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Imidazo- and pyrazolopyrimidine scaffolds as anticancer agents

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Abstract: Cancer is a global serious life threatening disease; it exerts massive impacts on diseased human body, and causes high rate of mortality in different parts of the world. It arises from irregular cell growth forming heterogenous tissues affecting normal ones' efficacies. Additionally, it can affect any body part and possess ability to migrate to another body organ, which is called metastasis. The real awful effect of cancer motivated many researchers to achieve synthesis of effective and safe anticancer drugs with the least possible side effects on normal body tissues. Among these trials heterocyclic derivatives gained vast interest, especially the imidazo- and pyrazopyrimidine ones. Many of these analogs exhibited good antitumor effects, even some of them were approved by FDA as effective anticancer drugs. Through this review, we aimed to cover recent publications concerning synthesis of pyrimidine derivatives with either imidazole, or pyrazole moieties and their effects as anticancer agents.

Keywords: Anticancer; pyrimidine; imidazopyrimidine; pyrazolopyrimidine; synthesis.

1. INTRODUCTION

Cancer is a globally wide spreading disease; it exerts deadly effects on sick people. Cancer tissues can proliferate at a higher rate when compared to the normal ones[1]. It caused about 9.6 billion deaths in 2018[2]. In addition, both incidence and mortalities rates increase in the Gulf and eastern Mediterranean areas, it's assumed to be 1.8 fold by 2030[2]. Breast, liver, bladder, non-Hodgkin lymphoma, lung, leukemia, brain, CNS, and prostate cancers are widespread in Egypt[3]. Liver, bladder, and non-Hodgkin lymphoma cancers are ranked first in males[4]. Moreover, breast, non-Hodgkin lymphoma, and liver cancers are the most commonly represented in females[4]. The leakage of information about breast cancer among Egyptian women caused the late discovery of the disease in many cases[5]. It is proposed that the breast and liver cancers ratio will be increased through the following years[5,6]. In addition, HCV, HBV, alcohol, and smoking are considered as the most common cause of developing liver cancer in Egypt[6,7]. The used protocols for cancer treatments could be divided into surgery, radiation, immunotherapy, and chemotherapy[8]. From the above, the design of a new effective treatment represented an urgent need.

The pyrimidine nucleus is a basic participant in both ribonucleotide and deoxyribonucleotide bases[9]; as a result, it displayed a rich field for scientists to synthesize pyrimidine analogs, which showed diversified pharmacological effects. Many of imidazo-, and pyrazolopyrimidines revealed assorted efficacies as antibacterial[10,11], antifungal[12,13], antiviral[14-16], hyoptenstive[17,18], anti-alzheimer[19,20], analgesic, antiinflammatory[21,22], anixolytic[23,24] and anticancer[26-28]. It was reported that many of the anticancer drugs carry imidazo[4,5-d]pyrimidine,

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pyrazolo[1,5-a]pyrimidine, and pyrazole[4,5-d]pyrimidine moieties, or carry the two nuclei as separated rings as fludarabine phosphate[29], tirabrutinib[30], roscovitine[31], nilotinib[29], zanubrutinib[30], dinaciclib[31], ibrutinib[30], parsaclisib[32], sapanisertib[32], umbralisib[32], ruxolitinib[31] and encorafenib[33] (Figure 1).

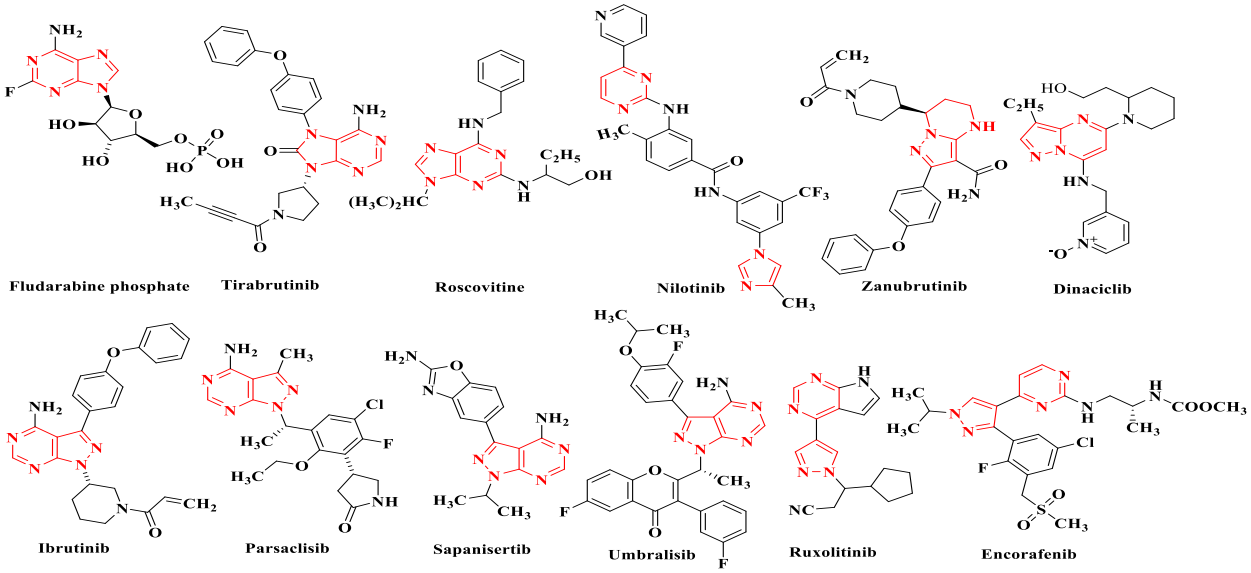
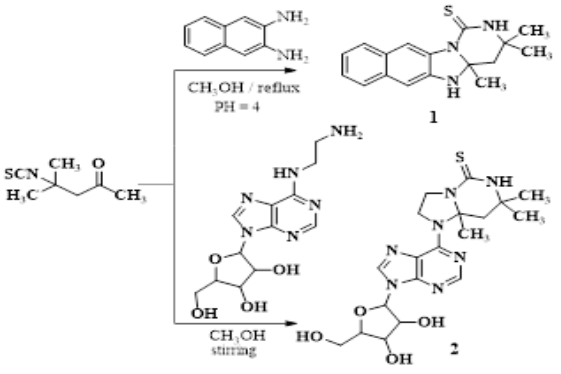


Figure 1. Reported anticancer pyrimidine containing drugs.

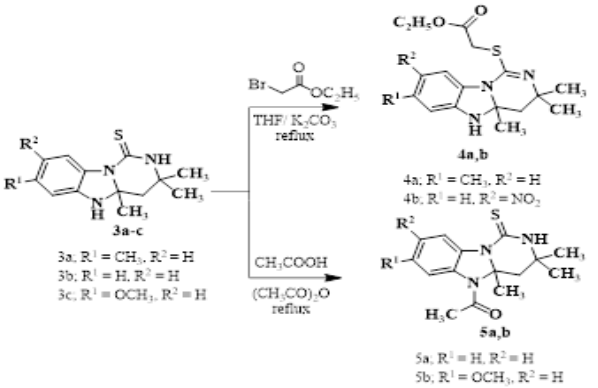
2. Imidazo and pyrazolopyrimidines anticancer agents

2.1. Imidazopyrimidine derivatives

It was found that condensation of 4-isothiocyanato-4-methyl-2-pentanone with 2,3-diaminonaphthalene, and *N*-aminoethyladenosine allowed the synthesis of compounds **1** and **2**. However, compounds **4a,b** were prepared by refluxing of **3a,b** with ethyl bromoacetate, whereas acetylation by refluxing of compounds **3a,c** in acetic anhydride/acetic acid mixture accomplished synthesis of **5a,b**. These derivatives were tested against DU145, PC3, HT29, LOX, SK-MEL-5, MCF-7, MCF7/ADR, IGROV1, and U251b cell lines; the highest efficacy was exerted by compound **5b** against U251 CNS cell line with GI_{50} 5.02 µM. Its activity was much higher than **4a,b**'s activities, this may be attributed to the ethylmercaptoacetate, and acetyl moieties. Moreover, the methoxy group at position 7 greatly increased its effect over **5a**[34]. Schemes 1&2.



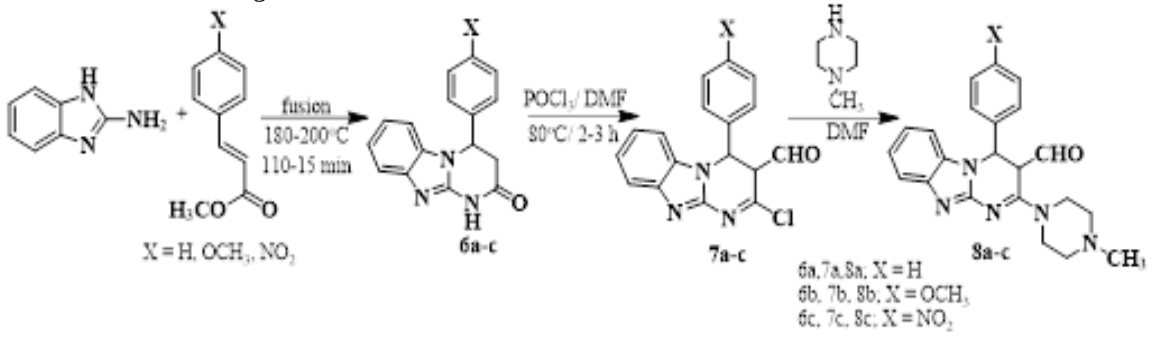
Scheme1. Synthesis of compounds 1–2.



Scheme 2. Synthesis of compounds 4a,b – 5a,b.

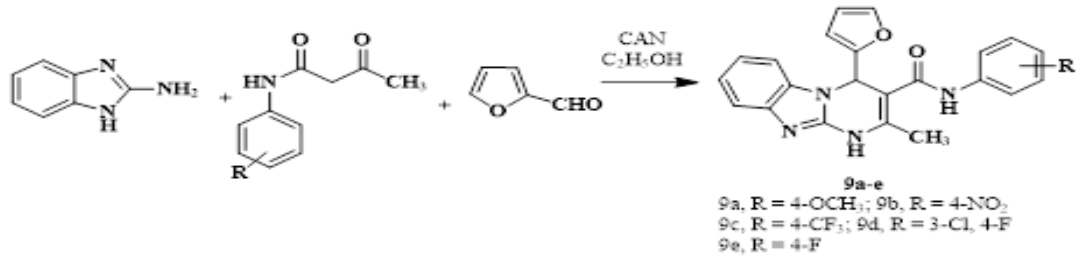
As outlined in Scheme 3; more derivatives were synthesized by fusion of 2-aminobenzimidazole, and substituted cinnamates representing compound **6**, that upon chlorination using phosphorous oxychloride; compounds **7a-c** were produced. These derivatives were stirred with 1-methylpiprazine at

60º C producing **8a-c**. Among these compounds; **7a, 7c,** and **8b** showed good anticancer effects. Compound **8b** showed high activity against MOLT-4 cell line with GI_{50} < -8.00 M[35].



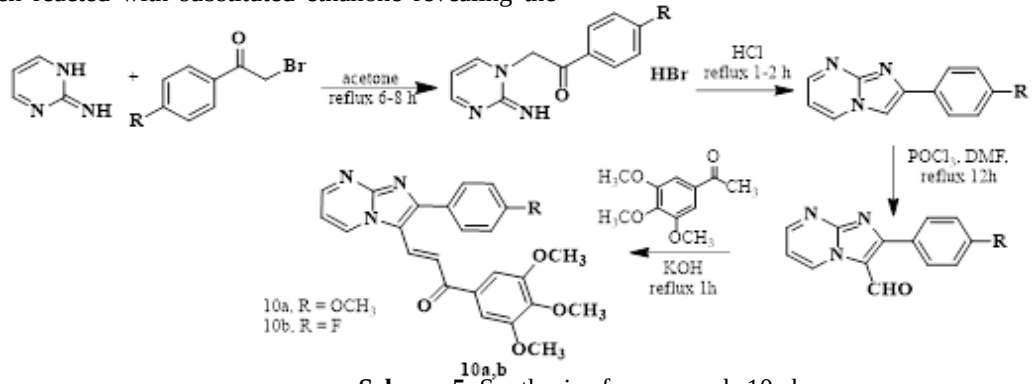
Scheme 3. Synthesis of compounds 6a-c – 8a-c.

Compounds **9a-e** were prepared *via* heating a mixture of 2-aminobenzimidazole, appropriate substituted 3-oxo-*N*-phenylbutanamide, 2-furaldehyde, and ceric ammonium nitrate (CAN) at 50º C with stirring. Among the produced compounds; **9a,b** were active against the HCT-116 cell line with IC_{50} 8.71 µM, and 4.96 µM, respectively and Hep-G2 cell line with IC_{50} 4.97 µM, and 7.38 µM, respectively. These compounds showed KSP inhibition and Aurora-A kinase inhibition[36]. Scheme 4.



Scheme 4. Synthesis of compounds 9a-e.

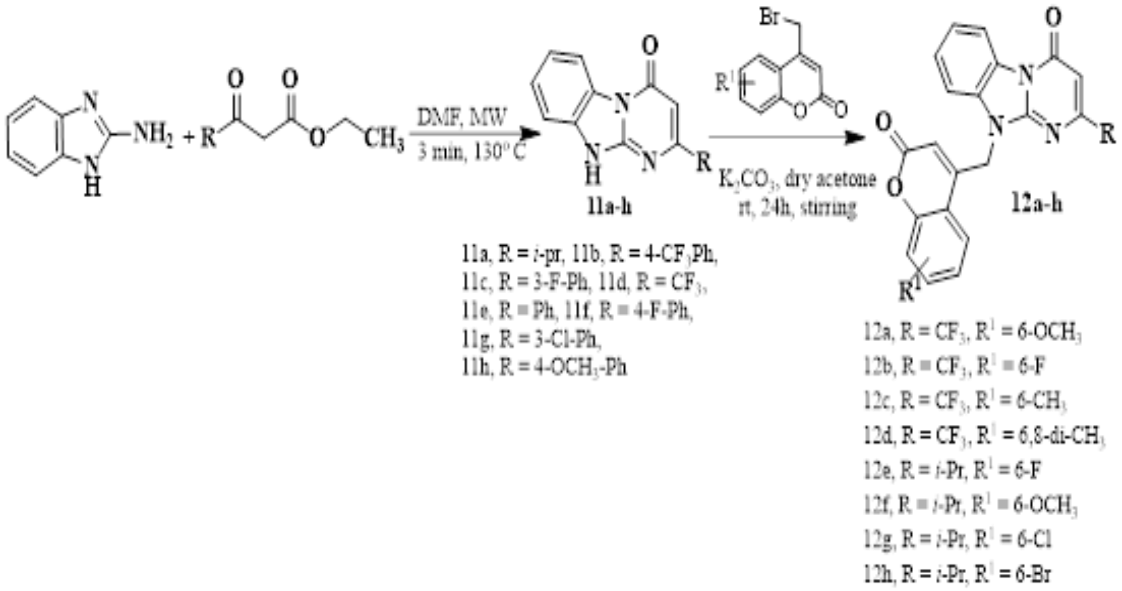
Additionally, Kamal *et al*,[37] synthesized imidazo-pyrimidine scaffold by first reacting pyrimidin- 2(1*H*)-imine with substituted 2-bromoethanone, followed by cyclization, and synthesis of imidazole ring using hydrochloric acid. Then it underwent Vilsmeier reaction and converted into an aldehydic analog, which then reacted with substituted ethanone revealing the desired structures **10a,b**. The synthesized derivatives were subjected to MTT assay at NCI, and delivered good anticancer effects against tested 60 cell lines in NCI[37]. Scheme 5.



Scheme 5. Synthesis of compounds 10a,b.

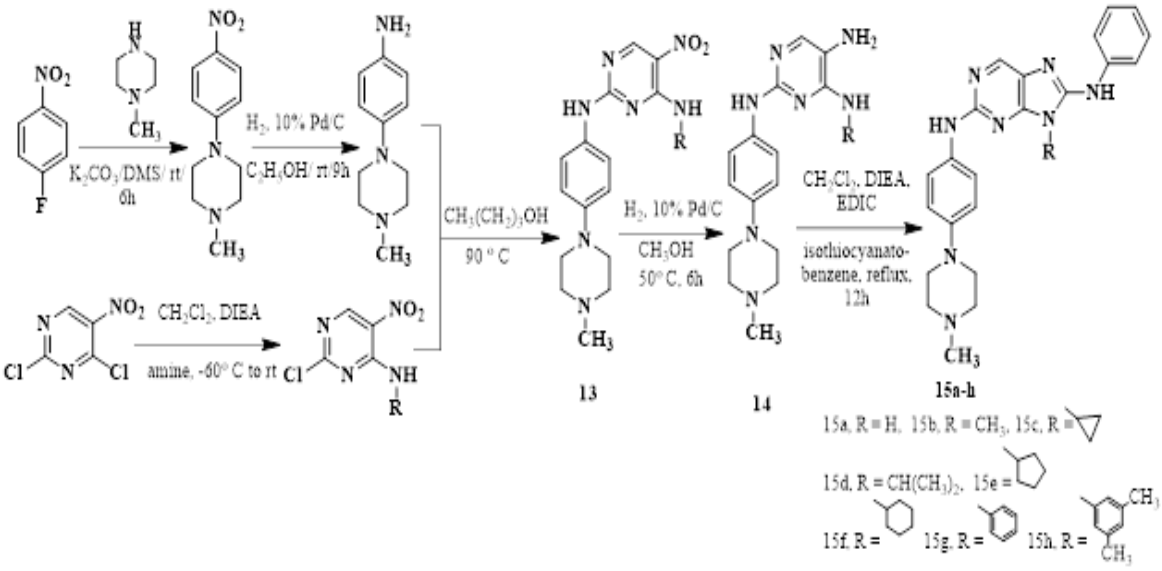
Puttaraju *et al,* [38] accomplished the synthesis of imidazopyrimidine by reaction of 2-aminobenz-imidazole with appropriate substituted 1,3-di-carbonyls. This was followed by the reaction with 4-bromomethyl coumarins. Compounds **11d**, **11b**, **12b**, **12d**, **12e**, and **12g** showed good anticancer effects against Dalton's ascitic lymphoma cell line; compound **12g** was the most active derivative, it

caused 88% death of cells at the concentration of 100 µg/mL[38]. Scheme 6.



Scheme 6. Synthesis of compounds 11a-h - 12a-h.

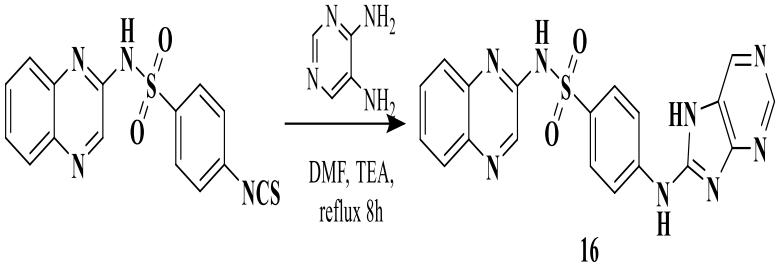
Compounds **15a-h** were synthesized as described in scheme 7; first 1-methyl-4-(4-nitro-phenyl)piperazine was synthesized *via* reaction of 4-fluoronitrobenzene, and 1-methylpiperazine, this was followed by hydrogenation and conversion of the nitro group into amino one. The nucleophilic substitution reaction of 4-(4-methyl-piperazin-1-yl) aniline with 2-chloropyrimidine produced compound **13**. The preceding compound was subjected to hydrogenation releasing compound **14**. Cyclization was fulfilled by using isothiocyanate benzene to synthesize **15a-h** derivatives. Compound **15e** manifested a high anticancer effect against HCC827, H1975, and Hep-G2 cell lines with IC_{50} < 0.00001 µM, 0.36 µM, and > 5.00 µM, respectively. The better activity may be related to the five- membered rings at N-9, it also revealed a high EGFR kinase inhibiting effect[39].



Scheme 7. Synthesis of compounds 13–15a-h.

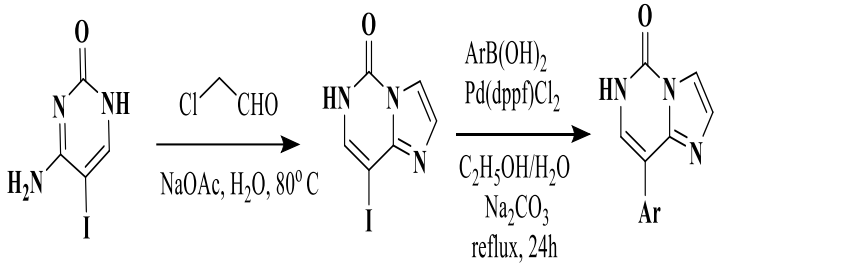
Upon refluxing of 4-isothiocyanato-*N*-(quinoxalin-2-yl)benzenesulfonamide with 4,5-di-amino pyrimidine in DMF; the imidazo pyrimidine moiety's synthesis was achieved. This revealed compound **16**, which showed in-vitro anticancer activity against Hep-G2 cell line with IC_{50} 38.12 µM

and exhibited more activity than 5-fluorouracil[40].
Scheme 8



Scheme 8. Synthesis of compound 16.

Compounds **17a-j** were synthesized by the reaction of 4-aminopyrimidinone with 2-chloro-acetaldhyde. The iodo atom was then substituted by variable aryl moities allowing the synthesis of derivatives **17a-j**. Compounds **17b,h** revealed good cytotoxic effect against CCRF-CEM, CEM-DNR bulk, K562, K562-Tax, A549, HCT-116, HCT-116p53-/-, MRC-5, and BJ cell lines. The highest efficacy was exerted by **17b** against the BJ cell line, and by **17h** against CCRF-CEM cell line with IC_{50} 0.66 μM, and 1.45 μM, respectively[41]. Scheme 9

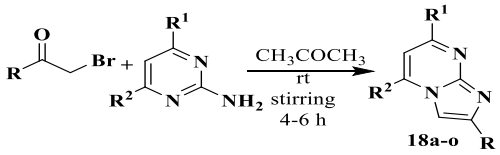


17a, Ar = Ph, 17b, Ar = biPh-4-yl
17c, Ar = 4-OCH_3-Ph, 17d, Ar = 4-Cl-Ph
17e, Ar = 4-CF_3-Ph, 17f, 4-CHO-Ph
17g, Ar = 4-COOH-Ph, 17h, Ar = 4-CN-Ph
17i, Ar = thiophen-2-yl, 17j, Ar = pyridin-4-yl

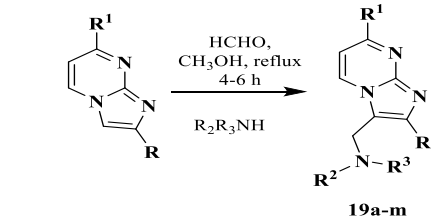
Scheme 9. Synthesis of compounds 17a-j.

In 2015, the imidazopyrimidine skeleton was synthesized by stirring 2-aminopyrimidines and substituted α-haloketones. The produced compounds **18a-o** underwent reaction with different amines permitting the synthesis of compounds **19a-m**, **20a-c**, and **21a-l**. It was found that compounds **19e**, **20b**, and **21k** showed considerable anticancer effects against A-549, HeLa, Panc-1, and MDA-MB-23 when compared to doxorubicin. Compound **19e** was highly active against A-549 with 0.05 μM GI_{50}, while < 0.01 μM GI_{50} was demonstrated by **20b**, and **21k** against MDA-MB-231[42]. Scheme 10

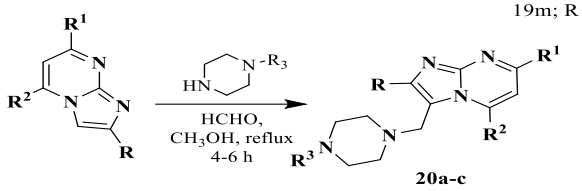
Kamal and co-workers[43] synthesized different analogs **22a-o** as expected anticancer agents. These compounds were tested against Hela, A-549, DU-145, and B-16 cell lines. Potent anticancer effect against A-549 cell line was revealed by compounds **22k**, and **22n** with 1.92 μM, and 2.19 μM IC_{50}, respectively. Cyclization of substituted 2-(2-imino-pyrimidin-1(2*H*)-yl)ethanone achieved synthesis of imdazopyrimidines. Vilsmeier reaction allowed the insertion of an aldehydic group that paved the synthesis of benzimidazole moiety by reaction with phenylenediamine[43]. Scheme 11



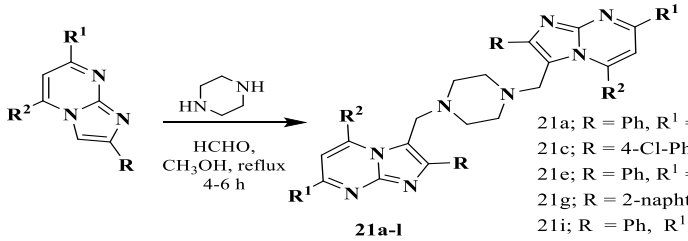
18a; R = Ph, $R^1 = R^2 = H$; 18b; R = 4-tolyl, $R^1 = R^2 = H$;
18c; R = 4-Cl-Ph, $R^1 = R^2 = H$ 18d; R = 2,4-di-Cl-Ph, $R^1 = R^2 = H$;
18e; R = 2-naphthyl, $R^1 = R^2 = H$; 18f; R = 2-thiophenyl, $R^1 = R^2 = H$
18g; R= 2-tolyl, $R^1 = R^2 = H$ 18h; R = 2-Br-Ph, $R^1 = R^2 = H$
18i; R = *tert*butyl, $R^1 = R^2 = H$ 18j; R = 4-OH-Ph, $R^1 = R^2 = H$
18k; R = Ph, $R^1 = CH_3$, $R^2 = H$ 18l; R = 4-Cl-Ph, $R^1 = CH_3$, $R^2 = H$
18m; R = 4-OH-Ph, $R_1 = CH_3$, $R_2 = H$ 18n; R = *tert*butyl, $R^1 = CH_3$, $R^2 = H$
18o; R = Ph, $R^1 = R^2 = OCH_3$



19a; R = Ph, $R^1 = H$, R^2R^3N = morpholinyl
19b; R = Ph, $R^1 = CH_3$, R^2R^3N = piperidinyl
19c; R = 4-OH-Ph, $R^1 = H$, R^2R^3N = piperidinyl
19d; R = 4-OH-Ph, $R^1 = CH_3$, R^2R^3N = pyrrolidinyl
19e; R = Ph, $R^1 = H$, R^2R^3N = pyrrolidinyl
19f; R = Ph, $R_1 = H$, R^2R^3N = piperidinyl
19g; R = *ter*-butyl, $R^1 = H$, R^2R^3N = piperidinyl
19h;R = Ph, $R^1 = H$, $R^2 = CH_3$, $R^3 = Ph$
19i; R = *ter*-butyl, $R^1 = CH_3$, R^2R^3N = morpholinyl
19j; R = Ph, $R^1 = CH_3$, R^2R^3N = morpholinyl
19k; R = 4-Cl-Ph, $R^1 = CH_3$, R^2R^3N = morpholinyl
19l; R = Ph, $R^1 = CH_3$, R^2R^3N = pyrrolidinyl
19m; R = 2-thiophenyl, $R^1 = H$, R^2R^3N = pyrrolidinyl

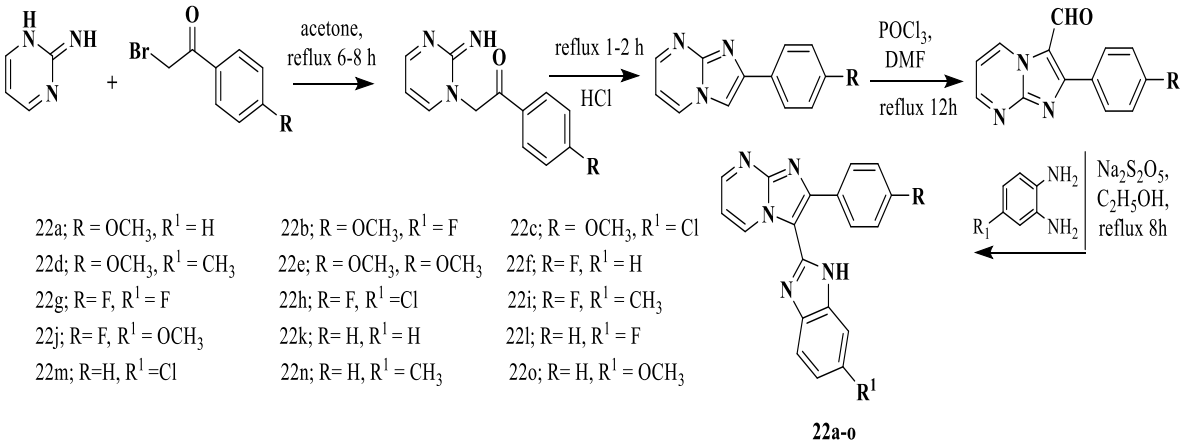


20a, R = Phenyl, $R^1 = R^2 = R^3 = H$
20b, R = Phenyl, $R^1 = R^2 = H$, $R^3 = CH_3$
20c, R = Phenyl, $R^1 = R^2 = H$, R^3 = tosyl



21a; R = Ph, $R^1 = R^2 = H$ 21b; R = 4-tolyl, $R^1 = R^2 = H$
21c; R = 4-Cl-Ph, $R^1 = R^2 = H$ 21d; R = *ter*-butyl, $R^1 = R^2 = H$
21e; R = Ph, $R^1 = CH_3$, $R^2 = H$ 21f; R = *ter*-butyl, $R^1 = CH_3$, $R^2 = H$
21g; R = 2-naphthyl, $R^1 = R^2 = H$ 21h;R = 2,4-diCl-Ph, $R^1 = R^2 = H$
21i; R = Ph, $R^1 = R^2 = OCH_3$ 21j; R = Ph, $R^1 = R^2 = OCH_3$
21k; R = 2-tolyl, $R^1 = R^2 = H$ 21l; R = 4-Br-Ph, $R^1 = R^2 = H$

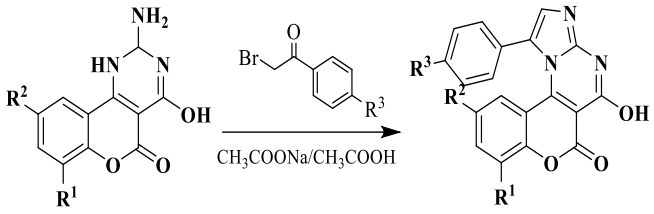
Scheme 10. Synthesis of compounds 18a-o –21a-l.



22a; R = OCH_3, $R^1 = H$ 22b; R = OCH_3, $R^1 = F$ 22c; R = OCH_3, $R^1 = Cl$
22d; R = OCH_3, $R^1 = CH_3$ 22e; R = OCH_3, R = OCH_3 22f; R= F, $R^1 = H$
22g; R= F, $R^1 = F$ 22h; R= F, R^1 =Cl 22i; R= F, $R^1 = CH_3$
22j; R= F, $R^1 = OCH_3$ 22k; R= H, $R^1 = H$ 22l; R= H, $R^1 = F$
22m; R=H, R^1 =Cl 22n; R= H, $R^1 = CH_3$ 22o; R= H, $R^1 = OCH_3$

Scheme 11. Synthesis of compounds 22a-o.

In scheme 12, a mixture of suitable chromeno pyrimidin derivative, bromomethyl aryl ketones, and sodium acetate was refluxed for 4 hours. The produced imidazo pyrimidine derivative **23a** was more active than **23b** against the Hep-G2 cell line[44].

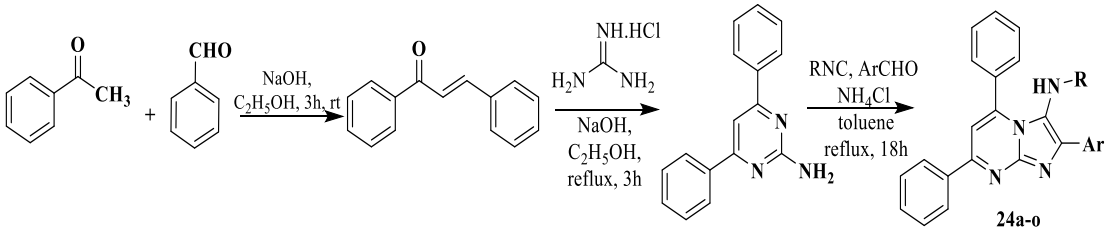


23a,b

23a; R^1 = OCH_3 R^2 = H, R^3 = CH_3
23b; R^1 = H R^2 = Br, R^3 = OCH_3

Scheme 12. Synthesis of compounds 23a,b.

Mahdavi *et al*,[45] fulfilled synthesis of **24a-o** *via* Groebke-Blackburn-Bienaymé reaction of 4,6-di-phenylpyrimidin-2-amine, substituted aldehyde, and substituted isocyanide. They were tested as anticancer drugs against MCF-7, MDA-MB-231, and T-47D cell lines. Most of them showed good activity against them, especially **24a-c**, and **24k**, moreover, **24c** analog was the most potent derivative with IC_{50} 10.92 µM, 10.43 µM, and 6.72 µM, in correspondence. This may be related to the hydroxy, methoxy, and cyclohexyl substituents[45]. Scheme 13

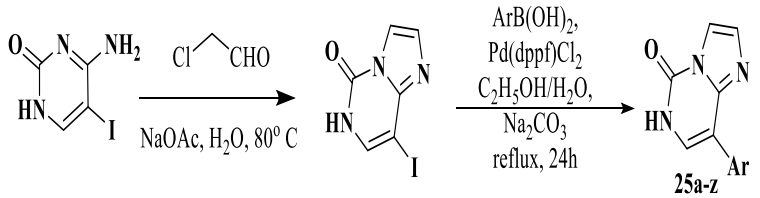


24a-o

24a; Ar = 4-OH-Ph	R = cyclohexyl	24b; Ar = 2-OCH_3-Ph	R = cyclohexyl
24c; Ar = 3-OH-4-OCH_3-Ph	R = cyclohexyl	24d; Ar = 3-CH_3-Ph	R = cyclohexyl
24e; Ar = 2-F-Ph	R = cyclohexyl	24f; Ar = 4-F-Ph	R = cyclohexyl
24g; Ar = 3-Cl-Ph	R = cyclohexyl	24h; 2,4-di-Cl-Ph	R = cyclohexyl
24j; 2-thienyl	R = cyclohexyl	24k; Ar = 2-OCH_3-Ph	R = *tert*-butyl
24l; Ar = 3-CH_3-Ph	R = *tert*-butyl	24m; Ar = 4-F-Ph	R = *tert*-butyl
24n; Ar = 4-Cl-Ph	R = *tert*-butyl	24o; 3-NO_2-Ph,	R = *tert*-butyl

Scheme 13. Synthesis of compounds 24a-o.

It was found that the reaction of 2-chloroacetaldehyde, and 4-amino-5-iodopyrimid inone permitted the synthesis of the imidazo-pyrimidine scaffold. This was followed by nucleophilic aromatic substitution reaction to produce compounds **25a-z**. The activity of these compounds as CDK2 inhibitors were related to the size of the aryl substituent; increasing the size decreased the activity. Compound 25j demonstrated the best activity with 1.30 µM IC_{50}[46]. Scheme 14

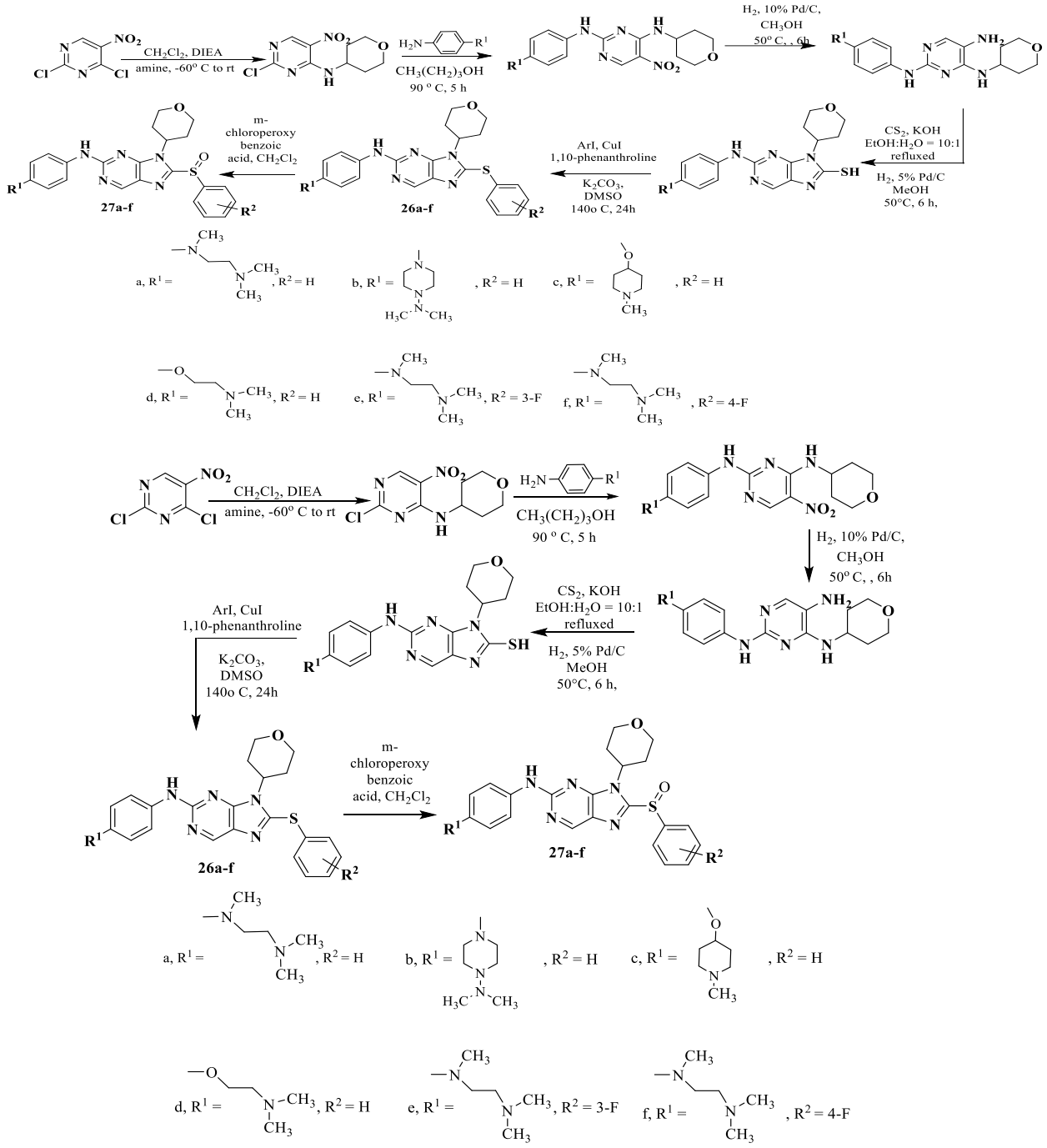


25a-z

25a; Ar = 2-thienyl	25b; Ar = Ph	25c; Ar = 4-pyridinyl
25d; Ar = 3-pyridinyl	25e; Ar = 2-Cl-Ph	25f; Ar = 4-Cl-Ph
25g; Ar = 2-SCH_3-Ph	25h; Ar = 2-C_2H_5-5-Cl-Ph	25i; Ar = 2-diF-Ph
25j; Ar = 2,3-diF-Ph	25k; Ar = 3,5-diF-Ph	25l; Ar = 4-OH-Ph
25m; Ar = 4-NH_2-PH	25n; Ar = 4-CN-Ph	25o; 4-CHO-Ph
25p; Ar = 4-OCH_3-Ph	25q; Ar = 4-COOH-Ph	25r; Ar = 4-CF_3-Ph
25s; Ar = 4-[NHCOOC$(CH_3)_3$]-Ph	25t; Ar = 4-[CO-(pyrrolidin-1-yl)]	25u; Ar = 1-naphthyl
25v; Ar = 1,1'-biphenyl-2-yl	25w; 1,1'-biphenyl-4-yl	25x; Ar = 4'-NH_2-1,1'-biphenyl-4-yl
25y; Ar = 3'-NH_2-1,1'-biphenyl-4-yl	25z; Ar = 4'-OCH_3-1,1'-biphenyl-4-yl	

Scheme 14. Synthesis of compounds 25a-z

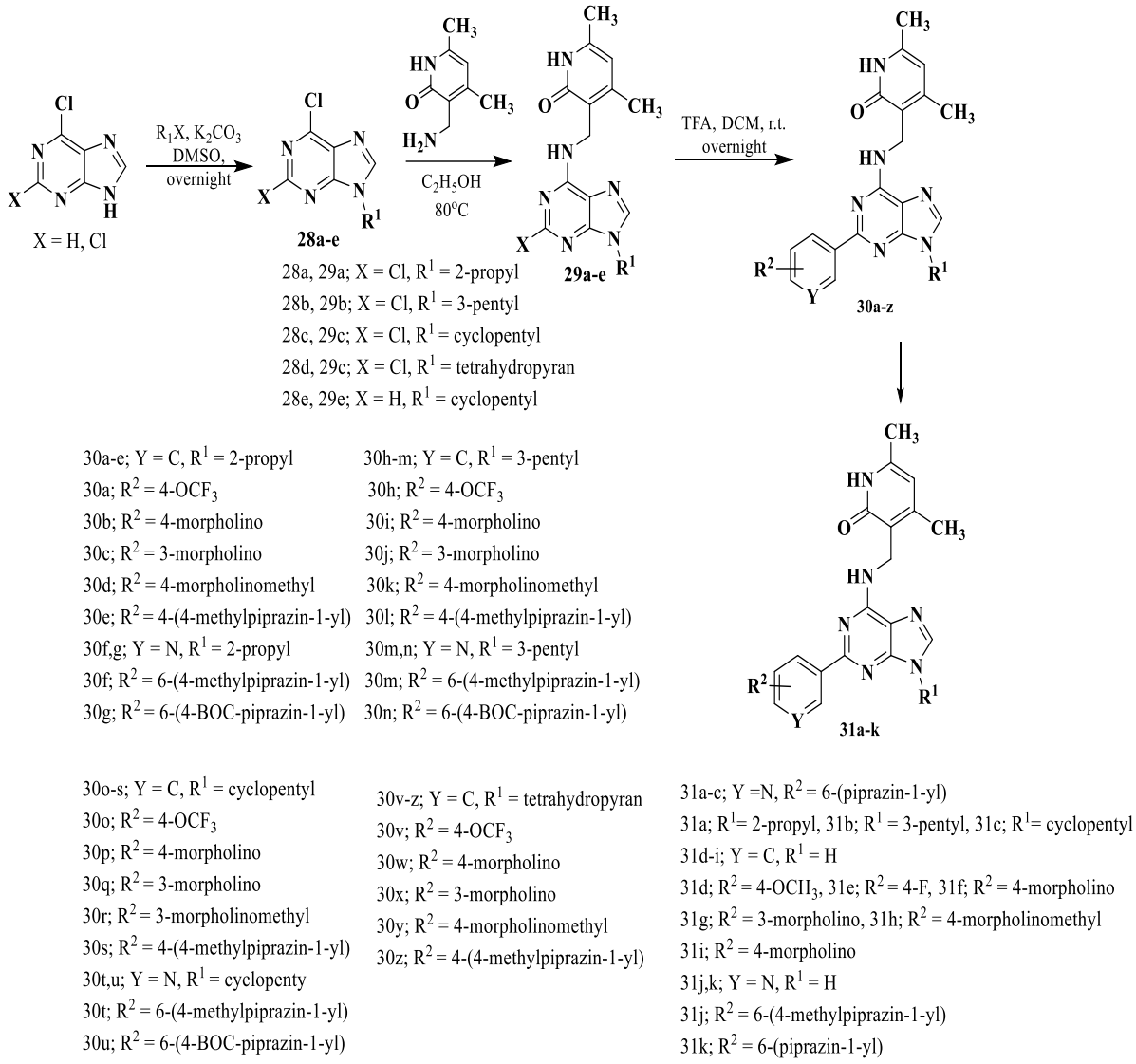
More derivatives; **26a-f** were synthesized, and tested as anticancer compounds against HCC827 cell line. Compound **26c** showed the most potent effect with 29.40 nM IC_{50}. In addition, it revealed 1.90 nM IC_{50} against EGFR. Additionally, compound **26f** showed moderate inhibitory activity against EGFR, and compound **27a** showed a potent antiproliferative effect with an IC_{50} value of 50.30 nM. The team work followed the synthetic route as described in scheme 15; first the 2,4-dichloro-5-nitropyrimidine underwent nucleophilic substitution reactions using appropriate amines; this was followed by hydrogenation. The diamino pyrimidine analog was cyclized permitting synthesis of the imidazopyrimidine, which reacted with substituted iodobenzene preparing **26a-f** derivatives. 3-chloroperoxybenzoic acid accomplished oxidation of **26a-f,** and synthesis of more imidazopyrimdines **27a-f**[47].



Scheme 15. Synthesis of compounds 26a-f -27a-f.

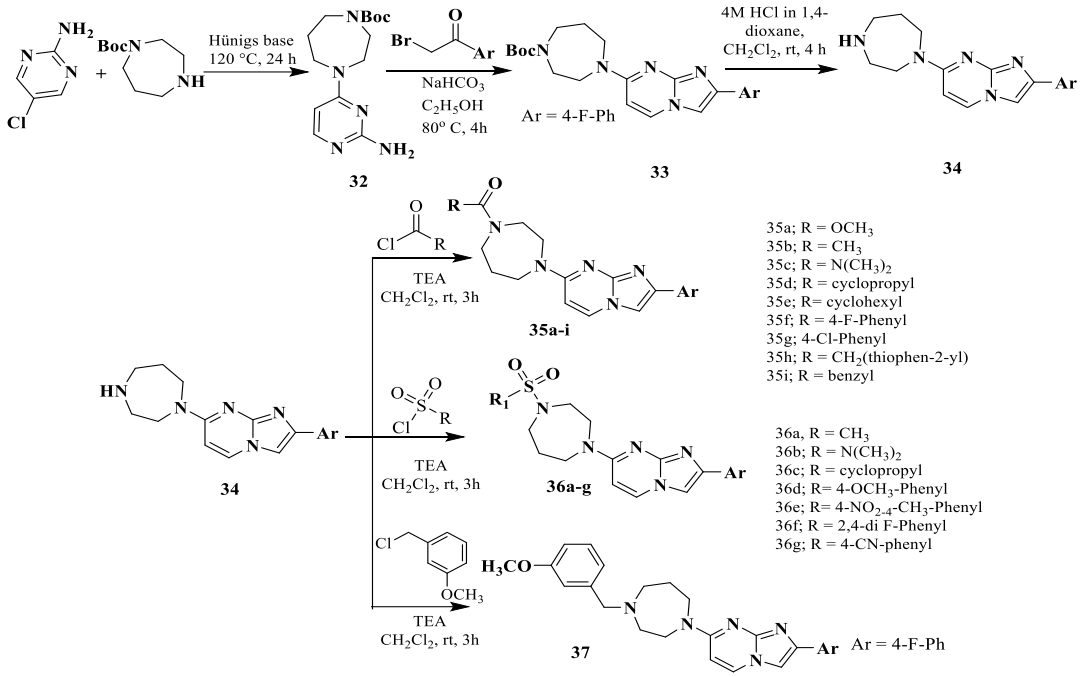
Other compounds were synthesized and tested for their efficacies as antitumor agents against Hep-G2, HCT-116, and A-549 cell lines. They were synthesized starting with disubstituted purine, and alkylhalide reaction, then nucleophilic substitution by 3-(aminomethyl)-4,6-dimethylpyridin-2(1*H*)-one

producing **29a-e**. Suzuki-Miyaura coupling reaction fulfilled the synthesis of **30a-z** derivatives. More derivatives **31a-k** were synthesized by deprotection of their precursors. The biological assay revealed that compound **29c** was the most active compound against Hep-G2, HCT-116, and A-549, it displayed IC_{50} as 0.08 µM, 0.06 µM, and 0.10 µM, respectively [48]. Scheme 16



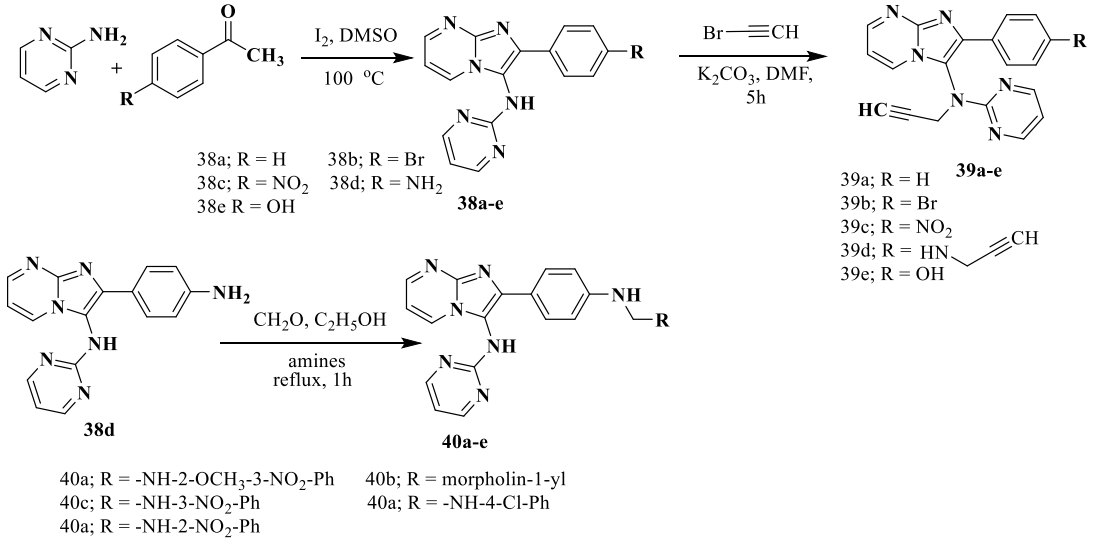
Scheme 16. synthesis of compounds 28a-e – 31a-k.

Synthesis of imidazo[1,2-a]pyrimidine **34** was fulfilled by condensation of substituted 2-amino-pyrimidine **32** with 2-bromo-1-(4-fluorophenyl) ethanone, and deprotection of compound **33**. Nucleophilic substitution reaction using acid chloride, sulfonyl chlorides, or benzyl chloride afforded the required analogs **35a-i**, **36a-g** and **37**. Compound **37** was the most active derivative against A-549 cell line, in addition, **35a**, **35c,** and **36a** delivered potent effect against the same cell line. When they were tested against the Hela cell line, compounds **35f**, **37**, and **35g** showed IC_{50} values of 6.12 µM, 6.54 µM, and 8.55 µM, in correspondence. Compound **37** was also the most active against DU145 cell line with IC_{50} 6.24 µM. Finally, **36f** showed the best anticancer effect against SKOV3 cell line with IC_{50} 10.02 µM[49]. Scheme 17



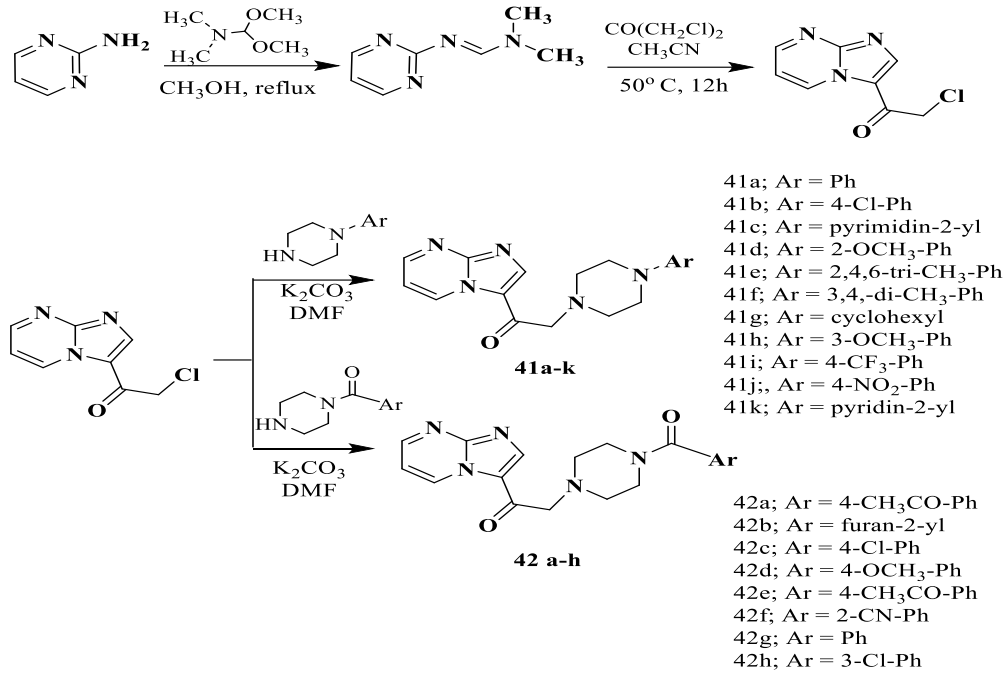
Scheme17. Synthesis of compounds 32–37.

In 2021, Rehan *et al.*[23] reported the synthesis of some imidazopyrimidines as antioxidants through refluxing of acetophenone derivatives in DMSO, followed by the addition of substituted 2-amino-pyrimidines, and heating for 2 hours allowed the synthesis of **38a-e** analogs. In DMF solvent; mixtures of compounds **38a-e**, propargylbromide and K_2CO_3 were refluxed for 5 hours to produce **39a-e** analogs. Compounds **40a-e** were produced *via* the reaction of **38d**, formaldehyde, and suitable amines. Compound **39d** showed the most potent DPPH scavenging effect[23]. Scheme 18



Scheme 18. Synthesis of compounds 38a-e – 40a-e.

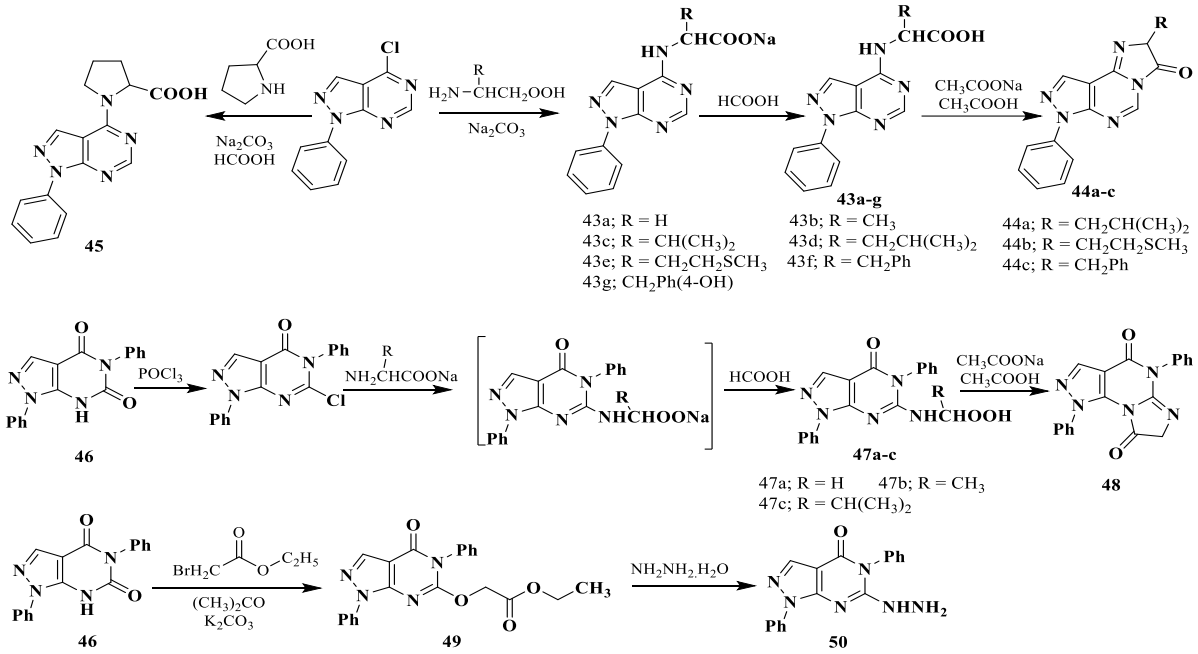
Variable imidazopyrimidine derivatives were synthesized *via* a reaction of 2-aminopyrimidine with *N,N*-dimethylformamide dimethyl acetal to give *N,N*-dimethyl-N'-(pyrimidin-2-yl)formimidamide. The latter structure was then reacted with 1,3 dichloroacetone forming imidiazopyrimidine block, which finally was reacted with substituted piperazines producing compounds **41a-k**, and **42a-h**. They were tested against MCF-7, Colo-205, and A-549 cell lines using imatinib as a reference drug; compound **41f** delivered the most potent efficacy against MCF-7 cell line with IC_{50} 10.54 µM, while **41j** was the most active derivative against colo-205 with IC_{50} 29.15 µM. Additionally, The highest activity against A-549 was demonstrated by **41h** with IC_{50} 11.67 µM[50]. Scheme 19



Scheme 19. Synthesis of compound 41a-k – 42a-h.

2.2. Pyrazolopyrimidine derivatives

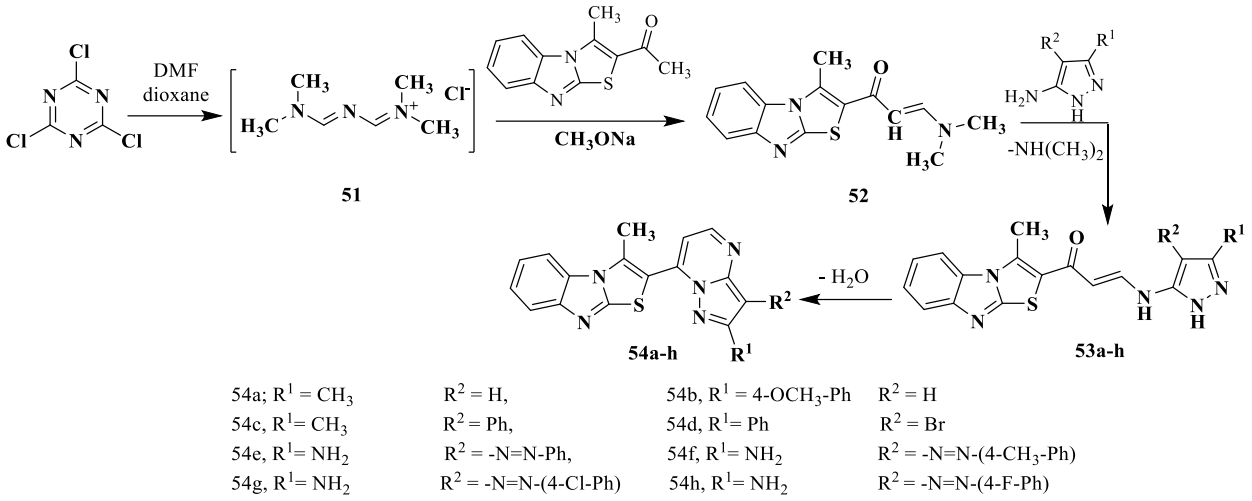
Pyrazolopyrimidine derivatives garnered vast interest from researchers as compounds **43a-g −50** which were synthesized by Ghorab *et al.* [51] adopting the outlined scheme 20. Compounds **43d,b** revealed high anticancer effect with IC_{50} 30.00 µM, and 35.00 µM, in correspondence. The presence of the amino group at position 4 in compounds **43d,b**, provided them with a better anticancer effect over other analogs[51].



Scheme 20. synthesis of compounds 43a-g – 50.

Synthesis of more derivatives was achieved by Abdel-Aziz and his team[52]. Firstly, compound **51** was formed by refluxing a mixture of cyanuric chloride, and DMF using dioxane as solvent. The former product was then refluxed with 1-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)ethanone in sodium methoxide allowing the synthesis of compound **52**, which was reacted with substituted

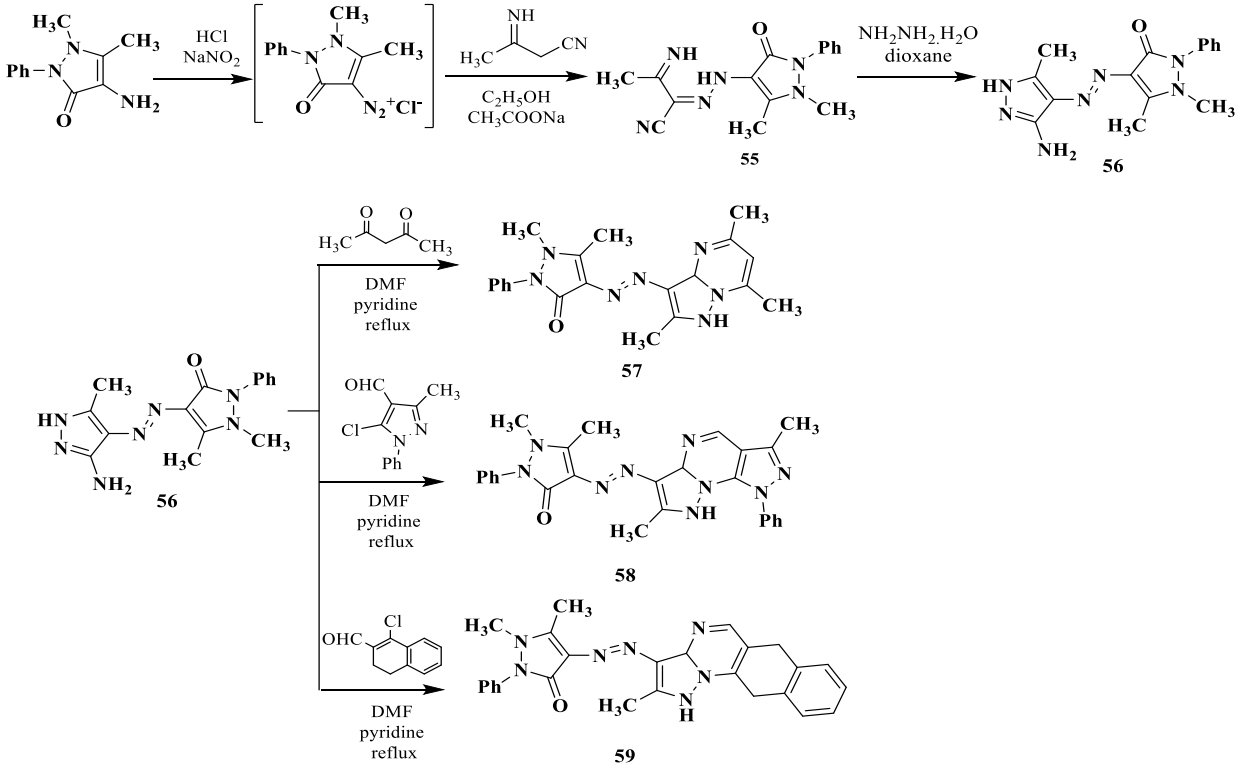
pyrazoles in glacial acetic acid / sulphuric acid mixture fulfilling synthesis of compounds **53a-h**, that upon dehydration, pyrazolopyrimidine analogs **54a-h** were synthesized. Compound **54h** exhibited the highest antitumor activity against the CaCo-2 colon cell line with IC_{50} 0.50 µM, where **54d** was the most active derivative against BHK cell line with IC_{50} 0.54 µM[52]. Scheme 21



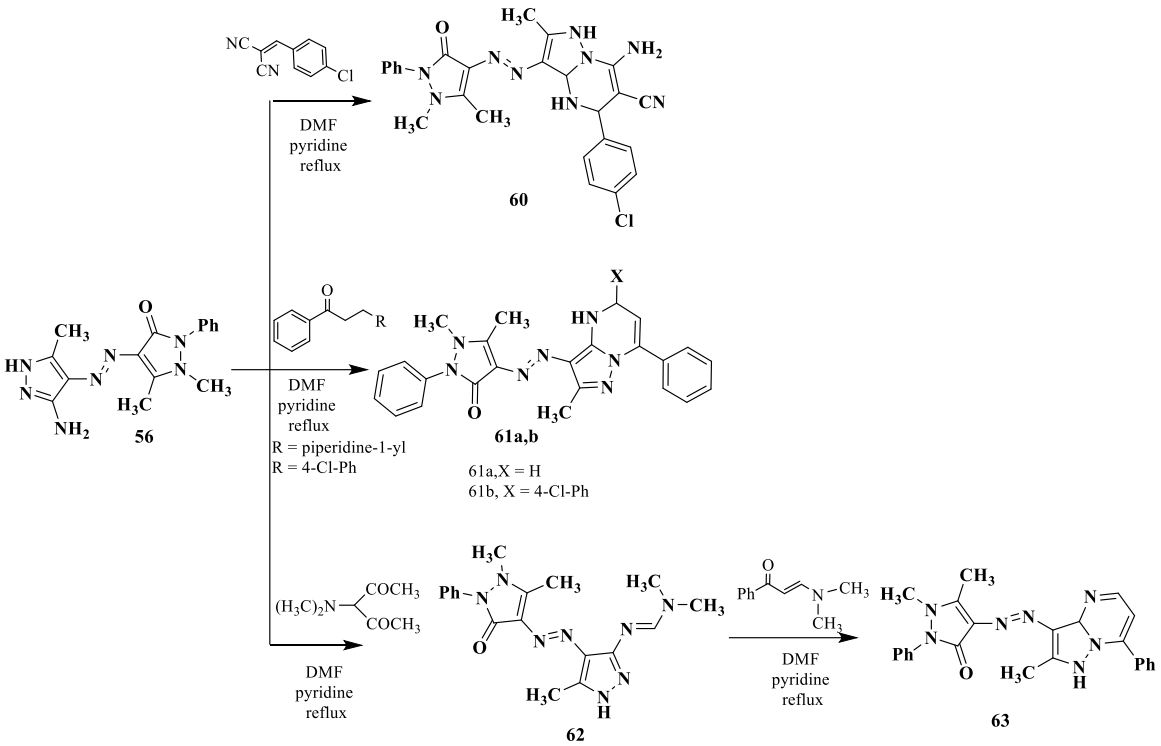
54a; $R^1 = CH_3$ R^2 = H, 54b, R^1 = 4-OCH_3-Ph R^2 = H
54c, $R^1 = CH_3$ R^2 = Ph, 54d, R^1 = Ph R^2 = Br
54e, $R^1 = NH_2$ R^2 = -N=N-Ph, 54f, $R^1 = NH_2$ R^2 = -N=N-(4-CH_3-Ph)
54g, $R^1 = NH_2$ R^2 = -N=N-(4-Cl-Ph) 54h, $R^1 = NH_2$ R^2 = -N=N-(4-F-Ph)

Scheme 21. synthesis of compounds 51 – 54a-h.

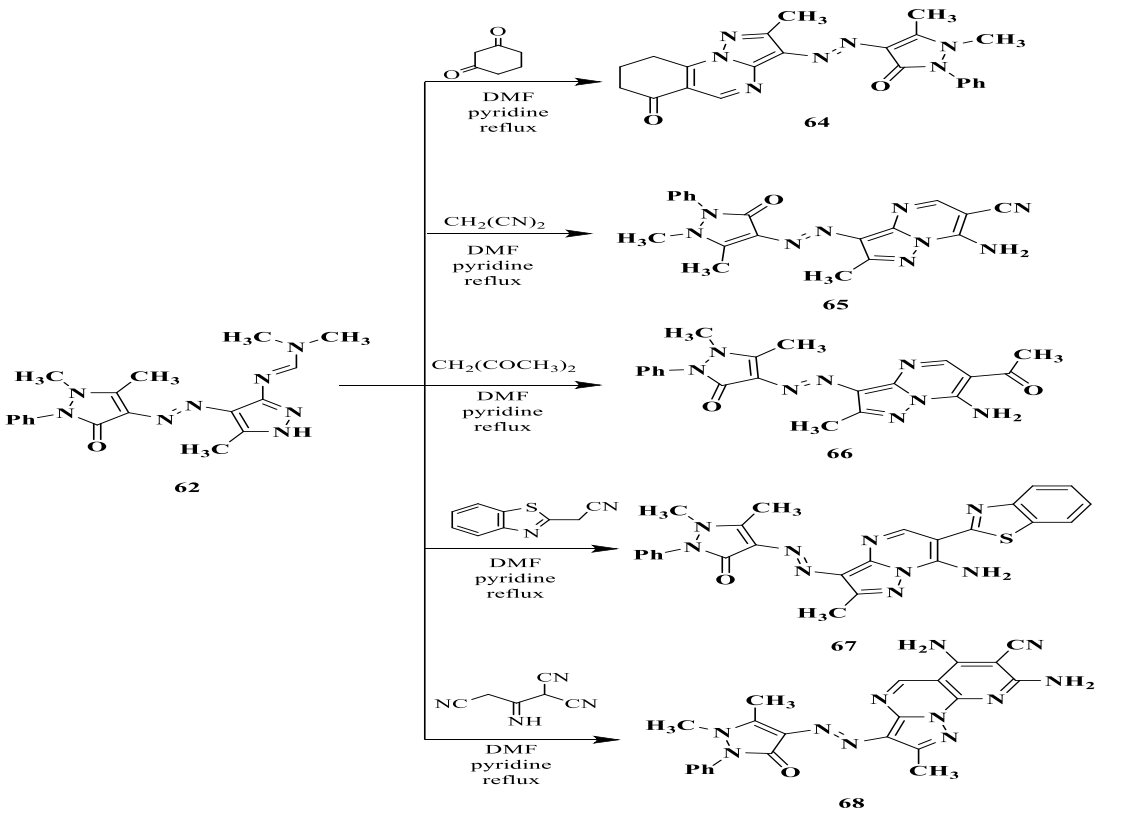
Cyclization and synthesis of pyrimidine ring was achieved in a single step reaction delivering compounds **57−61.** Moreover, compound **63** was synthesized by first reaction with 3-(dimethylamino) pentane-2,4-dione followed by cyclization using 3-(dimethylamino)-1-phenylprop-2-en-1-one. In a similar procedure; compounds **64−68** were synthesized. Compound **61a** exhibited considerable antitumor effect with IC_{50} 3.13 µM[53]. Schemes 22−24



Scheme 22. Synthesis of compounds 55 – 59.



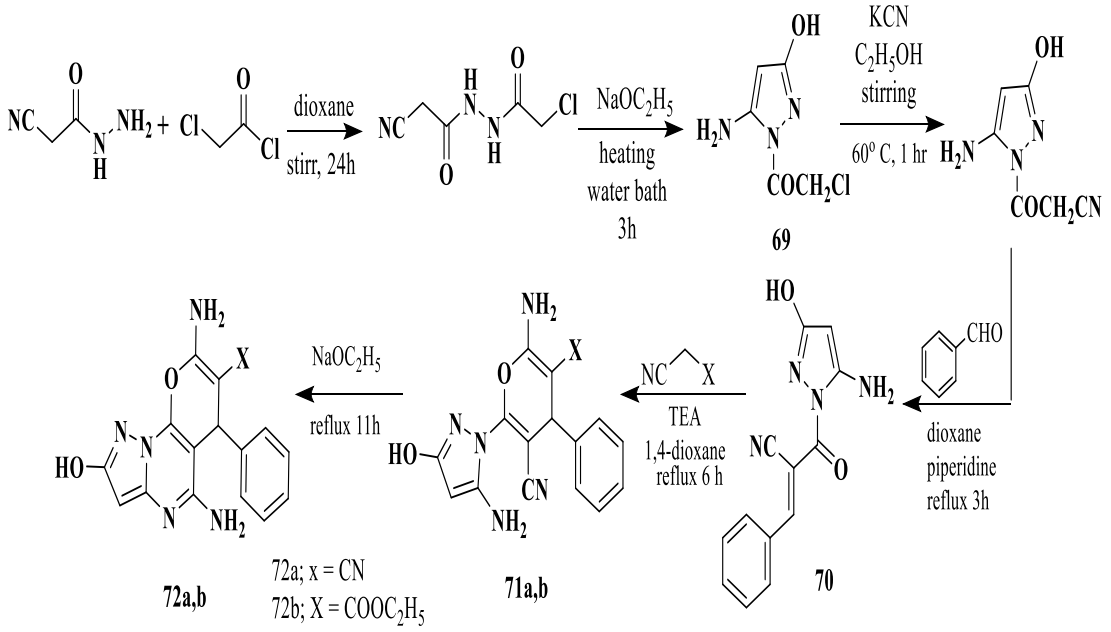
Scheme 23. Synthesis of compounds 60–63.



Scheme 24. Synthesis of compounds 64–68.

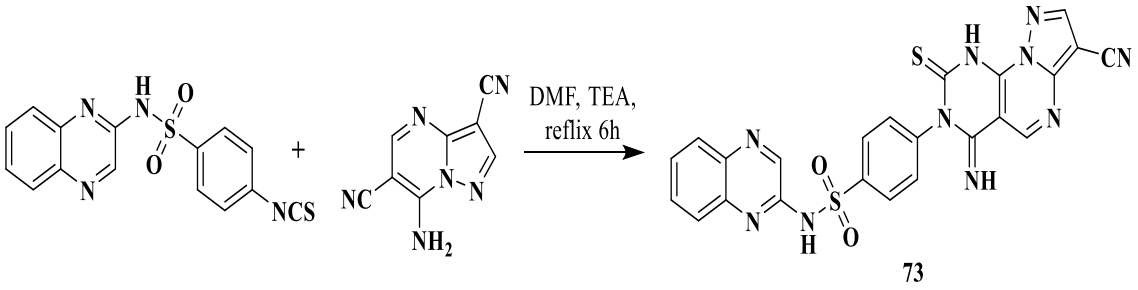
As shown in Scheme 25, the synthesis of pyrazolopyranopyrimidines **72a,b** could be verified through a series of chemical reactions. The first reaction of cyanoacetylhydrazine, and chloroacetyl chloride allowed the synthesis of 2-chloro-*N*'- (2-cyanoacetyl)acetohydrazide, which was refluxed in

sodium ethoxide permitting the synthesis of the cyclized product **69**. The reaction of the latter compound with potassium cyanide fulfilled the synthesis of pyrazolo compound with a cyano group, after, the reaction with benzaldehyde allowed the synthesis of compound **70**. This was followed by a reaction with malononitrile, or ethyl cyanoacetate liberating pyrano pyrazolo compound **71a,b**, which was refluxed in sodium ethoxide giving release to the desired derivatives **72a,b**. The antitumor activity was evaluated against MCF-7, NCI-H460, and SF-268. Compound **72a** showed higher activity than doxorubicin with GI_{50} 0.01 mol L^{-1}, 0.01 mol L^{-1}, and 0.02 mol L^{-1}, respectively. It was more active than **72b** which may be attributed to the existence of cyano group[54].



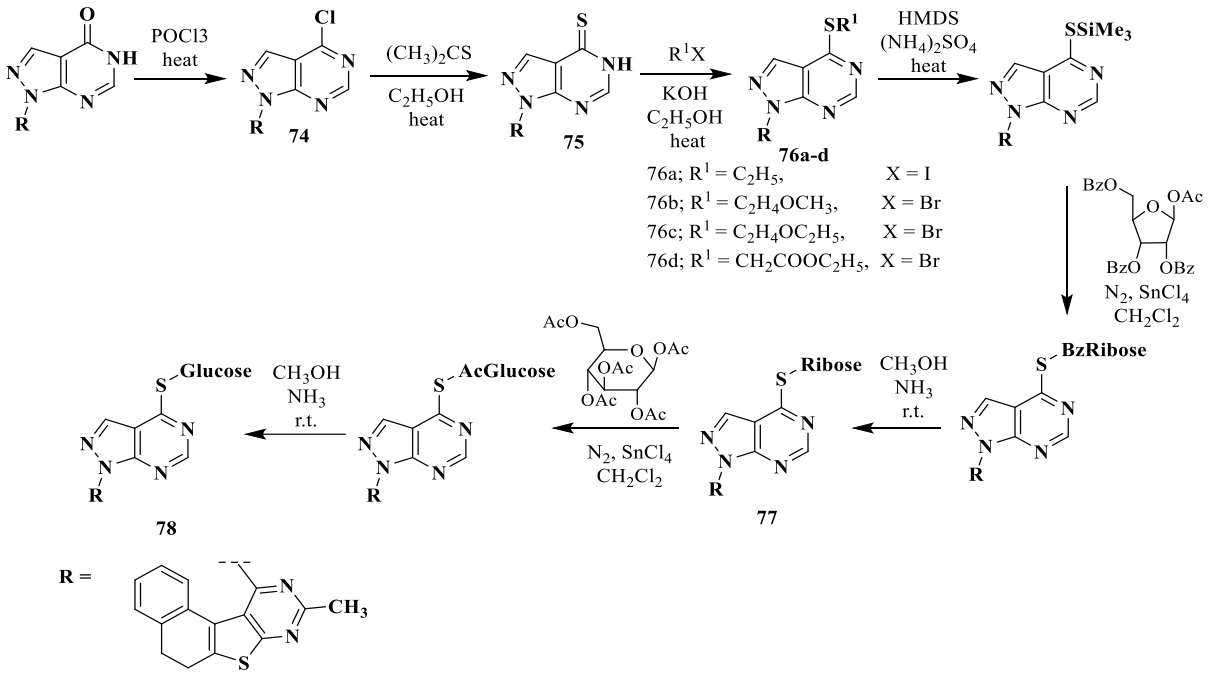
Scheme 25. Synthesis of compounds 72a,b.

Moreover, pyrazolopyrimidine derivative **73** was synthesized *via* refluxing 4-isothiocyanato-*N*-(quinoxalin-2-yl)benzenesulfonamide with pyrazolo pyrimidine-o-aminocarbonitrile in DMF in presence of triethylamine. It showed higher activity than 5-fluorouracil against Hep-G2 cell line with IC_{50} 26.84 μM[40]. Scheme 26



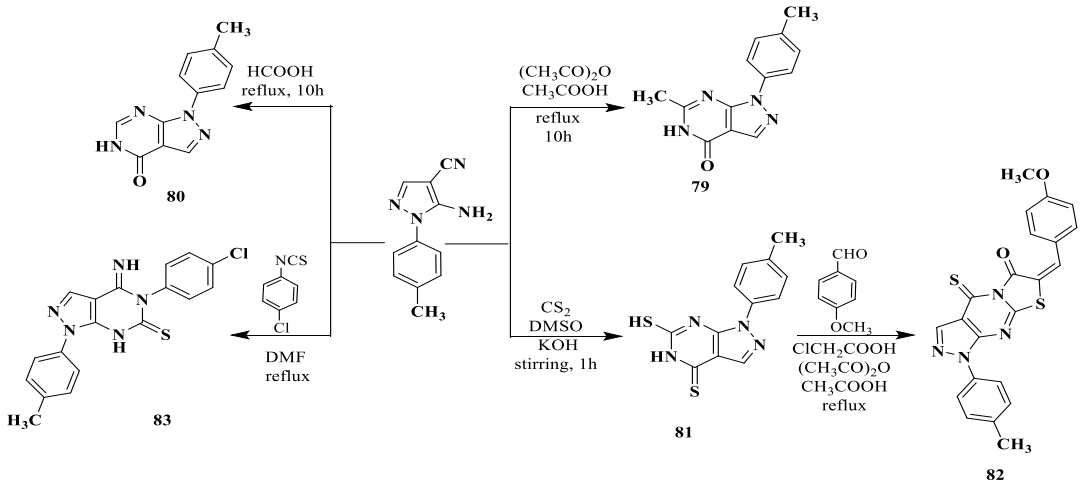
Scheme 26. Synthesis of compounds 73.

As outlined below (Scheme 27), the chlorinated analog **74** of the pyrazolopyrimidinone was prepared using phosphorus oxychloride. Refluxing with thiourea fulfilled the synthesis of pyrazolo [3,4-d]pyrimidine-5(4*H*)-thione **75**. It enabled later preparation of **76a-d** *via* stirring with various alkyl halides at 70 ° C. Nevertheless, compounds **77,** and **78** were prepared by first reaction with hexamethyl-disilazane followed by treating with either 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose or β-D-glycopyranose pentaacetate, then debenzoylation, and deacetylation. The synthesized compounds were tested against the MCF-7 cell line as anticancer agents in comparison with cisplatin as a reference drug; compound **76a** was the most active analog against the MCF-7 cell line with IC_{50} 3.00 μg/ml[55].



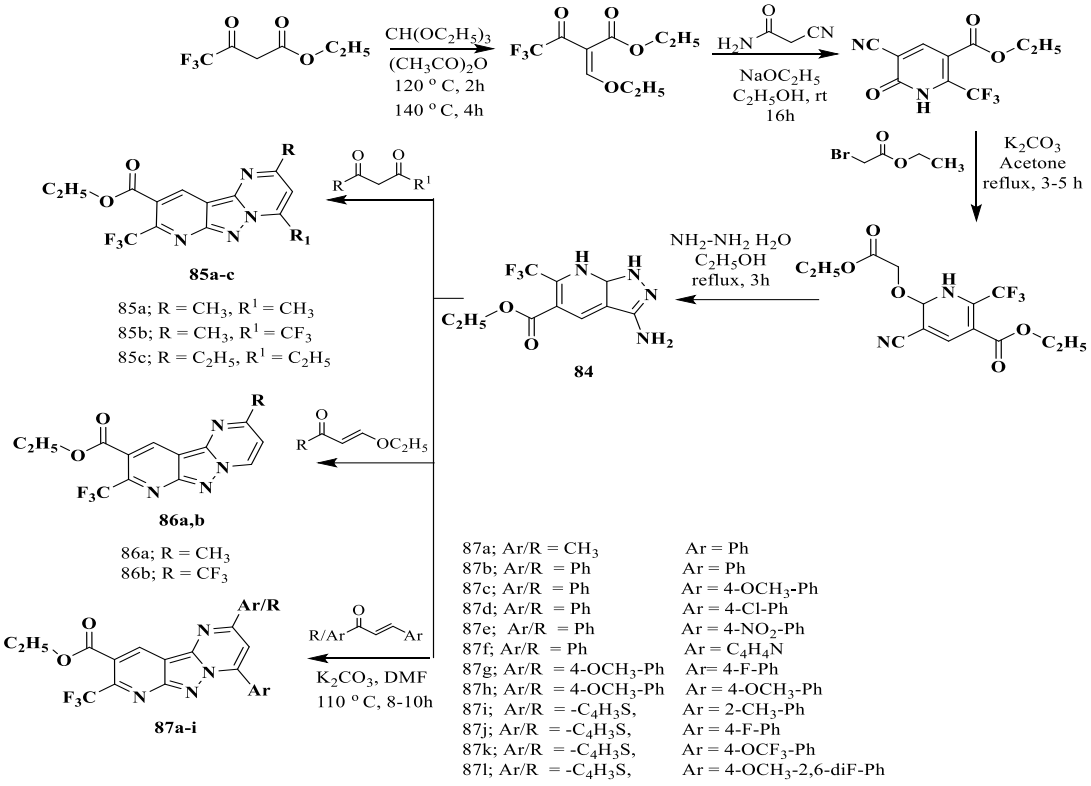
Scheme 27. Synthesis of compounds 74–78.

In 2014, more derivatives **79**–**81**, and **83** were synthesized through refluxing of 5-amino-1-(*p*-tolyl) -1*H*-pyrazole-4-carbonitrile with acetic anhydride, formic acid, carbon disulfide, and 1-chloro-4-isothiocyanatobenzene, respectively. Moreover, compound **82** was synthesized *via* refluxing of compound **81**, chloroacetic acid, 4-methoxy-benzaldehyde, and anhydrous sodium acetate in a glacial acetic acid/acetic anhydride mixture. The anticancer activity was evaluated against MCF-7, and Hep-G2 cell lines using doxorubicin as a reference drug; compound **79** showed the highest activity against MCF-7, and Hep-G2 cell lines with 5.00 µg/ml, and 6.20 µg/ml as IC_{50} values, respectively[56]. Scheme 28



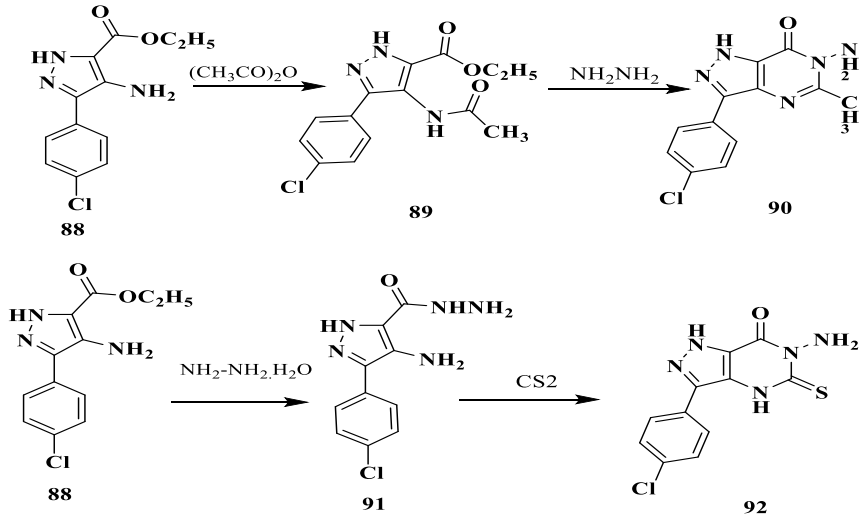
Scheme 28. Synthesis of compounnds 79–83.

In addition, synthesis of the pyridocarboxylate derivative was achieved through reaction of β-ketoester and triethylorthoformate followed by a reaction with cyanoacetamide. Later, it was refluxed with ethyl 2-bromoacetate in acetone followed by a reaction with hydrazine hydrate producing compound **84**, which act as key analogue for further synthesis of compounds **85**–**87** by reaction with 1,3-diketone, α,β-unsaturated keto ethyl ethers, and α,β-unsaturated ketones. These analogs were tested as anticancer agents against PC-3, MDA-MB-231, Hep-G2, and HeLa cell lines. Compounds **86a** revealed the highest efficacies with IC_{50} 11.40 µM, 12.10 µM, 11.80 µM, and 10.60 µM, respectively. Moreover, **86a**, and **87f** were able to inhibit the human topoisomerase I[1]. Scheme 29

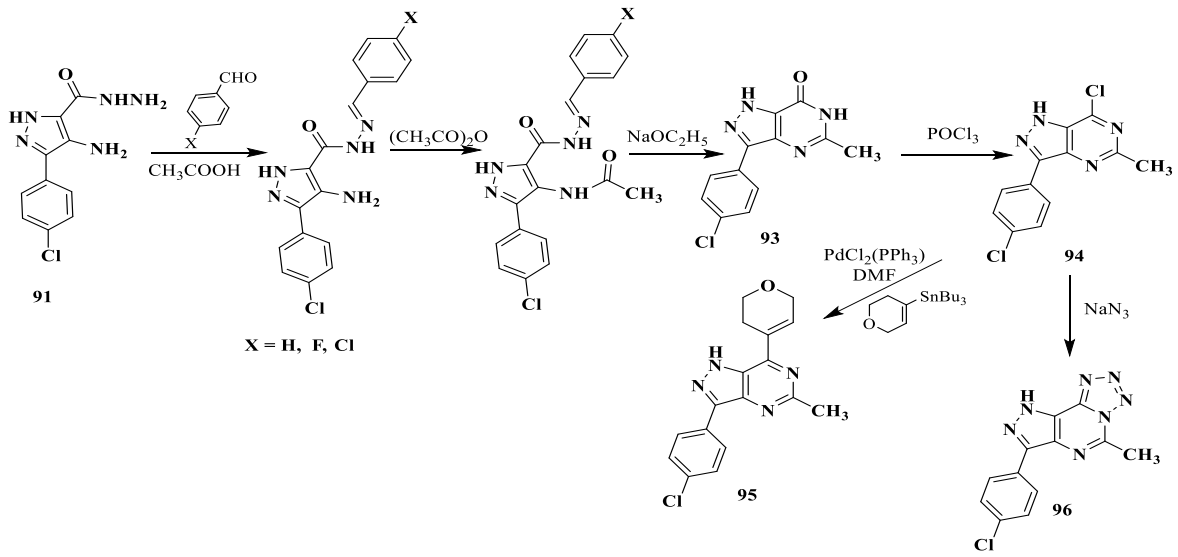


Scheme 29. Synthesis of compounds 84–87a-l.

Hafez *et al*, [57] synthesized further derivatives, and tested them for their efficacies as anticancer agents against HT29, Hep-G2, and MCF-7 cell lines in comparison with doxorubicin as a reference drug. Compound **96** was the most active derivative; it displayed 0.29 µM, 0.36 µM, and 0.13 µM as IC_{50} values, in correspondence. Acylation of compound **88** accomplished the synthesis of compound **89**, which upon treatment with hydrazine fulfilled the synthesis of **90**. Compound **88** was reacted with hydrazine hydrate releasing compound **91**, that when treated with carbon disulfide, compound **92** was synthesized. Nevertheless, pyrazolo pyrimidines **93−96** were synthesized starting with compound **91** which underwent Schiff's base reaction followed by acetylation using acetic anhydride then cyclization with sodium ethoxide. Phosphorus oxychloride verified the chlorination and synthesis of compound **94**, through which compounds **95,** and **96** were synthesized *via* reaction with tributyl(3,6-dihydro-2*H*-pyran-4-yl)stannane, and sodium azide, in correspondence[57]. Schemes 30&31

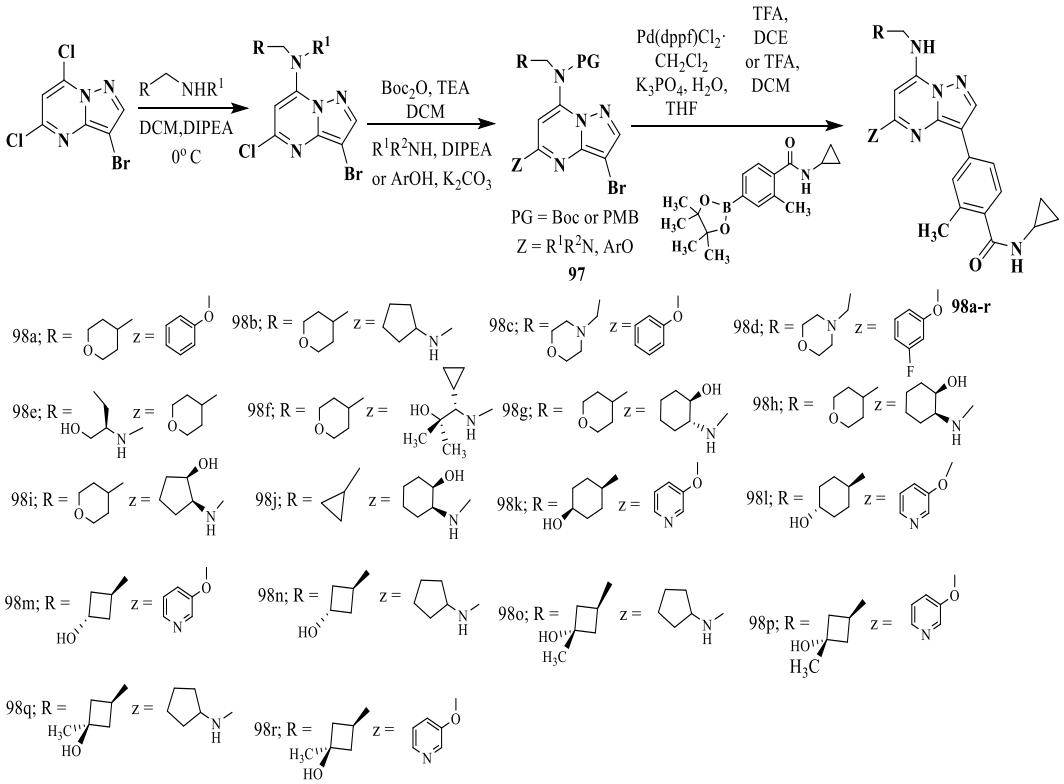


Scheme 30. Synthesis of compounds 89–92.



Scheme 31. Synthesis of compounds 93–96.

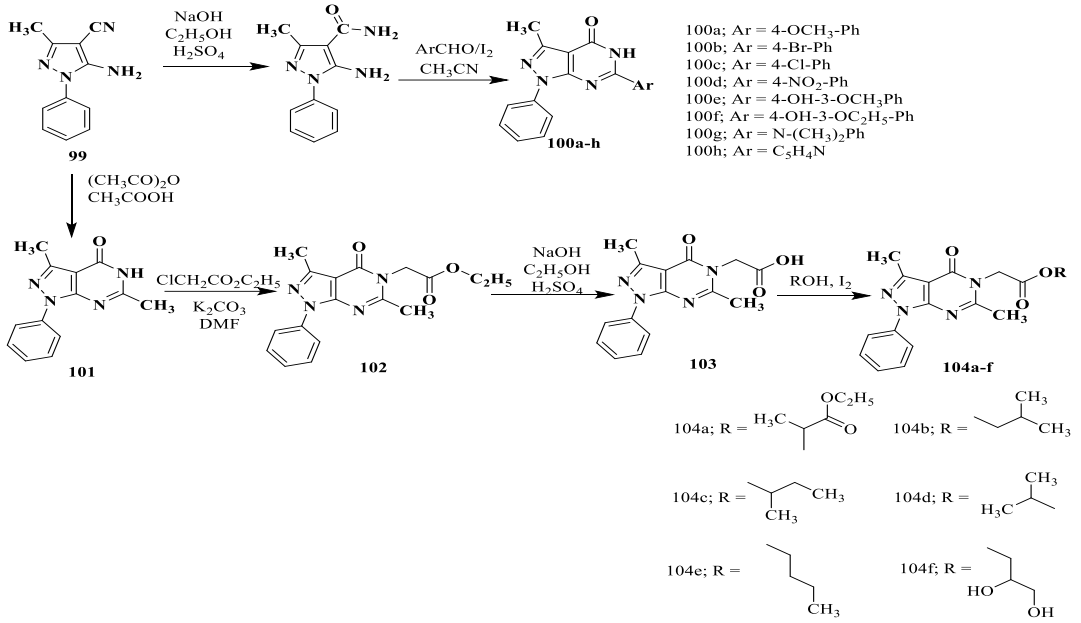
Liu *et al*. [58] synthesized compounds **98a-r** starting with 3-bromo-5,7-dichloro-pyrazolo[1,5-a] pyrimidine followed by nucleophilic aromatic substitution, and production of compound **97**. The latter derivative underwent Suzuki-Miyaura coupling, and deprotection to synthesize the desired derivatives. **98m,r** revealed the highest efficacies against MDA-MB-468 with IC_{50} 0.002 μM. The most potent anticancer effect against the HCT-116 cell line was revealed by compounds **98d,g** with IC_{50} 0.001 μM. However, **98r** showed the most remarkable activity against the OVCAR-3 cell line with IC_{50} 0.004 μM, also it acted as a highly selective inhibitor of exogenous TTK autophosphorylation[58]. Scheme 32



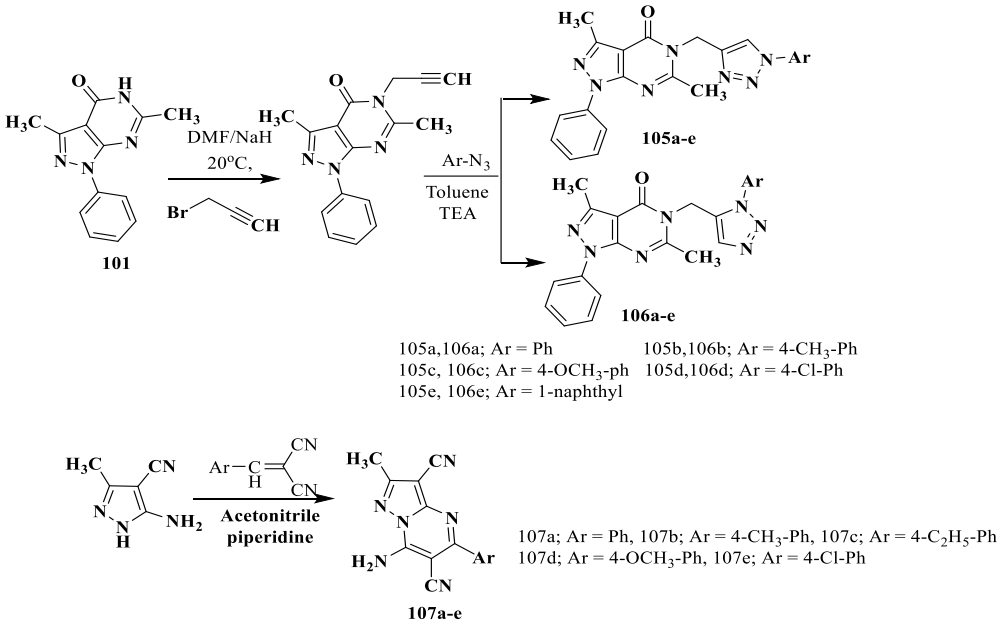
Scheme 32. Synthesis of compunds 98a–r.

In 2016, 5-amino-3-methyl-1-phenyl-1*H*-pyr azole-4-carbonitrile (**99**) was used to synthesize variable derivatives either in two, or one-step reactions as in the preparation of compounds **100a-**

h, and **101**. Compound **101** was then reacted with ethyl acetate chloride producing compound **102**. This was followed by treatment with NaOH solution and acidification using sulphuric acid producing compound **103**, which was then esteritified with different alcohols to prepare **104a-f**. Nevertheless, two triazolo derivatives **105**, and **106** were prepared in another synthetic route by first reaction with 3-bromoprop-1-yne, then cyclization *via* refluxing with arylazides. More compounds **107a-e** could be synthesized by refluxing α-cyanocinnamonitriles with 5-amino-3-methyl-1*H*-pyrazole-4-carbo-nitrile using piperidine as a catalyst. In between the tested derivatives against HCT-116, and MCF-7 cell lines; compounds **105b**,**c**,**d**,**e** revealed the most potent effects. GI% exerted by **105d** was 75.40%, moreover compounds **100e**, and **100f** showed the highest inhibitory effects against 5-lipoxygenase with 68.00%, and 72.20%, respectively[59]. Schemes 33&34



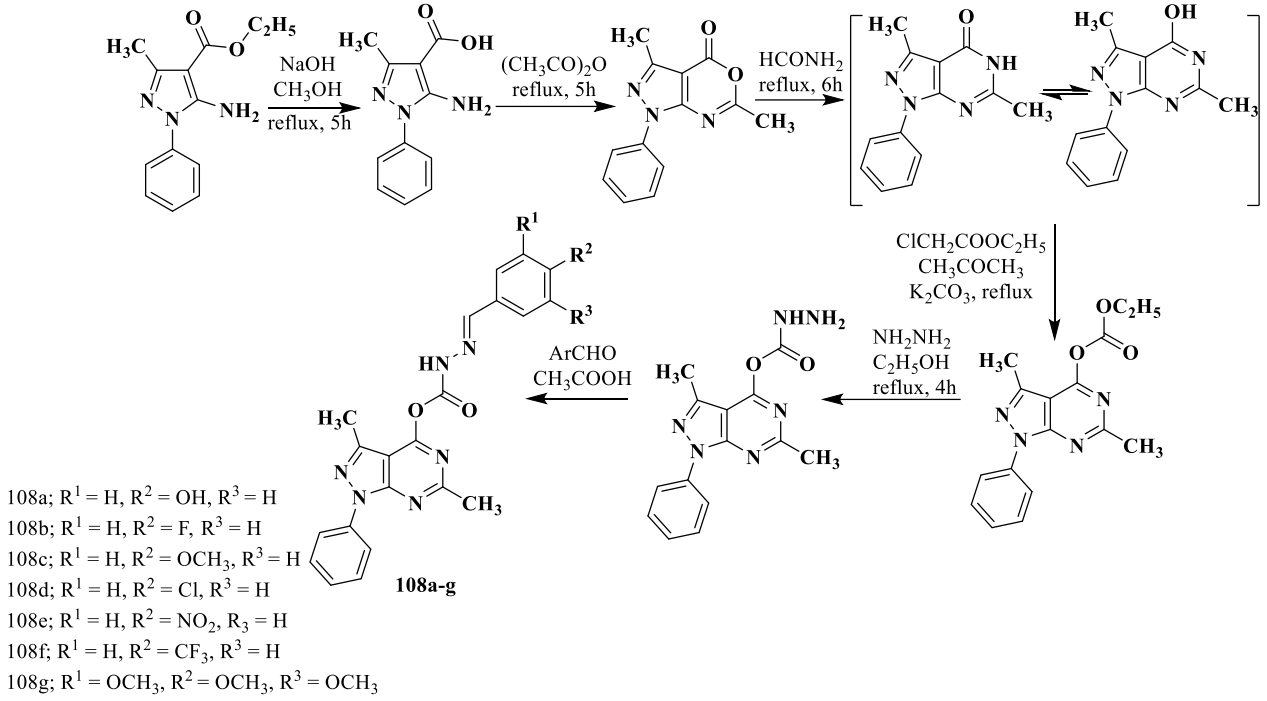
Scheme 33. Synthesis of compounds 100 –104a-f.



Scheme 34. Synthesis of compounds 105a-e –107a-e.

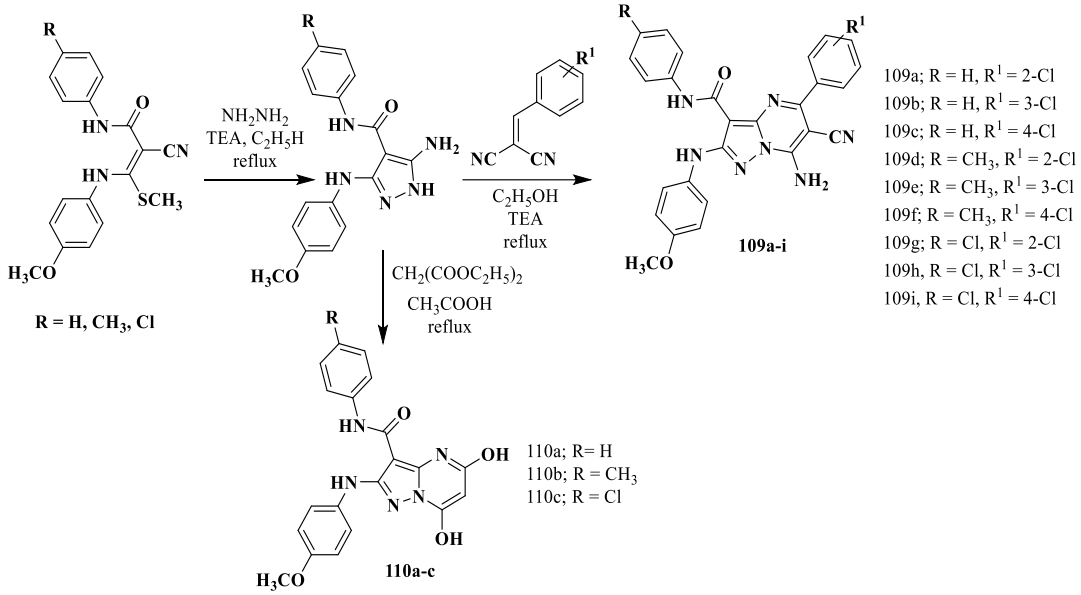
Abdelgawad *et al*, [60] synthesized novel pyrazopyrimidines as outlined in scheme 35; first the pyrazolo-carboxylate derivative was basically hydrolyzed to its carboxylic analog. The latter compound was then cyclized forming oxazine derivative *via* reflux with acetic anhydride. The

phenylpyrazolooxazine derivative underwent reflux with formamide achieving synthesis of the pyrazolo-pyrimidine analog. Esterification, hydrazinolysis, and Schiff's reaction allowed the synthesis of compounds **108a-g**. These analogs were evaluated against MCF-7, A-549, and HT-29 cell lines. They showed potent activity against these cell lines; compound **108g** showed the highest anticancer efficacy, it demonstrated 6.14 µM, 9.09 µM, and 5.36 µM as IC_{50}, respectively[60].



Scheme 35. Synthesis of compounds 108a-g.

Further pyrazolopyrimidine analogs **109a-i** were synthesized by a reaction of pyrazole-4-carboxamides with benzylidene malononitriles. More derivatives **110a-c** were synthesized *via* refluxing of 2-amino substituted pyrazole ring with 1,3-diketone. Compound **110a** revealed IC_{50} values as 58.44 µM, and 64.58 µM against HCT-116, and PC-3 cell lines, respectively[61]. Scheme 36

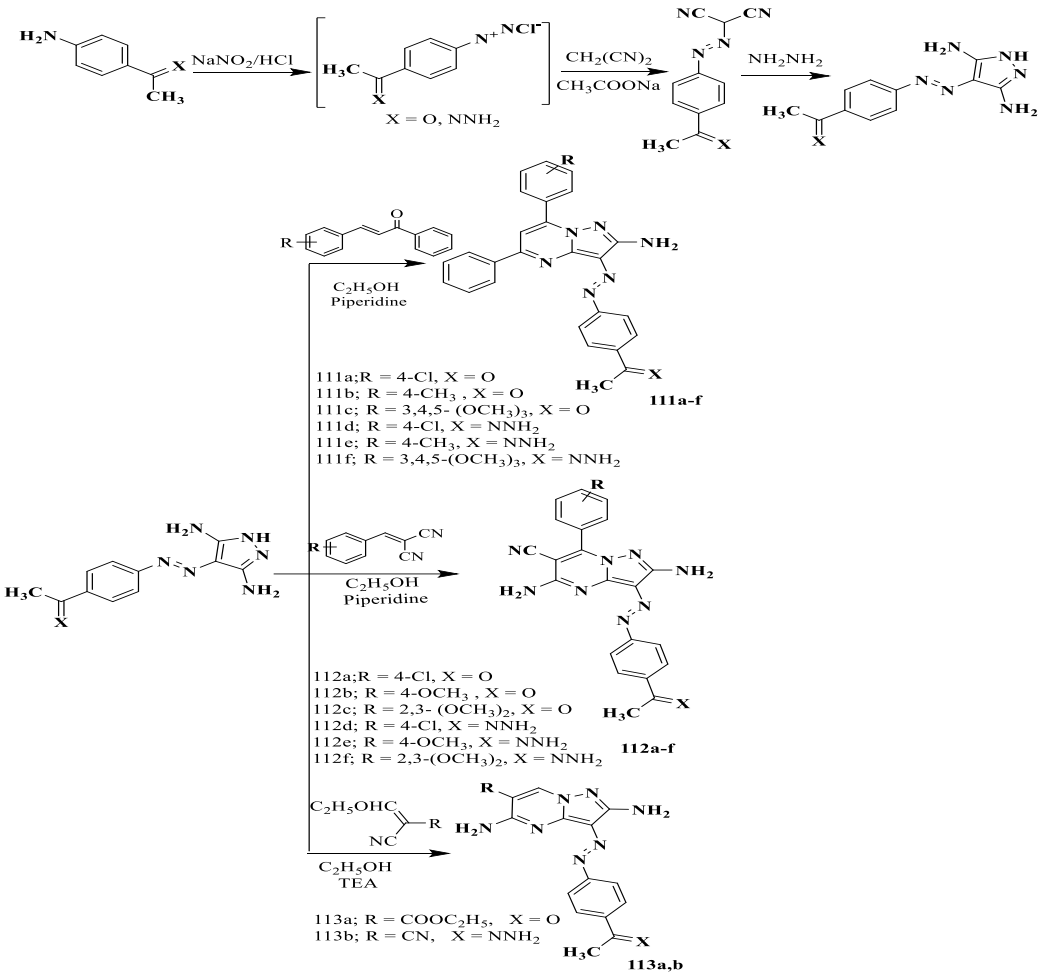


Scheme 36. Synthesis of compounds109a-i – 110a-c.

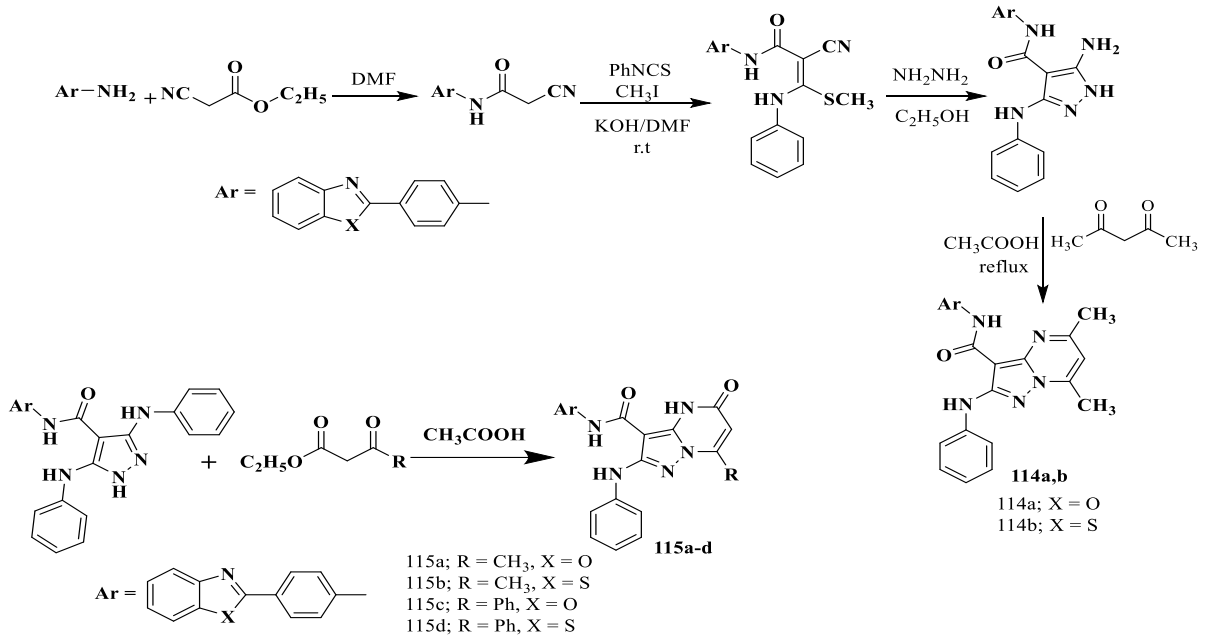
Moreover, 2-((4-acetylphenyl)diazenyl)malononitrile was synthesized *via* a reaction of the diaza derivative malononitrile. Reaction with hydrazine hydrate allowed cyclization, and synthesis of pyrazole moiety. Moreover, the pyrimidine ring was synthesized through a reaction with appropriate chalcones, arylidenemalononitriles, and ethyl 2-cyano-3-ethoxyacrylate. These derivatives were tested for their anticancer efficacies against the MCF-7 cell line; among them; compound **112a** was the most active one with 3.25 µM IC_{50}[62]. Scheme 37

In addition, Abdelal *et al.*[63] achieved the synthesis of pyrazolopyrimidine-benzothiazole / benzimidazole hybrids **114a,b**, and **115a-d** by refluxing a mixture of the appropriate amino-pyrazole, and acetylacetone, ethyl acetoacetate, or ethyl-3-oxo-3-phenylpropanoate in glacial acetic acid. Their anticancer activities were tested against MCF-7, BT474, and A-549 cell lines; compounds **115b,** and **115d** revealed the highest activities. This may be attributed to the thiazole moiety. In addition **115d** was more reactive than **115b** which could be related to the phenyl ring, it showed IC_{50} 1.98 µM, 2.20 µM, and 2.61 µM against MCF-7, BT474, and A-549 cell lines, respectively[63]. Scheme 38

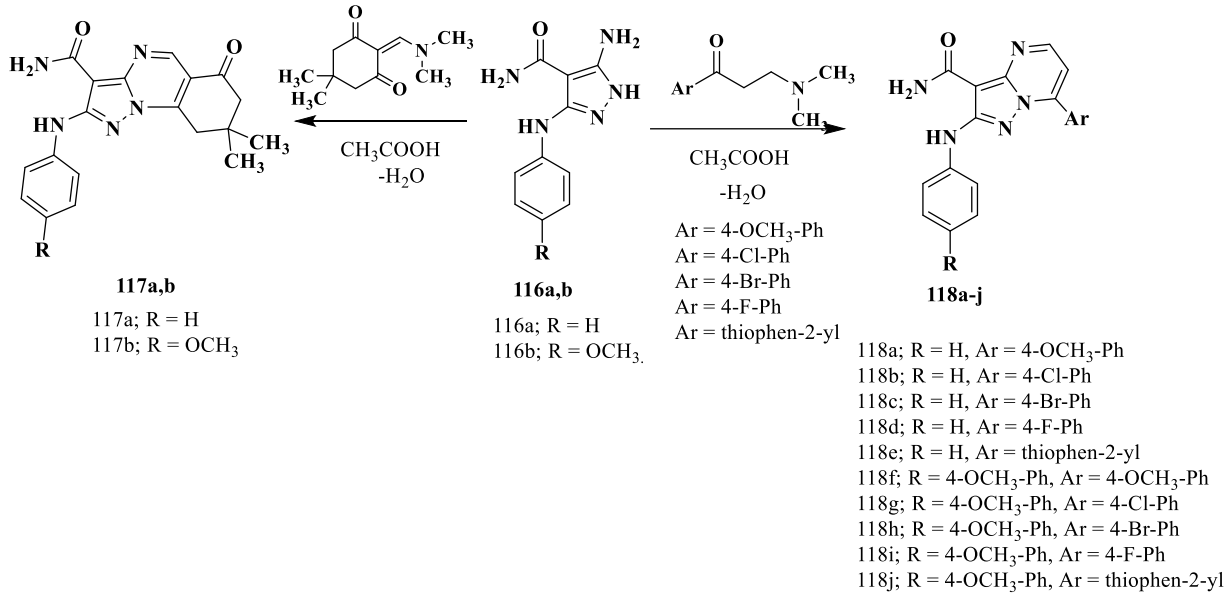
Condensation reaction allowed the synthesis of two pyrazolopyrimidine derivatives **117a,b,** and **118a-j** by Hassan and his team[64]. These compounds were synthesized by reaction of compounds **116a,b** with 2-((di-methylamino)methylene)-5,5-dimethyl cyclohexane-1,3-dione, and 3-(dimethylamino)-1-aryl-prop-2-en-1-ones, in correspondence. These analogs were tested for their anticancer effects against MCF-7, and Hep-G2 cell lines. Compound **118b** revealed the most remarkable activity against the MCF-7 cell line with IC_{50} 63.20 µg/ml, where compound **118h** exhibited the highest activity against Hep-G2 with 70.30 µg/ml IC_{50}[64]. Scheme 39



Scheme 37. Synthesis of compounds 111a-f – 113a,b.

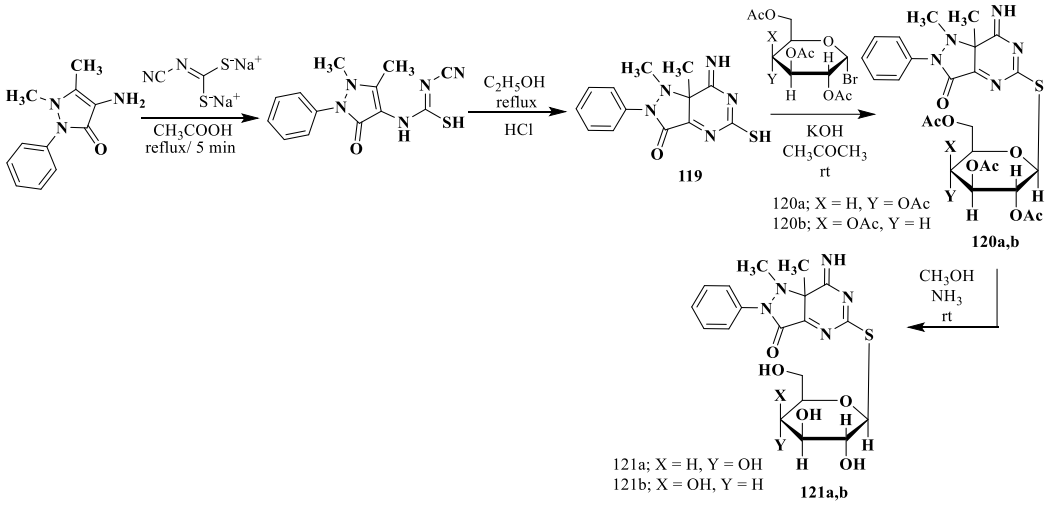


Scheme 38. Synthesis of compounds 114a,b – 115a-d.



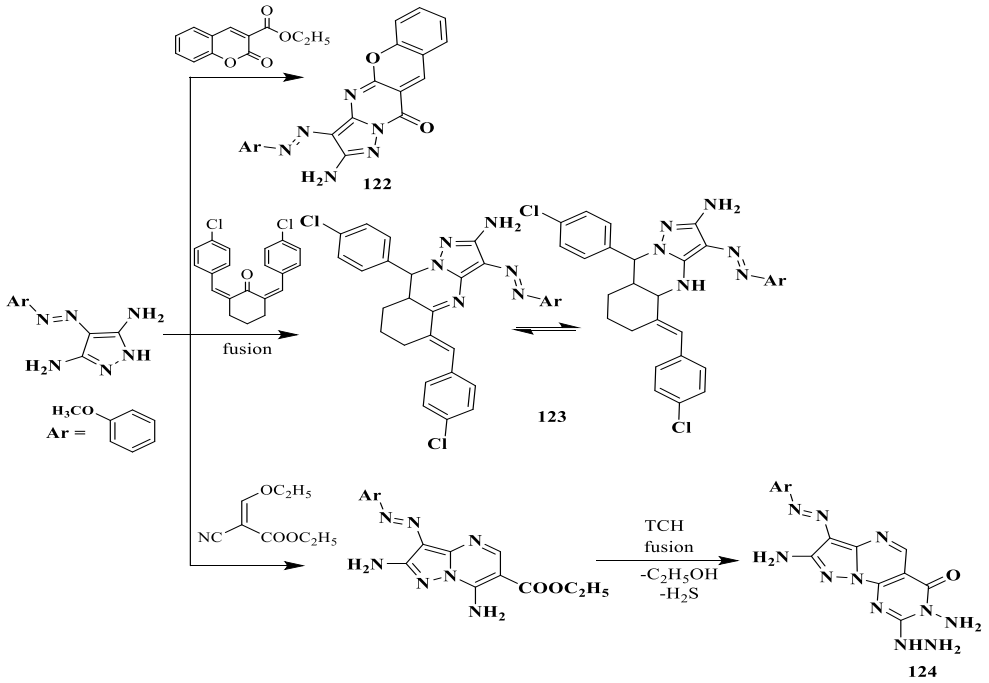
Scheme 39. Synthesis of compounds 117a,b – 118a-j.

As shown in Scheme 40, the synthesis of pyrazolopyrimidine moiety was completed through two-step reaction; first, *N*-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)carbamimidothioic acid was synthesized *via* reaction of antipyrine, and sodium cyanocarbonimidodithioate. This was followed by cyclization by being refluxed in an ethanol / hydrochloric acid mixture. Both α-acetobromoglucose, and α-acetobromogalactose react with compound **119** permitting synthesis of **120a,b**, which upon deprotection; the free glycosides are obtained. Compound **121b** was the most cytotoxic drug against the Hep-G2 cell line, it showed 36.30 μM IC_{50}[65].

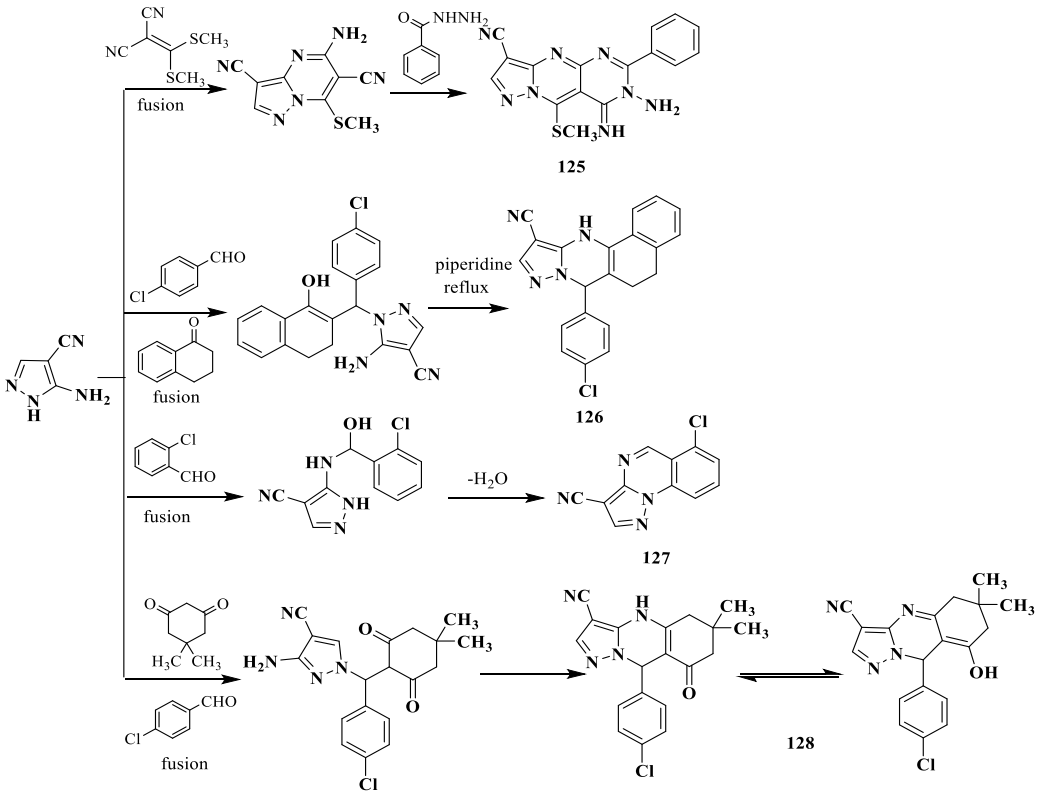


Scheme 40. Synthesis of compounds 119 – 121a,b.

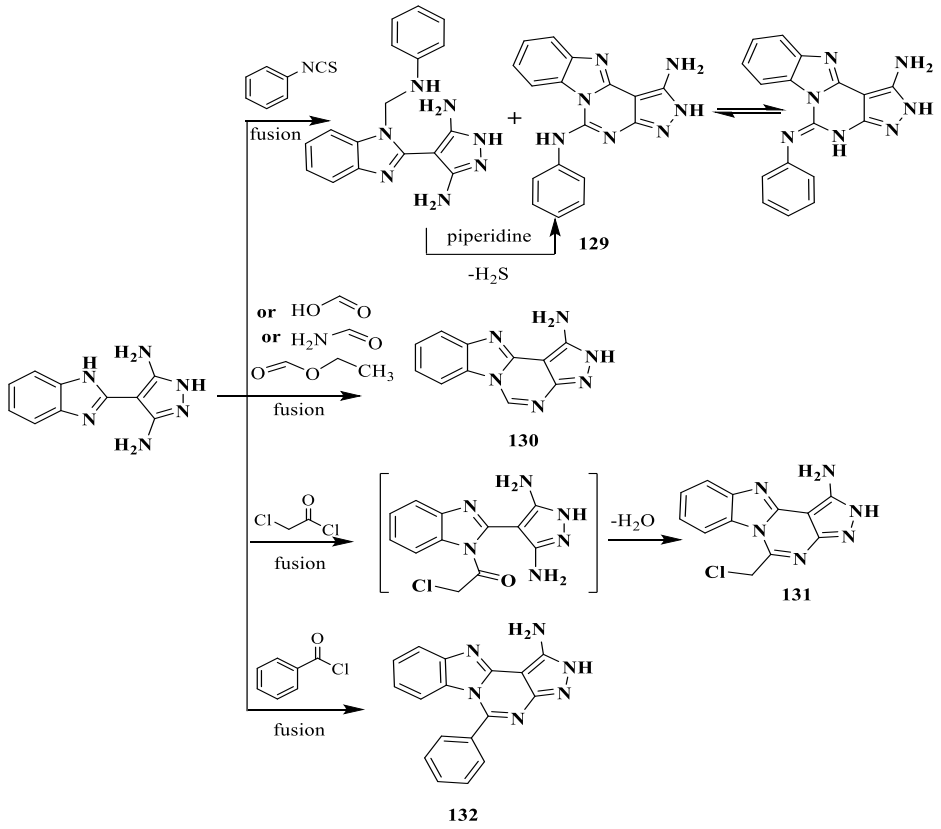
In 2020, many pyarazolopyrimidines **122−136** were synthesized starting with substituted pyrazole-3,5-diamine, 5-amino-1*H*-pyrazole-4-carbonitrile, and 4-(1*H*-benzo[d]imidazol-2-yl)-1*H*-pyrazole-3,5-diamine by fusion pathway as illustrated below. These derivatives were tested as anticancer agents against leukemia, non-small cell lung cancer, colon, CNS, melanoma, ovarian cancer renal, prostate, and breast cancer cell lines. Among them; compound **136** exhibited moderate to strong anticancer activity[66]. Schemes 41−44



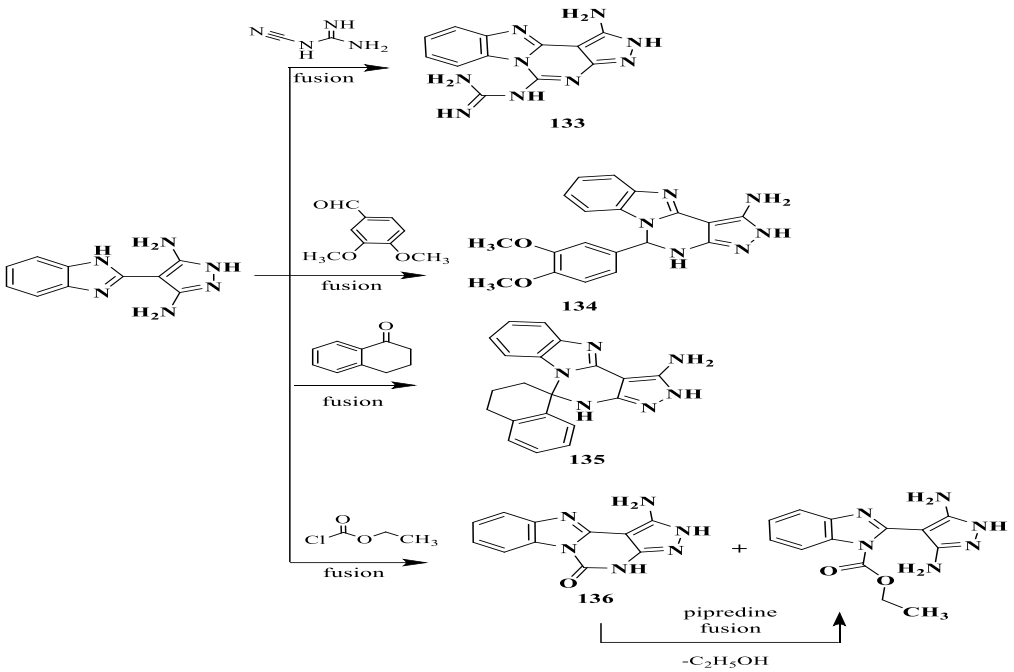
Scheme 41. Synthesis of compounds 122–124.



Scheme 42. Synthesis of compounds 125 – 128.

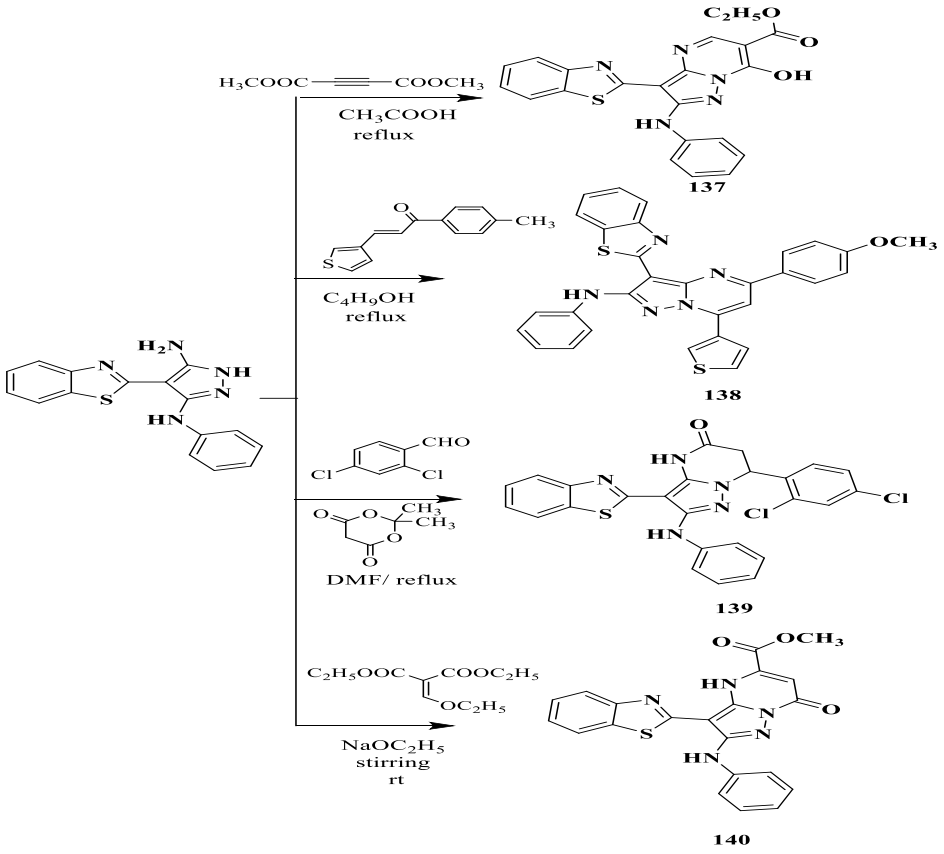


Scheme 43. Synthesis of compounds 129 – 132.



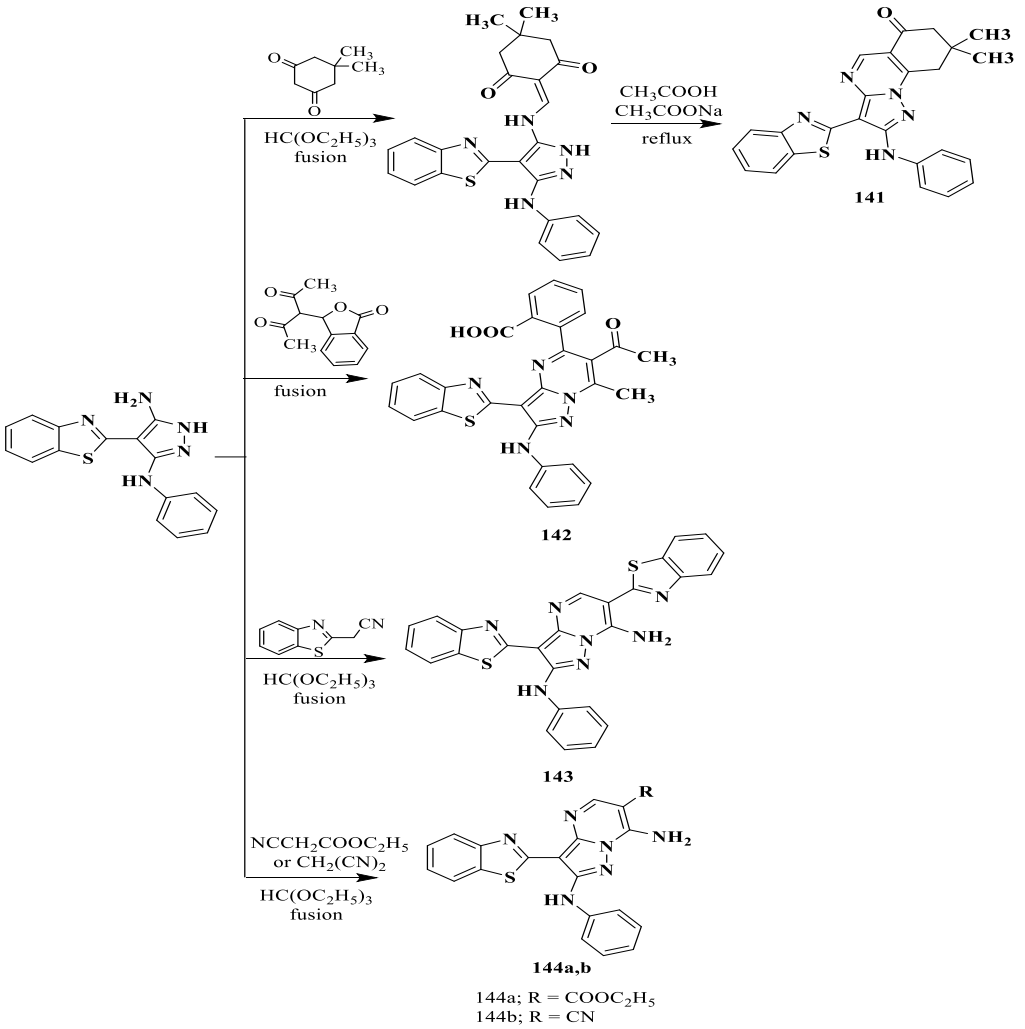
Scheme 44. Synthesis of compounds 133 – 136.

It was found that the reaction of 4-(benzo[*d*]thiazol-2-yl)–N^3-phenyl-1*H*-pyrazole-3, 5-diamine with variable reagents either by refluxing, stirring at room temperature, or fusion accomplished synthesis of compounds **137**−**144**. Compound **137** revealed an apoptosis effect, and exerted high KDM1, and CDK1 inhibitory activity. Moreover, it elucidated 16.34 μM, 3.54 μM, and 7.79 μM IC_{50} values against CCRF-CEM, HOP-92, and Hep-G2 cell lines, respectively[31]. Schemes 45&46

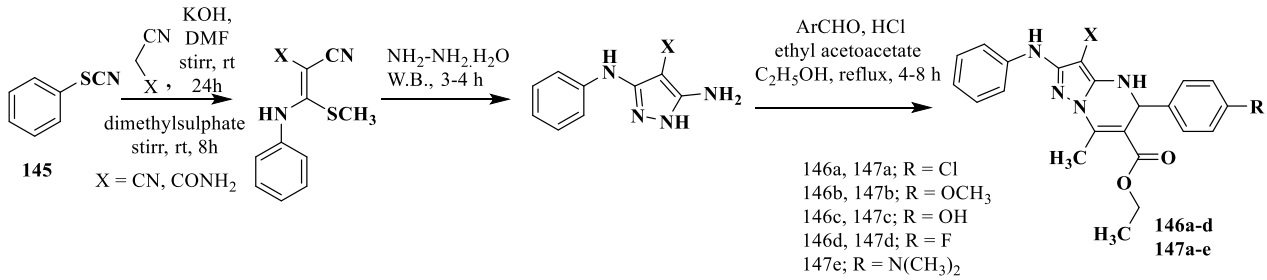


Scheme 45. Synthesis of compounds 137 – 140.

Ali *et al*,[67] followed a specified synthetic route to produce the desired derivatives by first nucleophilic addition reaction of phenyl isothiocyanate **(145)** with various derivatives containing active methylene group either as cyanoacetamide, or malononitrile. The produced compound underwent cyclization by fusion with hydrazine hydrate. Moreover, the Biginelli reaction verified the synthesis of compounds **146a-d**, and **147a-e**. Nevertheless, **146d**, and **147b** were the most potent compounds against Hep-G2, MCF-7, A549, and Caco2 cell lines. Compounds **146d**'s and **147b's** highest activity were exerted against the MCF-7 cell line with 14.12 µM, and 10.05 µM IC_{50} values[67]. Scheme 47

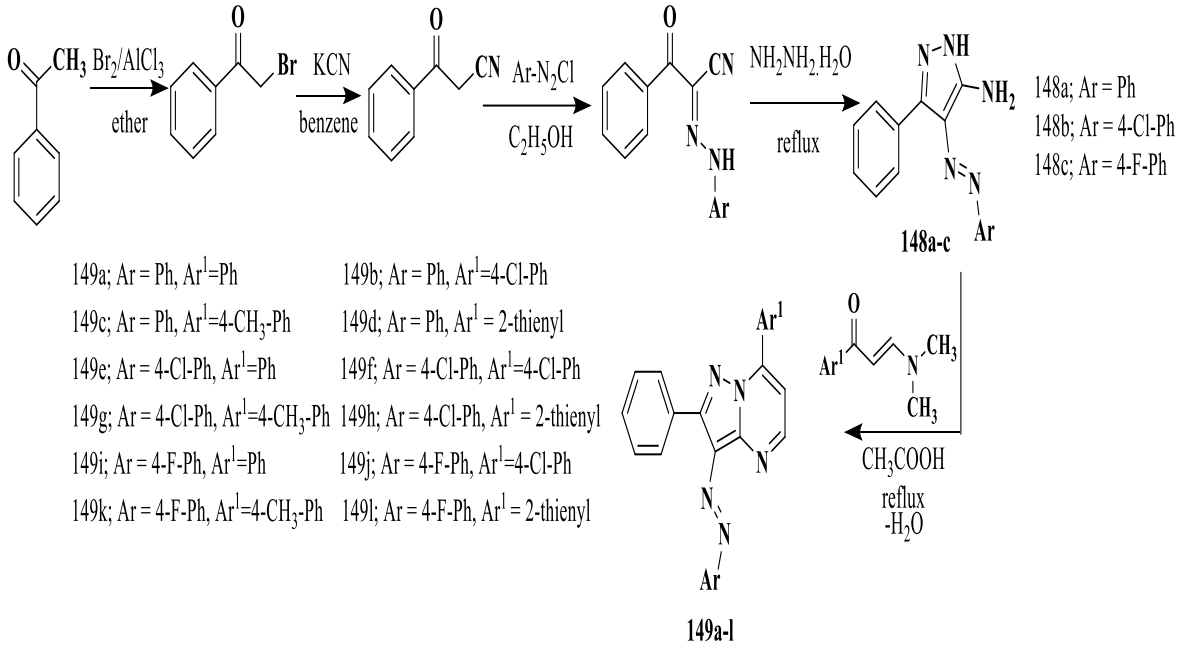


Scheme 46. Synthesis of compounds 141 – 144a,b.



Scheme 47. Synthesis of compounds 146a-d –147a-e.

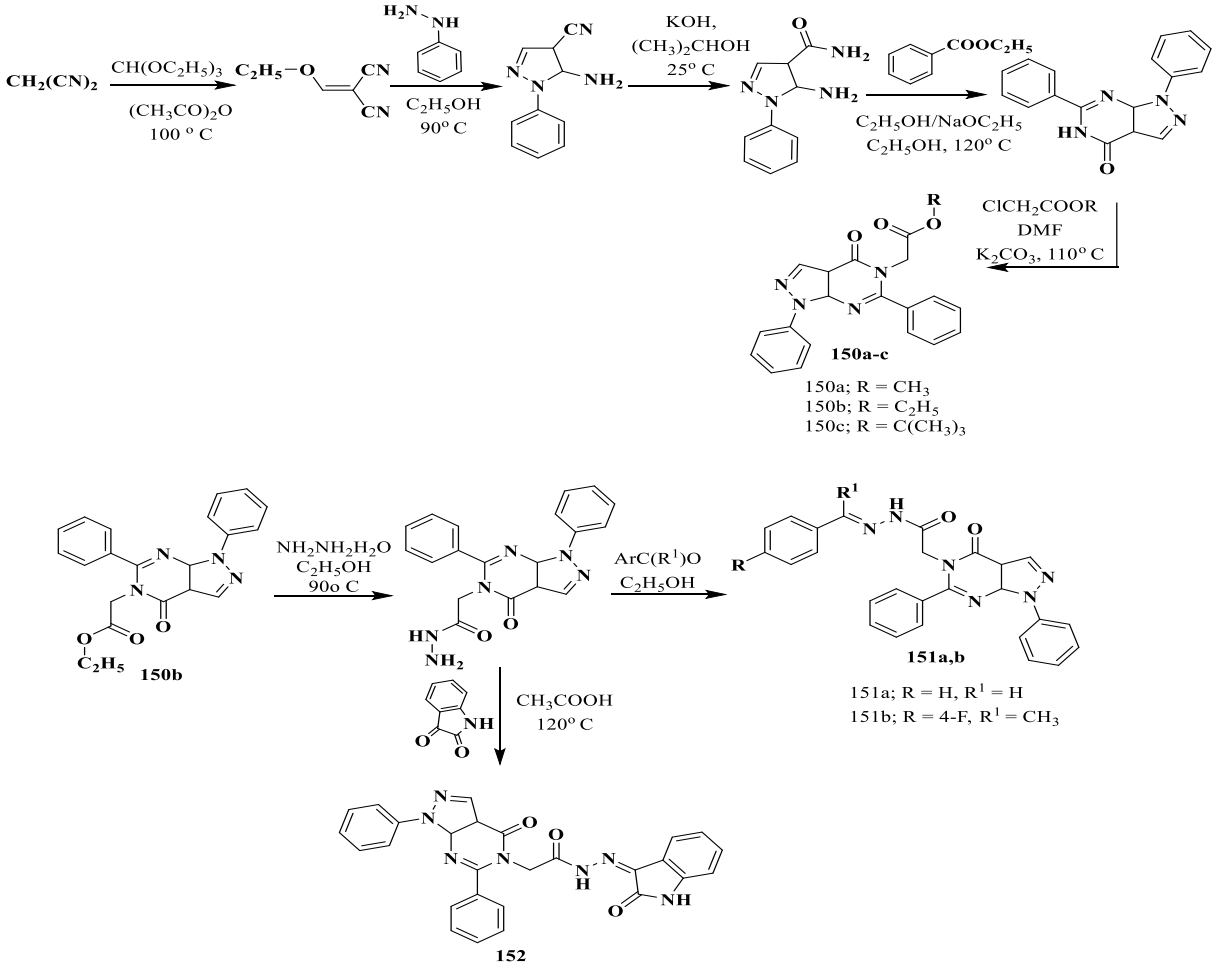
More substituted pyrazolo compounds **148a-c** were synthesized as outlined in Scheme 48. This was followed by a reaction with different enamin- ones producing compounds **149a-l**. They were tested against HepG-2, and MCF-7 as anticancer agents. Compound **149c** showed the highest efficacy against the Hep-G2 cell line with IC_{50} 29.10 μM, moreover, compound **149l** revealed the highest activity against the MCF-7 cell line with 7.30 μM as IC_{50} value[68].



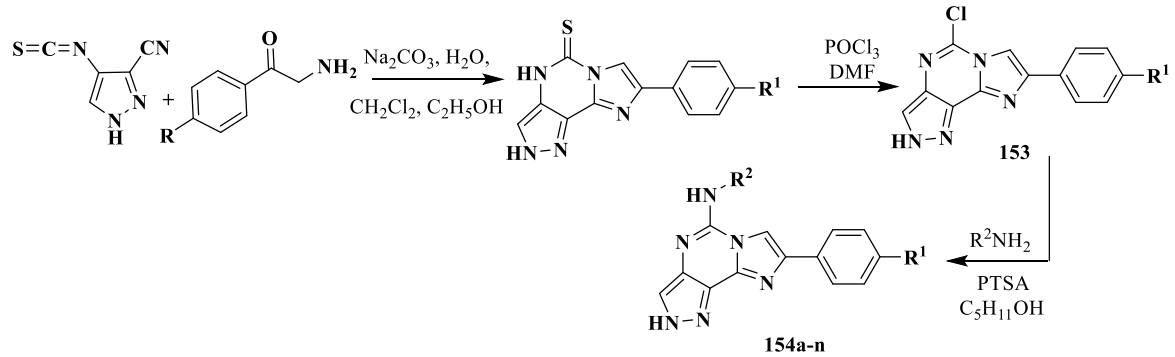
Scheme 48. Synthesis of compounds 148a-c –149a-l.

5-Amino-1-phenyl-1*H*-pyrazole-4-carbonitrile was synthesized *via* reacting malononitrile with a triethylorthoformate producing intermediate, that was reacted with phenylhydrazine. After hydrolysis, the produced 5-amino-1-phenyl-4,5-dihydro-1*H*-pyrazole-4-carboxamide was condensed with ethyl benzoate. The synthesized pyrazolopyrimidine was reacted with ethyl 2-chloroacetate affording the synthesis of compounds **150a-c**. Compound **150b** was reacted with hydrazine hydrate producing the intermediate that reacted with ketones, and isatin producing hydrazone derivatives **151a,b**, and **152**. They were tested as anticancer agents against the MCF-7 cell line; Compound **151b** exhibited the highest activity with IC_{50} 2.89 μM[69]. Scheme 49

More analogs with imidazo, or pyrazolo moieties were synthesized by a reaction of 4-isothiocyanato-1*H*-pyrazole-3-carbonitrile, and variable different substituted aminoethanone. The produced products were then subject to chlorination using phosphorus oxychloride allowing the synthesis of compound **153**. Nucleophilic substitution reaction allowed the synthesis of derivatives **154a-n**; some of them were tested as anticancer agents against K562, U937, HCT-116, and HT-29 cell lines. The derivatives **154b**, **154e**, **154j**, and **154m** showed potent growth inhibition. While **154k**, **154a**, and **154n** revealed much less effect than the former derivatives. This may be attributed to the methyl, bromo, and fluoro substituents. Compound **154m** revealed IC_{50} values as 0.44 μM, 4.44 μM, 1.02 μM, and 1.72 μM, respectively against the used cell lines[27]. Scheme 50



Scheme 49. Synthesis of compounds 150a-c –152.

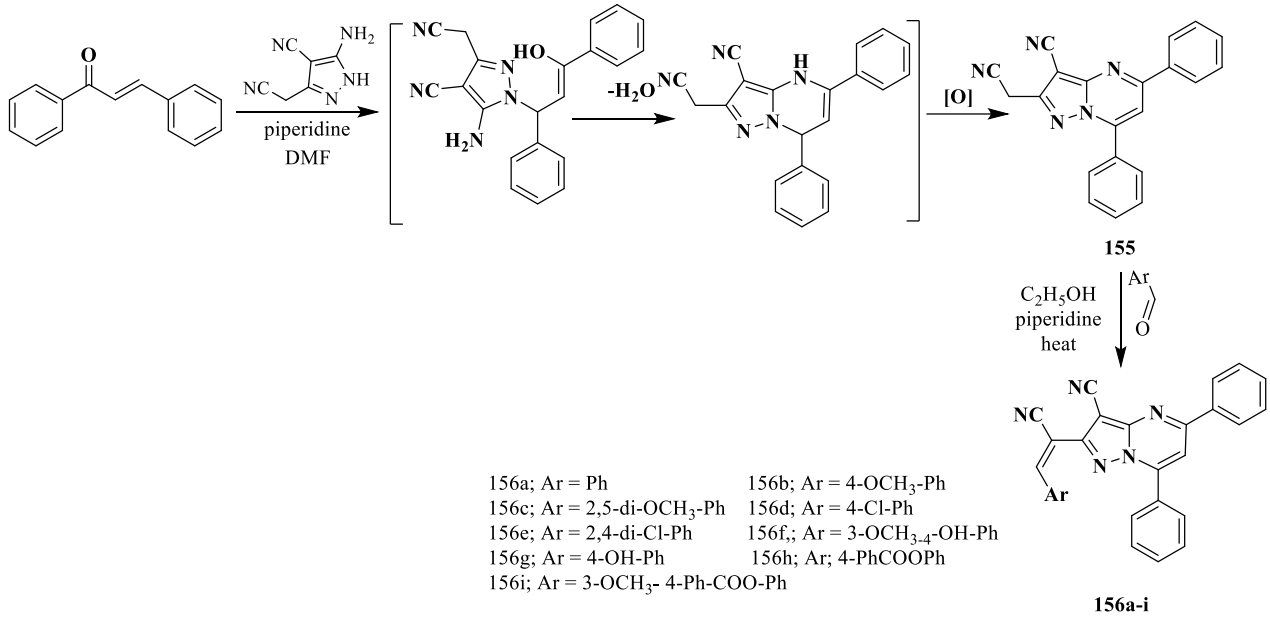


154a; R^1 = CH_3, R^2 = 4-OCH_3-Ph
154b; R^1 = CH_3, R^2 = 3-Cl-4-F-Ph
154c; R^1 = CH_3, R^2 = cyclopropyl
154d; R^1 = CH_3, R^2 = cyclopentyl
154e; R^1 = CH_3, R^2 = 4-NO_2-Ph
154f; R^1 = Br, R^2 = 4-OCH_3-Ph
154g; R^1 = Br, R^2 = 3-Cl-4-F-Ph
154h; R^1 = Br, R^2 = cyclopropyl
154i; R^1 = Br, R^2 = cyclopentyl
154j; R^1 = F, R^2 = 4-OCH_3-Phenyl
154k; R^1 = F, R^2 = 3-Cl-4-FPhenyl
154l; R^1 = F, R^2 = cyclopropyl
154m; R^1 = F, R^2 = cyclopentyl
154n; R^1 = F, R^2 = 4-NO_2-Phenyl

Scheme 50. Synthesis of compounds 153 –154a-n.

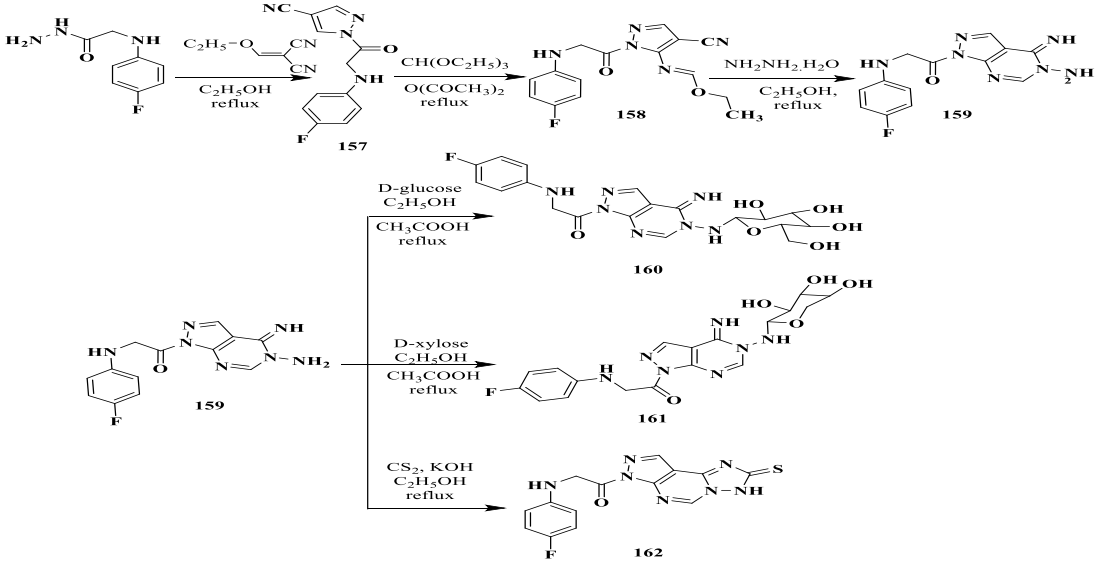
The reaction of 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile, and 1,3-diphenylpropane-1,3-dione fulfilled synthesis of pyrazolopyrimidine analog **155**, which was reacted with aldehydes allowing the synthesis of compounds **156a-i**. These derivatives were tested against Hep-G2, MCF-7, and

Hela cell lines as anticancer agents. **156f** was the most active compound, it exhibited IC_{50} values as 3.53 μM, 6.71 μM, and 5.16 μM, respectively[70]. Scheme 51

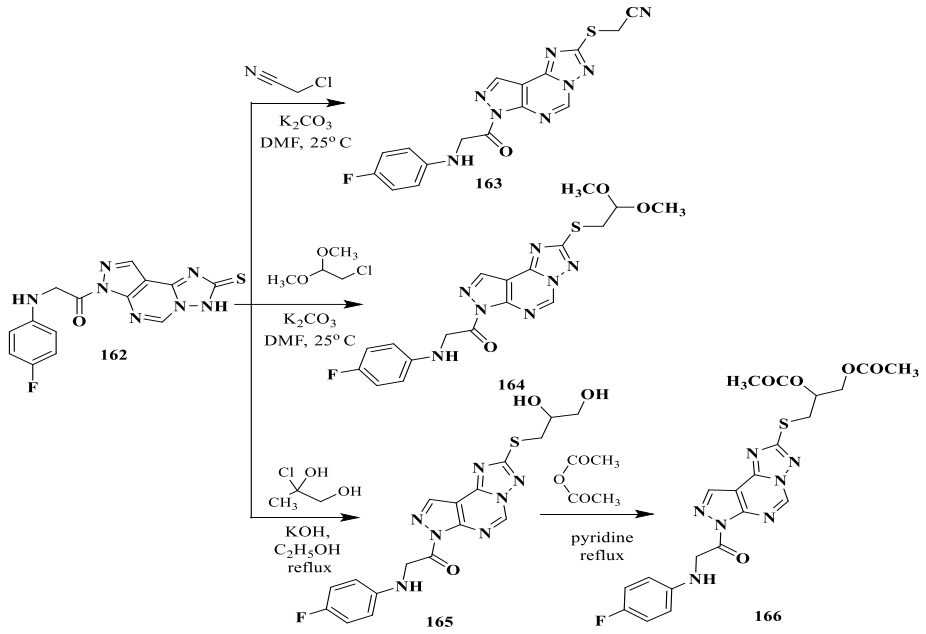


Scheme 51. Synthesis of compounds 155 –156a-j.

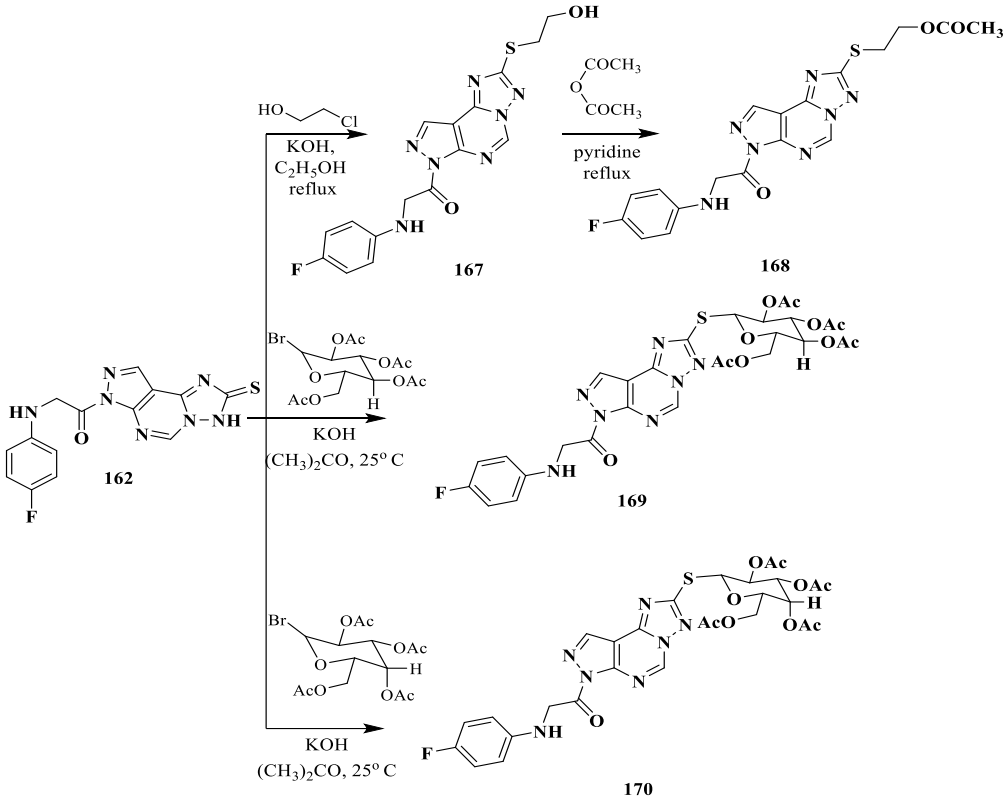
Otherwise, *via* a series of chemical reactions; pyrazolopyrimidine nucleus was synthesized. First, pyrazolo derivative **157** was synthesized by refluxing 2-(ethoxymethylene)malononitrile, and 2- ((4-fluorophenyl) amino)acetohydrazide. Refluxing of hydrazine hydrate with compound **158** achieved the synthesis of compound **159**. Furthermore, refluxing of compound **159** with aldose sugars fulfilled the synthesis of compounds **160,** and **161**. The reaction of compound **159** with carbondisulfide allowed compound **162**'s synthesis which paved the synthesis of compounds **163, 164, 165,** and **167** through reaction with alkyl halides, while compounds **166,** and **168** were synthesized *via* esterification using acetic anhydride. Finally, the reaction with glycosyl bromide accomplished the synthesis of compounds **169,** and **170**. The compounds were tested against MCF-7, HepG-2, and HCT-116 cell lines. Compound **169** was the most active compound with IC_{50} 7.00 μM, 7.00 μM, and 6.00 μM, respectively. In addition, compound **170** revealed IC_{50} value as 0.061 μM, when tested for its CDK2/cyclin A2 inhibitory activity[71]. Schemes 52−54



Scheme 52. Synthesis of compounds 157 – 162.

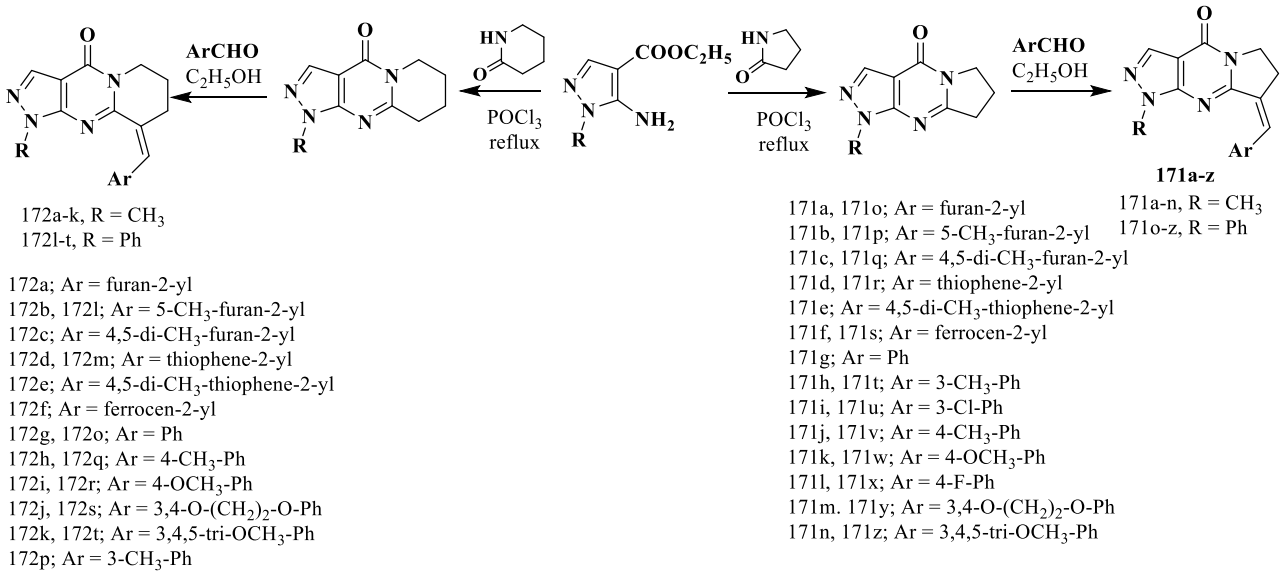


Scheme 53. Synthesis of compounds 163 – 166.



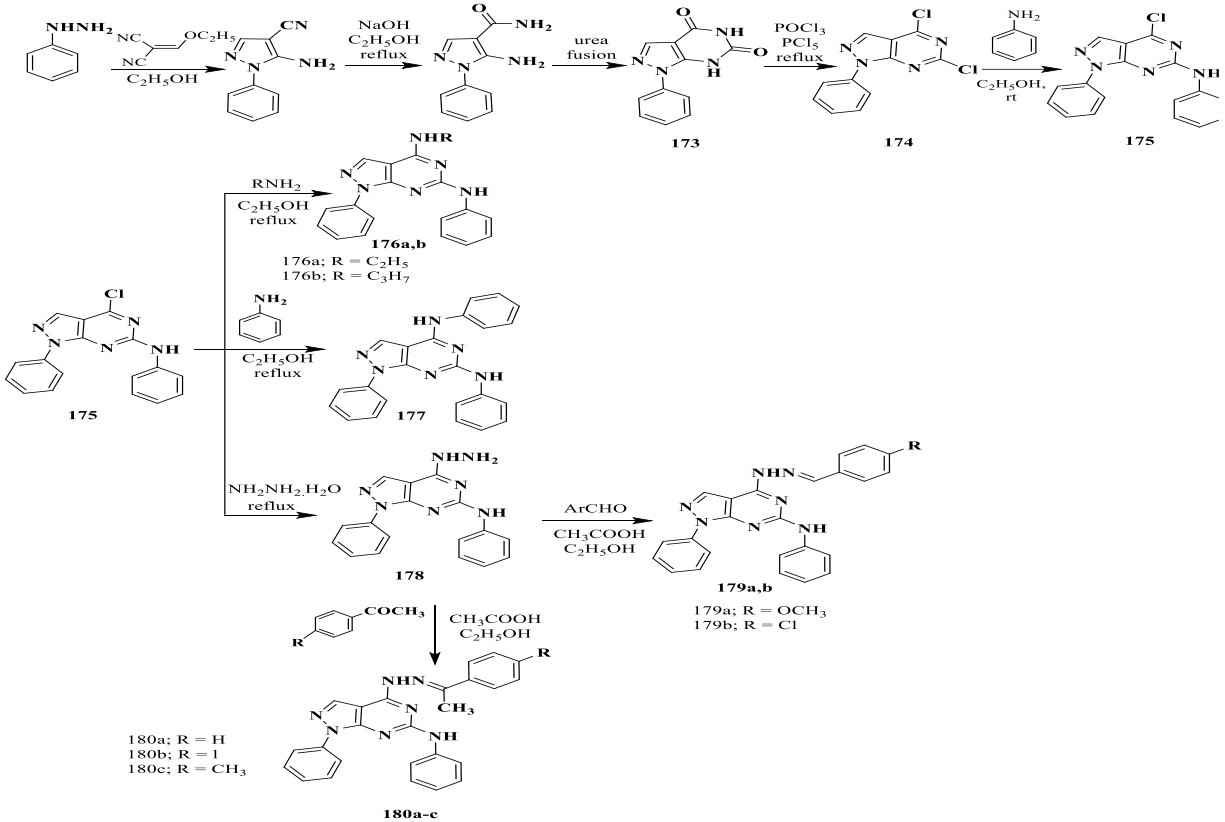
Scheme 54. Synthesis of compounds 167 – 170.

Pyrazolopyrimidines were synthesized by refluxing the reactants in $POCl_3$, whereas; condensation reaction with appropriate aldehyde allowed synthesis of **171a-z**, and **172a-t**. These derivatives were tested as anticancer agents against HT-29, HCT-116, HGC-27, HeLa, and MDA-MB231 cell lines using doxorubicin as a reference drug. Compound **172k** revealed the highest activity against the mentioned cell lines with IC_{50} values as 0.03 µM, 0.04 µM, 0.19 µM, 0.09 µM, and 1.61 µM, respectively[72]. Scheme 55



Scheme 55. Synthesis of 171a-z – 172a-t.

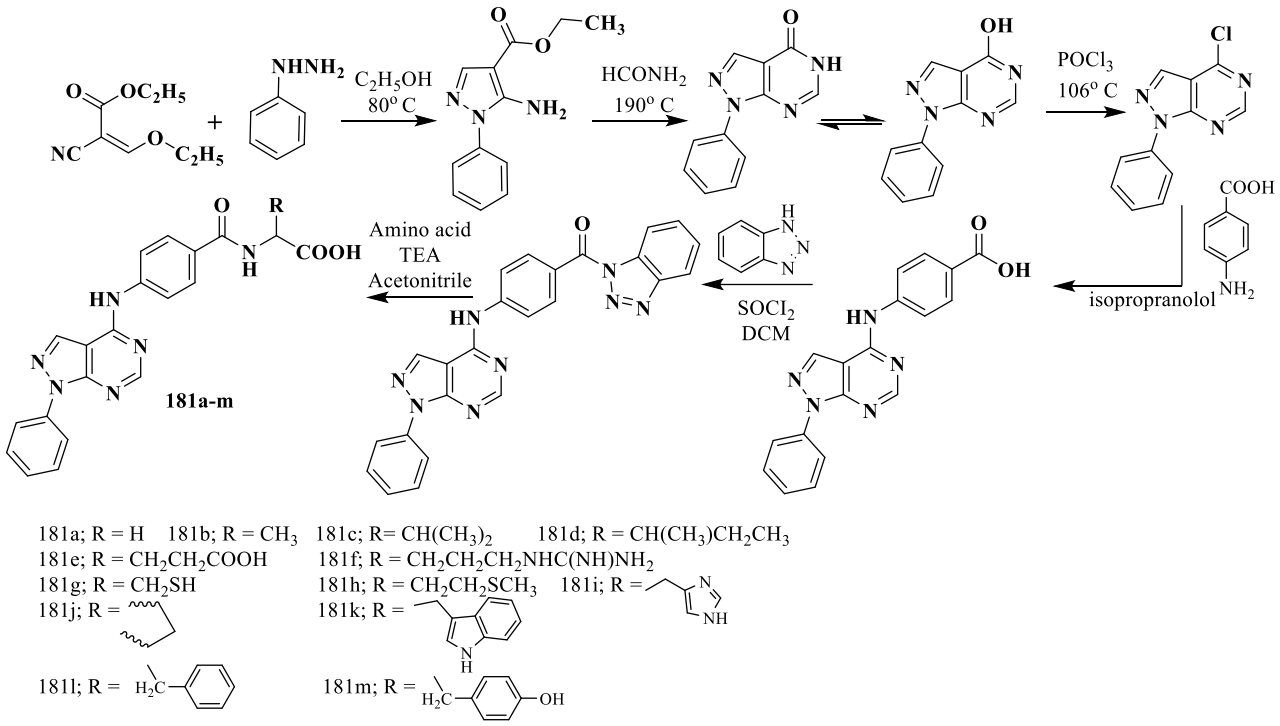
After the cyclization of the substituted pyrazole, and synthesis of compound **173**, chlorination verified the synthesis of compound **174**. Reaction with aniline allowed compound **175**'s synthesis as outlined in Scheme 56. This was followed by a reaction with various amines producing compounds **176−178**. Also Schiff's reaction accomplished the synthesis of **179a,b**, and **180a-c.** They were tested as anticancer agents against HCT-116, and A-549 cancer cell lines. Among them; compound **178** showed the highest activity against HCT-116 with 18.78 μM IC_{50}. Moreover, 8.21 μM IC_{50} was exerted by **180b** against the A-549 cell line[73].



Scheme 56. Synthesis of compounds 173 – 180a-c.

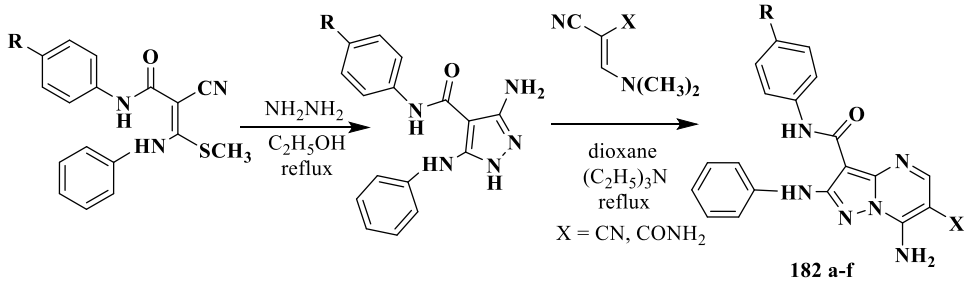
Ethyl-5-amino-1-cyclohexyl-1*H*-pyrazole-4-carboxylate was synthesized *via* a reaction of phenyl-hydrazine, and ethyl-2-cyano-3-ethoxyacrylate. Cyclization was achieved by refluxing of the former compound with formamide. Nucleophilic aromatic substitution fulfilled synthesis of 4-((1-phenyl-1*H*-

pyrazolo[3,4-d]pyrimidin-4-yl)amino)benzoic acid. This was followed by a reaction with 1*H*-benzo[d][1,2,3]triazole, then with appropriate amino acid. Compounds **181a-m** were tested against HeLa, PC-3, HCT-116, BxPC-3, HepG-2, MCF-7, DHFR, and HPDE cell lines; Compounds **181c, 181d, 181f, 1814j,** and **181l** revealed good anticancer efficacies. Compound **181f** was the most active derivative as it revealed IC_{50} values as 6.99 µM, 6.29 µM, 5.48 µM, 7.09 µM, 5.12 µM, 4.65 µM, and 0.31 µM, respectively [74]. Scheme 57



Scheme 57. Synthesis of compounds 181a-m.

Refluxing of 2-cyano-3-(methylthio)-*N*-phenyl -3-(phenylamino)acrylamide with hydrazine hydrate enabled synthesis of 3-amino-*N*-phenyl-5-(phenyl amino)-1*H*-pyrazole-4-carboxamide. The latter derivative was reacted with either 2-((dimethyl amino)methylene)malononitrile, or 2-cyano-3-(di methylamino)acrylamide permitting synthesis of the pyrazolpyrimidine nucleus. Compounds **182a-f** were tested as anticancer effects against MCF-7, PC3, Hep-2, and WI38 cell lines. The highest anticancer activity was exerted by compound **182f** against Hep-2, and MCF-7 cell lines with 8.85 µM, and 10.80 µM IC_{50}, respectively, compound **182c** against HepG-2 cell line with 19.62 µM IC_{50}, compound **182e** against PC-3 cell line with 24.90 µM IC_{50}, and compound **182a** against W138 cell line with 26.15 µM IC_{50} [75]. Scheme 58



Scheme 58. Synthesis of compounds 182a-f.

5. CONCLUSIONS

Through our review, it was elucidated that the synthesized imidazo pyrimidines were mainly synthesized as four basic categories depending on four different nuclei. These nuclei are benzo[4,5] imidazo[1,2-c]pyrimidine as in compounds **5a,b**, **8a-c**, **9a-c**, and **12a-h**, imidazo[1,2-a]pyrimidine as in compounds **18a-o**–**24a-o**, and **33**–**42a-h**, imidazo [1,2-c]pyrimidin as in compounds **17a-j**, and **25a-z**, and imidazo[4,5-d]pyrimidine as in compounds **15a-h**, **16**, and **26a-f**–**31a-k**. Nevertheless, the pyrazolopyrimidine derivatives were synthesized targeting pyrazolo[3,4-d]pyrimidine nucleus as in compounds **43a-g**–**50**, **74**–**83**, **90**, **92**–**96**, **100a-h**–**106a-e**, **108a-g**, **120a,b 121a,b**, **129**–**136**, **150a-c**–**152**, and **159**–**181a-m**, and pyrazolo[1,5-a]pyrimidine nucleus as in compounds **54a-h**, **57**–**61a,b**, **63** – **68**, **72a,b**, **73**, **85a-c, 86a,b, 87a-i, 97**, **98a-r**, **107a-e**, **109a-i**, **110a-c**, **112a-f**–**115a-d**, **117a,b**, **118a-j**, **122**–**128**, **137**–**144a,b**, **146a-d**, **147a-e**, **149a-i**, **153**–**156a-i**, and **182a-f**. These derivatives revealed potent anticancer effects and vast antitumor efficacy against variable types of cancer as CNS, leukemia, colon, breast, lung, liver, skin, cervical, and ovarian.

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Author Contribution: Azza T. Taher was responsible for the review's conception, design and critical review. Marwa T. M. Sarg and Moshira A. El Deeb were responsible for reviewing the manuscript. Amira A. Helwa and Ghada S. Rady were responsible for the review's writing and the data collection.

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