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Role of Pyrimidine Derivatives in the Treatment of Cancer

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ABSTRACT

The study of the chemistry of pyrimidines is contributing to the expansion of research into the therapeutic applications of these compounds. In the field of medicinal chemistry, the sheer number of pyrimidine synthesis methods and reactions that are available opens up a world of possibilities. These investigations have been inspired by the fact that pyrimidines can be used as building blocks for a wide variety of compounds that have a physiological effect. The pyrimidine ring and its fused derivatives, which include pyrazolo[3,4-d]pyrimidine, pyrido[2,3-d]pyrimidine, quinazoline, and furo[2,3-d]pyrimidine, have garnered a great deal of attention due to the extensive variety of biological potential that they possess. In addition, fused pyrimidines are considered to be bioisosteres with purines. As a consequence of this, numerous substances, such as pyrimidine and derivatives of fused pyrimidine, have demonstrated promising anticancer potential. Pyrimidine compounds have been shown to possess a number of beneficial qualities, including antibacterial, anticancer, anti-inflammatory, antidiabetic, and analgesic effects. The purpose of this study is to shed light on the anticancer significance of certain fused pyrimidine derivatives and privileged pyrimidines through the use of various types of inhibition. Additionally, the study reveals structure-activity relationships and provides specifics regarding the synthetic compounds that were utilized in the construction of these scaffolds. The hope is that this research will assist medicinal chemists in the development of highly selective pyrimidine anticancer agents. The focus of this review article is on recent research on synthetic pyrimidine compounds that have anticancer effects. Additionally, the paper examines the chemistry and biological activities of pyrimidines.

Keywords- Pyrimidine, cancer, heterocycle, cytotoxicity.

I. INTRODUCTION

The study of heterocyclic compounds accounts for fifty percent of all organic chemistry research conducted on a global basis. The heterocyclic structure is the foundation for a wide variety of pharmaceutical, agricultural, and veterinary medicinal goods [1]. There is a group of molecules that are known as heterocycles, and they are incredibly significant. There are approximately fifty percent of all organic compounds that are heterocycles. Histamine is a structural component that can be found in a number of naturally occurring drugs, such

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as quinine, papaverine, emetine, theophylline, atropine, procaine, codeine, morphine, and reserpine [2]. Certain luminophores, herbicides, insecticides, and dyes are more examples of substances that contain heterocyclic compounds. The creation of novel chemicals that have the potential to be used as therapeutic therapies for people is the shared objective that organic and medicinal chemists work toward and strive to achieve [3]. During the past ten years, the preferred structure library growth efforts in combinatorial chemistry have primarily concentrated on heterocyclic structures as their primary emphasis. The reason for this is that heterocyclic compounds belong to a category of molecules that have demonstrated potential in the field of medical chemistry [4].

In chemicals that are physiologically active, there is a high concentration of molecules that include six carbon atoms and two hetero atoms (figure 1). In the same way that pyridine and benzene are, pyrimidine is a heterocyclic aromatic molecule that consists of a six-membered ring and has two nitrogen atoms at three different places [5]. There are two other diazine analogues that share an isomer with it. As the number of nitrogen atoms in the ring rises, the ring pi electrons in a pyrimidine become less energetic, and the process of electrophilic aromatic substitution becomes more challenging. On the other hand, nucleophilic aromatic substitution gets easier [6]. Other than that, the ring is very similar to pyridine in many respects. For instance, the final type of reaction occurs when chlorine or its reverse enters into 2-aminopyrimidine and displaces the amino group. This is an example of the process. One possible outcome of lowering resonance stability of pyrimidines is the occurrence of addition and ring cleavage events, rather than substitution interactions. The Dimroth rearrangement is one example of a manifestation that fits this description. In comparison to pyridine, pyrimidines are less basic and exhibit more challenging N-alkylation and N-oxidation reactions with the following: A pKa value of 1.23 is assigned to protonated pyrimidine, which is significantly lower than the value of 5.30 that is assigned to pyridine. One such technique that can be utilized in a laboratory for the production of pyrimidines is known as organic synthesis. An strategy that is well-known is known as the Biginelli reaction. Ethylacetoacetate, an aryl aldehyde (such as benzaldehyde), and urea are the three components that are required for the Biginelli method, which is a multi-step procedure, in order to create 3,4-dihydropyrimidin-2(1H) ones [7].

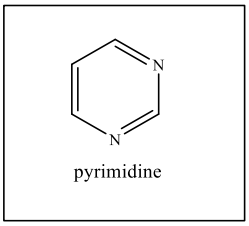

Fig. 1: Structure of pyrimidine

As a result of the numerous therapeutic applications that they offer, pyrimidine derivatives have earned an excellent reputation in the field of medicinal chemistry [8]. Thymine, cytosine, and uracil are the fundamental components of nucleic acids, DNA, and RNA. It is possible that the presence of a pyrimidine base is responsible for the activity of these three nucleotides [9]. Compounds with a pyrimidine nucleus have been shown to possess a wide variety of biological activities, including the following: 5-fluorouracil, which is anticancer; idoxuridine and trifluoridine, which are antiviral; zidovudine and stavudine, which are antiHIV; trimethoprim, sulfamethiazine, and sulfadiazine, which are antibacterial; sulfadoxin, which is both antimalarial and antibacterial; minoxidil and prazosin, which are antihypertensive; barbiturates, such as phenobarbitone, which are sedatives, hypnotics, and anticonvulsant; propylthiouracil, which is antithyroid; thionzylamine, which is an H1-antihistamine; and toxosavin and fervennuline, which are antibiotics fig 2 [10,11].

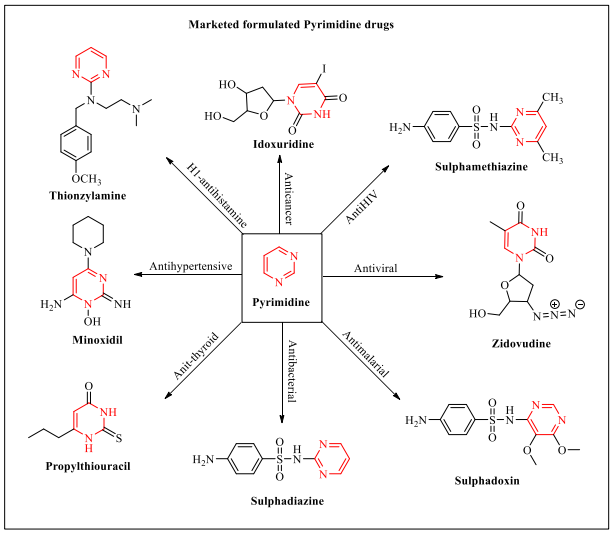

Fig. 2: Marketed formulation of some Pyrimidine moiety.

Cancer, which is considered to be one of the most devastating diseases in the world, is responsible for the deaths of approximately one million people every year. The introduction of novel treatments is not always sufficient to prevent the failure of therapy due to adverse effects and resistance to drugs [12]. Therefore, the most important thing is to continue developing new chemotherapeutic scaffolds that are capable of overcoming these constraints. There is little doubt that cancer is one of the most debilitating diseases in the world. Second only to heart diseases in terms of mortality rates, it is the second most common cause of death [13]. In terms of mortality caused by cancer around the world, colorectal cancer comes in at number four, with liver cancer earning the number two spot. Variations in DNA are accountable for the development of many types of cancer. A crucial weapon in the fight against cancer cells

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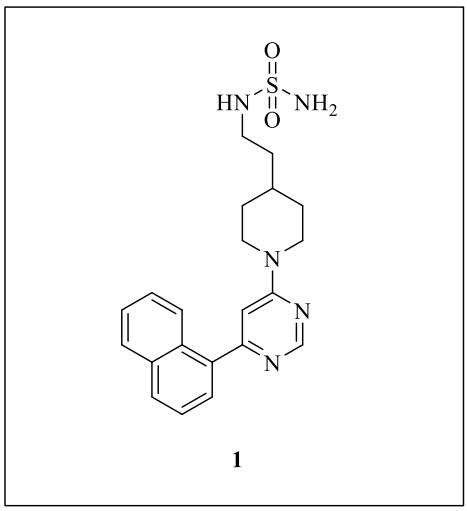
and their unrestrained cell proliferation and expansion is a medication that has the ability to disrupt the normal function of nucleic acids like DNA and RNA and interfere with the production of nucleic acids like DNA and RNA [14]. The reductive methylation of 2-deoxyuridine-5′-monophosphate (dUMP) is catalyzed by thymidylate synthase (TS) and the cofactor N5,N10-methylenetetrahydrofolate (MTHF), which results in the formation of the DNA building unit known as 2-deoxythymidine-5-monophosphate (dUMP). Due to the extraordinary pharmacological activity of pyrimidine derivatives, anticancer action has been the subject of a significant amount of research. This review places an emphasis on the anticancer capabilities that are possessed by pyrimidine derivatives [15].

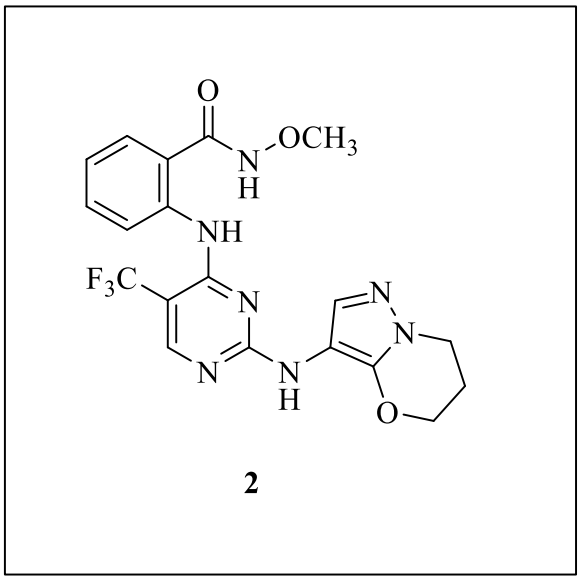
II. PYRIMIDINE AS ANTICANCER ACTIVITIES

Lefebvre *et al.*,The effectiveness of the in vitro growth suppression was evaluated using three human tumor cell lines (HT-29, M21, and MCF7). Additionally, two sets of novel substituted pyrimidine derivatives that contained a sulfamide group were synthesized. Compound 1, which displayed a GI50 value of less than 6 micromolar for all human tumor cell lines, was discovered to possess the most effective growth inhibition action. This activity was effectively enhanced by the incorporation of a substantial substituent into the aromatic ring. Furthermore, the data indicated that the selective action was improved by a shorter linker that extended from the piperidine to the sulfamide group. This proved to be the case. Experiments conducted on four different human invasive breast ductal carcinoma cell lines (MDA-MB-231, MDA-MB-468, SKBR3, and T47D) revealed that the MCF7 selective compounds were selective against the T47D cell line, with the exception of one instance. As a result of this discovery, the possibility of anti-estrogen action has been raised, which may prove to be beneficial in the fight against cancer treatment resistance [16].



1

Xie *et al.*, Biological tests were conducted to determine whether or not a novel series of pyridine or pyrimidine compounds containing a ring-fused pyrazoloamino group could be effective in inhibiting FAK and acting as anticancer drugs. There was a high degree of sensitivity of the FAK kinase to the majority of the medications. The chemical 2, which is highly effective, has an IC50 value of 46 μM and exhibits a significant inhibition of the growth of the MDA-MB-231 cell line. An further finding from the ELISA assay was that the FAK Y397 autophosphorylation in the MDA-MB-231 cell line was reduced in a dose-dependent manner. Compound 2 was found to be responsible for the death of 43.58% of the MDA-MB-231 cells when administered at a concentration of 12.5 μM, as demonstrated by the flow cytometry measurement. As a result of docking experiments conducted using computational models, it was discovered that compounds 2 and TAE-226 had comparable interactions with the FAK kinase domain [17].



2

Liu *et al.*, By synthesizing a number of novel 2,4-substituted pyrimidine derivatives, we were able to establish anti-proliferative activities against the PC-3, MGC-803, MCF-7, and H1975 cell lines. During the tests conducted against H1975 cells, compound 3 demonstrated the highest level of bioactivity. According to the findings of additional mechanistic research, compound 3 caused the cell cycle to stop at the G2/M phase and significantly impeded the migration and colony formation of H1975 cells. In addition, the results of tests such as DAPI staining, apoptosis, and western blotting revealed that compound 3 triggered the intrinsic apoptotic pathway, which ultimately resulted in the induction of apoptosis in H1975 cells. Through the use of molecular docking, it was discovered that compound 3 was able to successfully bind to the EGFR pocket (PDB designation: 5GNK) [18].

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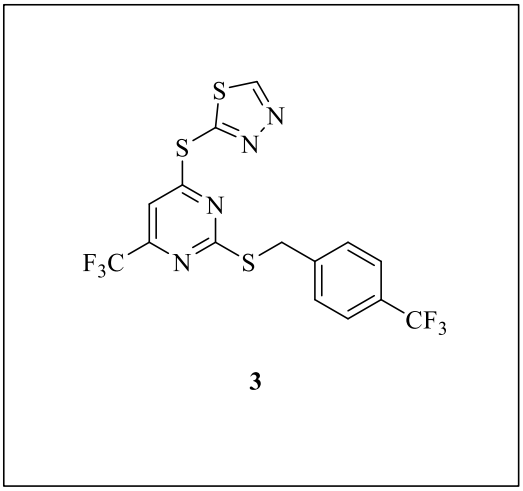
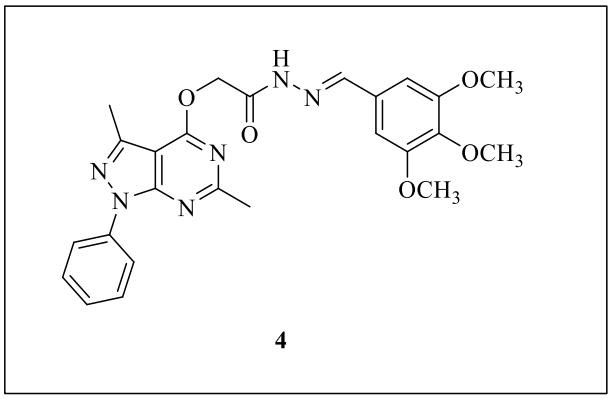


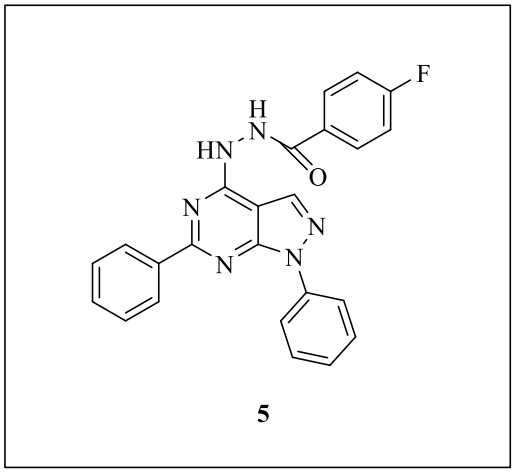
3

Abdelgawad *et al.*, The pyrazolo [3,4-d] pyrimidin-4-yloxy)-N-(4-substitutedbenzylidene) ring led to the development of a variety of novel acetohydrazide derivatives. For the purpose of determining whether or not they have cytotoxic properties, human colorectal adenocarcinoma (HT-29), non-small cell lung cancer (A549), breast carcinoma (MCF-7), and newly synthesized compounds were put through test. With an IC50 range of 5.36-9.09μM, N-(3,4,5-trimethoxybenzylidene)-2-(3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)aceto hydrazide 4 had the most potent anticancer activity among all the compounds that were investigated. These compounds were able to bind to the active site of EGFR-TK and potentially block these receptors, as indicated by the fact that compound 4 had the highest scoring energy (28.89 kcal/mol) among the target compounds [19].



4

Gaber *et al.*, A series of thirty-one pyrimidine derivatives that contain pyrazolo[3,4-d] groups was designed and manufactured by the researcher. After evaluating the inhibitory activity of the compounds that were produced against EGFRWT, a comparison was made between these compounds and erlotinib. The majority of the compounds that were synthesized in this study had an EGFRWT inhibitory activity that was more potent than the action of erlotinib compounds. The IC50 values of these compounds ranged from 0.09±0.11 to 0.41±0.21 μM. The anti-proliferative characteristics of these medications were investigated in respect to four cancer cell lines: MCF-7, HepG2, A549), H1975, and HCC827. Each of these cell lines carries the $EGFR^{WT}$ gene. Additionally, the HepG2 cell line was utilized in order to investigate the influence that the most active chemical, number 5, has on the progression of the cell cycle and the induction of apoptosis. The G0/G1 and G2/M phases of the cell cycle are both susceptible to being stopped by it, and it also has apoptotic effects. In addition, molecular docking studies were carried out in order to determine the pattern of binding that the synthetic molecules $EGFR^{T790M}$ and $EGFR^{WT}$ (PDB ID: 4HJO) exhibit. It was observed that the synthesized compounds exhibited suitable binding modes and binding energies that were satisfactory [20].



5

Elmetwally *et al.*, as well as planned, combined, and evaluated There were sixteen thieno [2,3-d] pyrimidine derivatives that were studied for their inhibitory actions against $EGFR^{WT}$, $EGFR^{T790M}$, and HER2 kinases. Next, we assessed the inhibitory activity of the compounds that were tested against four different cancer cell lines (HepG2, HCT-116, MCF-7, and A431) in vitro. We compared the compounds that were tested to erlotinib, which served as a positive control. Three of the compounds that were produced in this inquiry displayed an inhibitory effect on growing cell lines, with IC50 values ranging from 7.592±0.32 to 16.006±0.58μM. These values are equivalent to the standard control. Taking into consideration the outcomes of the SAR investigations, it would appear that the terminal hydrophobic head that incorporates the electron donating group substitution that is less burdensome is the most suitable alternative. The presence of a lengthy linker and a big hydrophobic head in 6 may be advantageous in certain circumstances. The ability of chemical 6 to cause cell death and influence the course of the cell cycle was another aspect that we investigated in MCF-7 cells. It was revealed that it produces apoptotic effects and has the ability to stop the cell cycle when it is in the G2/M phase. In addition, molecular docking experiments were carried

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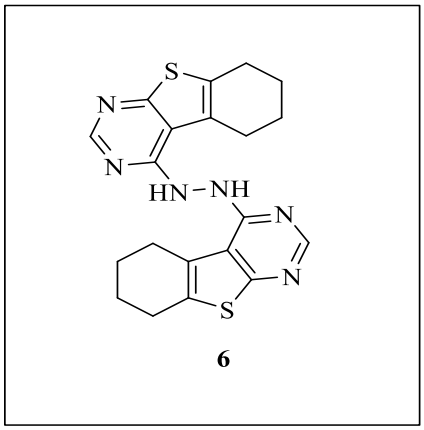
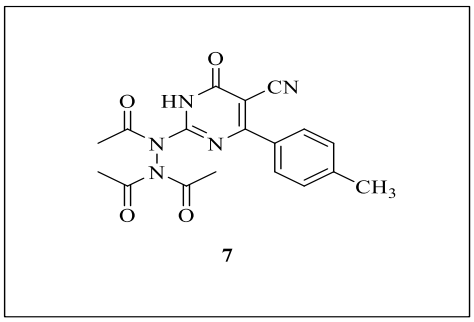
out in order to determine the pattern of binding that the compounds that were produced had against the $EGFR^{WT}$ and $EGFR^{T790M}$ receptors (PDB code: 4HJO). Significant binding modes and high binding energies were shown by the vast majority of the synthesized compounds [21].



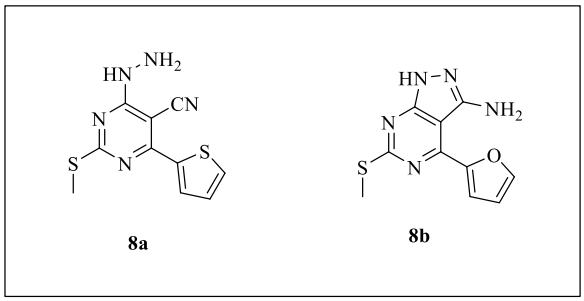
6

Amin *et al.*, In order to create and test a novel class of 6-aryl-5-cyano-pyrimidine derivatives as dual EGFR/HER2 inhibitors, we tested them against HePG-2, MCF-7, and HCT-116 cancer cell lines. An inhibitory effect on thymidylate synthase was observed to be exhibited by the compounds that appeared to be the most active. According to the data, compound 7 exhibited a significant anti-cancer activity and a substantial TS inhibitory impact, as indicated by its IC50 value of 3.89 µM. In order to evaluate the capability of chemical 7 to induce apoptosis, we carried out a series of apoptosis assays. According to the findings, the levels of active caspase 3 were shown to be enhanced by compound 7 by 7.3 times when compared to the control. When compared to the control, compound 8 exhibited a Bax/Bcl2 ratio that was 44 times higher than the control [22].



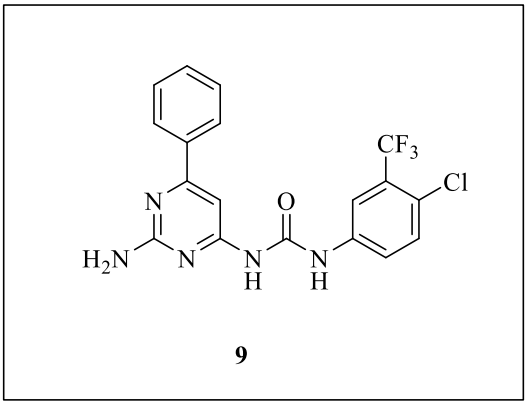
7

Ragab *et al.*, Utilizing three different sets of hydrazine pyrimidines, 2-pyr azolylpyrimidines, and 3-amino[3,4-d] pyrazolo pyrimidines, the National Cancer Institute (NCI) carried out cytotoxic activity testing in vitro on sixty different tumor cell lines. For the purpose of determining the IC50 values of five distinct derivatives, we conducted in vitro tests against cancer cell lines as well as normal cell lines. Among the compounds, compounds 8a and 8b were the most effective and specific in their targeting of the KM12 cell line. In order to determine whether the 8a or 8b derivatives were capable of activating caspases, the researchers utilized the KM12 cell line, which is a colon cancer cell line. The findings revealed a significant increase in the levels of caspase 3 (0.5217 and 0.5951 ng/mL) and caspase 9 (14.77 and 18.45 ng/mL) as compared to the untreated KM12 (0.04316 and 0.91 ng/mL, respectively). Both compound 8a and compound 8b were put through an in vitro Bcl-2 inhibition test in order to verify the apoptotic activity that they possessed. The annexin V-FITC labeling approach demonstrated that derivatives 5d and 7c had an apoptotic impact, and they also exhibited selective cytotoxic action against KM12 cells. It is probable that these derivatives could be useful as apoptosis inducers in the treatment of colon cancer [23].



8a **8b**

Kilic-Kurt *et al.*, The compounds 9 had the most pronounced cytotoxic impact against the SW480 cell line. These compounds were produced with a hydrophobic and stiff phenyl moiety at the 4-position of the pyrimidine ring. The IC_{50} value of these compounds was 11.08 µM. Compound 9 induced apoptosis in SW480 cells by elevating the expression of Bax, Ikb-α, and cleaved PARP, while simultaneously lowering the expression of Bcl-2. In addition, compound 9 has a considerable impact on the potential of the mitochondrial membrane in SW480 cells, which suggests that the intrinsic apoptosis pathway, which is mediated by mitochondria, is the cause of the apoptosis that is caused by compound 9. In light of these findings, it is clear that compound 9 possesses the potential to serve as a foundation for the creation of innovative anticancer medications [24].



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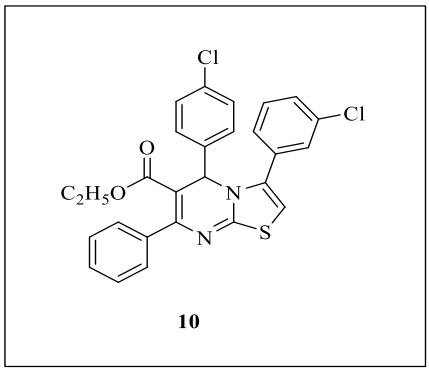
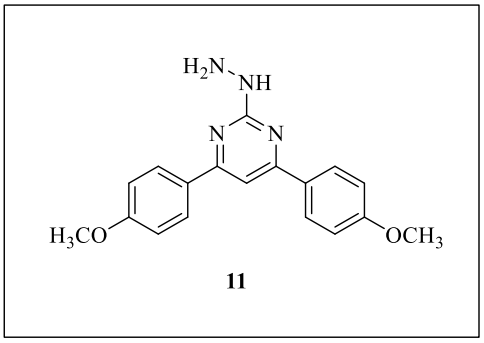
Nemr *et al.,* A variety of hydrobromides of triazolopyrimidines and thiazolopyrimidines were manufactured with the intention of evaluating the anticancer effects of these compounds on sixty distinct types of human cancer cells. Compound 10, which had an inhibition rate of 92.46% and an IC50 value of 3.5 µM, demonstrated a significant inhibitory effect on the renal cell line A498. Through the utilization of the MTT colorimetric experiment, it was established that compound 10 exhibited a higher level of inhibition on the A-498 renal cell line compared to doxorubicin (IC50 = 3.50µM versus 1.21µM). According to the results of the enzymatic assay, thiazolopyrimidine 10 exhibited a significant inhibitory impact on topoisomerase II, as evidenced by its IC_{50} value of 2.89 µM. This is in contrast to the reference chemical doxorubicin, which exhibited an IC50 value of 2.67 µM. A molecular modeling investigation of the generated molecule 10, with the PDB ID being 5GWK, provided validation for the results. The topoisomerase II complex exhibited a favorable docking contact energy of -5.436 kcal/mol throughout the process [25].



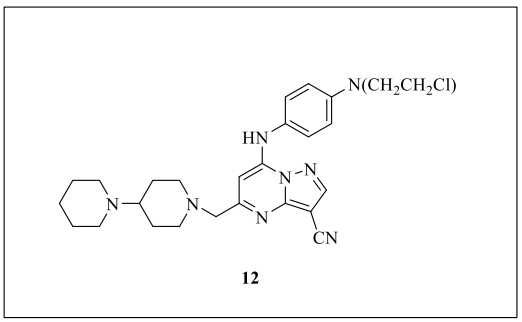
10

El-Naggar *et al.,* for the purpose of using them as inhibitors of both EGFR and VEGFR-2, two new series of pyrimidine and 4-methoxyphenyl pyrazole compounds were designed and synthesized. The anti-proliferative properties were evaluated using five distinct cancer cell lines: HepG-2, MCF-7, MDA-231, HCT-116, and Caco-2. Every one of these cell lines was tested. Compound 11 shown remarkable antiproliferative effects on all five cell lines that were evaluated, namely HepG-2, MCF-7, MDA-231, HCT-116, and Caco-2. The IC50 values for compound 11 were 3.74, 7.81, 4.85, 2.96, and 9.27 µM, respectively. With IC50 values of 12.49, 30.00, and 10.06 µM, respectively, compound 11 had a more potent antitumor impact against the Caco-2 cell line when compared to the three reference medicines. These medicines are doxorubicin, erlotinib, and sorafenib. Furthermore, compound 11, in particular, demonstrated superior performance in comparison to the reference drugs erlotinib (IC50 = 0.063 µM) and sorafenib (IC50 = 0.041 µM) when it came to inhibiting the activity of EGFR and VEGFR-2. The IC50 values for compound 11 were 0.071 and 0.098 µM, respectively. Compound 11, which had a 2-hydrazinopyrimidine ring and a 4-CH_3 phenyl group, was shown to have the most effective antiproliferative effects on the five cancer cell lines that were evaluated, as determined by the SAR analysis of the novel compounds [26].



11

Zhao *et al.,* For the purpose of conducting research on cancer, a battery of nitrogen mustard derivatives containing pyrazolo[1,5-a]pyrimidine rings was recently developed. When the N-mustard pharmacophore was linked at C-7 and various substituents were applied to the C-5 moiety, we demonstrated that a significant number of these pyrazolo[1,5-a]pyrimidine derivatives exhibited high levels of cytotoxicity in vitro. In the process of coupling the N mustard pharmacophore at C-5 and introducing a variety of aniline moieties to the C-7, derivatives were almost completely ineffective. The compound 12, which exhibited anti-proliferative activity against five distinct types of human cancer cells, was selected for further investigation. The IC50 values of this compound ranged from 0.22 to 8.32 µM, indicating that it was a promising candidate for further research. According to the findings of the researchers, compound 12 was able to trigger early cell death and block cell cycle arrest at the G1 phase stages. The previous research resulted in the selection of compound 12 for the purpose of evaluating its anticancer activity against a xenograft of human HepG2 HCC tumors in mice that were not exposed to any other substances. To a small extent, the results are superior to those obtained with cyclophosphamide and sorafenib, which are the medications that serve as the positive control. According on the information that has been supplied, compound 12 has the potential to be an effective anticancer agent [27].



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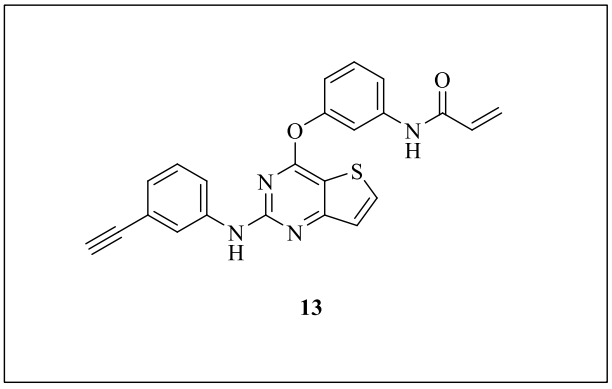
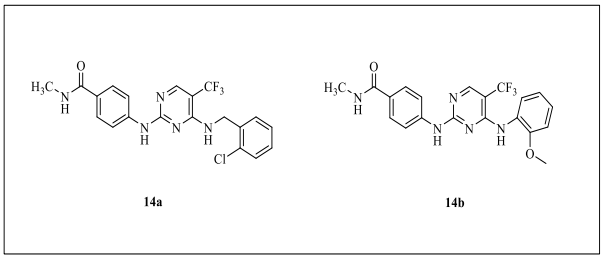
Xiao *et al.*, A total of five distinct series of thiophene pyrimidine derivatives were developed and manufactured by the authors of this work. The most promising chemical showed greater activity against A549, A431, and Hela, with values of 4.34 ± 0.60μM, 3.79 ± 0.57μM, and 6.39 ± 0.94μM, respectively. These values were virtually identical to the IC50 values of the lead drug Olmutinib. Specifically, compound 13 demonstrated its effectiveness against the H1975 cell line at the nanomolar level, with an IC50 value of 699.2μM. The IC50 values of target compounds are greater than 50 when they are evaluated against the normal cell line LO2, which indicates that they have the ability to selectively inhibit cancer cells. According to the findings of the inquiry into kinase activity, the chemical that was selected, number 13, possesses a high selectivity for EGFR, a low inhibition of KDR and CeMe, and a moderate activity toward PI3K and mTOR, all of which are located downstream of the EGFR signal pathway. EGFRT790M/L858R is specifically inhibited by 13 to the extent of 103.6% inhibitory efficacy. The use of acridine orange and Annexin V-FITC labeling in the tests further demonstrated that 13 has the potential to cause A431 cells to undergo late apoptosis in a dose-dependent manner [28].



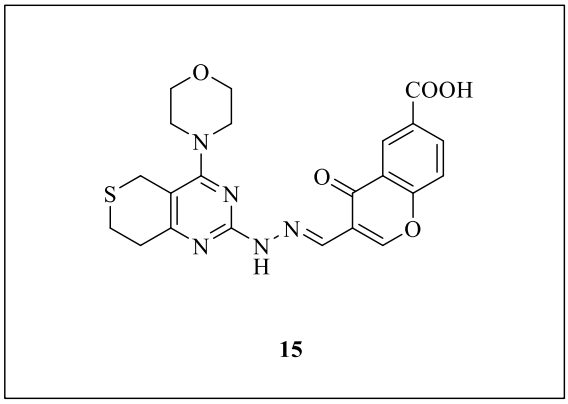
13

Wang *et al.*, An entire battery of N-alkylbenzamide-substituted DAPYs was designed, manufactured, and evaluated for their potential anti-cancer and anti-angiogenesis activities. The vast majority of the compounds were able to decrease the activity of the FAK enzyme in vitro. PANC-1 and BxPC-3, two of the pancreatic cancers that overexpress FAK, were among the seven human cancer cell lines that were severely inhibited by the two most effective inhibitors, 14a and 14b. These inhibitors were tested on seven different human cancer cell lines. Furthermore, in a dose-dependent manner, 14a and 14b were able to significantly limit the migration, invasion, and colony formation of PANC 1 cells. The anti-cancer effects of compounds 14a and 14b were confirmed by a flow cytometry assay. These compounds induced apoptosis in PANC-1 cells and stopped the cell cycle in the G2/M phase. Through their ability to inhibit the FAK/PI3K/Akt signal pathway, both compounds were able to significantly diminish the expression of cyclin D1 and Bcl-2. After conducting additional study on anti-angiogenesis, it was shown that 14a and 14b were able to successfully inhibit the antiproliferative, migratory, and tube formation processes of HUVEC neurons. When both compounds were delivered intravenously, they significantly reduced the amount of angiogenesis that occurred in zebrafish embryos [29].



14a **14b**

Sun *et al.*, designed, created, and evaluated a novel class of chromone-modified 4-morpholino-7,8-dihydro-5H-thiopyrano[4,3-d] pyrimidine derivatives for their anticancer activities against mTOR/PI3Ka kinases and five different cancer cell lines in vitro at the same time. According to the pharmacological data, the seven compounds that were synthesized exhibited cytotoxicity against the five cell lines that ranged from moderate to extraordinary. The IC50 values of these compounds ranged from 34.9 to 0.17 μM, which corresponded to the same level of chemical activity as the compound II that was reported before. With IC50 values of 1.1±0.10μM and 0.92±0.12μM, respectively, against mTOR kinase and PI3Ka kinase, compound 15, which is considered to be the most promising molecule, exhibited inhibitory effects that were comparable to or even greater than those of the lead compounds II and of compound III. In early SARs and docking investigations with mTOR and PI3Ka proteins, it was shown that the morpholine group, chromone moieties, and hydrazinyl group were necessary for these compounds to exhibit potent anticancer effects. This was determined by the fact that these compounds exhibited these effects. Alterations to the replacements of the chromone moieties had a significant impact on the activity, with the 6-COOH substitution producing the most successful outcomes [30].



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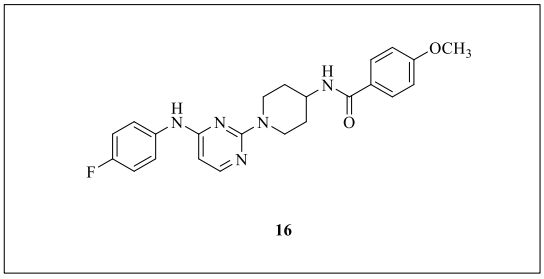
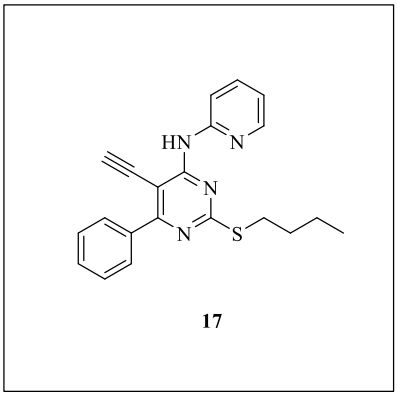
Wang *et al*., For the purpose of consideration as possible molecules, twenty-four structural analogs were developed. Through the utilization of molecular docking and MD modeling, it has been demonstrated that the complex system that involves compound 16-CDK2 is completely stable. The ability of compound 16 to induce S-phase arrest and apoptotic cell death appears to be responsible for this anti-proliferative impact. This is demonstrated by the time-dependent reduction in the proliferation of triple-negative breast cancer cells that was observed in the MTT assay. Both flow cytometry and western blotting, as well as fluorescence microscopy, provided additional evidence that compound 16 have the capability to induce cell death. The utilization of these findings will provide valuable insights for the development of small molecule medicines for the treatment of TNBC [31].



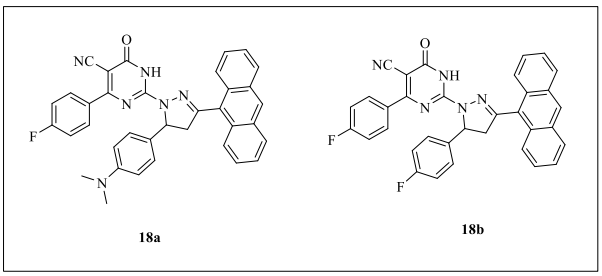
16

Eissa *et al*., a new class of pyrimidine-5 carbonitrile chemicals that serve as ATP-pretending tyrosine kinase inhibitors by targeting the EGFR (epidermal growth factor receptor) was created. Using four human malignant cell lines, the features of in vitro cytotoxicity were investigated. These cell lines were HCT-116 (colorectal carcinoma), HepG-2 (hepatocellular carcinoma), MCF-7 (breast cancer), and A549 (non-small cell lung cancer cells). An evaluation and synthesis of these analogues were carried out. In contrast to the EGFR inhibitor erlotinib, five target analogues were discovered that exhibited anti-proliferative activity against the cell lines that were investigated. These analogues had an average level of effectiveness. On HCT-116, MCF-7, A549, and HepG-2 cells, compound 17 in particular demonstrated an increase in erlotinib action that was between 4.5 and 8.4 times greater than the previous value. In addition, homogeneous time resolved fluorescence (HTRF) tests were utilized in order to assess the kinase inhibition capabilities of the highly cytotoxic analogues that demonstrated significant IC50 values when tested against the four cancer cell lines. The chemicals in question will be subjected to additional research in subsequent investigations. $EGFR^{WT}$ and $EGFR^{T790M}$ were exposed to Analogue 17, which proved to be the most effective of the three. The cell cycle and apoptotic tests indicate that compound 17 has the capability to produce considerable cell death in HepG-2, HCT-116, and MCF-7 cells. Additionally, at the G2/M stage of the cell cycle, compound 17 has the ability to arrest the cell cycle. Last but not least, the docking analysis was utilized in order to investigate the manner in which the synthesized analogues related to the predicted targets, which were $EGFR^{WT}$ and $EGFR^{T790M}$ [32].



17

Ahmed *et al*., Spectral and elemental studies were used to reveal the chemical structures of a new series of pyrimidine pyrazoline-anthracene hybrids. These hybrids were synthesized by a cyclo condensation technique that used 2-hydrazinopyrimdine derivatives and appropriate chalcones respectively. With DOX serving as a point of reference, we examined the antiproliferative properties of each of the compounds that were produced by testing them against normal fibroblast cells as well as two HCC cell lines, namely HepG2 and Huh-7. Not only that, but in their Huh-7 cell line activity testing, PPAD 18a and 18b performed better than DOX. The chemical 18a demonstrated a high level of effectiveness when tested against the HepG2 and Huh-7 cell lines. When further investigation into the mechanism of action was carried out, it was discovered that these compounds significantly activate caspase 3/7 at all of the dosages that were examined, hence causing apoptosis in the HepG2 and Huh-7 cell lines. The molecular modeling investigations came up with an additional hypothetical action mechanism that could be responsible for these compounds. In the same way as the DOX does, the tricyclic planar anthracene chromophore has the potential to intercalate with the DNA helix of the cancer cell. On the other hand, the remaining portion of the structure will be oriented in such a way as to establish a greater number of van der Waals interactions with the minor groove of the DNA [33].



18a 18b

μ

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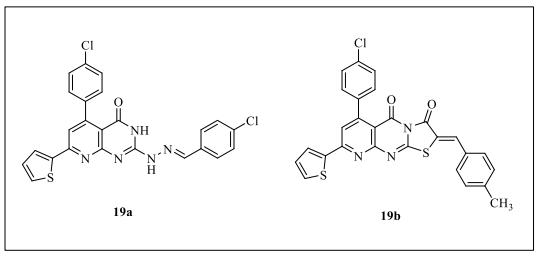
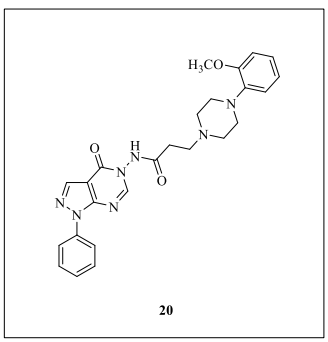
Abbas *et al*., In addition to normal fibroblasts (WI-38), we synthesized and analyzed a number of novel bicyclic and tricyclic pyridopyrimidines for their cytotoxic effects on breast, lung, and prostate cancer cell lines (MCF-7, A549, and PC-3, respectively). These cell lines were used to test the cytotoxic effects of the compounds. Among these, compounds 19a and 19b stood out because to their greater action against the cell lines that were evaluated at submicromolar levels in comparison to doxorubicin. Overall, they demonstrated moderate to strong activity. Compounds 19a and 19b were shown to induce apoptosis in MCF-7 and PC-3, respectively, by activating caspase-3 in PC-3, Bax, and p53, downregulating Bcl2, and inhibiting CDK4/6. These compounds were found to be responsible for these effects. Furthermore, it is worth noting that compound 19a exhibited direct inhibition of CDK6 with an IC50 value of 115.38 µM, whereas compound 19b exhibited an IC50 value of 726.25 µM [34].



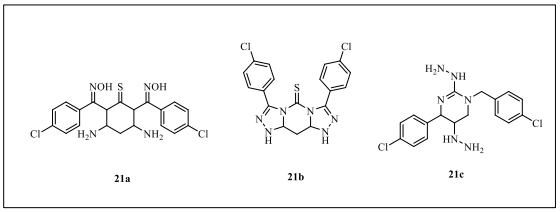
19a 19b

Abd El Razik *et al*., The purpose of this research was to create new pyrazolo[3,4-d] pyrimidines and investigate their anticancer and COX-2 inhibitory properties. The ultimate objective was to identify potential lead compounds that do not have the gastrointestinal side effects that are associated with conventional anticancer and nonsteroidal anti-inflammatory medications (NSAIDs). According to the findings, compound 20 demonstrated a significant inhibition of COX-2 protein expression in rat peripheral blood mononuclear cells that were stimulated by lipo polysaccharide (LPS) at a concentration of 25 micrograms per milliliter. As an additional point of interest, the findings of the antineoplastic activity tests were in agreement with these findings, with the exception of one molecule that did not exhibit any activity and twenty compounds that displayed inhibitory action that was relatively substantial [35].



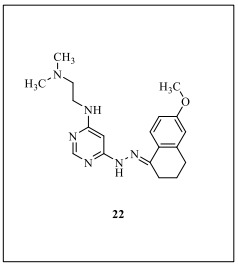
20

Abu-Hashem *et al*., Novel pyrimidine and thiourea compounds were created and manufactured by the company. The fact that a handful of the produced chemicals were shown to be sensitive to a number of human cancer cell lines provides evidence that these molecules may demonstrate cytotoxic properties. When compared to 5-fluorouracil, it was shown that compounds 21a, 22b, and 22c have substantial cytotoxic effects against cancer cell lines that were even more potent or comparable to those of 5-fluorouracil. Due to these findings, we have decided to continue our research on new thiourea and pyrimidine moieties in order to gain a deeper understanding of SAR and the mechanisms by which they exert their effects [36].



21a 21b 21c

Tylińska *et al*., A wide variety of responses were seen from a number of different cell lines in response to freshly synthesized pyrimidine derivatives. The findings suggest that the chemicals that were investigated might possess anticancer qualities; however, it is important to note that these properties might vary depending on the type of tumor that is being investigated. Based on the findings, it appears that the chemicals that are now being investigated might have beneficial therapeutic applications in the treatment of cancers that are resistant to doxorubicin. If the compounds under investigation have a stronger affinity to the 1-octanol phase, then they have a larger probability of infiltrating cancer cells, according to the findings of research on lipophilicity, which has the capacity to expose this information. The findings of this study indicate that Topo II is often overexpressed in a variety of tumor cell types, notably during the G2/M phase of the cell cycle and in particular. Their inhibition leads to the occurrence of apoptosis as well as double-strand breaks in DNA. According to the results of our investigation, the compounds that have been proposed have the ability to intercalate DNA and also block Topoisomerase II. Furthermore, it is feasible for all derivatives to decrease the number of cells that are in the S phase and the G2/M phase of the cell growth process. They all contribute to the demise of cells [37].



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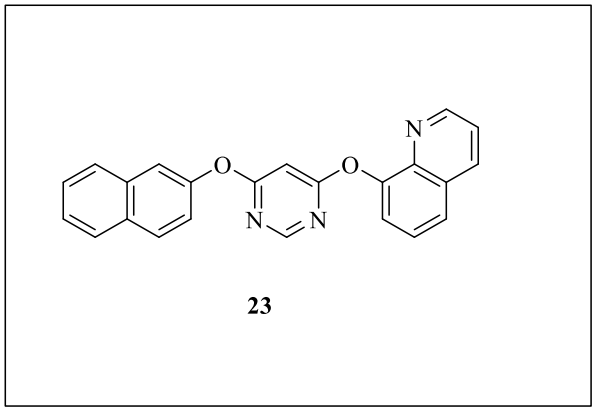
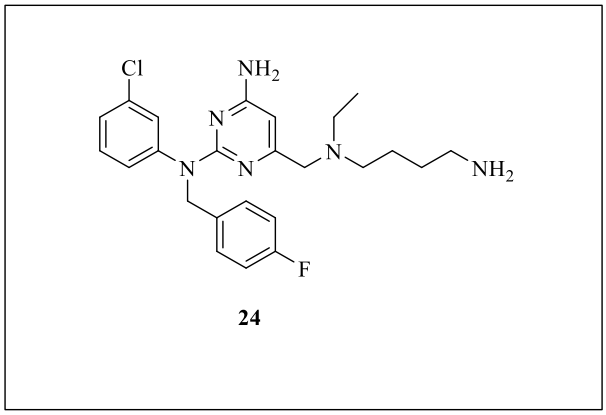
Jameel *et al.*, The results of his research showed that, despite the fact that CAMKIV plays a crucial part in the regulation of essential physiological processes, very little effort has been put into the development of inhibitors that specifically target this protein. Using this method, we were able to successfully construct seven candidate ligands of CAMKIV and then conduct tests to evaluate their cytotoxicity, anticancer capabilities, and PI characteristics. According to the findings of the study, compound 23 contains all of the necessary features to be studied as a potential pharmacophore. These experiments shed information on the search for potent CAMKIV inhibitors by further exploring target selectivity, cellular efficacy, therapeutic efficacy, and tolerance. These investigations were conducted in order to examine these topics. As a further point of interest, the results of our structural analysis inquiry have demonstrated that the CAMKIV exhibits a specific selectivity as well as a distinctive structural characteristic. The inhibition of CAMKIV may be helpful in a number of ways, including the prevention of phosphorylation activity and the disruption of protein-protein interactions, both of which are necessary for the end of several cellular cascades. Lastly, but certainly not least, the findings of our research on novel inhibitors pave the way for the potential application of pyrimidine derivatives in the treatment of disorders that are associated with CAMKIV [38].



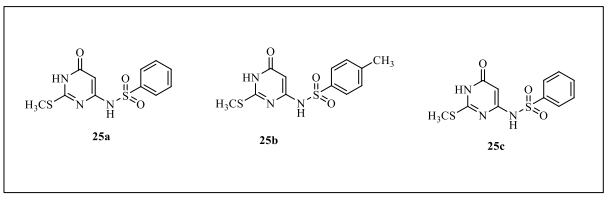
23

Madia *et al.*, A significant issue that has not yet been tackled is the development of innovative and effective anticancer medications. By making modifications to position 6 of the pyrimidine core and/or on the 2-aniline ring, we were able to synthesize a new series of aminopyrimidine derivatives that are structurally connected to RDS 3442. From our research on structure-activity relationships, we learned that the aminopyrimidine core can be enhanced by adding either: (i) a p-F benzyl ring to the aniline residue's nitrogen in 2-position and a primary aliphatic base, such as propanediamine, in 6-position; or (ii) a secondary aliphatic base, such as dipropylamine, in 6-position without the N-benzyl ring connected to the aniline substituent in position 2. 24 was the most effective molecule; it reduced cell viability across all cell lines studied at a rate that was four to thirteen times quicker than the hit compound, with EC50 values ranging from four to eight M. The N-benzyl analogue of RDS 3442 was the most effective molecule [39].



24

Awad *et al.*, Certain compounds that had been created and designed in the past underwent additional structural modifications in order to improve their effectiveness. The purpose of these investigations is to examine the role that the spacer plays in the particular biological anticancer action described above. In terms of the anticancer activity of the compounds that were investigated, the cell lines HT-29 (which represents colon cancer) and HEPG2 (which represents human liver) had the highest level of sensitivity. Compounds 25a, 25b, and 25c exhibited the highest levels of antiproliferative activity in comparison to other compounds when applied to human liver HEPG2 in this particular study. Only compound 25a, on the other hand, demonstrated a moderate effect when compared to the other compounds under consideration in the case of colon cancer HT 29 [40].



25a **25b** **25c**

III. CONCLUSION

As therapeutic chemistry and drug development targets, a number of pyrimidine ring and fused derivatives have proven to be effective. These include quinazoline, furo[2,3-d]pyrimidine, pyrazolo [3,4-d]pyrimidine, and pyrido[2,3-d]pyrimidine, among others. By inhibiting PKs, these scaffolds were able to exert their influence; PKs are enzymes that play a crucial role in controlling the proliferation, motility, and metabolism of cells. The field of pyrimidine chemistry is still expanding, despite the fact that there is a mountain of literature on pyrimidines. When compared to its predecessors, this more recent family of pyrimidines possesses significantly enhanced

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biological properties. As a result of the information that has been presented in this review, it is anticipated that new synthetic procedures will be created. These strategies are anticipated to result in the synthesis of molecules that are more effective, with better selectivity and anticancer activity.

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