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Research Article

Role of Pyridine and Pyrimidine-Based Kinase Inhibitors in Cancer Treatment: Selectivity, Resistance, and Next-Generation Designs

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Abstract
Pridine and pyrimidine scaffolds are important heterocyclic compounds; considerable attention is being paid to the development of anticancer drugs due to their utility as the foundational building blocks of DNA and RNA. Derivatives of pyridine are well established for their profound pharmacokinetic profiles, such as satisfactory solubility and metabolic stability, along with having demonstrably potent activity against important cancer targets like EGFR and VEGFR-2. Beyond their potential anticancer activity, a number of pyridine-based therapeutics offer diverse pharmacology, such as vasodilation and other relevant activities, broadening the scope of their therapeutic utility. The fused and standalone systems of pyrimidine derivatives have demonstrated impressive cytotoxic activity and interact with key molecular targets, primarily kinase enzymes, such as EGFR and VEGFR-2, which continue to be the focus of extensive investigation. This review, which includes the results from 2009 to 2024, synthesizes synthetic strategies. Compounds exhibiting kinase inhibition, DNA-binding affinity, and apoptosis induction are discussed, with emphasis on molecular docking insights and cytotoxic profiles across multiple cell lines. A comparative evaluation of their pharmacokinetic properties, scaffold advantages, and dual-inhibition strategies is also conducted. The review also outlines future directions for optimizing scaffolds, validating their mechanisms, and exploring their translational potential in oncology.

Keywords: Pyridine-Pyrimidine, Kinase & EGFR inhibition, VEGFR-2 targeting, Anticancer agents, SAR, Drug Resistance

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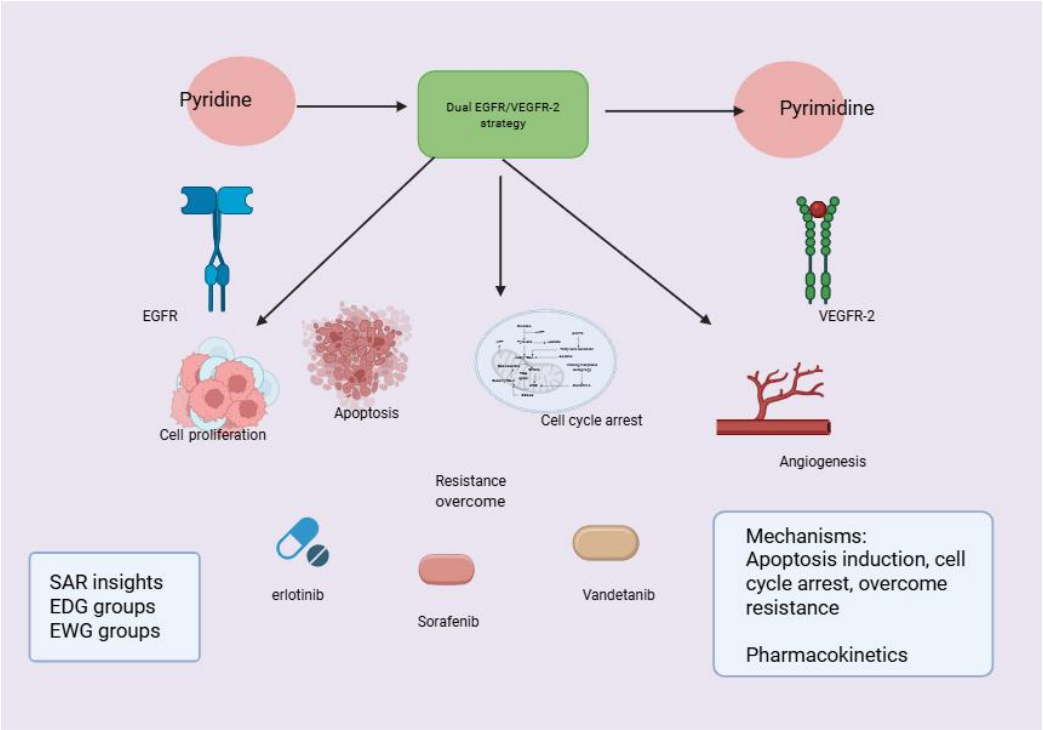


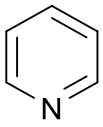
Fig: Key Aspects of Pyridine and Pyrimidine Scaffolds

1. Introduction

Despite advances in treatment, cancer remains one of the most challenging diseases facing modern medicine(1–4). In response to this critical health challenge, medicinal chemists are actively working on the creation of impactful and selective chemotherapeutic medications(5,6). These drugs are designed to suppress cancer cell proliferation, targeting the precise therapeutic binding sites, thereby minimizing damage to healthy cells(7,8). However, major challenges such as drug resistance, poor selectivity, and inefficient delivery affect the success of many therapeutic candidates(9,10). To address these limitations, there is growing interest in understanding the cellular and molecular mechanisms underlying cancer initiation, progression, and resistance(11,12). Protein kinases (PKs) are the top candidates in anticancer treatment, which have significant impact in regulating vital cellular functions including programmed cell death, cell cycle control, genomic maintenance, and cellular metabolism(13–16). Their Dysregulation or overexpression commonly results into various kinds of malignancies. The epidermal growth factor receptor (EGFR),a transmembrane tyrosine kinase, is frequently upregulated in tumors like colon, breast, and ovarian cancers, which serves as a specific identified target for developing cancer medications. Activation of EGFR initiates the signaling pathways for promoting cell growth, angiogenesis, and metastasis(17). The FDA-approved medication erlotinib is one example of a clinically established EGFR inhibitor in the treatment of cancer(18). Through binding to its receptors, VEGRF-2, EGFR activation stimulates the upregulation of VEGF (vascular endothelial growth factor), a major driver of tumor angiogenesis that promotes the formation of blood vessels and tumor growth(19). As a result, VEGFR-2 inhibitors like sorafenib have also gained FDA approval for their anticancer activity (20). Due to the interaction between the EGFR and VEGFR-2 pathways, dual inhibition of both receptors has become a promising therapeutic strategy. Inhibition of EGFR decreases VEGF expression, while blocking VEGFR-2 may enhance the effectiveness of EGFR inhibitors(21). Vandetanib, a dual EGFR/VEGFR-2 inhibitor, is already approved for treating thyroid cancer, demonstrating the clinical potential of this approach(22,23). Structurally, EGFR and VEGFR-2 inhibitors share key pharmacophoric features, particularly a hydrophobic head, a hydrogen bond donor (EGFR) or both donor and acceptor (VEGFR-2), a heteroaromatic spacer, and a hydrophobic tail. These common features allow for the strategic development of “dual-targeting inhibitors”(24–26). Pyrazole, pyridine, and pyrimidine-like scaffolds have shown high potential as kinase inhibitors, due to their ability to mimic ATP and form essential interactions in the kinase active site(27–32).

Pyridine and pyrimidine scaffolds offer strong anticancer potential to bind various kinase targets, including drug-resistant mutants such as EGFR T790M, due to their favorable electronic properties. Studies have revealed that several pyrimidine-based derivatives retained activity against resistant cancer forms by forming irreversible covalent bonds or accommodating conformational changes in mutant kinases. In this context, our study reports the creation of novel 4-thiophenyl-substituted compounds based on pyrazole, pyridine, and pyrimidine scaffolds as potential dual EGFR/VEGFR-2 inhibitors. In addition to their anticancer potential, these heterocyclic cores have also demonstrated promising antimicrobial properties

(33,34), which motivates us to evaluate the antibacterial and antifungal activities of the recently developed compounds, along with their anticancer potential. Moreover, this study aims to establish the critical parameters like structure-activity relationship (SAR) insights, compare pharmacokinetic profiles, and critically evaluate their potential to overcome significant clinical challenges such as drug resistance and lack of specificity.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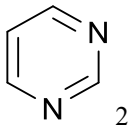
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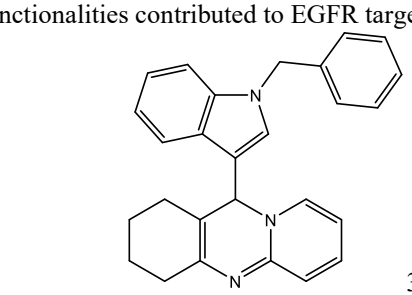
2. Pyridine scaffolds as anticancer agents: Targeting Key Biological Pathways

2.1 Biological action of Pyrimidine-based derivatives

2.1.1 Pyridine Derivatives Targeting Cell Cycle and Apoptosis

Post-translational regulation of cyclin-dependent kinases (CDKs) is crucial for cellular replication. These pyridine-based derivatives function as inhibitors of CDK (cyclin-dependent kinase) by influencing phosphorylation processes and interacting with regulatory proteins, such as cyclins, whose activity is finely regulated through targeted proteasomal degradation. Therefore, many researchers have targeted the cell cycle as a means to develop anticancer therapies. Pyridine, a nitrogen-containing heterocycle, has gained attention for its role in modulating key cellular pathways involved in tumorigenesis. This review focuses on synthetic pyridine derivatives and their anticancer activities, emphasizing their molecular targets, cytotoxic profiles, and SAR insights.

Bathula et al. (2019) synthesized pyrido[2,1-b]quinazoline derivatives. *Compound 3* showed potent cytotoxicity against A549 and NCI-H460 cells ($IC_{50} \approx$ 4.5–5.5 μM).SAR indicated that bulky benzyl-indole groups enhance EGFR kinase binding(33). **Eldehna et al. (2019)** developed phenylurea-linked pyridine derivatives. *Compound 4* induced apoptosis via Bax, p53, and caspase activation. Electron-donating groups improved potency; the urea linkage mimicked hydrogen bonding with EGFR(34). **AbdelHaleem et al. (2020)** introduced 3-cyano-6-naphthylpyridine inhibitors. *Compound 5* arrested the S-phase and upregulated p53/p21. Cyano and naphthyl groups enhanced VEGFR-2 binding and metabolic stability(35). **Boraei et al. (2021)** reported 4,6-diaryl-3-cyano-2-pyridone derivatives. *Compound 7* showed selective cytotoxicity against HepG2 cells. Cyano groups and π-donor substituents improved PIM-1 kinase inhibition(36). **Sigalapalli et al. (2021)** synthesized imidazo[1,2-a]pyridine–oxadiazole hybrids. *Compound 8* inhibited tubulin polymerization and showed strong lung cancer activity. SAR highlighted the importance of fused ring systems and oxadiazole linkages(37). **Dawood et al. (2021)** developed chromene–pyridine hybrids with vasodilatory and anticancer effects. *Compound 9* blocked cell cycle progression and activated caspase-3. Cycloheptyl rings and electron-rich aryl groups enhanced cytotoxicity(38). **Aruchamy et al. (2023)** investigated imidazole–pyridine hybrids. *Compound 10* inhibited GSK-3β and showed liver cancer efficacy. Docking studies supported steric and electronic contributions to potency(39). **Ashmawy et al. (2023)** synthesized thiazolyl–pyridine–thiophene hybrids. *Compound 12* (para-chloro-phenyl) showed high potency against A549 cells. Hydrazone and nitrile functionalities contributed to EGFR targeting(40)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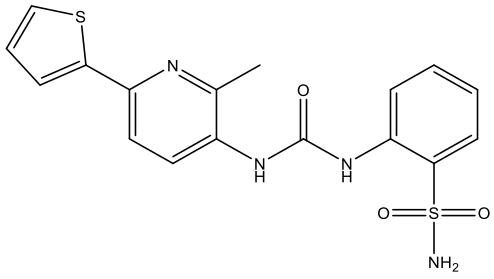
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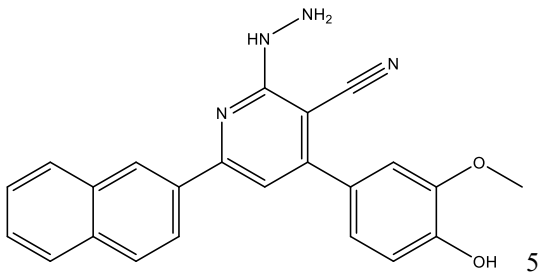
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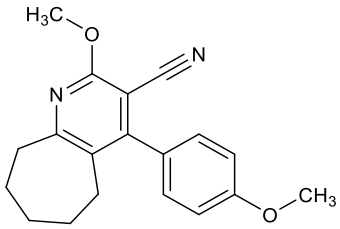
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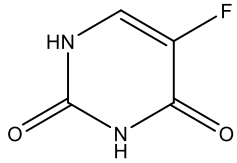
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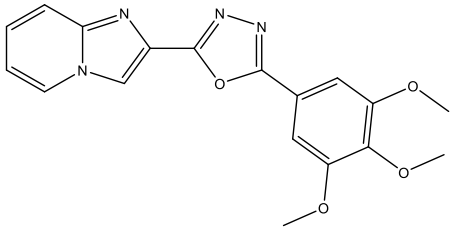
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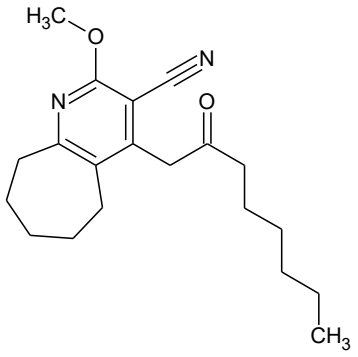

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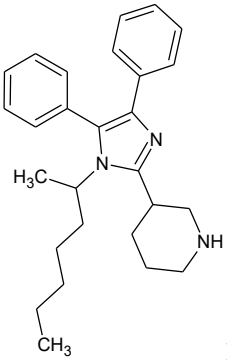

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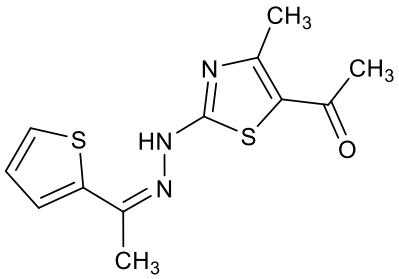

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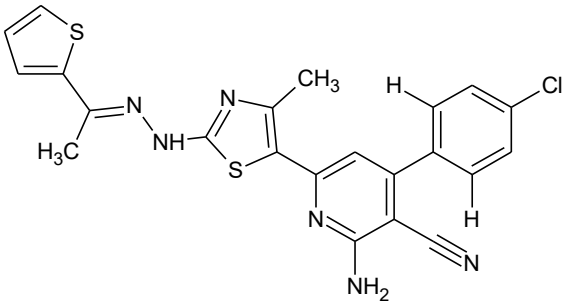

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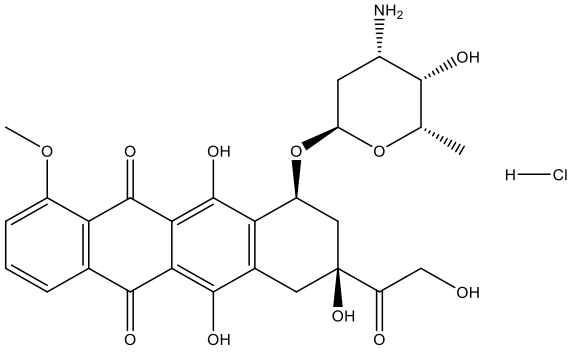
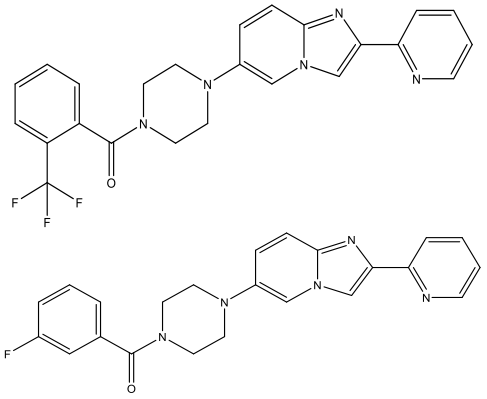


13(Doxorubicin)

2.1.2 Anti-Tumorigenic Properties of Synthetic Pyridine Derivatives

Several synthetic pyridine derivatives have demonstrated notable anti-tumorigenic activity, with evidence from molecular docking studies as well as in-vitro cytotoxicity suggesting therapeutic potential.

Gangireddy et al. (2019) created fluorinated imidazo[1,2-a]pyridines. *Compounds 14 & 15* showed cytotoxicity comparable to paclitaxel. Piperazine and CF_3 substitutions enhanced receptor binding(41). ***Prasad et al. (2020)*** synthesized imine-based phenanthroline derivatives. *Compounds 16 & 17* induced apoptosis via DNA interaction. Schiff-base linkers and hydroxyl groups improved solubility and activity(42). ***Silva B.R. and his team (2021)*** developed thieno[3,2-b]pyridine carboxylates. *Compound 18* selectively killed MDA-MB-231 cells. Para-chloro substitution and thieno-pyridine core were key SAR features(43)**.** ***Venugopal et al.(2015*** introduced pyrazoline–pyridine hybrids. *Compounds 19–21* showed strong activity against A549 and liver/breast cancers. Indole and carboxamide groups enhanced AhR binding. They used isatin (22) as a reference(44)**.** ***Alharthy et al. (2023)*** synthesized pyrazolo–pyridine/naphthyridine derivatives. *Compounds 23 & 24* halted cell cycle and activated intrinsic apoptosis. Chloro and methyl substitutions improved potency(45).



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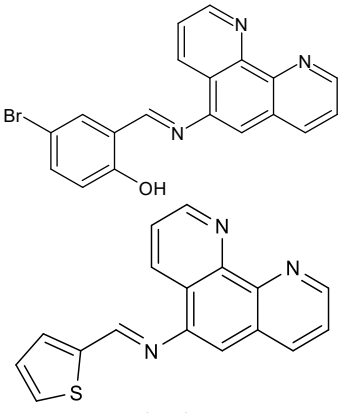

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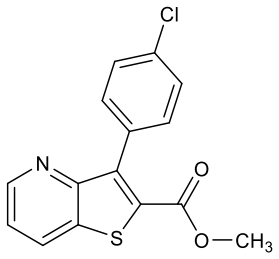

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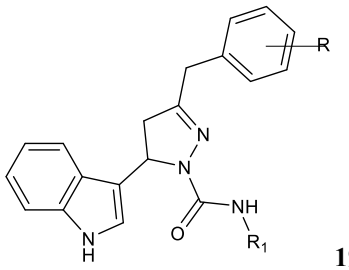

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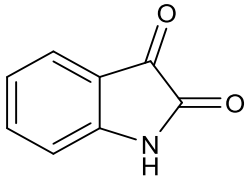
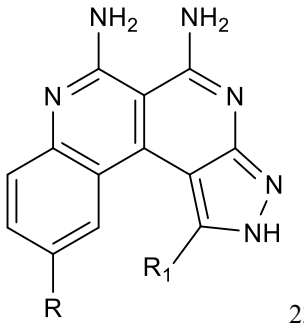


22

S.No	R	R1
19	**OH**	**Pyridin-2-yl**
20	**OH**	**Pyridin-4-yl**
21	**OH**	**Phenyl**

Table 1: Substitutions at R and R_1 position

Table 2: Different substitutions at R and R_1 position



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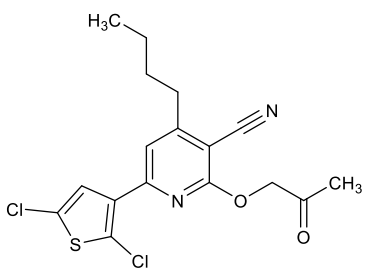
S. No	R	R1
23	F	CH_3
24	Cl	CH_3

2.1.3. Cytotoxic Potential of Synthetic Pyridine Derivatives

Ibrahim et al. (2019) developed nicotinonitrile and furo[2,3-b]pyridine compounds. Compounds 25 & 26 showed high selectivity for cancer cells over fibroblasts(46). ***Murugavel et al. (2019)*** developed the topoisomerase IIα moiety targeting BTPTs , where Compound 27 showed sub-micromolar potency and favorable ADMET profile(47). ***Ivasecho et.al.(2022)*** reported pyridine thiazole hybrids. Compound 28 disrupted DNA replication and showed synergy with PARP1 inhibitors(48). ***Elmorsy et al. (2022)*** synthesized multi-scaffold heterocycles. Compounds 31–34 showed ATP-site binding and broad-spectrum efficacy(49). ***Chakraborty et al. (2022)*** developed 1,2,4-triazole–pyridine hybrids. Compound 35 showed moderate activity against melanoma cells(50). ***Shaban et al. (2023)*** synthesized oxadiazole–nicotinonitrile hybrids. Compound 36 inhibited PIM-1 and induced apoptosis in MCF-7 cells(51). ***Mehany and coworkers (2024)*** used green chemistry to create pentose-linked pyridine analogues. Compound 37 was the top-notch molecule, proven by in vivo tumor suppression and sarcoma targeting (52). Pyridine–based scaffolds, which have a range of structural variations that target specifically essential oncogenic pathways, play a critical role in the development of anticancer therapies. Continued exploration of SAR, mechanistic studies, and in vivo validations will be essential to translate these promising compounds into clinical candidates.



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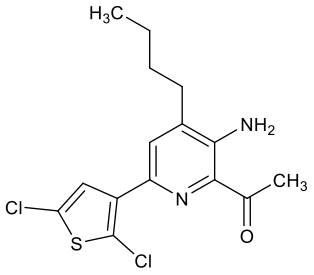

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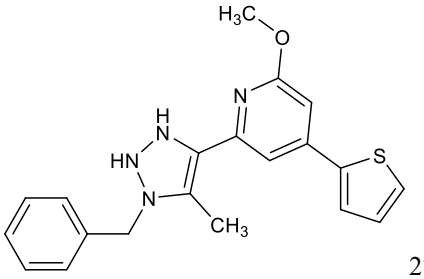

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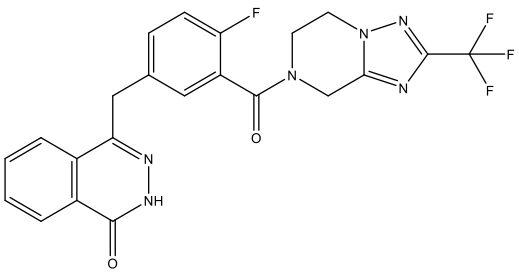

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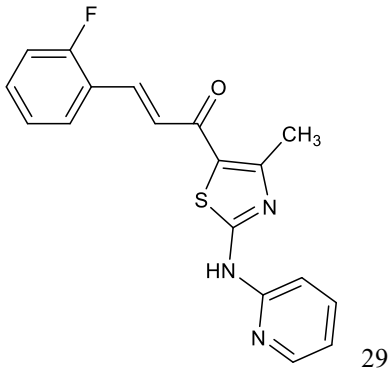

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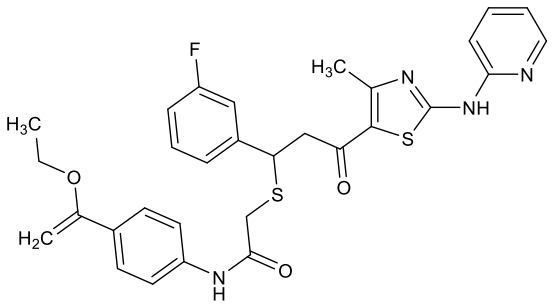

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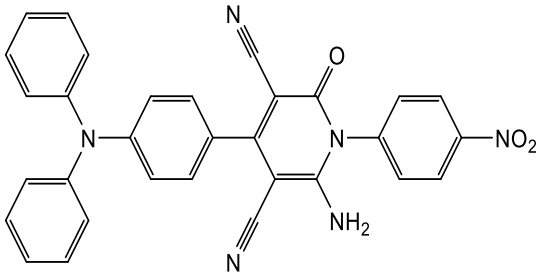

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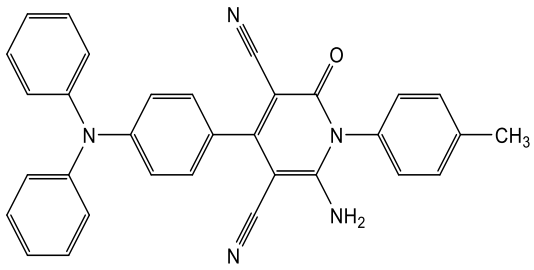

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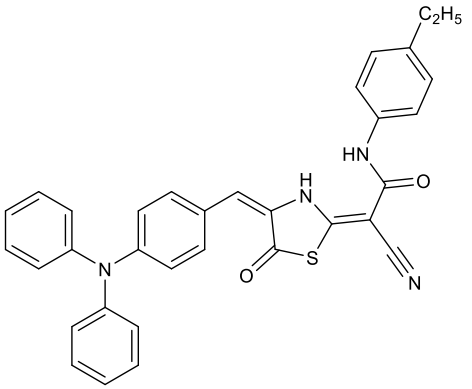

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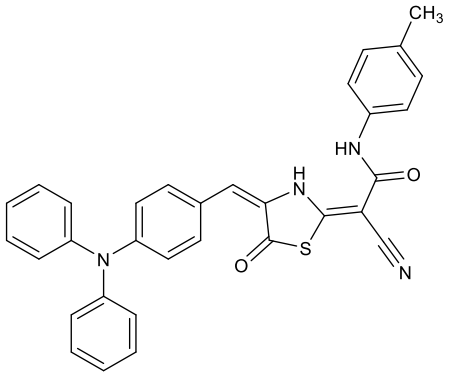

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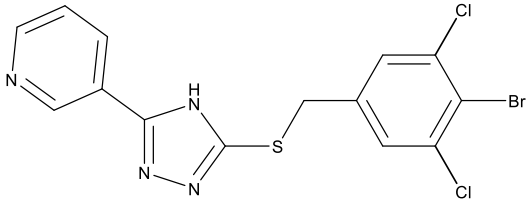

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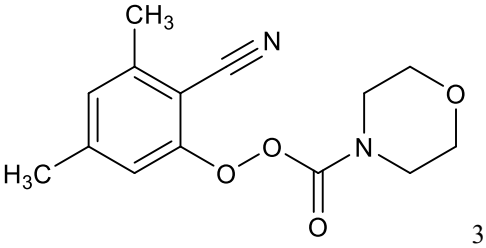

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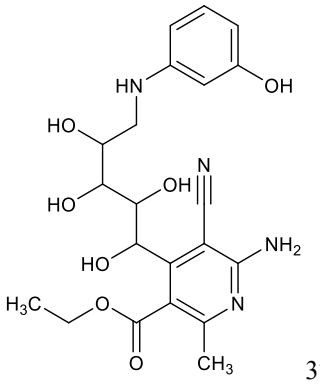

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Table 3. Pyridine derivatives targeting EGFR and VEGFR-2

Compound/Series	Target	IC_{50} / Activity	SAR Insight	Reference
3	EGFR kinase	A549 IC_{50} = 4.57 µM; NCI-H460 IC_{50} = 5.53 µM	enzyl-indole at position 11 enhances EGFR binding	Bathula et al., 2019
4	EGFR kinase	A549 IC_{50} = 3.22 µM; HCT-116 IC_{50} = 2.71 µM	Electron-donating aryl groups improve potency; urea linkage aids H-bonding	Eldehna et al., 2019
5	VEGFR-2	Sub-nanomolar IC_{50}; cytotoxicity against MCF-7, PC3	6-Naphthyl substituent essential for hydrophobic interactions; cyano group enhances binding	AbdelHaleem et al., 2020
7	PIM kinase	HepG2 IC_{50} = 6.98 µM	Cyano group at C3 improves H-bonding; aryl substituents at C4/C6 modulate potency	Boraei et al., 2021
8	Tubulin	IC_{50} = 3.45 µM	Imidazo[1,2-a]pyridine–	Sigalapalli et

	polymerization		oxadiazole hybrid enhances tubulin binding	al., 2021
9	EGFR / Apoptosis induction	MCF-7 IC_{50} = 4.55 μM; MDA-MB-231 IC_{50} = 9.87 μM	Pyridine-3-carbonitrile core essential; cycloheptyl substitution increases potency	Dawood et al., 2021
10	GSK-3β	Significant cytotoxicity (H1299, HCT116)	Imidazole–pyridine hybrid drives GSK-3β binding and activity	Aruchamy et al., 2023
11–12	Predicted EGFR kinase	A549 IC_{50} = 0.302 μM	Thiophene–thiazole–hydrazone–pyridine hybrids increase potency; para-Cl improves activity	Ashmawy et al., 2023
14–15	Estrogen receptor / general cytotoxicity	Compound 14 HeLa IC_{50} = 5.8 μM; Compound 15 HeLa IC_{50} = 3.5 μM; others varied	Piperazine-linked imidazo[1,2-a]pyridine increases activity; Ar-CF3 affects potency	Gangireddy et al., 2019
16–17	DNA-binding / general cytotoxicity	IC_{50} range ≈ 14.82–23.86 μM	Imine (Schiff-base) linker modulates potency; hydroxyl improves solubility	Prasad et al., 2020
18	General cytotoxicity (TNBC)	GI_{50} (MDA-MB-231) = 13 μM	Para-chloro phenyl improves activity; electron-donating groups reduce potency	Silva et al., 2021
19–21	AhR-ARNT complex related cytotoxicity	IC_{50} = 2.32–3.02 μM (A549)	Hydroxyphenyl and indole/carboxamide motifs enhance activity	Venugopal et al., 2015
23–24	General cytotoxicity (HeLa, MCF-7)	HeLa ~6.4 μM; MCF-7 ~2.03 μM	The methyl group and chloro substitution enhance cytotoxicity	Alharthy et al., 2023
25–26	Panel screening (multiple targets)	IC_{50} < 20 μM; high selectivity (40–287 fold over normal fibroblasts)	Furo[2,3-b]pyridine scaffold superior to nicotinonitrile; thiophene and benzoyl-chlorophenyl substituents are important	Ibrahim et al., 2019
27	Topoisomerase IIα	MDA-MB-231 IC_{50} = 0.88 μM	Planar thiophene–triazole–pyridine scaffold enhances Topo IIα inhibition via π–π stacking	Murugavel et al., 2019
28–30	PARP1 / general cytotoxicity	Compound 28 (HL-60) IC_{50} = 0.57 μM; compounds 29–30 active	2-Fluorophenyl and thiazole linkage increase potency; PARP1 synergy with Fluzaparib	Elmorsy et al., 2022
31–34	ATP-site targeting (various)	Compounds 31–32 IC_{50} ≈ 0.0103–0.0147 μM; compound 33 best docking (−9.35 kcal/mol)	Electron-rich aryls and N, N-dimethylaniline substitutions favor potency; active methylene substitution reduces activity.	Elmorsy et al., 2022
35	General cytotoxicity (B16F10 melanoma)	IC_{50} range 41.12–61.11 μM; compound 35 IC_{50} = 41.12 μM	1,2,4-Triazole–pyridine core moderate activity; para-halogen (Br) improves potency	Chakraborty et al., 2022
36	PIM-1 kinase	PIM-1 inhibition 97.5% (IC_{50} = 14.3 nM); ↑ apoptosis in MCF-7	Cyano-dimethylphenyl morpholine derivative; PIM-1 engagement and S-alkyl/galactosyl modifications explored	Shaban et al., 2023
37	General cytotoxicity	Notable cytotoxicity	Pentose/pentyl-like	Mehany et al.,

	/ in vivo sarcoma model	against MCF-7 (comparable to doxorubicin); in vivo tumor reduction 42.1%	substitution (tetrahydroxy pentyl) on nicotinate enhances tumor targeting and potency.	2024

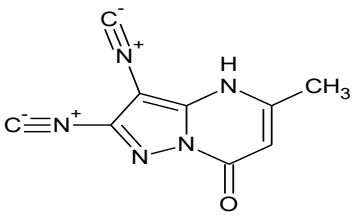
3. Biological targets of pyrimidine derivatives

3.1. Pyrimidine analogues classified on the therapeutic activity

3.1.1 Artificially Designed Pyrimidines as Regulators of the Cell Cycle in Cancer

Metwally et al. (2019) synthesized novel pyrazolo[1,5-a]pyrimidine derivatives. Compounds 38–40 exhibited highly significant cytotoxic effects against human breast cancer and cervical cancer cells, with IC_{50} values of 13.91 ± 1.4 μM and 22.37 ± 1.8 μM for the breast and HeLa cell lines, respectively. These derivatives also demonstrated significant inhibitory activity against histone lysine demethylases (KDMs), with Compound 38 showing strong KDM inhibition (IC_{50} = 1.91 μM)(53). ***Alblew and team (2019)*** developed novel β-enaminonitrile/ester derivatives and imidates, serving as precursors for 2-substituted 4H-benzo[h]chromene and 7H-benzo[h]chromeno[2,3–d]pyrimidine analogs. Compound 43 is highly cytotoxic, with IC_{50} values surpassing or comparable to standard chemotherapeutics against MCF-7, HCT-116, and HepG-2, at both the synthesis and G2/M checkpoints, alongside inhibition of migration and invasion. The hydrophilic groups and fused ring systems enhance anticancer activity(54). ***Abbas et al. (2019)*** synthesized pyrido[2,3-d]pyrimidines and fused tricyclic analogues. Compounds 44(inhibiting CDK4/6) and 45(inhibiting CDK6) exhibited notable cytotoxicity against PC-3 and MCF-7 cell lines, respectively(55). ***Mghwary and coworkers (2019***) synthesized thienopyrimidine derivatives as dual EGFR/VEGFR-2 inhibitors. Compound 46 was the most potent against MCF-7 breast cancer cells, exhibited strong VEGFR-2 inhibition (IC_{50} = 1.23 μM) and EGFR inhibition. Activity was favored by chloro and methyl substituents, while fluoro reduced potency surpassing erlotinib and doxorubicin in efficacy(56). ***An. et al. (2019)*** synthesized novel osimertinib (AZD9291) analogues featuring a sulfoxide group at the C-4 aniline moiety(47). Compound 48 showed the strongest EGFR kinase inhibition (IC_{50} = 4.10 μM) and L858R/T790M mutant cell growth suppression (IC_{50} = 10 μM. The compound exhibited favorable pharmacokinetic properties(AUC0-inf: 1294.74 h mg/mL), oral bioavailability (73.69%), a relatively shorter half-life (t1/2 = 1.12 h) and less toxic than AZD9291(57). ***Nemr et al. (2020)*** reported thiazolopyrimidine-based hydrobromide topoisomerase II inhibitors; compound 51 blocked G_2/M transition and apoptosis in A498 renal cancer cells (IC_{50} = 3.5 μM), with dual chloro substituents driving potency(58). ***Kilic-Kurt et al. (2020)*** synthesized Aryl urea–pyrimidines derivatives; compound 52 induced apoptosis and G_2/M arrest in SW480 cells (IC_{50} = 11 μM) by increased Bax, IκB-α, and cleaved PARP levels. Activity was enhanced by optimized aryl substitutions, though in vivo data were lacking(59). ***Diao and colleagues (2020)*** reported Pyrimidine–benzothiazoles based CDK2 inhibitors. Among these, compound 53 displayed strong cytotoxicity across multiple lines (IC_{50} = 0.45–1.8 μM) compared to the reference drug AZD5438(compound 54), supported by docking to CDK2(60). **AboulWafa et. al. (2020)** identified Pyrazolone/hydrazone pyrimidines compounds 55–57 as potent EGFR/ARO inhibitors, inducing G_2/M arrest and apoptosis with submicromolar activity. These compounds showed strong activity against MDA-MB-231 and MCF-7. SAR showed the pyrimidine core with nitrile, phenyl modifications greatly enhanced potency (IC_{50} down to 0.27 μM)(61). ***El-Saidi and team (2020)*** reported Thiouracil-based pyrimidines based DNA-mimetic derivatives; bulky aromatic substituents improved CDK2 and BCL-2 binding in docking studies, though experimental validation is pendingstudies assessed their interactions . Compound 58, featuring a bulky naphthoyl group, showed the strongest binding due to enhanced hydrophobic and hydrogen bonding interactions with CDK2 and BCL-2, key proteins in cancer progression(62). ***Farghaly et. al. (2020)*** synthesized novel thiazole-based chalcones. Compounds (59–62) with strong activity against MCF-7, HepG2, and A549, reduced normal-cell toxicity, and CDK1/2/4 inhibition. Compound 59 emerged as the most active.compounds exhibiting selective anticancer activity. Investigations into underlying biological mechanism**s also** revealed that derivative 62 upregulated G2/M proliferation arrest and increased pre-G1 apoptotic populations in A549 cells. CDK1, CDK2, and CDK4 inhibition assays confirmed moderate to strong activity, supported by in silico ATP-binding site of CDK1 docking(63).***Tyinska et al***. **(2021)** developed Hydrazone–pyrimidines hybrids (63–66) with selective cytotoxicity in multiple lines, sparing normal NHDF cells. DNA intercalation and topoisomerase IIα inhibition were proposed mechanisms with 20% greater inhibition of MCF-7 cells than doxorubicin(64). ***Ahmed et al. (2021)*** synthesized indolyl-pyrimidine hybrids with potent in vitro and in vivo efficacy. Compound 67 inhibited EGFR (IC_{50} = 0.25 μM) and showed activity comparable to erlotinib. SAR analysis revealed that hydrazone substituents with electron-withdrawing aryl groups at C-5 enhanced activity(65). ***Gaber et al. (2022) and Ruzi et al. (2022)*** reported Pyrazolo[3,4-d]pyrimidine derivatives with nanomolar EGFR/VEGFR-2 inhibition and strong tumor suppression. Compound 68 inhibited EGFR T790M (IC_{50} = 0.236 μM), while compound 69 showing potent cytotoxicity (IC_{50} = 0.03–1.6 μM) combined with VEGFR-2 and tubulin inhibition, inducing G_2/M arrest(11,66). In 2022, ***Elzahabi and others*** synthesized Pyrido[2,3-d]pyrimidines analogues (70–73) with dual EGFR inhibition, including T790M mutants (IC_{50} ≈ 0.1 μM), and caspase-dependent apoptosis. These

compounds were screened at 100 μM for cytotoxicity against PC-3, A-549, HCT-116, and MCF-7 cancer cells. Compound 70 emerged as the lead candidate, exhibiting strong dual inhibition of EGFRT790M (IC_{50} values of 0.099 and 0.123 μM, respectively)(67). In 2023, ***Sroor et al.*** created Pyrrolo[2,3-d]pyrimidines derivatives (74–77) outperforming doxorubicin in breast cancer models. .having 2-trichloromethyl and 4,6-dichloro substitutions, structurally confirmed via spectroscopic methods, elemental analysis, and single-crystal X-ray diffraction. Mechanistic studies confirmed apoptosis induction, Bcl-2 downregulation, and caspase activation (68).In 2023, ***Li and authors*** developed Thiadiazole–pyrimidines reported compound 78 with selective activity against colorectal cancer ($IC_{50} \approx 5–8$ μM), inducing mitochondrial-mediated apoptosis and MEK/ERK pathway inhibition. Compound 78 selectively inhibited HCT116 cell proliferation, while exhibiting minimal cytotoxicity toward normal NCM460 cells as compared to 5-flourouracil(compound 79)(69).



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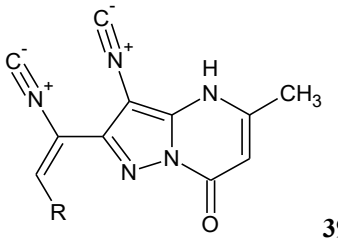
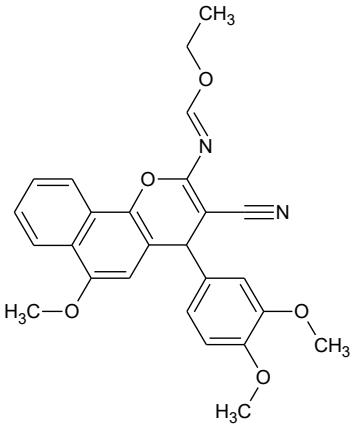


39-40

Table 4: Substitution at R position

S.No.	R
39	2-furyl
40	4-OH, 3-$OMeC_6H_5$



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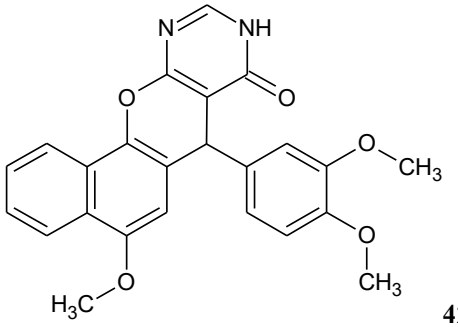

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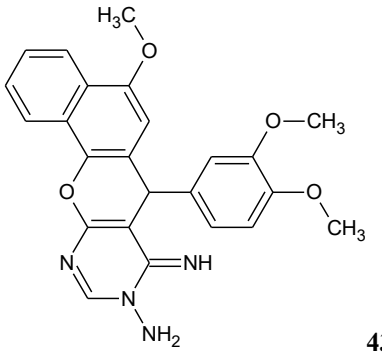

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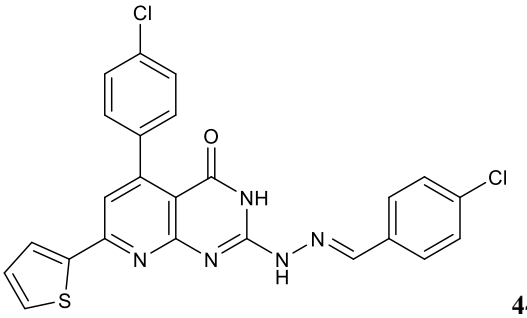

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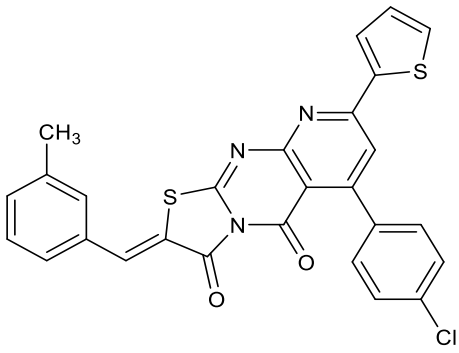

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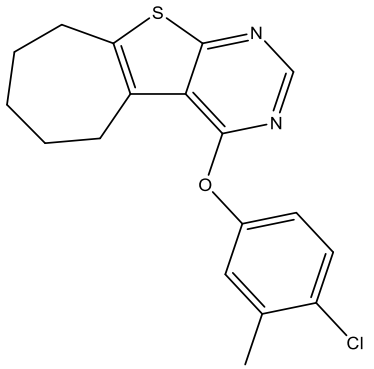

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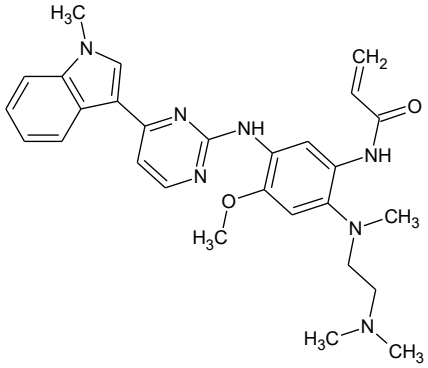
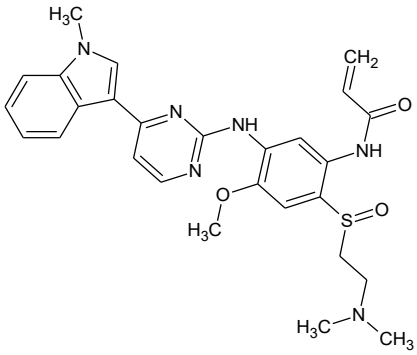


47 (AZD9291 osimertinib)



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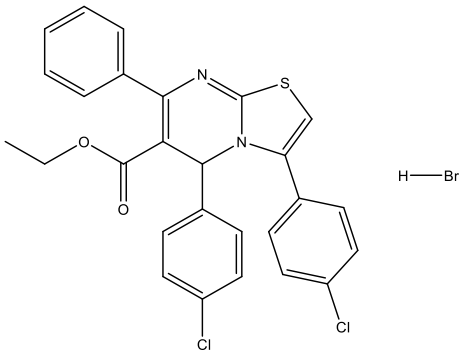

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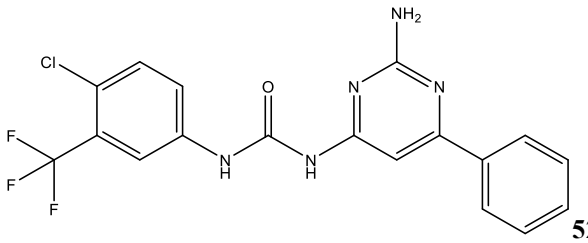

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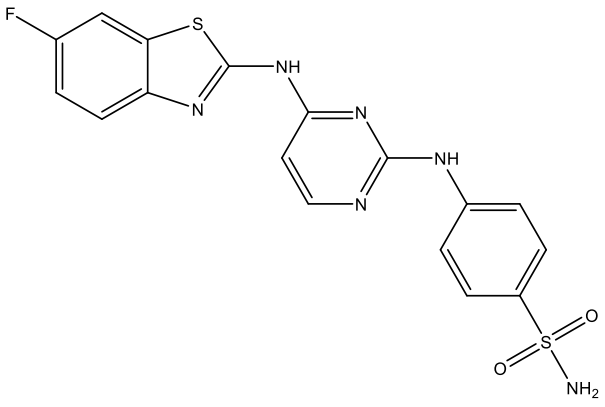

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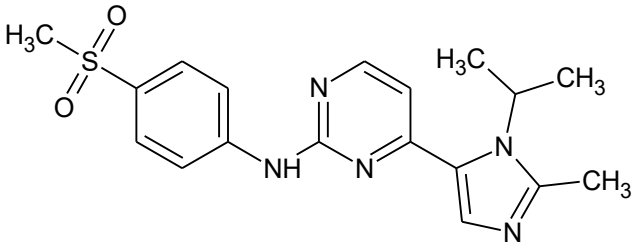

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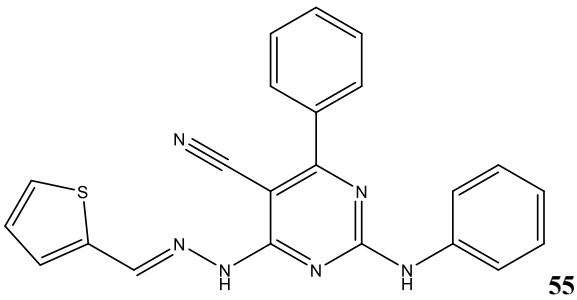

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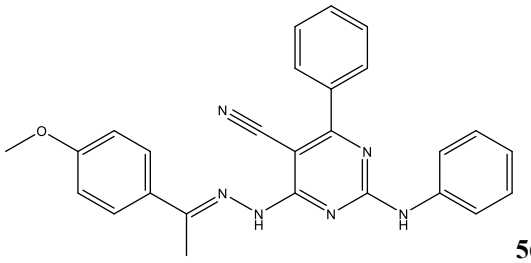

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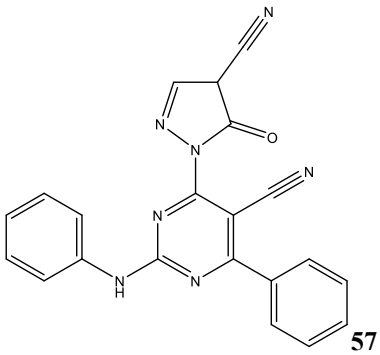

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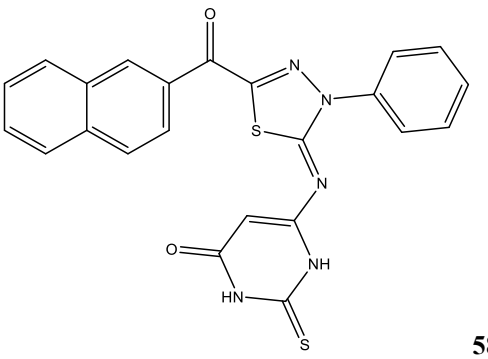

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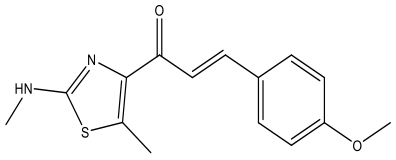

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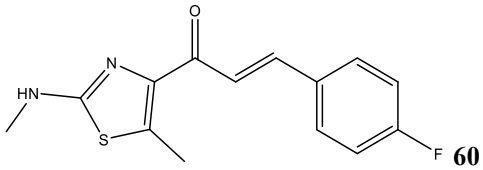

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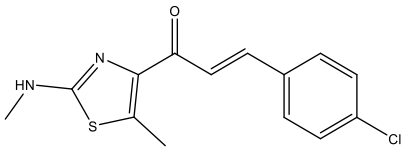

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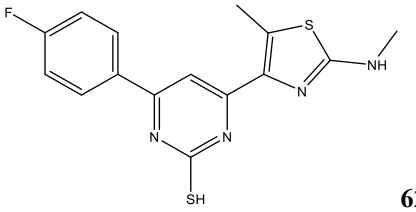

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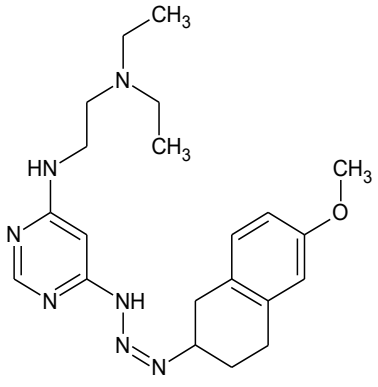

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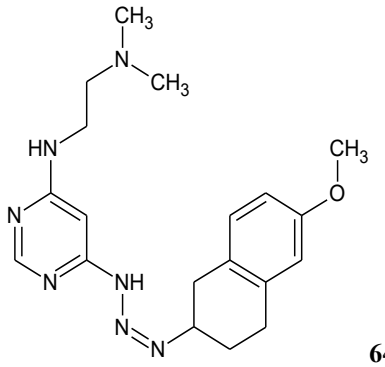

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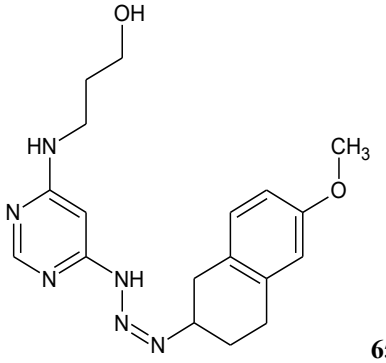

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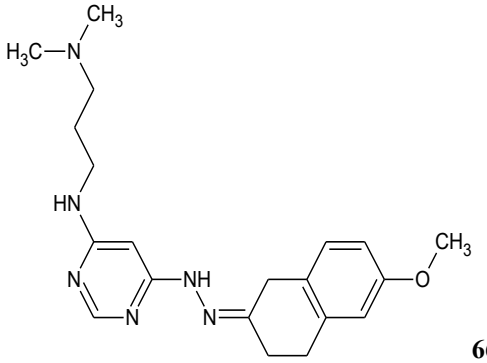

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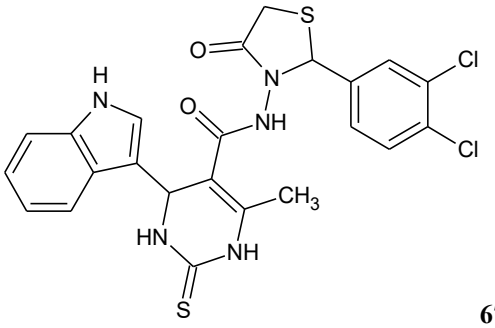

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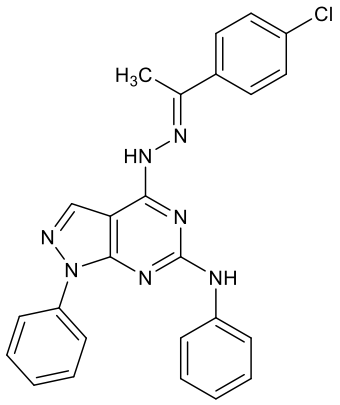

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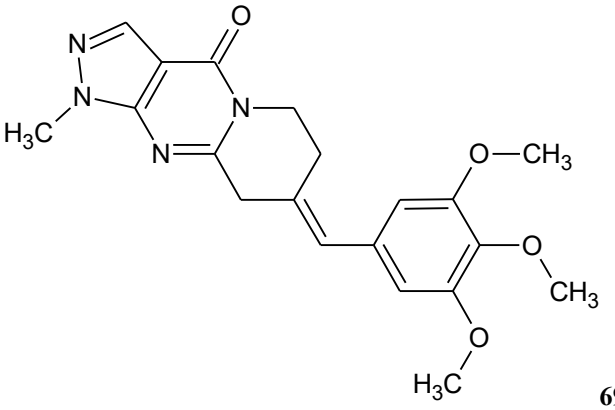

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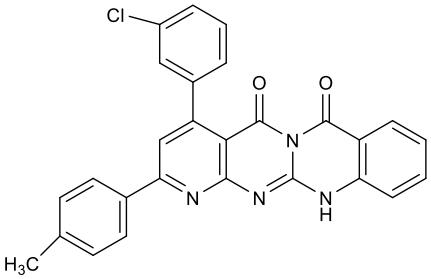

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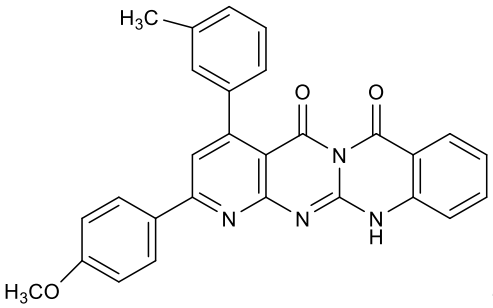

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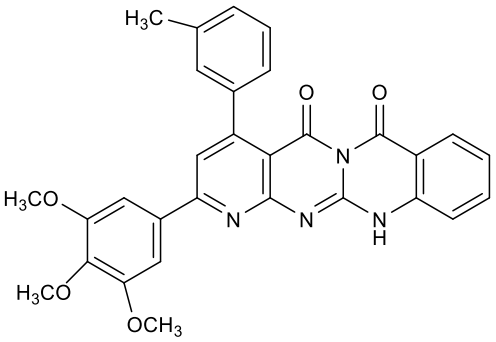

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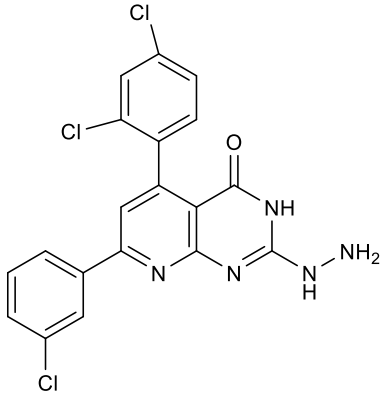

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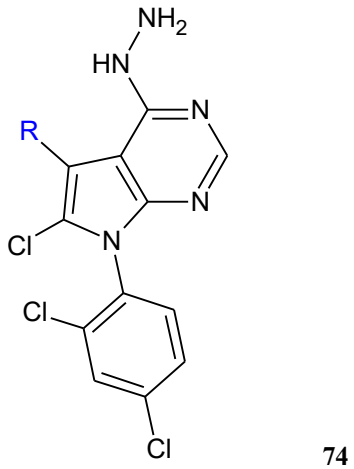

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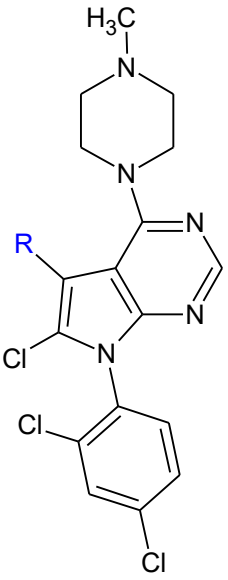

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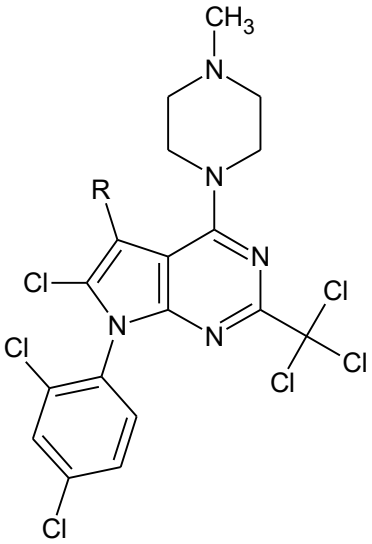

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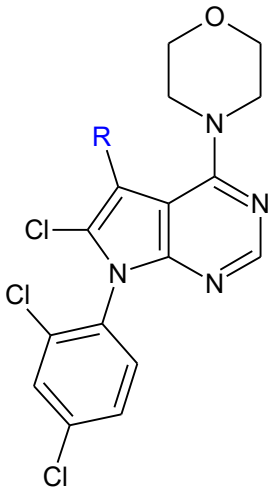

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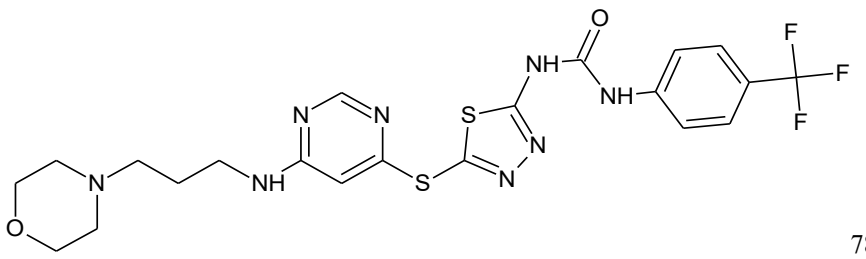
Table 5: Substitution at R position

Compound	R
74	4-Br-C_6H_4
75	3,4-OMe-C_6H_3
76	4-Br-C_6H_4
77	3,4-OMe-C_6H_3



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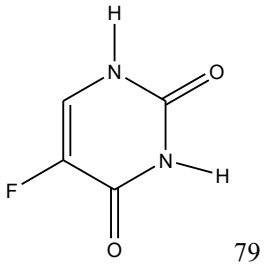
3.1.2 Pyrimidine-based Compounds with Cytotoxic Properties

Amin et al. **(2019)** in their research, synthesized and assessed a range of 6-aryl-5-cyano-pyrimidines. Among the synthesized compounds, compound 80 demonstrated significant anticancer activity (33.66–74.98%) against HCT-116, MCF-7, and HePG-2 cell lines, with an IC50 of 3.89nM, indicating potential to inhibit the thymidylate synthase (TS) enzyme, surpassing 5-Fluorouracil (79) as the reference(70).***Fouda et al. (2019)*** synthesized novel 3,6-diarylazo-2,5,7-triaminopyrazolo[1,5-a]pyrimidines(compounds 81-85) with potent anticancer activity, particularly compound 83, which showed broad cytotoxicity across MCF-7, HepG2, and HCT-116 cell lines (IC_{50}: 0.3–3.4 µg/mL). Despite promising efficacy, the study lacked detailed SAR, mechanistic insights, and pharmacokinetic data(71). ***Huang et al. (2019)*** developed oxacalix[2]arene[2]pyrimidine derivatives with promising in vitro anticancer activity, notably compound 86 (IC_{50} = 12.37 µM against HepG2), which induced apoptosis. However, SAR, mechanistic insights, and in vivo validation remain unexplored, warranting further investigation(72). ***Li et al. (2019)*** identified a triazole-fused pyrimidine (compound 87) as a potent, selective LSD1 inhibitor ($IC_{50} \approx 49$ nM) with strong antiproliferative effects and differentiation induction in leukemia cells. While promising, further SAR refinement, mechanistic studies, and in vivo validation are needed to advance its therapeutic potential(73). ***Hosseinzadeh et al. (2019***) reported DHPM derivatives with notable cytotoxicity, especially compound 88 ($IC_{50} \approx 0.17$ µg/mL against MCF-7), supported by docking to kinesin Eg5(74).



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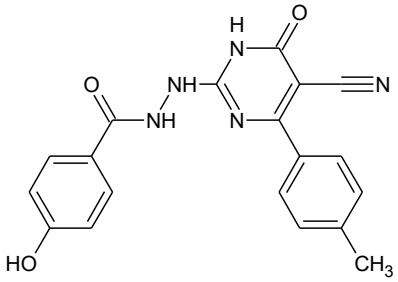

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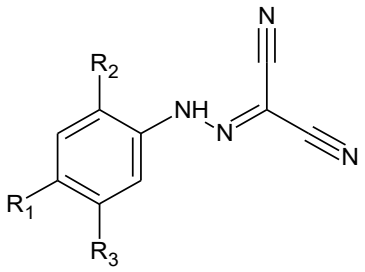
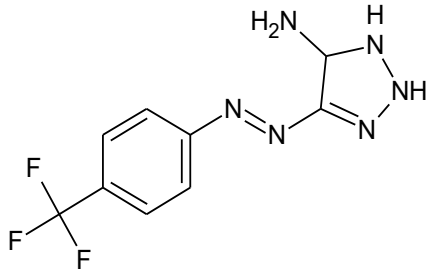


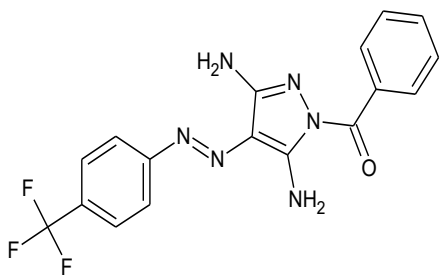
81,82



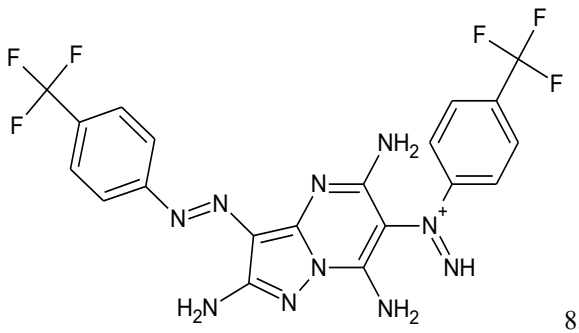
83

Table 6: different substitutions at R_1, R_2, and R_3 positions

Compound	R_1	R_2	R_3
81	F	H	H
82	CF_3	H	H



84



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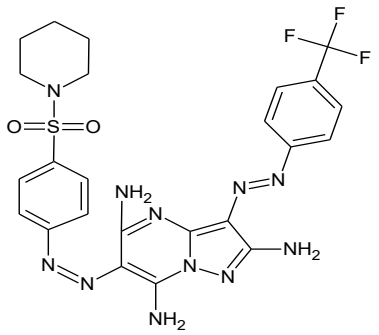

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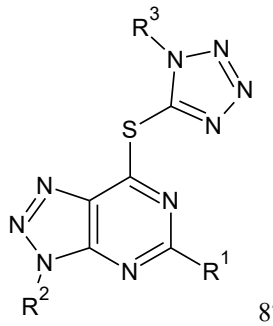
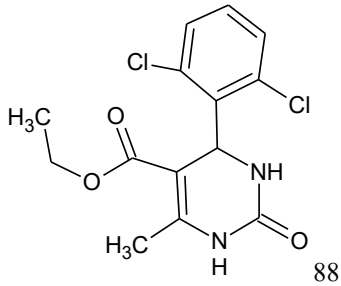


87

Table 7 different substitution at R_1, R_2 and R_3 positions

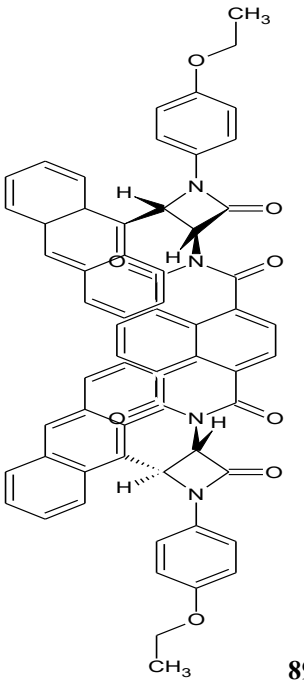
Compound	R^1	R^2	R^3
87	Propargyl-S-	2-Cl-Bn-	Ph-



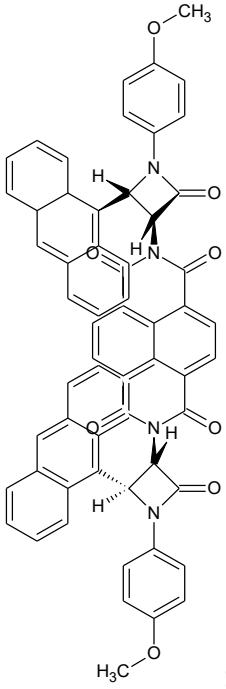
88

Borazjani et al. (2020) synthesized β-lactam naphthalimido derivatives (compounds 89 and 90) with moderate anticancer activity against MCF-7 and TC-1 cells, outperforming gemcitabine(75). ***Al-Rashood et al. (2020)*** developed thiazolopyrimidine derivatives with potent anticancer activity, notably compound 91 (GI_{50} = 1.07 μM), showing strong DNA-binding comparable to doxorubicin. Compound 92 exhibited the highest DNA affinity, underscoring the scaffold's potential for nucleic acid-targeted therapies(76). ***Bakhotmah et al. (2020)*** synthesized diverse pyrano[2,3-c]pyrazole-malononitrile derivatives via base-catalyzed heterocyclization, with compounds 93 and 94 showing notable cytotoxicity. Enhanced activity was linked to chromone and pyran moieties, suggesting improved conjugation and molecular stabilit(77). ***Marwa H. Ahmed et al. (2020)*** developed pyrimidine-bearing chalcone derivatives targeting DHFR, with compounds 95–97 showing superior antiproliferative activity against MCF-7 and HepG2 cells compared to doxorubicin, alongside reduced toxicity. This highlights their promise as potent, low-toxicity anticancer agents(78). ***Nasser et al. (2020***) developed pyrimidine-5-carbonitrile analogues as ATP-mimetic EGFR inhibitors, effectively targeting both wild-type and T790M-mutant forms. Compounds 98–102 showed superior antiproliferative activity over erlotinib, with compound 99 exhibiting strong EGFRT790M inhibition (IC_{50} = 4.03 μM)(79). ***Abu El-Azm et al. (2020***) synthesized chromeno[2,3-d]pyrimidine and chromenotriazolo[1,5-c]pyrimidine derivatives, with compounds 103 and 104 showing selective cytotoxicity against MCF-7 and HepG2 cells while sparing normal WI-38 fibroblasts. These scaffolds highlight promising cancer-selective therapeutic potential(80). ***Xu et al. (2020)*** developed 2,4-disubstituted pyrimidines as Aurora kinase inhibitors, with compound 105 showing strong antiproliferative activity and apoptosis induction via Bax/Bcl-xl modulation. While promising, SAR exploration beyond compound 105 remains limited, warranting further scaffold optimization(81). ***Sakr et al. (2020)*** synthesized diphenyl-4-thioxo-1,4-dihydropyrimidin-5-yl ethan-1-one derivatives with versatile reactivity, yielding diverse analogues. Compound 106 showed the most promising cytotoxicity against A-549 lung cancer cells, highlighting its potential as an antitumor lead(82). ***Thuraka Sekhar et al. (2020)*** synthesized thiazolo[3,2-a]pyrimidine derivatives via a one-pot method, with compounds 107 and 108 showing potent cytotoxicity against A549 and

HeLa cells (IC_{50} = 2.2 and 5.6 μM), outperforming doxorubicin in select assays. These findings highlight their promise as anticancer leads(83). ***Chhikara et al. (2020)*** synthesized N^1-(α,β-alkene)-substituted phenylthiazolopyrimidines inspired by Ibrutinib's core, with compound 108 showing selective inhibition of c-Src, Btk, and Lck kinases and potent antiproliferative activity against HT-29 and SK-OV-3 cells (IC_{50} = 21.7 μM)(84). ***Madia et al. (2021)*** designed aminopyrimidine-based multitarget anticancer agents by modifying RDS 3442, with compound 109 showing selective activity against CAL 27 cells, compound 110 (N-benzyl) displaying enhanced potency (EC_{50} = 10–26 μM), and compound 111 exhibiting broad-spectrum antiproliferative effects(85).



89



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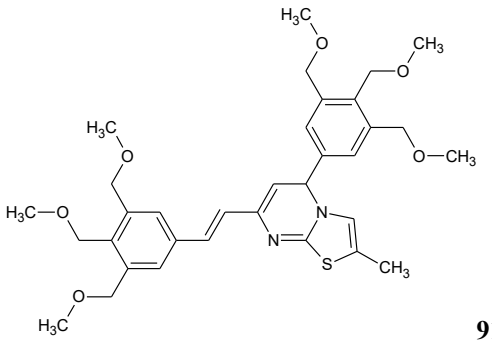

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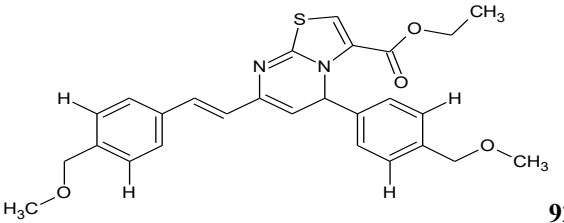

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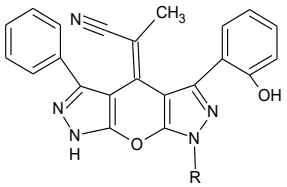
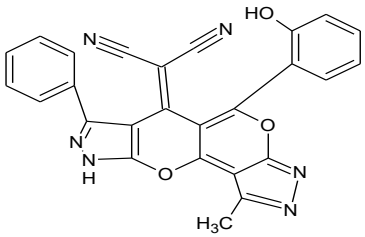


93, R=Ph



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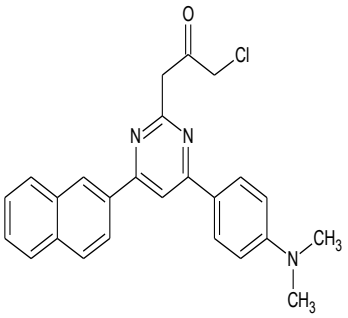

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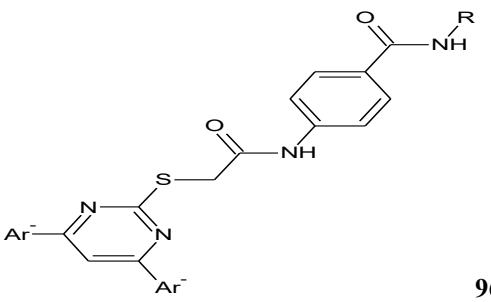
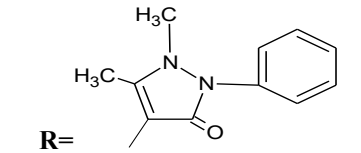
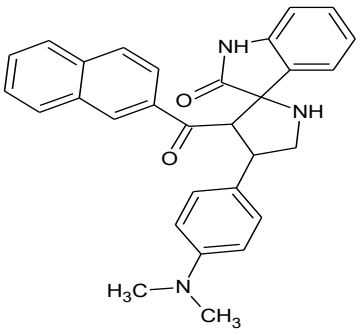


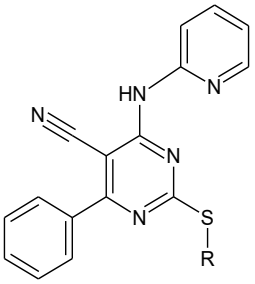
96

R=

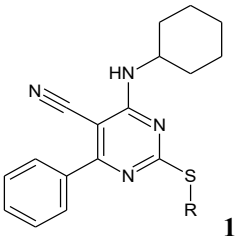




97



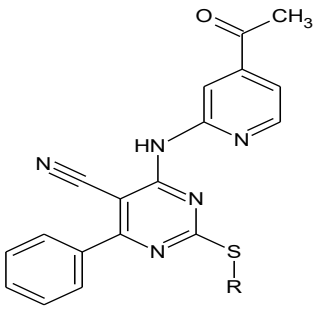
98, 99



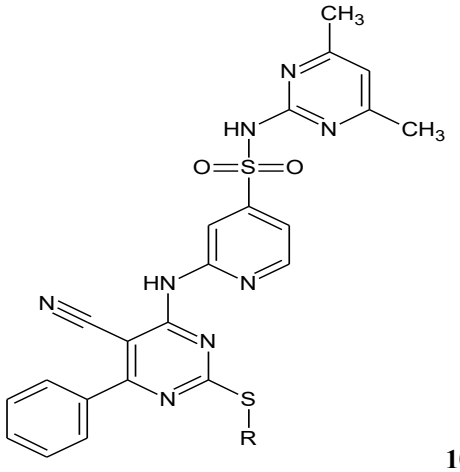
100, R= C_4H_9

Table 8: Different substitutions at R position

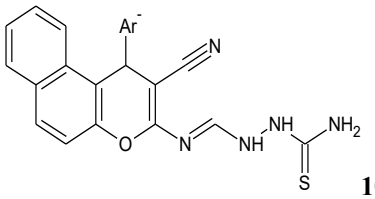
Compound	R
98	C_2H_5
99	C_4H_9



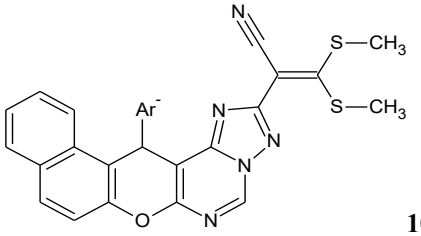
101;R=C_4H_9



102;R=C_2H_5



103



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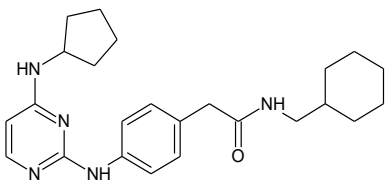

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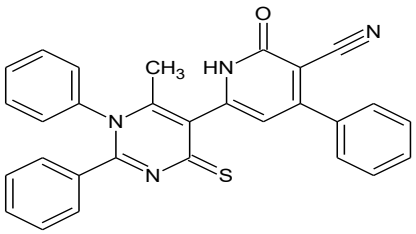
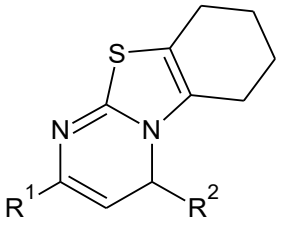


106

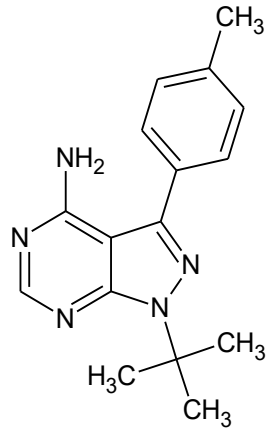
Table 9: Different substitutions at R1 and R2 position



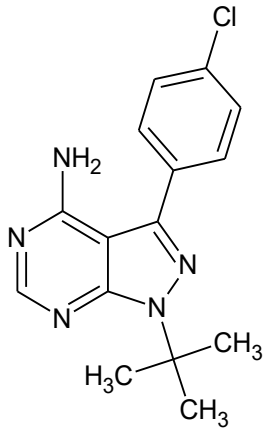
HBr

107, 108

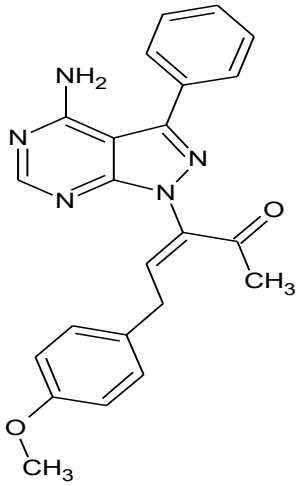
Compound	R^1	R^2
107	2-Naphtrhyl	3-bromophenyl
108	2-Naphtrhyl	3,4,5-trimethoxyphenyl



PP1



PP2



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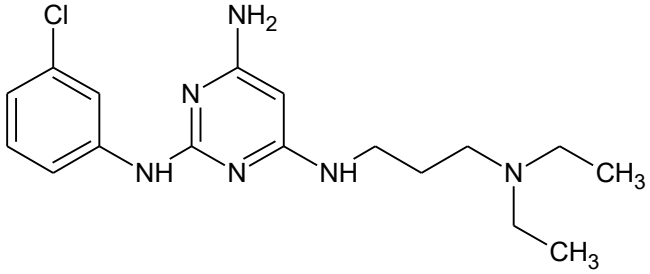
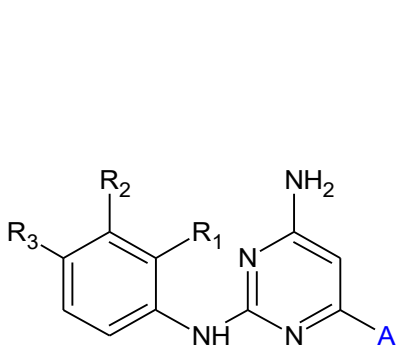
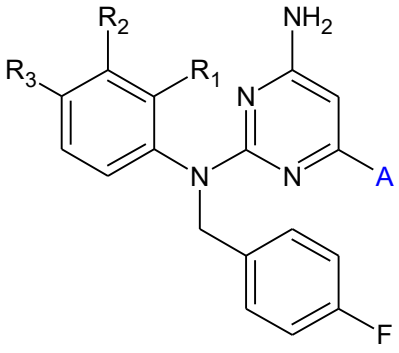


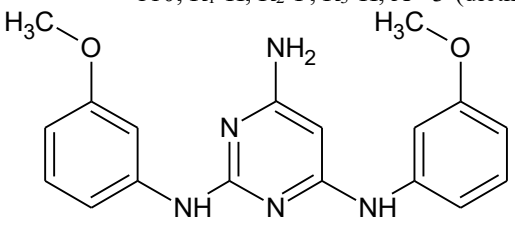
RDS3442 (previously reported aminopyrimidine compound)



109



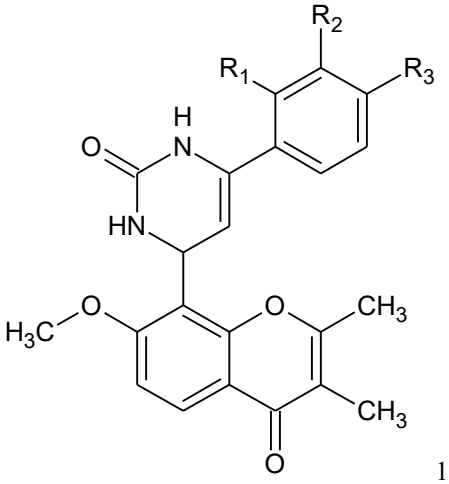
110; R_1=H, R_2=F, R_3=H, A= 3-(diethylamino)propylamino



111

Kantankar et al. (2021) developed chromone-fused pyrimidine derivatives via a modified Biginelli reaction, yielding two potent series (112 and 113). Compounds such as 112a–c, 112f, and 113a–b showed strong, selective cytotoxicity against various cancer cell lines, particularly hematological malignancies(86). ***Bandaru et al. (2021)*** created a new array of thiazole–pyrimidine analogs incorporating a fused imidazo–pyrazole core, designed to enhance antitumor activity. Among these, compound 114 exhibited potent cytotoxicity across MCF-7, A549, Colo-205, and A2780 cell lines (IC_{50}: 0.043–0.87 mM), outperforming etoposide(87). ***Ćwikła (2022)*** developed oxazolo[5,4-d]pyrimidine derivatives bearing isoxazole and amino side chains, structurally analogous to purines, and evaluated their antitumor potential against A549, MCF7, LoVo, and HT29 cell lines. Compound 115, featuring a 3-(N, N-dimethylamino)propyl group, showed superior activity against HT29 (IC_{50} = 58.4 µM) and favorable selectivity over cisplatin and fluorouracil(88). ***Myriagkou, with his colleagues(2023***), synthesized pyrido[2,3-d]pyrimidine derivatives targeting inflammation-associated cancer pathways, with compounds 117 and 119 showing significant lipoxygenase inhibition (IC_{50} = 47.5 and 42 µM)(89). ***Pattabi et al. (2024)*** developed aryl urea oxazole–pyrimidine derivatives (134a–j) with potent antiproliferative activity (IC_{50}: 0.01–10.6 µM), outperforming etoposide across multiple cancer cell lines. SAR highlights the key role of aryl substituents on the urea moiety in enhancing cytotoxicity(90).

Table 10: Different substitutions at the R1, R2, and R3 positions

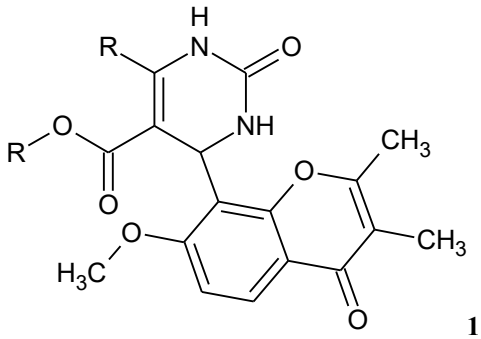


112(a-j)

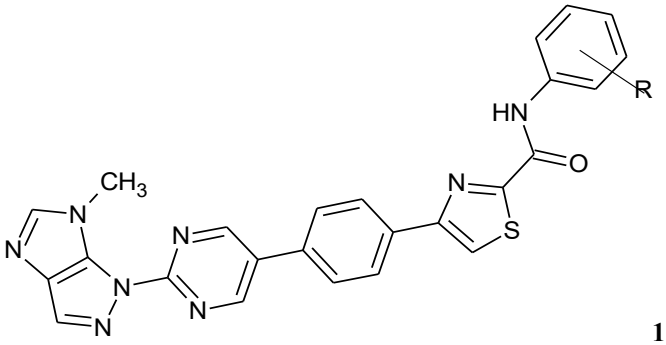
S.No	Co No.	R1	R2	R3
1	112a	H	H	F
2	112b	F	H	H
3	112c	H	H	OCH_3
4	112d	H	H	H
5	112e	H	OCH3	OCH3
6	112f	H	H	OCH3
7	112g	H	H	CH3
8	112h	H	Br	H
9	112i	H	H	Br
10	112j	H	H	Cl

Table 11: Different substitutions at R1, R2

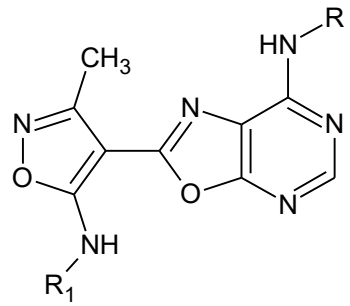
S.No	Co No.	R1	R2
1	113a	CH2OCH3	-CH3
2	113b	CH3	C2H5
3	113c	-C2H5	-CH3
4	113d	i-C3H7	C2H5
5	113e	CH3	-CH2-ph



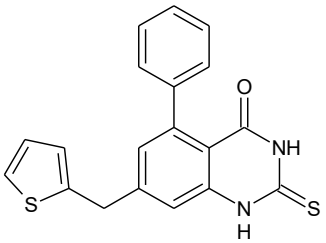
113(a-e)



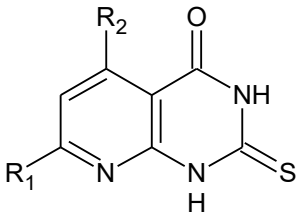
114; R= 3,4,5-timethoxy



115; R= 3-(N,N-dimethylamino)propyl, R1=Ethyl



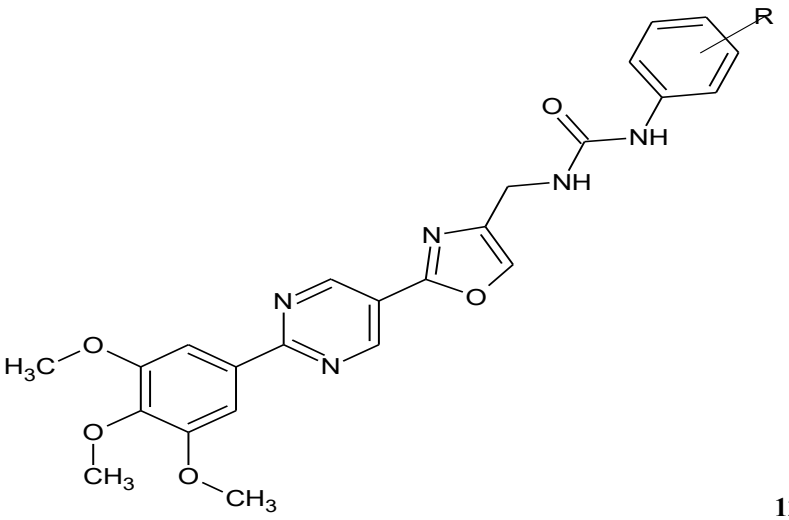
116



117-119

Table 12: Different substitution at R1, R2 position

Compounds No.	R1	R2
117	C_6H_5	C_6H_5
118	$4ClC_6H_4$	2-thienyl
119	$4ClC_6H_4$	$4ClC_6H_4$



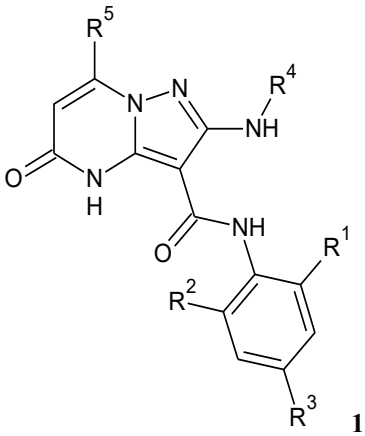
120(a-j)

Table 13: Different substitutions at the R position

S.No	Compound No.	R
1	120a	3,4,5-timethoxy
2	120b	3,5-dimethoxy
3	120c	4-methoxy
4	120d	4-cyano
5	120e	4-Nitro
6	120f	3,5-dinitro
7	120g	4-chloro
8	120h	4-bromo
9	120i	4-methyl
10	120j	3,5-dimethyl

3.***1.3 Anti-tumor activity of Pyrimidine derivatives***

Philoppes (2020) synthesized pyrazolo[1,5-a]pyrimidine derivatives with confirmed regioselectivity via HMBC and NOESY, showing potent cytotoxicity (IC_{50}: 0.67–7.68 μM) against MCF-7 and HCT-116 cells. Strong PIM-1 kinase inhibition and stable binding profiles suggest promising anticancer potential(91). ***Luo et al. (2020)*** developed 5-methylpyrazolo[1,5-a]pyrimidine derivatives as potent c-Met kinase inhibitors, with compounds 125 and 126 (IC_{50} ≈ 5.2 nM) showing efficacy comparable to cabozantinib. SAR revealed nitrogen heterocycles at R_2 enhance c-Met inhibition, while aryl groups boost activity against A549 cells(92). ***Amr et al. (2020)*** synthesized cyclo(Nα-pyrido)-bis-[(L-valinyl)-L-ornithinyl acid hydrazide] (compound 127), showing potent VEGFR-2 inhibition and broad-spectrum cytotoxicity. In vivo, it achieved significant antitumor efficacy in a prostate cancer model, outperforming flutamide by ~7-fold (ED_{50} = 1.65 μM)(93). ***Al-Tuwaijri et al. (2023)*** developed indazol-pyrimidine derivatives with strong cytotoxicity against MCF-7 cells (IC_{50} = 1.629–4.798 μM), surpassing the reference drug. Compounds 130 and 132 induced apoptosis via caspase-3/7 activation, with additional potency against A549 and Caco-2 cells(94). ***Lamie et al. (2023)*** synthesized indole-pyrimidine hybrids as potent Mcl-1 inhibitors, with compounds 133–136 showing nanomolar K_i values and selective activity against Bcl-2 family proteins. Compounds 133 and 135 exhibited dual inhibition and strong antiproliferative effects in PC-3, K-562, and MDA-MB-231 cells(95). In 2024, ***Shuai et al.*** identified compound 137, a (thiophen-3-yl)aminopyrimidine-based ERK1/2 inhibitor, with potent activity against RAS/BRAF-mutant triple-negative breast and colorectal cancers (IC_{50}: ERK1 = 0.11 nM, ERK2 = 0.08 nM)(96).

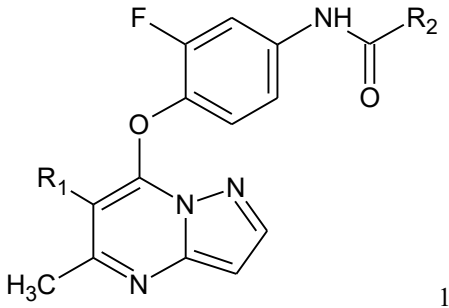


121-123

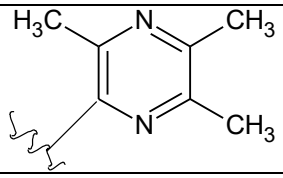
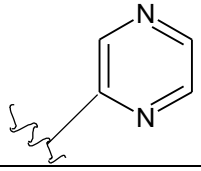
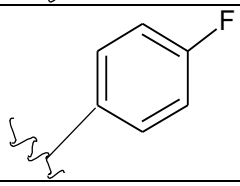
Table 14 Different substitution at R1, R2, R3,R4,R5 position

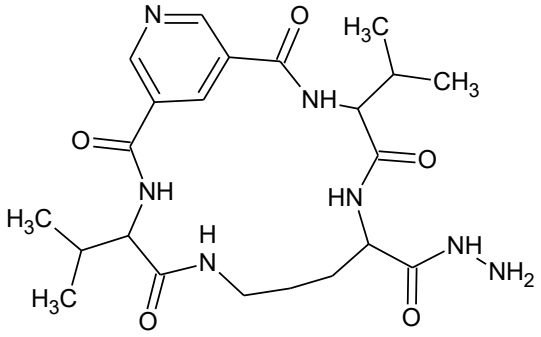
Compound	R1	R2	R3	R4	R5
121	H	H	NO_2	C_2H_5	CH_3
122	H	H	NO_2	C_2H_5	CH_3
123	H	H	NO_2	C_6H_5	CH_3

Table 15 Different substitutions at R1, R2



124-126

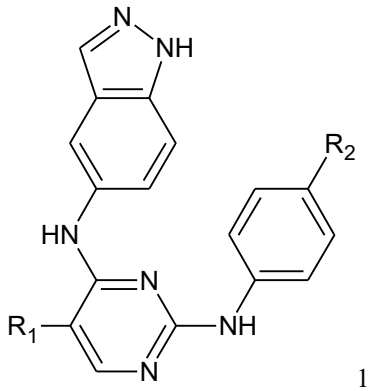
Compound	R1	R2
124	H	
125	H	
126	H	



127

Table 16: Different substitution R1, R2

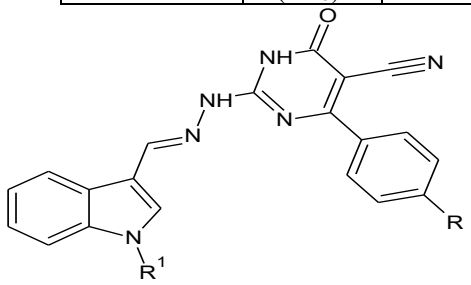
Compound	R1	R2
128	F	N-(pyrimidin-2-yl)sulfonamide
129	F	3,4,5-triMeO
130	F	morpholine
131	H	P-SO2NH2
132	H	3,4,5-triMeO



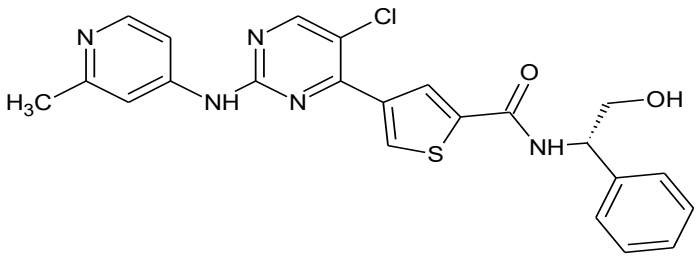
128- 132

Table 17: different substitutions at R, R1

Compound	R	R1
133	OCH_3	SO_2Ph
134	Cl	H
135	Cl	SO_2Ph
136	$N(CH_3)_2$	SO_2CH_3



133–136

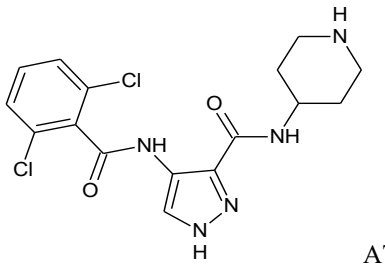


137

3.1.4 Chemically Produced Pyrimidine Variants Exhibiting Blocking Effects

Ali et al. (2019) synthesized pyrazole and pyrazolo[1,5-a]pyrimidine analogues as inhibitors of CDK2/cyclin A2, with compounds 152 and 153 showing notable cytotoxicity across Caco-2, MCF-7, A549, and HepG2 cell lines(97). ***Shu et al. (2020)*** developed 4- and 6-phenyl-pyrimidine derivatives targeting JAK3 via covalent Cys909 thiolization. Among these, compound 140 exhibited potent JAK3 selectivity (IC_{50} = 1.7 nM) with >588-fold isoform specificity(98). ***Sana et al. (2020)*** introduced urea-linked thioindole–pyrimidine hybrids via molecular hybridization, with compound 141 showing notable anticancer activity across multiple cell lines (IC_{50}: 5.85–10.43 μM) and potent VEGFR-2 inhibition (IC_{50}: 310–920 nM)(99). ***Nassar et al. (2022)*** synthesized a fresh CDK2 inhibitors library featuring pyrazolo[3,4-d]pyrimidine and thioglycoside-linked scaffolds. Compounds 142 and 143 demonstrated potent antiproliferative activity (IC_{50}: 6–48 nM) across MCF-7, HCT-116, and HepG2 cell lines, surpassing sorafenib. Compound 143 selectively inhibited CDK2/cyclin A2 (IC_{50}: 0.057–0.119 μM), induced G1 arrest and apoptosis, and showed strong binding affinity (ΔG = −62.79 kcal/mol) with key interactions at Leu83. (100). ***In 2022, Mandoura A.A. and colleagues*** synthesized a series of pyrazolopyrimidine analogues(144–146) as potential CDK2 inhibitors with antitumor potential against MCF-7 and HCT-116 cells, surpassing Sorafenib, while compounds showed notable efficacy against HepG2 cells. Compound 146(IC_{50} = 0.061 ± 0.003 mM), demonstrating strong CDK2/cyclin A2 inhibition (IC_{50} = 0.061 ± 0.003 mM), was the lead candidate in HCT-116 cells, with minimal toxicity toward normal cells(101). ***Warhi et al. (2022)*** developed tetracyano pyridone-based derivatives with strong cytotoxicity against HepG2 and MCF-7 cells. Compound 147 outperformed Taxol (IC_{50} = 1.77 μM) and showed notable VEGFR-2 and HER-2 inhibition, indicating promising dual-target anticancer potential(102). ***Zoghbi et al. (2023)*** synthesized thiazolopyrimidine derivatives with strong anticancer activity, notably compound 148 as a potent Topo II inhibitor (IC_{50} = 0.23 mM), surpassing etoposide and doxorubicin. Compound 161 further induced cell cycle arrest and apoptosis in A549 cells, highlighting

therapeutic promise(103). ***Binjawhar et al. (2024)*** developed imidazolone-sulphonamide-pyrimidine hybrids as EGFR-targeted anticancer agents, with compound 149 showing superior cytotoxicity against MCF-7 cells (IC_{50} ≈ 1.05 µM) and potent EGFR inhibition (IC_{50} ≈ 0.09 µM), comparable to lapatinib(104).



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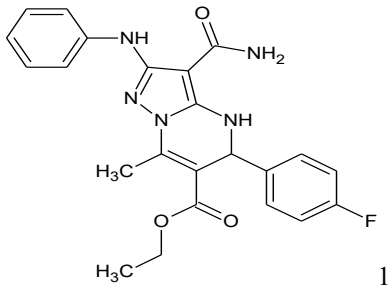

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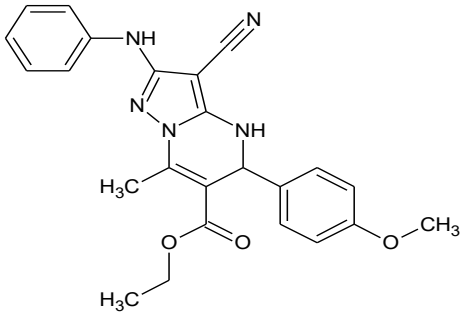

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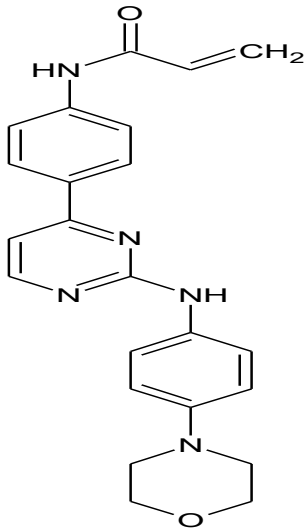

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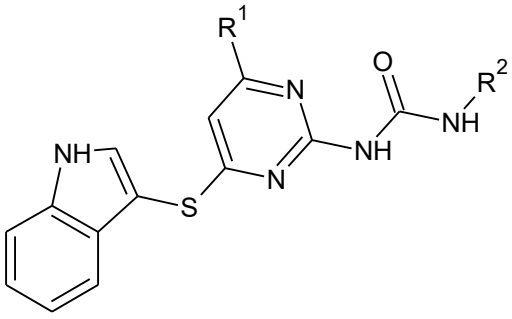
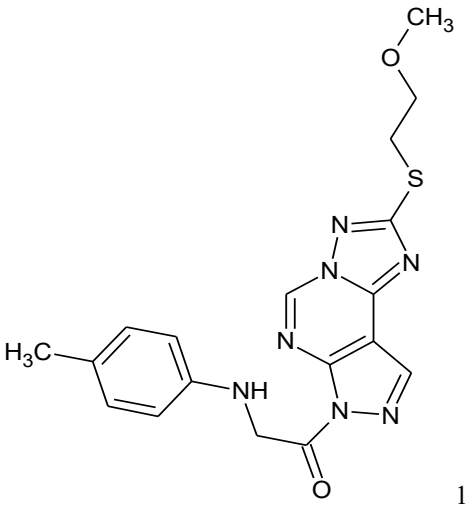


141

R1=pyrrolidin 1-yl,R2= 4-Chloro phenyl



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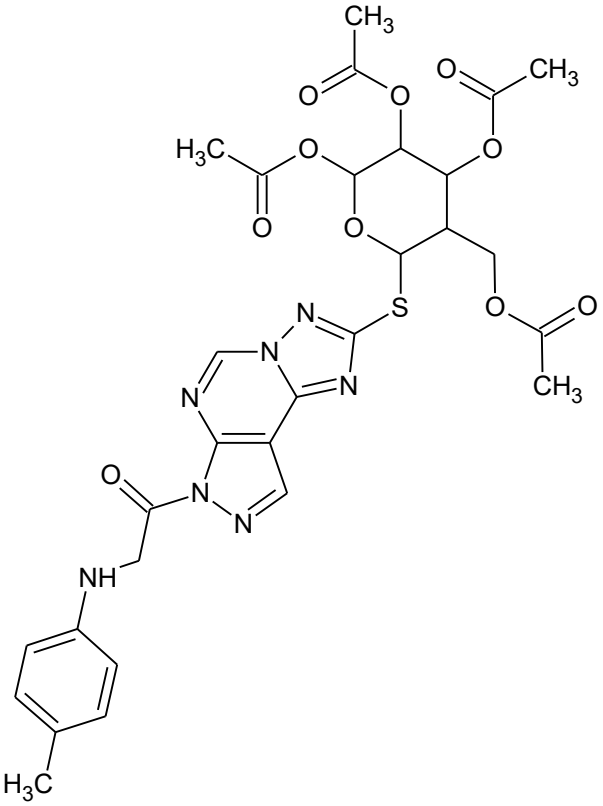

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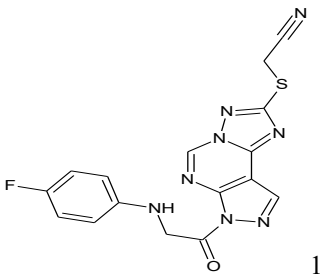

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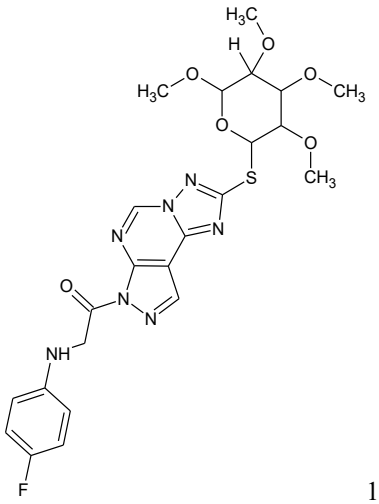

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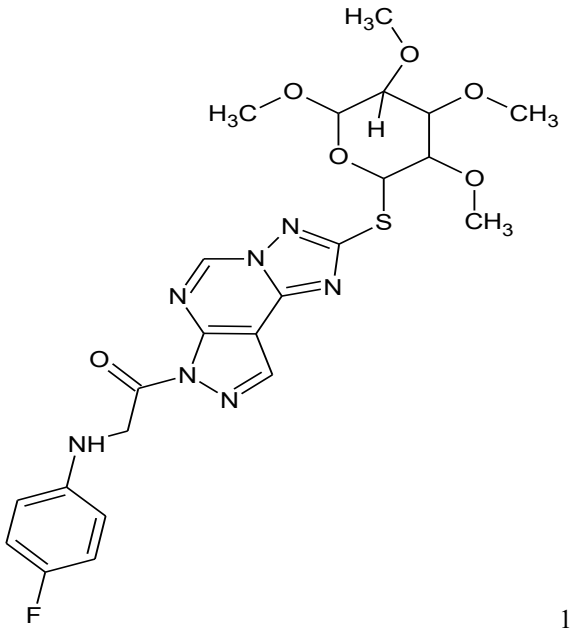

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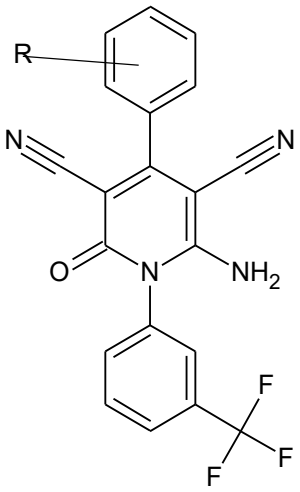
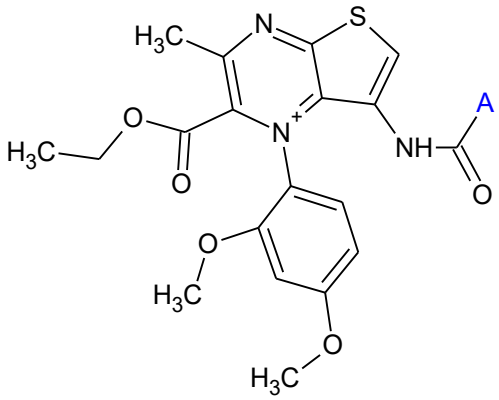
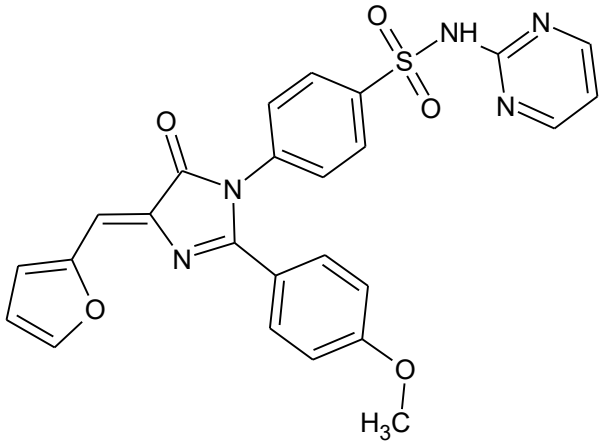


147; R=H, 5e; R= 2,4-$(Cl)_2$



148; A= 2,4,6-tri Cl-C_6H_2



149

Table 18. Pyrimidine derivatives targeting EGFR and VEGFR-2

Compound/Series	Target	IC_{50} / Activity	SAR Insight	Reference
38	KDM (histone lysine demethylase)	KDM IC_{50} = 1.91 µM; Breast cancer IC_{50} ≈13.91 µM	Pyrazolo[1,5-a]pyrimidine core; substituents at R modulate enzymatic and cytotoxic activity	Metwally et al., 2019
39–40	KDM / cytotoxicity	HeLa IC_{50} ≈22.37 µM (series)	Specific modifications on pyrazolopyrimidine improve activity; SAR dependent on R groups	Metwally et al., 2019
41–43	General cytotoxicity, cell cycle	Compound 43 highly cytotoxic (IC_{50} comparable to standards)	β-enaminonitrile/ester precursors; fused ring systems and hydrophilic groups enhance activity	Alblew et al., 2019
44–45	CDK4/6	Noted cytotoxicity vs PC-3 and MCF-7 (IC_{50} in low µM range)	Pyrido[2,3-d]pyrimidine scaffold; tricyclic fusion improves CDK inhibition	Abbas et al., 2019
46	EGFR / VEGFR-2 (dual)	VEGFR-2 IC_{50} = 1.23 µM; superior cytotoxicity vs erlotinib in MCF-7	C-4 chloro/methyl favored; fluoro reduced potency; interaction with Lys721	Mghwary et al., 2019
47–48	EGFR (L858R/T790M mutant)	Compound 48 EGFR IC_{50} = 4.10 µM; mutant cell growth IC_{50} = 10 µM	Sulfoxide at C-4 aniline enhances mutant EGFR inhibition; dimethylamine side chain aids hinge binding	An et al., 2019
51	Topoisomerase II	Topo II IC_{50} = 2.89 µM; A498 GI% = 92.46%; cytotoxic IC_{50} ≈3.5 µM	Thiazolopyrimidine core; dual p-Cl on phenyl rings increases potency; S-isomer favored	Nemr et al., 2020
52	Apoptosis / cell cycle (SW480)	SW480 IC_{50} = 11.08 µM	Aryl urea substituents promote G2/M arrest and apoptosis;	Kilic-Kurt et al., 2020

			aryl urea tuning affects potency	
53–54	CDK2 / cell proliferation	CDK2 IC_{50} ~15.4 µM (analogue 54); antiproliferative IC_{50}s 0.45–1.8 µM across lines	Benzothiazole–pyrimidine linkage; 6-fluoro improves activity; benzenesulfonamide motif useful	Diao et al., 2020
55–57	EGFR / ARO	Compound 57 EGFR ≈ 139.6 ng/mL (~0.14 µg/mL); hydrazone/pyrazolone series IC_{50} down to 0.27 µM	C5 nitrile and C6 phenyl on pyrimidine core essential; C4 hydrazone/pyrazolone increases potency	AboulWafa et al., 2020
58	CDK2 / BCL-2 (docking)	Docking shows strong binding (no experimental IC_{50} reported)	Bulky naphthoyl groups enhance hydrophobic/H-bond interactions; larger aromatics favorable	El-Saidi et al., 2020
59–62	CDK1/2/4 / apoptosis	Selected compounds show potent cytotoxicity (varied IC_{50}s); compound 62 upregulated G2/M arrest	Thiazole-based chalcone scaffold; electron-donating phenyls ↑ potency	Farghaly et al., 2020
63–66	Topoisomerase IIα / DNA intercalation	Up to 20% greater inhibition of MCF-7 vs doxorubicin; potent across panel	4,6-substitution and lipophilicity improve uptake; hydrazone/dihydronaphthalene motifs favorable	Tyinska et al., 2021
67	EGFR	IC_{50} (EGFR) = 0.25 µM; antiproliferative IC_{50} 5.1–6.6 µM; in vivo EAC tumor reduction	Indolyl-pyrimidine hybrids; hydrazone with electron-withdrawing aryl groups at C-5 enhances activity	Ahmed et al., 2021
68	EGFR WT / T790M mutant	EGFR WT IC_{50} = 0.016 µM; T790M mutant IC_{50} = 0.236 µM	1H-pyrazolo[3,4-d]pyrimidine core; substitutions confer isoform selectivity and ATP-pocket binding	Gaber et al., 2022
69	VEGFR-2 / Tubulin	Cytotoxic IC_{50} = 0.03–1.6 µM across lines; tumor suppression in xenograft	Trimethoxy arylidenes and tricyclic scaffold enhance VEGFR-2 and tubulin disruption	Ruzi et al., 2022
70–73	EGFR / EGFRT790M	EGFR T790M IC_{50} ≈ 0.099–0.123 µM; potent antiproliferative activity in vitro	Pyrido[2,3-d]pyrimidin-4(3H)-one core; specific substitutions enable dual EGFR inhibition	Elzahabi et al., 2022
74–77	Bcl-2 / general cytotoxicity	IC_{50} range 1.7–5.7 µg/mL against breast cancer lines; compound 76 active in other lines	2-trichloromethyl and 4,6-dichloro substitutions and 3,4-dimethoxyphenyl at C-5 enhance activity	Sroor et al., 2023
78	MEK/ERK pathway / CRC	HCT116 IC_{50} = 8.04 µM (48h); 5.52 µM (72h)	4-(1,3,4-thiadiazole-2-ylthio)pyrimidine scaffold; thiadiazole–pyrimidine core crucial	Li et al., 2023
79–80	Thymidylate synthase (TS)	Compound 80 TS IC_{50} = 3.89 nM; antiproliferative activity significant	6-aryl-5-cyano-pyrimidines; 5-cyano and 6-aryl critical for TS inhibition	Amin et al., 2019
81–85	General cytotoxicity	IC_{50} values 0.3–3.4 µg/mL across MCF-7, HepG2, HCT-116	Pyrazolopyrimidine core with diarylazo substitutions; aryl variations modulate potency	Fouda et al., 2019
86	General cytotoxicity (HepG2)	HepG2 IC_{50} = 12.37 µM	Oxacalixarene-pyrimidine scaffold; ethanolamine highlighted, SAR underexplored	Huang et al., 2019
87	LSD1 (enzyme)	IC_{50} ≈ 49 nM (LSD1); antiproliferative IC_{50} 0.45–1.79 µM in leukemia lines	Triazole-fused pyrimidine; triazole-pyrimidine fusion enhances enzymatic potency	Li et al., 2019

88	Kinesin Eg5 (docking) / cytotoxicity	MCF-7 $IC_{50} \approx 0.17$ µg/mL; AGS ≈ 4.97 µg/mL	3,4-dihydropyrimidinone (DHPM) scaffold; hydrogen-bonding to Eg5 predicted	Hosseinzadeh et al., 2019
89–90	General cytotoxicity / DNA affinity	MCF-7 $IC_{50} \approx 136$ and 132 µM; TC-1 IC_{50} 65–85 µM	β-lactam naphthalimido core; anthracenyl and electron-rich aryls increased activity	Borazjani et al., 2020
91–92	DNA-binding / antiproliferative	GI_{50} = 1.07 µM; TGI = 6.61 µM; LC_{50} = 34.7 µM (compound 91)	Thiazolopyrimidine core with DNA affinity; intercalative/groove binding tendency	Al-Rashood et al., 2020
93–94	General cytotoxicity	Compounds 93/94 among most potent in series (varied IC_{50}s)	Chromone/pyran fused frameworks; chromone/pyran moieties enhance activity	Bakhotmah et al., 2020
95–97	DHFR-targeting (proposed)	Noted antiproliferative activity vs MCF-7 and HepG2 (IC values not specified)	Pyrimidine-bearing chalcone; dimethylamino-phenyl motif suggested DHFR engagement	Marwa H. Ahmed et al., 2020
98–102	EGFR WT and T790M (ATP-mimetic)	Compound 99 EGFR T790M IC_{50} = 4.03 µM; others low micromolar	Pyrimidine-5-carbonitrile core as ATP mimic; carbonitrile important for binding	Nasser et al., 2020
103–104	Tubulin (predicted) / antiproliferative	Selective cytotoxicity vs MCF-7 and HepG2 (IC_{50}s reported in manuscript)	Chromeno-pyrimidine and chromeno-triazolo-pyrimidine scaffolds; tubulin-binding predicted	Abu El-Azm et al.
105	Aurora A / Aurora B kinases	Aurora A $IC_{50} \approx 309$ nM; Aurora B $IC_{50} \approx 293$ nM; antiproliferative activity noted	2,4-disubstituted pyrimidines; substitution pattern at 2,4 positions modulates kinase selectivity	Xu et al., 2020
106	General cytotoxicity (A-549)	Compound 106 reported as most active vs A-549 (IC_{50} not quantified)	Diphenyl-4-thioxo-1,4-dihydropyrimidin scaffold; nucleophile modifications expand diversity	Sakr et al., 2020
107–108	General cytotoxicity / kinases (c-Src, Btk, Lck)	Compound 107 IC_{50} = 2.2 µM (A549); Compound 108 IC_{50} = 5.6 µM (HeLa) / 21.7 µM (kinase assay)	Thiazolo[3,2-a]pyrimidine and phenylthiazolopyrimidine cores; substituted naphthyl and trimethoxy groups influence potency	Thuraka Sekhar et al., 2020; Chhikara et al., 2020
109–111	General cytotoxicity	EC_{50} range 10–26 µM for lead analogues	Aminopyrimidine scaffold; N-benzyl substitution improves potency	Madia et al., 2021
112–113	Putative BCR-ABL (docking) / cytotoxicity	Several compounds active vs cervical, lung and erythroleukemia lines (IC_{50}s not all reported)	Chromone-fused pyrimidines; halogens on pyrimidine and electron-donating chromone improve activity	Kantankar et al., 2021
114–121	Various kinase and antiproliferative targets	Multiple compounds reported with micromolar activities across cancer lines	Thiazole–pyrimidine, imidazo-pyrazole fused cores; substitution patterns modulate selectivity and potency	Bandaru et al. and others,
115	VEGFR-2 (predicted, docking)	HT29 IC_{50} = 58.4 µM	Moderate lipophilicity at C-7 and proton at C-5 ↑ potency; dimethylamino-propyl group favored	Ćwikła, 2022
116–119	Lipid peroxidase / Lipoxygenase	117 IC_{50} = 47.5 µM; 119 IC_{50} = 42 µM	Substitutions at R1/R2 control LOX/LPO activity; aromatic/halogen enhance potency	Myriagkou, 2023
120a–j	General cytotoxicity (A549, Colo-205, A2780, MCF-7)	IC_{50} range: 0.01–10.6 µM	Aryl substituents on urea moiety critically influence potency	Pattabi, 2024

121–123	PIM-1 kinase	IC_{50} = 0.67–7.68 μM	Pyrazolo[1,5-a]pyrimidine core; nitro group at R3 ↑ potency	Philoppes, 2020
124–126	c-Met kinase	IC_{50} ≈ 5.2 nM (125,126)	N-heterocycles at R2 improve c-Met inhibition; aryl substitutions ↑ A549 activity	Luo et al., 2020
127	VEGFR-2 kinase / antiangiogenic	ED_{50} = 1.65 μM (in vivo prostate cancer model)	Nanoparticle physicochemical traits linked to potency	Amr A.E., 2020
128–132	General cytotoxicity (MCF-7, A549, Caco-2)	IC_{50} = 1.629–4.798 μM	Indazol-pyrimidine scaffold; R1/R2 substitutions control activity & apoptosis induction	Al-Tuwaijri, 2023
133–136	Mcl-1 inhibitors (Bcl-2 family)	K_i = 11.19–15.21 nM	Indole-pyrimidine hybrids; R/R1 substituents drive selectivity	Lamie, 2023
137	ERK1/2 (RAS/BRAF mutant cancers)	ERK1 IC_{50} = 0.11 nM; ERK2 IC_{50} = 0.08 nM	Thiophen-3-yl aminopyrimidine; PROTAC-PD-L1 strategy suggested	Shuai, 2024
138–139	CDK2/cyclin A2	Notable cytotoxicity vs MCF-7, Caco-2, A549, HepG2	Pyrazolo[1,5-a]pyrimidine core; apoptosis and G0/G1 arrest observed	Ali, 2019
140	JAK3 kinase	IC_{50} = 1.7 nM; >588-fold selectivity	4/6-phenyl pyrimidine covalent binding at Cys909	Shu, 2020
141	VEGFR-2 inhibitor	IC_{50} = 310–920 nM; cytotoxicity IC_{50} = 5.85–10.43 μM	Urea-linked thioindole–pyrimidine; apoptosis via ROS, DNA damage	Sana, 2020
142–143	CDK2/cyclin A2	IC_{50} = 6–48 nM	Pyrazolo[3,4-d]pyrimidine & thioglycoside hybrids; strong CDK2 binding	Nassar, 2022
144–146	CDK2 inhibitors	146: IC_{50} = 0.061 mM	Pyrazolopyrimidine analogues; Leu83 binding critical	Mandoura, 2022
147	VEGFR-2 & HER-2	IC_{50} = 1.77 μM (better than Taxol)	2,4-dichlorophenyl moiety enhances dual-target activity	Warhi, 2022
148,161	Topo II inhibitors	148: IC_{50} = 0.23 μM	Thiazolopyrimidines; apoptosis and cell cycle arrest in A549	Zoghbi, 2023
149	EGFR inhibitor	Cytotoxicity IC_{50} = 1.05 μM (MCF-7); EGFR IC_{50} = 0.09 μM	Imidazolone–sulphonamide–pyrimidine hybrid; furan-2-ylmethylene critical	Binjawhar, 2024

Comparative Evaluation: Pyridine vs. Pyrimidine Scaffolds

Both pyridine and pyrimidine moieties are nitrogen-containing heterocycles, often favored in anticancer design.The key differences in drugs of both moieties can be summerized as:

Table: 19 Comparative study of Pyridine and Pyrimidine scaffolds

Feature	**Pyridine**	**Pyrimidine**
Aromaticity	Monocyclic with one nitrogen	Also monocyclic, but with two nitrogens
Kinase Binding Potential	High (EGFR, VEGFR-2, CDKs)	Very High (EGFR T790M, PI3K, etc.)
Resistance Handling	Moderate	High (better for resistant mutations)
Pharmacokinetics	Generally good	Excellent, widely optimized
Clinical Relevance	Investigational/Preclinical	FDA-approved (e.g., Erlotinib)

Conclusion

Pyrimidine and pyridine both have higher promise as a whole in anticancer drug design. Derivatives of pyrimidine are more generalizable as kinase inhibitors and cytotoxics compared to pyrimidine analogs. Based on the SAR data, substituents such as cyano, nitro, halogens, and fused heterocycles tend to augment potency by enhancing kinase binding or DNA binding. Here, we emphasized the recent progress in pyridines and pyrimidines in the context of their promising biological properties and therapeutic relevance. Pyrimidine analogues were discovered to be excellent biomolecules, corroborating the correlation between their structural elements and pharmacological profiles,

due to their intense biological activity. Such versatile heterocycles have played an immense role in managing important and varied molecular processes, accentuating their significance in drug development. This review provides a comprehensive overview of structure–activity relationships (SAR), which is a class case of rational design methodology to the synthesis of new compounds with improved bioactivity. The pyridine molecule has been found to have a good range and could be designed for the action of multifunctionality—such as vasodilatory and anticancer activity at the same time—but pyrimidines are more effective in breaking drug resistance, particularly in cases involving EGFR T790M mutations. The results presented here offer an excellent platform to medicinal chemists who are engaged in designing clinical candidates with improved potency, selectivity, and resistance profiles. The outcomes of the present research are likely to further accelerate current research and pave the avenues for designing innovative, safer, and more effective pyrimidine-based therapies. With limited data for target validation, selectivity, PK, or in vivo potency, most of the publications are limited to in vitro tests. In an attempt to convert these scaffolds into useful anticancer leads, future research will be required to focus on thorough SAR exploration, mechanistic verification (e.g., CETSA, dTMP rescue), and uniting ADMET profiling with resistant animals

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