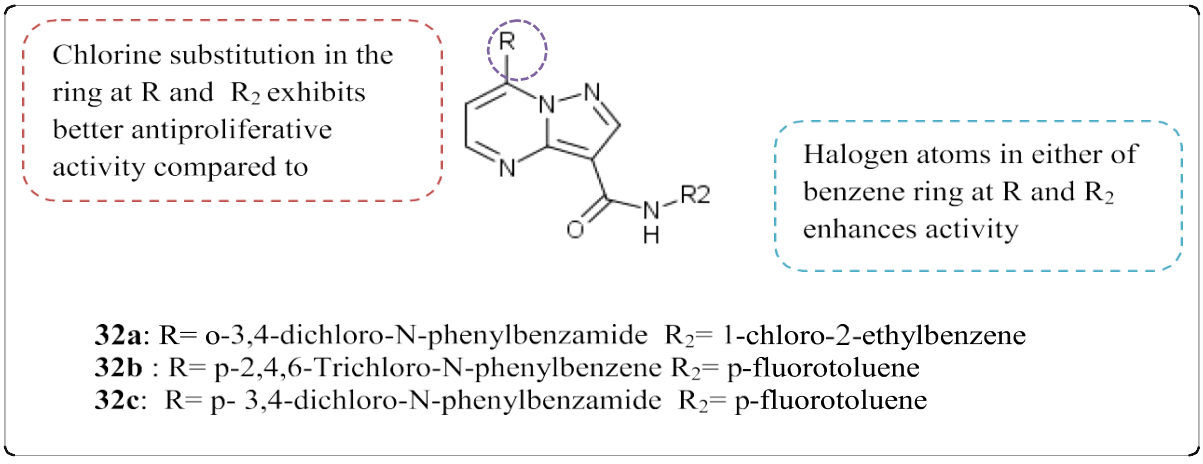

Fig. 11: Structure and SAR studies of diamide substituted pyrazolo [1, 5-a] pyrimidine

The MTT assay was used to investigate the anticancer activity of the pyrazolo [1, 5-a] pyrimidine derivatives having nitrogen mustard moiety against the A549, SH-SY5Y, HepG2, MCF-7, and DU145 cell lines. With an IC50 range of 0.2 to 8.3 μM, 34 reduced cell proliferation in all five cancer cell lines during the G1 phase of the cell cycle by causing apoptosis. The medicine showed superior efficacy than the positive control drug sorafenib and cyclophosphamide while also being less harmful to normal human cells when tested against human HepG2, HCC tumor xenograft in nude mice. The pyrrazolo-pyrimidine derivatives demonstrated strong in vitro cytotoxicity when N-mustard pharmacophore was attached at C-7 and another substituent at C-5, but the resulting drug was found to be ineffective when N-mustard

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pharmacophore was attached at C-5 and other aniline moieties at C-7 [31]. In a subsequent investigation, regioselective synthesis of pyrazolo [1, 5-a] pyrimidine derivatives were carried out with the use of ultrasound and KHSO4(aq). Results showed that compound 35 significantly decreased the metabolism of MTT (Fig. 12), which is the concentration at which metabolically viable cells cleave MTT to purple forzman [32].

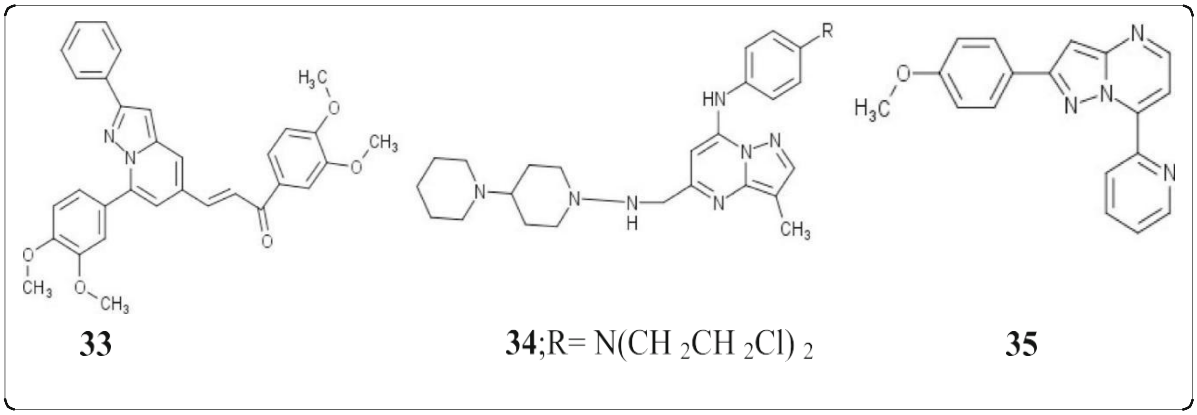

Fig.12: Chemical structures of pyrazolo [1, 5-a] pyrimidines

It has been documented that pyrazolo [1,5-a] pyrimidine is cytotoxic in vitro to the cell lines HCT-116, A549, HepG2, and MCF-7. Compared to the usual medication DOX, 36a and 36b show superior cytotoxicity and cancer cell growth inhibitory characteristics. Phenyl groups were most active in substituted pyrazolo [1,5-a] pyrimidines, followed by 4-chlorophenyl groups and then 4-methylphenyl groups [33]. Additionally, certain brand-new pyrazolo [1,5-a] pyrimidines have been identified as CDK9 inhibitors, which are frequently associated with cancer. Using PIK-75 as a positive reference, the study discovered that the synthesized compound 37 (IC50 = 203-> 1000 nM) is a superior lead compound to PIK-75 because it has less structural liabilities. The drug was also efficient against FLT3 and MV4, two cancer cell lines that have 11 (IC50 = 0.177 and 219 μM, respectively) (Fig. 13) [34].

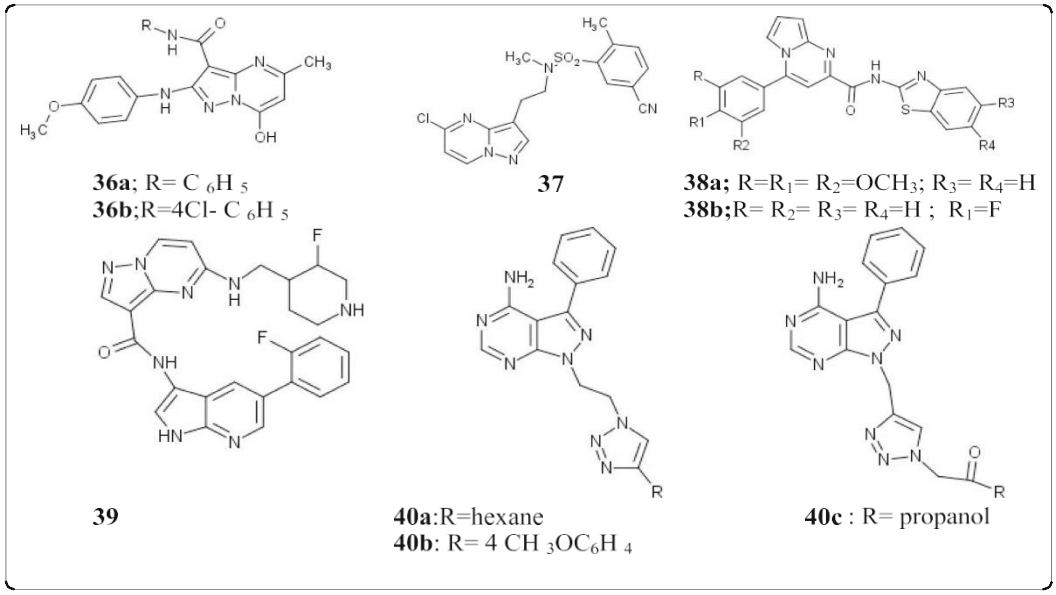

Fig. 13: Chemical structures of pyrazolo [1, 5-a] pyrimidines

Pyrazolo [3,4-d] pyrimidine derivatives

Novel pyrazolo [3,4 d] pyrimidine derivatives acted as inhibitors of ROS-induced apoptosis and malignancy in human cancer cells. A panel of 60 cancer cell lines was utilized to evaluate the compounds, and it was discovered that 41 had a dose-dependent effect on cell line development at an IC50 of 2 M and also produced ROS species [35]. Previously, a group of 4,6-disubstituted pyrazolo [3, 4-d]pyrimidine analogs demonstrated anticancer properties against MCF-7 and K-562 cell lines and reduced the activity of the enzymes CDK2/cyclin E and Abl kinases. The most effective compound was 42, which has IC50 values of 19.8 M (K-562) and 18.9 M (MCF-7) and is not harmful to normal human cells, according to findings on the CHO cell line [36].

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A second investigation found that compound 43 has strong anticancer activity against the K-562 and MCF-7 cell lines, as well as the best anticancer activity against the CDK2/cyclin E Abl kinases. Comparatively to compounds with thiopentane at C-6 and disubstituted aniline at C-4, compounds with thiophenethyl group at C-6 and monosubstituted aniline at C-4 locations showed better CDK2 inhibition. Compounds containing 2-chloro, 3-nitro, and 4-methythio anilines at C-4 were found to have significant enzyme inhibitory action [37].

Pyrazolo [4,3-d]-pyrimidine

Pyrido pyrimidine derivatives

Derivatives of pyrido [1,2-a]pyrimidine Using 5-FU as a positive control, the pyrido[1,2-a]pyrimidine 3-carboxamide derivatives were evaluated against the cancer cells DU145, A549, SiHa, and MCF-7. With respective IC50 values of 3.6±0.11 and 3.2±0.12 g/mL against A544, 78b and 78a demonstrated substantially higher activity. The SAR revealed that the compounds had improved activity when thien-2-yl groups were used in place of phenyl groups at the sixth position (Fig. 14) [38].

Pyrido[2,3-b]pyrimidine derivatives

There have been reported new pyrido[3′,2′:4,5] furo [3,2-d]pyrimidines. Using the MTT assay, the drugs were tested against the Hela, neuro-2a, Colo 205, and A549 tumor cell lines. The most powerful compounds were 79a and 79b, having an IC50 range of 5.8 to 3.6 M. Furo [2, 3-b] pyridine ring system was less active than the pyrimidinone ring. The cytotoxicity was only slightly reduced when nitrogen was substituted for N3 (Fig. 14) [39]. In a concurrent investigation, novel pyrido[2,3-d]pyrimidine derivatives were used to screen HepG-2 and HCT-116 cancer cell lines, and 80(a-d) was determined to be the most effective (Fig. 14) [40].

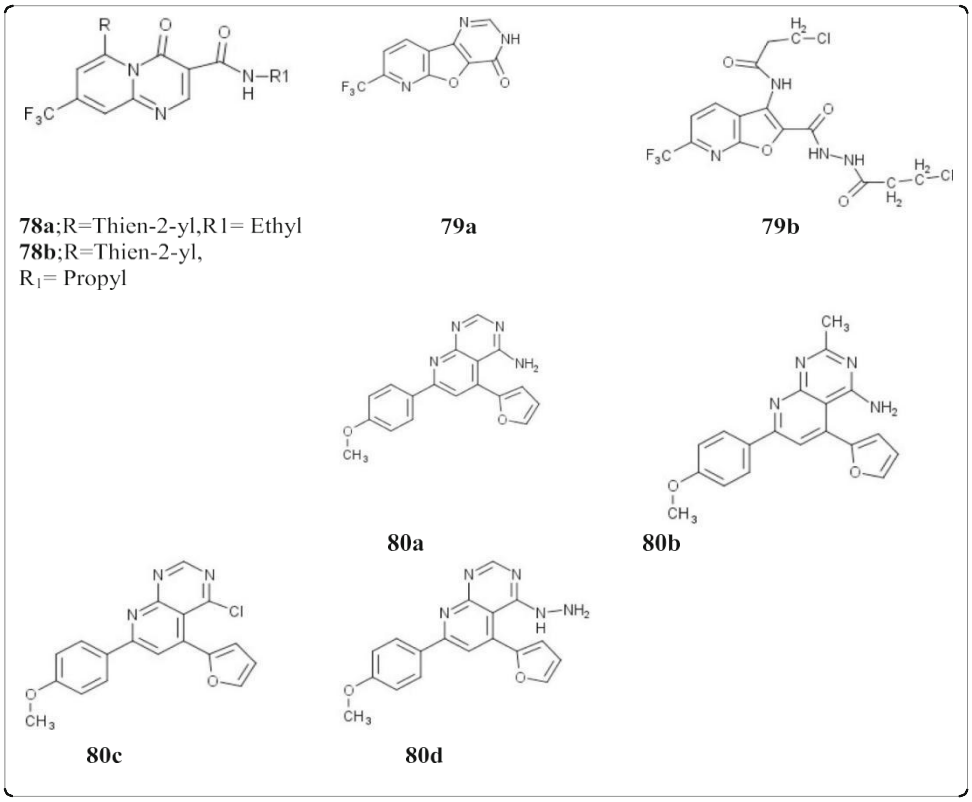

Fig. 14: Chemical structures of pyrido pyrimidine

Pyrido[2,3-d] [1,2,4]pyrido [2,3-d] and triazolo[4,3-a]pyrimidine derivatives81 (IC50 = 0.36 M) shown activity against both the cell lines with 5-FU (positive control), but was more responsive on cell line PC-3. Pyrimidines were assessed against two cancer cell lines, PC-3 and A549. The induction of apoptosis in the PC-3 cell line was caused by a caspase-3 dependent mechanism, and the cell cycle was halted at the G1 phase. Fig. 15 in [41] provides an illustration of SAR.

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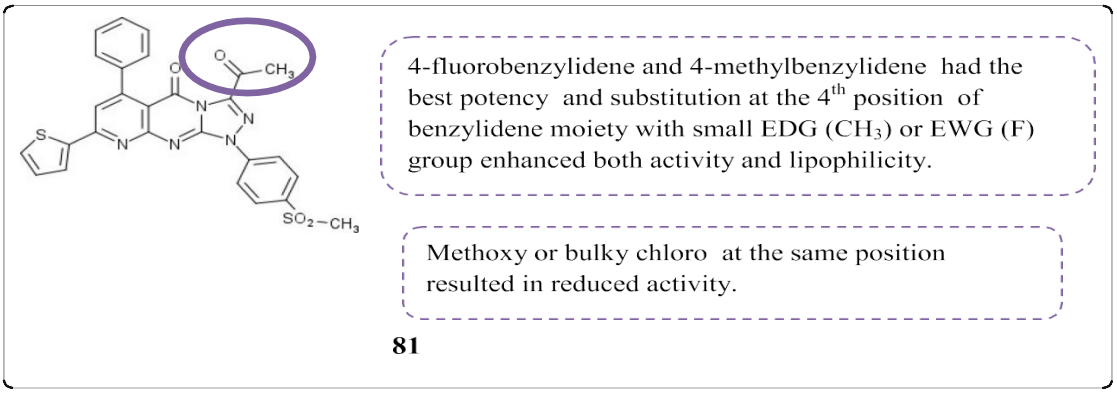

Fig. 15: SAR studies and chemical structures of pyrido[2,3-d] [1,2,4]triazolo[4,3-a]pyrimidine derivatives and pyrido [2,3-d]pyrimidine

Conclusions

Pyrimidine is a significant scaffold since it occurs in naturally occurring nucleotides, and its anticancer profile is currently being thoroughly investigated. The anticancer potential of pyrimidine substituted at different places as well as pyrimidine fused with other heterocyclic rings has been covered in the current work. The anticancer activity is greatly influenced by substitutions at the pyrimidine core's C-2, C-4, and C-6 positions, particularly a thio or amino group at C-2 and a modified phenyl group at C-4. In comparison to six member rings like pyrido and quinazoline, pyrididine fused with five member rings such as pyrazolo, pyrrolo, triazolo, imidazole, oxazolo, thiazolo, and thieno demonstrated more distinct anticancer action. Pyrimidine analogs have a variety of anticancer effects, including inhibition of kinase (erbB2, raf, CDK, Src, etc.) enzymes, cell cycle arrest, activation of oncogenes, reduction of mitochondrial membrane potential, increase in ROS, and induction of apoptosis by upregulation of apoptotic and downregulation of anti-apoptotic proteins. The current manuscript can be helpful to scientists and researchers worldwide.

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