DOI 10.1007/s11094-021-02346-8
Pharmaceutical Chemistry Journal, Vol. 54, No. 12, March, 2021 (Russian Original Vol. 54, No. 12, December, 2020)

DEVELOPMENT OF FUSED AND SUBSTITUTED PYRIMIDINE DERIVATIVES AS POTENT ANTICANCER AGENTS (A REVIEW)

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Original article submitted December 19, 2019.

The pyrimidine scaffold is a versatile lead heterocycle in pharmaceutical development. It has diverse chemical reactivity, accessibility and a wide range of biological activities. In the past few years, the pyrimidine derivatives have been developed drastically as potent anticancer agents. This review highlights the current status of pyrimidine molecules in cancer therapy. The *in vivo* models have been enumerated for the specific types of cancer. The structure – activity relationship (SAR) of fused and substituted pyrimidine derivatives for anticancer activity is discussed. Electron withdrawing groups on aryl moiety attached to both substituted and fused pyrimidine influenced positively, and enhanced potency of novel small molecules as anticancer agents. Electron donating groups reduced the antiproliferative activity. Thus, scientists and researchers of medicinal chemistry discipline could design small molecules with a pyrimidine scaffold possessing more promising anticancer potential.

Keywords: apoptosis; antiproliferative; fused pyrimidines; substituted pyrimidines; structure – activity relationship; *in vivo* methods.

1. INTRODUCTION

Cancer is a major cause of death in the whole world [1], the mortality being mostly due to stomach, liver, bone, lung, colon, and breast cancers [2, 3]. Chemotherapy, hormone therapy, radiotherapy, surgical removal, and immunotherapy are used in the treatment of cancer [4]. Nowadays several anticancer agents have been developed both from natural sources and by synthetic approaches [5, 6]. Unfortunately, currently available anticancer drugs produce severe side effects [7]. Hence, there is a need for discovery of potent anticancer agents with minimum or no side effects.

Substituted and fused pyrimidines are widely used heterocyclic moieties in drug discovery and development process. In particular, 1,3-diazine is the building unit of DNA and RNA. Pyrimidine and its derivatives exhibit numerous biological activities including antiviral [8], antimicrobial [9], antileishmanial [10], anti-inflammatory [11], neuroprotective [12], and cardiovascular [13]. Gemcitabine, Vandetanib, Gefitinib, Pazopatinib, Lapatinib, Imatinib, Dasatinib, Nilotinib, Uramustine, Tegafur, Cytarabine, Methotrexate, 5-Fluorouracil are anticancer drugs with a pyrimidine scaffold. Many pyrimidine derivatives are in clinical phase trials. Table 1 lists some of the well-known drug candidates (in clinical trials) having pyrimidine moiety, displays their structures with biological targets, and indicates applications.

Pyrimidine is also present in drugs for other applications, e.g., Stavudine is used as an anti-HIV agent. Fervennuline and Iclaprim are used as antibiotics. Minoxidil is used as an antihypertensive agent. Sulfamethiazine and Trimethoprim are used in treatment against bacterial diseases. Phenobarbitone is used as a sedative-hypnotic as well as anticonvulsant. Triflouridine and Idoxuridine are used in treatment against various viral infections. Aronixil is used as antilipedimic. Thonzylamine is an antihistamine. Risperidone is used as antipsychotic. Propylthiouracil is used as antithyroid agent [14]. Figure 1 displays structures of marketed drugs with pyrimidine nucleus.

Fused and substituted pyrimidine derivatives displayed excellent anticancer activities in various *in vitro* and *in vivo* models.

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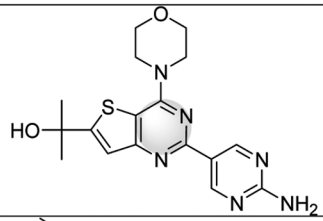
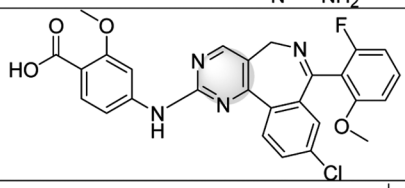
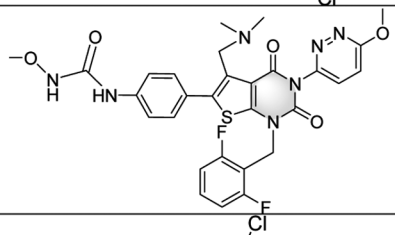
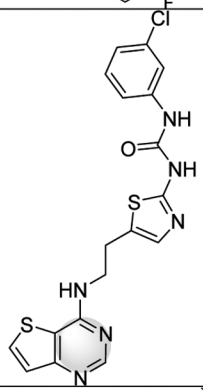
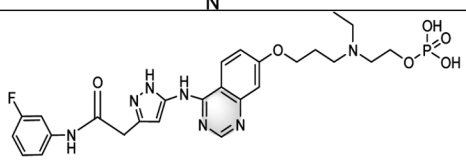
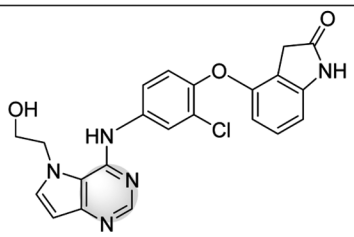
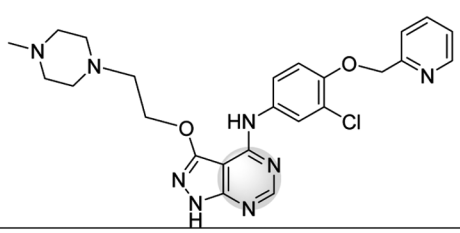
TABLE 1. Structures, Biological Targets and Applications of Some Drug Candidates Possessing the Pyrimidine Moiety (Found in www.cancer.gov/about-cancer/treatment/clinical)

Compound	Structure	Current status	Target	Application
GNE-493		Phase II	PI3K inhibitor (IC_{50} = 3.4 nM) mTOR (IC_{50} = 32 nM)	Breast cancer
Alisertib		Phase II	Aurora B kinase Inhibitor (IC_{50} = 1.2 nM)	Neuroendocrine Prostate Cancer
Relugolix (TAK-385) Takeda		Phase III	-GnRHR Antagonist (IC_{50} = 0.12 nM)	Prostate cancer Endometriosis
SNS-314		Phase I	Aurora A kinase inhibitor (IC_{50} = 9 nM) Aurora B kinase inhibitor (IC_{50} = 31nM) Aurora C kinase inhibitor (IC_{50} = 3 nM)	Advanced solid tumors
Barasertib (AZD1152),		Phase I	Aurora B kinase Inhibitor (IC_{50} = 0.37 nM)	SCLC Myeloid Leukemia
TAK-285 (6)		Phase I	EGFR inhibitor (IC_{50} = 3 nM) and HER-2 (IC_{50} = 1.6 nM)	Breast cancer
TAK-285 (9)		Phase I	EGFR/HER2 (IC_{50} = 5 nM and 1 nM)	Breast cancer

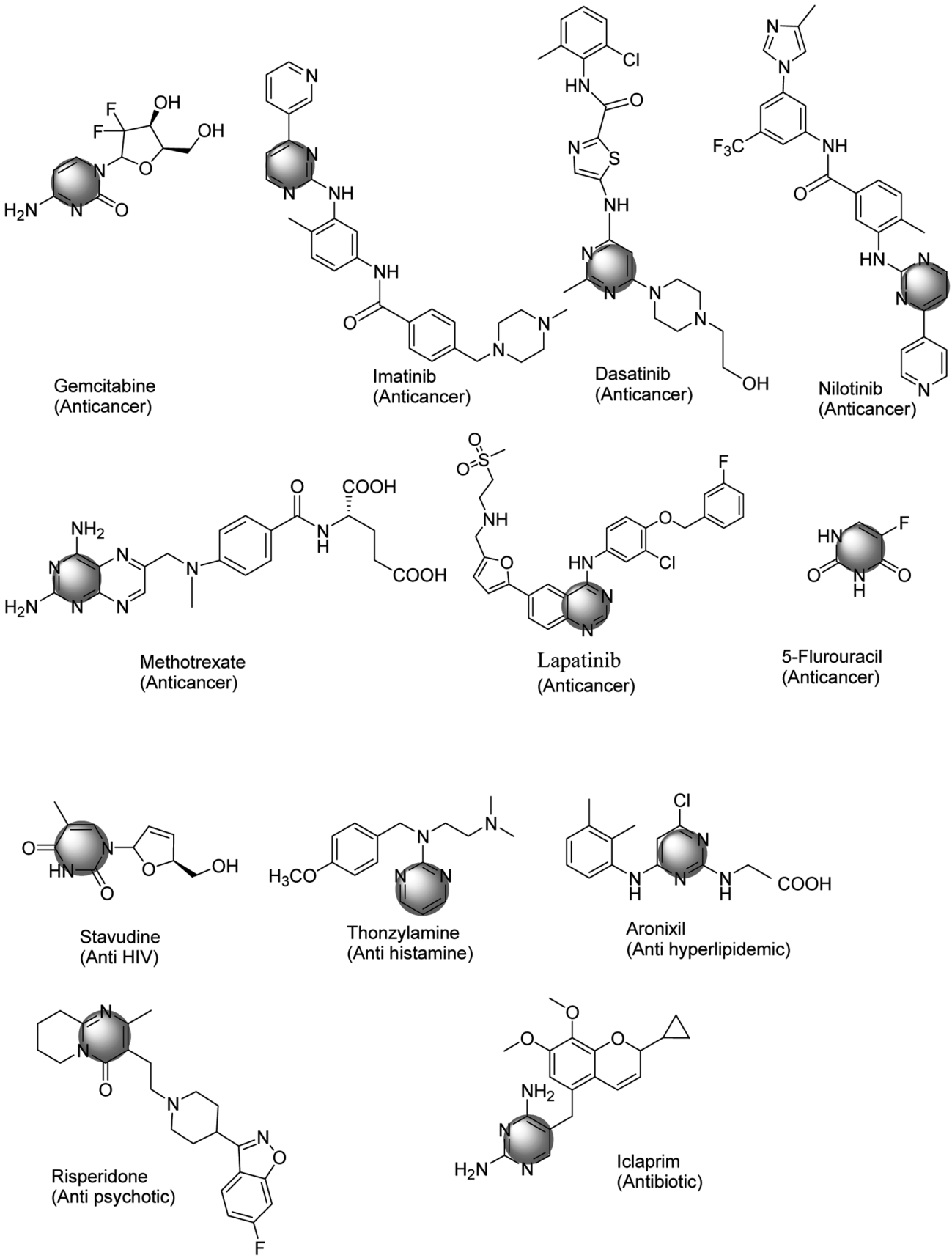
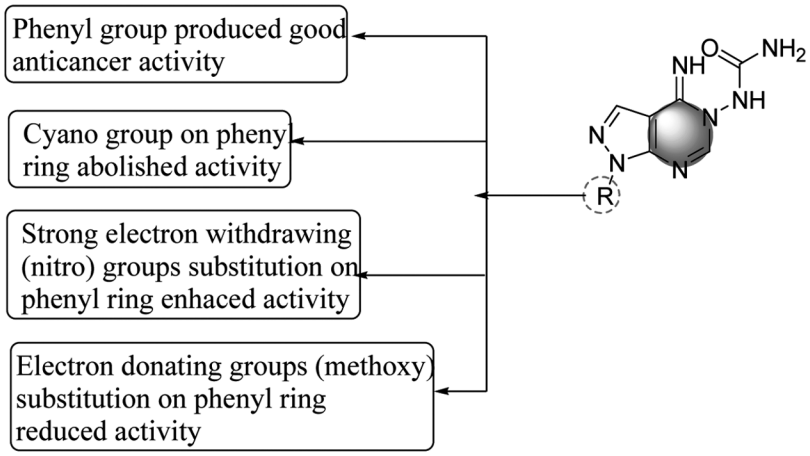


Fig. 1. Drugs with pyrimidine nucleus.



Comp1:R= phenyl Comp 2: R= *p*-fluorophenyl Comp 3: R= *m*-bromophenyl
Comp 4: *m*-nitrophenyl Comp 5: *p*-nitrophenyl

Compound	Activity against cell line ($IC_{50,}$ μM)			
	Hela	A549	MCF-7	HepG-2
1	13.57	12.17	14.87	11.35
2	25.36	10.92	14.73	9.78
3	23.76	11.35	16.59	16.45
4	9.21	8.67	13.54	18.61
5	14.34	5.28	7.93	8.472
Doxorubicin	14.52	8.27	21.9	17.31

Fig. 2. Structure – activity relationship of pyrazolo[3,4-d]pyrimidines.

2. STUDY OF STRUCTURE – ACTIVITY RELATIONSHIP IN FUSED AND SUBSTITUTED PYRIMIDINES

2.1. Pyrazolopyrimidines

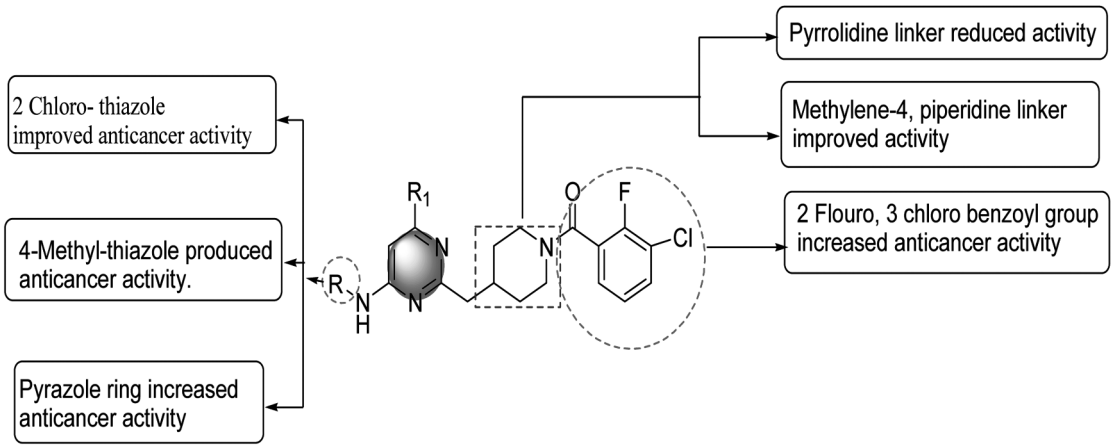
Mishra, et al. [15] in 2016 designed and synthesized a series of pyrazolo[3,4-d]pyrimidine and urea hybrids. Anticancer activity was evaluated by using *in vitro* and *in vivo* cancer models (Fig. 2). Among these, compounds **1 – 5** showed promising cytotoxicity against tested cancer cell lines. Compound **5** was the most potent derivative and it exhibited better cytotoxicity against all tested cell lines when compared to Doxorubicin. Compound **5** successfully inhibited cell cycle progression and displayed admirable apoptosis in A549 cells. It significantly induced caspase-3 activation and suppressed NF-êB and IL-6 activation. Additionally, it displayed tumoricidal effects in lung adenocarcinoma *in vivo* xenograft nude mice model [15].

2.2. Trisubstituted Pyrimidines

Vasilevich, et al. [16] in 2016 developed a pharmacophore model for Ser/Thr kinases. Using the model they screened ASINEX proprietary library database for molecules having Aurora A, Aurora B, and Haspin inhibitory activity. After optimization of the molecules against Aurora A kinase, several hit molecules with activity in the 3–5 nM range were found. These molecules were synthesized by Buchwald reaction, followed by Boc-deprotection and acylation. Antiproliferative assay was done against 16 cancer cell lines [16]. Compounds **6 – 10** exhibited anticancer activity. Compound **10** was found to be the most potent with IC_{50} Aurora A kinase inhibition at 3.5 ± 0.29 nM as displayed in Fig 3.

2.3. Disubstituted Pyrimidines

Xu, et al. [17] in 2020 designed, synthesized and evaluated a series of new 2,4-disubstituted pyrimidines for their



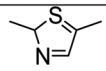
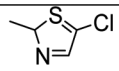
Compound	R	R_1	IC_{50} (nM) Aurora A kinase
6		-	12.0±1.1
7		CH_3	35.1±0.36
8		CH_3	4.1±0.35
9		CH_3	5.3±0.46
10		-	3.5±0.29

Fig. 3. Structure – activity relationship of trisubstituted pyrimidines.

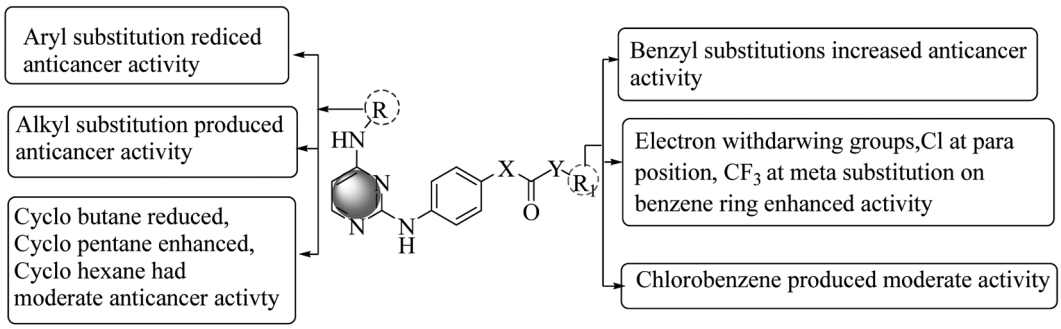
in-vitro anti-proliferative activities against A549, HCT-116 and MCF-7 cell lines. Compounds **11 – 18** exhibited anticancer activity. Among these, compound **18** produced antiproliferative effect with IC_{50} = 12.05 ± 0.45 μM, IC_{50} = = 1.31 ± 0.41 μM, IC_{50} = 20.53 ± 6.13 μM on A549, HCT-116 and MCF-7 cells, respectively. It produced inhibitory effect with the IC_{50} values of 309 nM and 293 nM, respectively, for Aurora A and Aurora B. Furthermore, it induced apoptosis by upregulating the pro apoptotic proteins Bax and decreased the anti-apoptotic protein Bcl-xl in HCT-116 cells [17]. The SAR data are illustrated in Fig 4.

2.4. Triazolopyrimidines

El-Sayed, et al. [18] in [2017] designed and synthesized novel substituted pyrimidine and triazolopyrimidine derivatives. The N3-glycosides of both heterocyclic systems and acyclic oxygenated alkyl derivatives were also prepared. The antiproliferative activity against human prostatic adenocarcinoma (PC3), human colorectal carcinoma (HCT-116) and human breast adenocarcinoma (MCF-7) cell lines in addition to their effect on human normal retinal pigmented epithelial cell line (RPE1) was studied. Compounds **19 – 22** exhibited good anticancer activity (Fig. 5). The results showed N3-substitution in the pyrimidine enhanced antiproliferative activity [18].

2.5. Pyridopyrimidines

Zhang, et al. [19] in 2018 designed and synthesized a new class of compounds containing pyrido[3,4-d]pyrimidine scaffold with an acrylamide moiety as irreversible EGFR-TKIs to overcome acquired EGFR-T790M resistance. Compounds **23 – 28** had antiproliferative activity (Fig. 6). The most promising compound 28 inhibited HCC827 and H1975 cells growth with IC_{50} values of 0.025 μM and 0.49 μM, respectively. Compound 28 also displayed potent inhibitory activity against the EGFRL858R (IC_{50} = 1.7 nM) and EGFRL858R/T790M (IC_{50} = 23.3 nM). It suppressed EGFR phosphorylation in HCC827 and H1975 cell lines and significantly induce the apoptosis of HCC827 cells. Additionally, compound 28 could remarkably inhibit cancer growth in established HCC827 xenograft mouse model at 50 mg/kg *in vivo*. The study revealed that 2,4-disubstituted



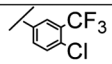
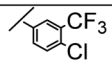
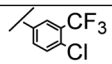
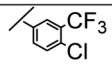
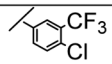
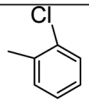
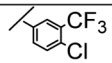
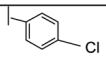
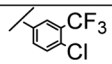
Compound	X	Y	R	R_1	A459 IC_{50} (μM)	HCT-116 IC_{50} (μM)	MCF-7 IC_{50} (μM)
11	NH	NH			7.43±1.08	5.95±0.24	10.75±2.96
12	NH	NH			5.88±1.97	2.51±0.09	2.33±0.42
13	NH	NH			18.52±3.86	16.41±1.36	38.25±3.9
14	NH	NH			7.32±1.96	4.24±0.54	4.61±0.04
15	NH	NH			>50	>50	>50
16	NH	NH			18.57±6.5	8.10±2.18	27.93±2.45
17	NH	NH			6.32±0.69	4.66±0.64	12.83±1.06
18	CH_2	NH			3.40±0.57	2.50±0.19	16.41±2.26
VX-680	-	-	-	-	3.90±0.42	1.49±0.65	17.39±4.55

Fig. 4. Structure – activity relationship of disubstituted pyrimidines.

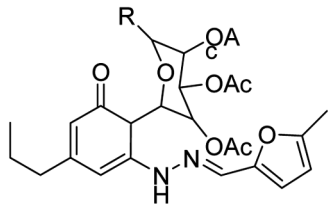
6-(5-substituted pyridin-2-amino)pyrido[3,4-d]pyrimidine derivatives could be effective EGFR inhibitors and potent anticancer agents [19].

2.6. Pyrolopyrimidines

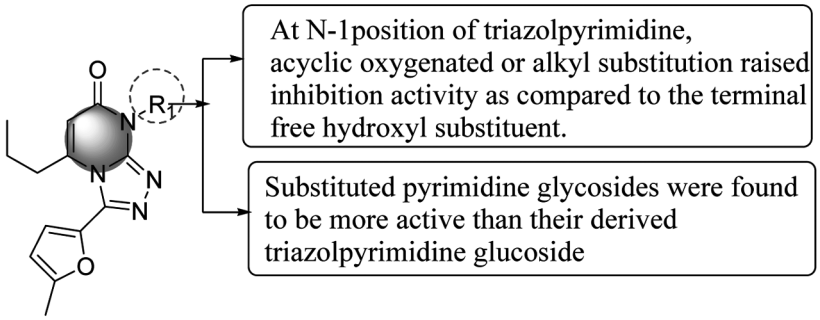
Targeting multiple kinases, simultaneous inhibition provides synergistic effects by inhibition of tumor growth and resistance [20 – 28]. Kurup, et al. [29] in 2018 designed, synthesized, and evaluated a series of 18 compounds incorporating pyrrolo[2,3-d]pyrimidine scaffold for dual inhibition of epidermal growth factor receptor kinase (EGFR) and aurora kinase A (AURKA). All the synthesized small molecules had nanomolar inhibition of EGFR and micromolar inhibition of AURKA (Fig. 7). Compounds **29 – 47** inhibited EGFR and AURKA. Compound 30 was the most potent inhibitor of EGFR and AURKA. Compound 30 was further evaluated in four different squamous cell head and neck cancer cell lines for downstream effects resulting from AURKA and EGFR inhibition [29].

2.7. Thienopyrimidines

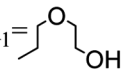
Saddik et.al. [30] in 2018 synthesized a series of thieno[2,3-d] pyrimidine derivatives. The new derivatives were tested against two (MCF-7 and HeLa) cancer cell lines in comparison with Paclitaxel as a reference standard (Fig. 8). Compounds **48 – 51** exhibited antiapoptotic potential. Compound **48** produced more pronounced cell inhibition than the standard drug for MCF-7 cancer cell line. The anticancer activity data showed that all the new compounds have good and excellent cytotoxicity activities as compared



Compound 19: R=H Compound 20:R=CH_2OH



Compound 21: R_1=H Compound 22: R_1=



Compound	PC3 IC_{50} (μM)	HCT-116 IC_{50} (μM)	MCF-7 IC_{50} (μM)	RPE1 IC_{50} (μM)
19	75±4	93±8	-	66±6
20	70±9	95±16	-	93±9
21	98±9	101±7	103±9	-
22	87±7	-	-	148±18
Doxorubicin	6.8±1.2	2.2±3.1	12.8±1	-

Fig. 5. Structure – activity relationship of triazolopyrimidines.

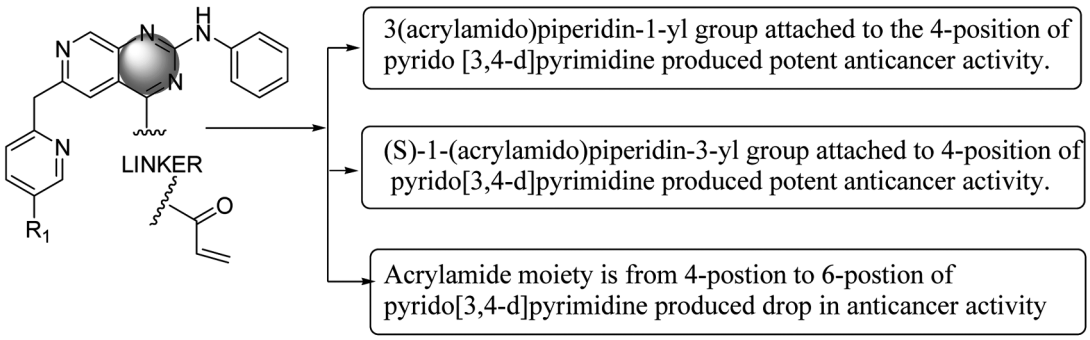
to that of Paclitaxel. The SAR data are briefly is illustrated in Fig. 8 [30].

2.8. 7H-Benzo[H]chromeno[2,3-d]pyrimidines

The synthesis of new compounds as anticancer agents for drug replacement, is an area of high interest in literature in order to overcome the drug resistance issue [31 – 34]. Rawda M. Okasha et. al., in 2017 synthesized novel 4H-benzo[h]-chromene-, 7H-benzo[h]chromeno[2,3-d]pyrimidine- and 14H-benzo[h]-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives, starting from 2-amino-4-(4methoxyphenyl)-6-methoxy-4H-benzo[h]chromene-3-carbonitrile and ethyl 2-amino-4-(4-methoxyphenyl)-6-methoxy-4H-benzo-[h]chromene-3-carboxylate. The new molecules have been evaluated for their antitumor activities against three cancer cell lines: breast adenocarcinoma (MCF-7), human colon carcinoma (HCT-116) and hepatocellular carcinoma (HepG-2) (Fig. 9). Compounds 52 – 54 had potent anticancer activity. Most of these synthesized compounds having pyrimidine rings exhibited good antitumor activities towards the tested cell lines [35].

2.9. Quinazolines

Allam et. al. [36] in 2020 synthesized 6-bromo-2-(pyridin-3-yl)-4-substituted quinazolines starting from 4-chloro derivative via the reaction with either phenolic compounds to obtain 2-amino-6-(un)substituted benzothiazole to produce hydrazine hydrate derivatives. Reaction of the hydrazino functionality of these compounds with appropriate acid anhydride, acid chloride or aldehyde affords 2,4,6-trisubstitu-



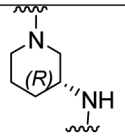
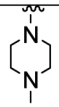
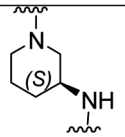
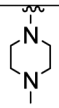
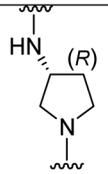
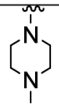
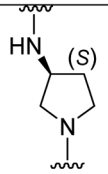
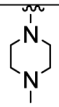
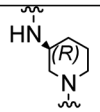
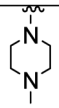
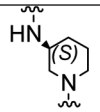
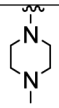
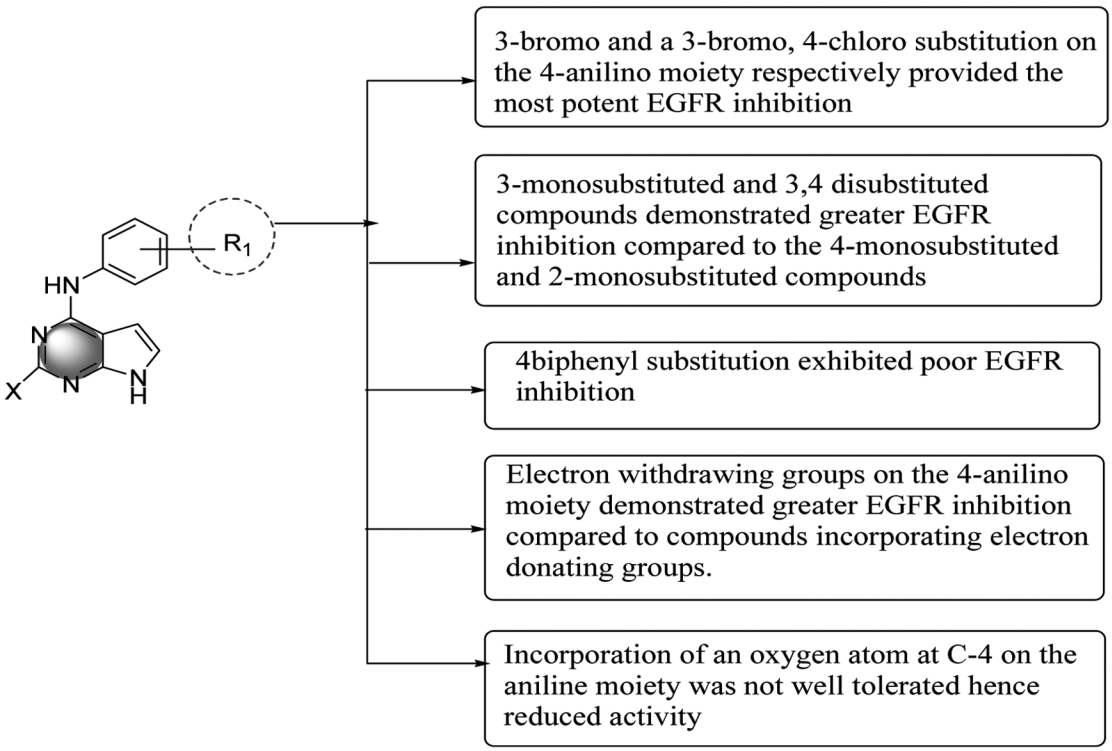
Compound			HCC827 IC_{50} (μM)	H1975 IC_{50} (μM)	A549 IC_{50} (μM)
23			0.054±0.023	1.75±0.42	0.81±0.02
24			0.073±0.005	1.4±0.02	0.81±0.26
25			0.17±0.01	0.44±0.08	0.65±0.10
26			0.27±0.02	0.86±0.25	1.67±0.40
27			0.16±0.02	1.40±0.24	0.81±0.05
28			0.025±0.005	0.49±0.08	0.99±0.04
Osimertinib	-	-	0.027±0.01	0.019±0.008	0.53±0.09

Fig. 6. Structure – activity relationship of pyridopyrimidines.

ted quinazoline derivatives. The target compounds were screened for their efficacy as EGFR inhibitors compared to Gefitinib. Compounds were further screened for their *in vitro* cytotoxicity against MCF7 (breast) and A549 (lung) cancer cell lines. Compounds showed potent inhibitory activity on wild-type EGFR were screened against mutant EGFR. They were assayed for their cytotoxicity against mutant EGFR-expressing cell lines PC9 and HCC827. The unsubstituted benzothiazol-2-amine compounds **55 – 56** displayed anticancer activity (Fig. 10). Compound **55** exhibited EGFR inhibition (IC_{50} = 0.096 μM) and anticancer activity against MCF-7 cell line (IC_{50} = 2.49 μM) [36].

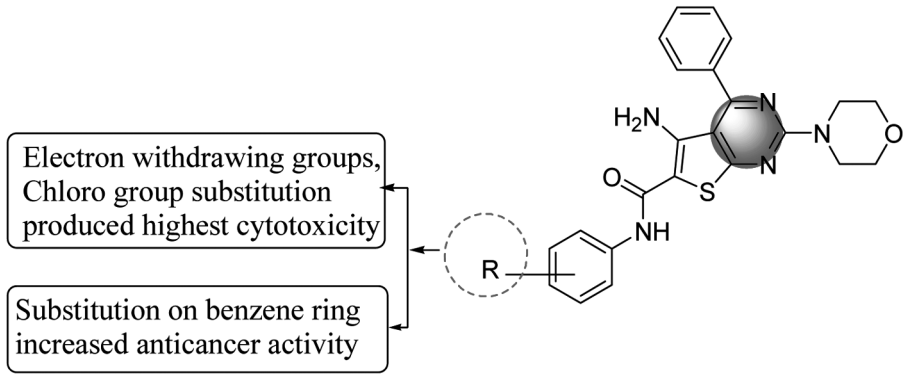


Compound	R_1	X	AURKA (IC_{50}±SD, μM)	EGFR (IC_{50}±SD, nM)
29	H	H	5.58±0.66	254.13±25.97
30	3-Br	H	1.99±0.05	3.76±0.12
31	3-F, 4-Cl	H	3.29±0.15	5.98±0.61
32	4-Cl	H	5.15±0.37	84.92±15.92
33	3,4-diCl	H	3.91±0.11	6.70±0.25
34	4-OCH_3	H	6.68±0.54	2936.67±94.40
35	3-Br, 4-Cl	H	3.23±0.31	3.63±0.43
36	3-Br	NH_2	4.54±0.93	383.7±65.50
37	4-CH_3	H	5.45±0.36	667.13±141.53
38	4-Br	H	3.73±0.12	125.33±16.44
39	3-Cl	H	3.13±0.75	6.63±0.98
40	3-CH3	H	3.43±0.12	20.01±3.60
41	3-CF_3	H	5.78±0.43	43.57±7.77
42	2-Cl	H	5.66±0.43	470.67±114.47
43	2-CH_3	H	8.56±1.74	1230±201.12
44	4-BiPh	H	74.36±25.25	>100
46	4-OPh	H	13.27±3.57	110.97±15.14
47	4-CH_2Ph	H	4.95±0.69	63.29±4.58
Staurosporine	-	-	0.46±0.03	430.57±25.44

Fig. 7. Structural activity relationship of pyrolo pyrimidine

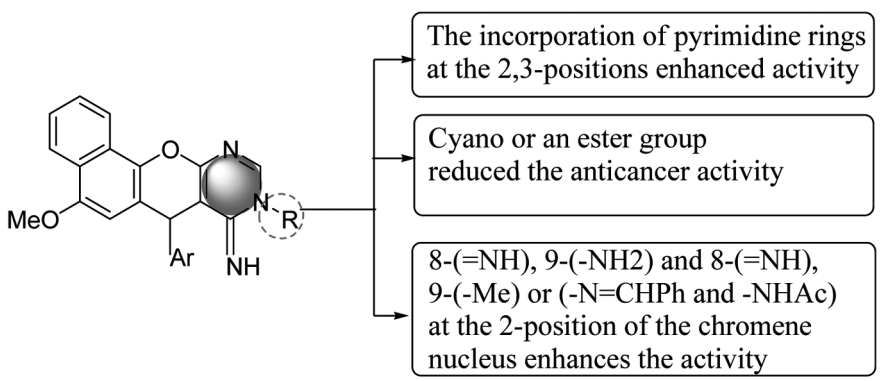
3. CONCLUSION

The SAR studies revealed that linkers like amide, urea, and thiourea groups enhance the binding with the molecular targets. Biphenyl and glycoside groups hindered anticancer activity. Electron withdrawing groups on aryl moiety attached to both substituted and fused pyrimidine influenced positively and enhanced potency of new small molecules as



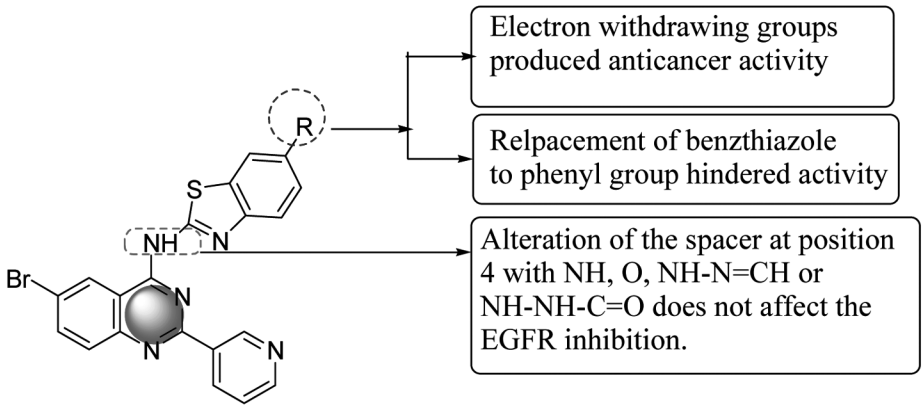
Compound	R	MCF-7 (IC_{50}±SD, µM)	HeLa (IC_{50}±SD, µM)
48	p-Cl	18.87±0.2	49.95±1.9
49	p-OCH_3	27.81±1.0	61.89±2.9
50	p-I	42.81±3.5	60.75±1.8
51	H	52.59±0.3	40.74±1.7
Paclitaxel	-	40.37±1.7	45.78±0.8

Fig. 8. Structure – activity relationship of thienopyrimidines.



Compound	R	MCF-7 (IC_{50}±SD, µg/mL)	HCT-116 (IC_{50}±SD, µg/mL)	HepG-2 (IC_{50}±SD, µg/mL)
52	Me	0.9±0.06	0.9±0.05	0.9±0.11
53	NH_2	1.1±0.14	0.8±0.12	0.8±0.08
54	N=CHPh	10.0±0.9	14.5±0.5	W
Doxorubicin	-	0.4±0.01	0.5±0.02	0.9±0.04

Fig. 9. Structure – activity relationship of 7H-benzo[h]chromeno[2,3-d]pyrimidines.



Compound	R	A45 (IC_{50}±SD, µg/mL)	MCF-7 (IC_{50}±SD, µM)
55	H	178±8.9	2.49±0.12
56	NO_2	24.55±1.22	3.195±0.15
Gefitinib	-	4.389±0.21	4.972±0.24

Fig. 10. Structure – activity relationship of 6-bromo-2-(pyridin-3-yl)-4-substituted quinazolines.

anticancer agents. Electron donating groups reduced the antiproliferative activity. The bulky groups like hydrazines, methoxy, and long chain alkyl groups hindered the activity. This review provides insight for researchers to design and develop new potent anticancer agents.

ACKNOWLEDGEMENT

We would like to thank government of India, for providing SERB grant no. DST No: EMR/2016/005073

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