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Section B: Pharmaceutical Analytical & Organic Chemistry, Medicinal & Biochemistry

Pyrimidines as Anticancer and Antiviral: Synthesis & Reactions (A Review)

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ABSTRACT

Background: The interest of many medicinal and organic chemists has been attracted to the synthesis of pyrimidines and their analogues due to their highly biological and medicinal properties. **Objectives& Methodology:** Based on these activities, this review discusses the various recent methods for the synthesis of these heterocyclic compounds during the period of 2017 to 2021 with certain two main medicinal actions. **Conclusion:** Pyrimidine moiety bearing compounds, are synthesized, and reacted either through one-pot synthesis or multi-step synthesis pathways, in catalytic and solvent free condition or using catalysts and solvent.

Keywords: *Pyrimidine; Pyrimidine analogues; Anticancer; Antiviral; Reactions; Synthesis.*

INTRODUCTION

Pyrimidines are sex membered heterocyclic compounds with two nitrogen hetero atoms at 1, 3 positions. They form the core part of Deoxyribonucleic acids (DNA) and ribonucleic acid (RNA), so they have diverse biological activities[1–3]. Among these activities, are anti-inflammatory[4–7], analgesic [8,9], antioxidant[10–12], antimalarial[13–15], antimicrobial activity[16–20], antitumor [21–28] and antiviral[29–36]. In this investigation we surveyed the synthesis and reaction of pyrimidines with antiviral and anticancer activity through the last five years.

Synthesis and Reaction of Pyrimidines

Synthesis And Reactions of Pyrimidines with Anticancer Activity

In 2017, A.S. Hassan *et al.* reported[37] the synthesis and anticancer activity of fused pyrazolo[1,5-*a*] pyrimidine **1** against both breast and liver cancer *via* refluxing amino-1*H*-pyrazoles with 3-(dimethylamino)-1-aryl-prop-2-en-1-ones using *N*-methylmethanamine as a basic catalyst in acetic acid as a solvent. (Scheme 1). For anti-breast cancer cell line MCF-7 compound **1** (Ar = phenyl and Ar^1 = 4-methoxyphenyl) exhibited the highest potency using doxorubicin (IC_{50} at 63.2 ± 3.6 µM and 65.6 ± 4.2 µM respectively). On the other hand, derivative **1** (Ar = 4-methoxyphenyl and Ar^1 = 4-bromophenyl) recorded the highest activity compared to doxorubicin with IC_{50} at 70.3 ± 4 µM and 80.9 ± 2.1 µM respectively.

Also, during 2017, A.M. El-Naggar *et al.* reacted[38] certain thiouracils **2** with dibromoethane, chloroacetyl chloride or methylene chloride using catalytic amount of anhydrous potassium carbonate

(K_2CO_3) and tetrabutylammonium bromide (TBAB) in dry tetrahydrofuran (THF) to afford cyclized pyrimidine derivatives **3,** **4** and 2,2'-[methylenebis(sulfanediyl)]bis[4-(4-methoxyphenyl)-6-oxo-1,6-dihydro pyrimidine-5-carbonitrile] **(5)** (Scheme 2).

When they reacted **2** with halo derivatives like chloroacetic acid, ethylchloro acetate, ethylchloro formate, allyl bromide or diethyl bromomalonate using anhydrous K_2CO_3 and TBAB in dry THF, S alkylation occurred to give **6-10**, respectively. While S, N alkylation product **11** obtained when **2** refluxed with two molecules of benzyl chloride (Scheme 3).

They also synthesized new derivatives of thiouracils **12-15** *via* reaction of **2** with different amines in dioxane through Mannich reaction (Scheme 4). These compounds showed potent activity as thymidylate synthases (TS) inhibitor with IC_{50} value ranging from 1.57 to 3.89 µM using 5-fluorouracil as a reference.

M. Wang and coworkers, also in 2017, reported[39] the synthesis of some fused 2,4 dichloropyrido[3,2-*d*]pyrimidines **16** *via* the reaction of 2,4 dihydroxypyrido[3,2-*d*]pyrimidines with phosphorus oxychloride ($POCl_3$) in catalytic amount of triethyl amine (Et_3N). The produced 2,4 dichloropyrido[3,2-*d*] pyrimidines **16** were further converted to the corresponding 2,4 aminopyrido[3,2-*d*] pyrimidines **17** by using ammonia saturated solution in dry methanol. To obtain the reduced products **18**, which have a potent anticancer activity through inhibition of recombinant human dihydrofolate reductase enzyme (rhDHFR), compounds **17** were treated with Pd/C in ethanol (Scheme 5). The reduced products **18** exhibited broad spectrum antitumor activity on four different cell lines with IC_{50} value ranging from 0.07 to 23 µM, and potent inhibitory activity against rhDHFR with IC_{50} value ranging from 0.2 to 1.0 µM.

Also in the same year, M.M. Mohamed *et al*. reacted[40] thioxopyrimidine with hydrazine hydrate in ethanol to obtain hydrazine derivatives **19** which were further refluxed with acetic anhydride to gain the acetylated derivative **20**. While thiazolopyrimidine analogues **21** were synthesized *via* the reaction of thioxopyrimidine analogue with chloroacetic acid and certain aldehydes (Scheme 6). Compound **20** and some derivatives of **21** showed equipotent activity as TS inhibitor compared to the reference drug 5-fluorouracil IC_{50} value 41.53 ± 2.3 µM against MCF-7 cell line and 38.44 ± 2.14 µM against HEPG-2 cell line.

Also, during 2017, our coworkers reported[41] the synthesis of fused pyrrolopyrimidine analogues **22-24** *via* the reaction of 2-amino-3-cyanopyrroles with formic acid or acetic anhydride, formamide or phenyl isocyanate respectively (Scheme 7). These compounds exhibited a promising antitumor activity especially against both breast and liver cancer as these compounds recorded IC_{50} value ranging from 2.57 to 33.87 µM against MCF-7 cell line compared to doxorubicin (IC_{50} value 58.5 µM) and for hepatic cancer (HEPG-2 cell line) these compounds recorded IC_{50} value ranging from 23.26 to 40.42 µM compared to doxorubicin (IC_{50} value 46.4 µM).

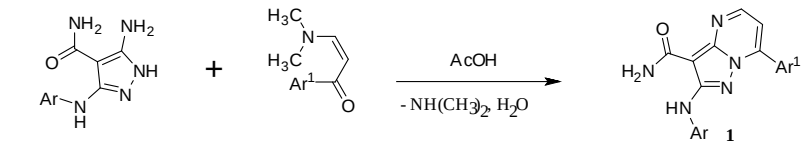
One year later, A.A. Helwa and co-workers refluxed[42] a substituted pyrimidine with certain aldehydes, benzoyl chloride or acetophenone to gain pyrimidine hydrazone analogues **25-27**. While their reaction with either ethyl acetoacetate or ethyl cyanoacetate afforded the cyclized products **28, 29** (Scheme 8). Compound **25** (Ar^1= 4-flurophenyl), among the other compounds, recorded the highest activity on MCF-7, A549 and Caco-2 cell lines with IC_{50} values 1.42, 1.98 and 9.50 µM respectively compared to 5-fluorouracil (IC_{50} = 1.71, 10.32 and 20.22 µM).

Starting from 2-chloro-4-floro-aniline, in 2018, R. Chikhale *et al*. reported[43] the synthesis of a tyrosine kinase inhibitor **30** *via* the reaction of 2-chloro-4-floro-aniline with ethyl acetoacetate and the produced compound was further refluxed with guanidine derivative and finally the product was dehydrogenated using CAN/HCl to afford the intended compound **30** (Scheme 9). Compared to the two standards lapatinib (IC_{50} = 0.0108 µM) and Dasatinib (IC_{50} = 0.005 µM), compound **30** showed significant activity with IC_{50} at 0.0711 µM.

In 2019, N.M. Ahmed and co-authors reported[44] the synthesis of substituted pyrimidines **31** *via* cyclocondensation of certain propenones, obtained *via* Claisen Schmidt condensation of the appropriate aldehydes with acetyl anthracene, with hydrazinopyrimidines (Scheme 10). The analogue **31** (Ar and Ar^1= 4-fluorophenyl) exhibited equipotent activity (IC_{50} values of 5.34 and 6.13) on HepG-2 and Huh-7 cell lines to that of doxorubicin (IC_{50} = 5.43 and 6.40 µM, respectively).

Also during 2019, S.E.S. Abass *et al*. reported[45] the reaction of thiopyrido[2,3-*d*]pyrimidine derivatives with either hydrazine hydrate or phenyl hydrazine to obtain hydrazino-derivatives **32**, **33**. Compound **32** was reacted separately with N, N dimethyl formamide, CS_2, acetyl and/ or benzyl chloride to get the anticancer compounds **34-36** respectively (Scheme 11). Compounds **32-36** showed broad spectrum anticancer activity against breast, prostate and lung cancer *via* activation of certain caspases and inhibition of both CDK4 and CDK6 using doxorubicin as a reference standard.

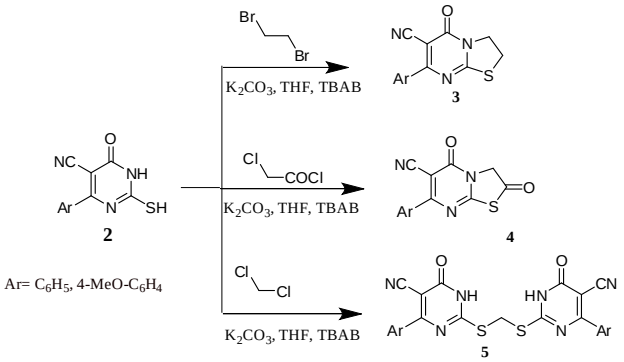
S.A. Elmetwally and co-workers in the same year, reported[46] the synthesis of a certain thieno[2,3-*d*] pyrimidine **37** *via* fusion of the amino-cyano derivative with formic acid then the produced pyrimidinone was refluxed with $POCl_3$. Finally, the substituted chloro compound was allowed to react with either thiourea derivative or hydrazine to produce thienopyrimidines **38**



Ar= C_6H_5, 4-MeOC_6H_4

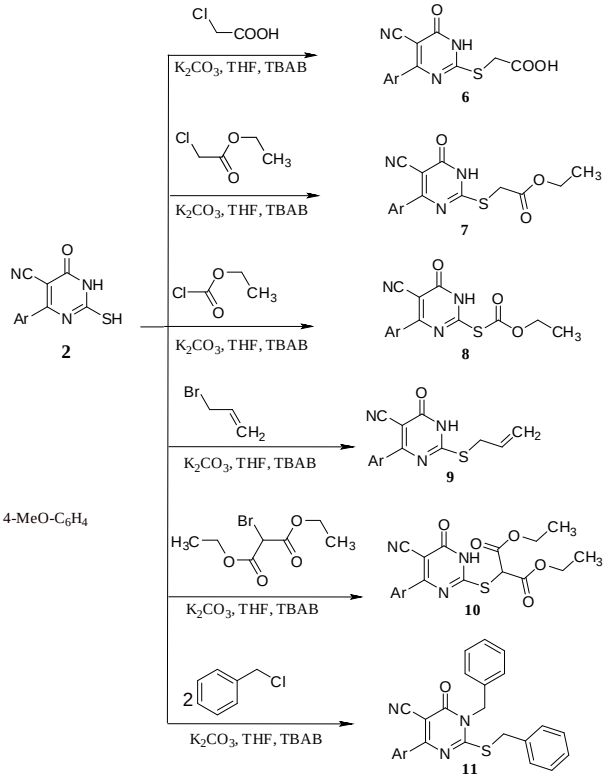
Ar^1 = 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-thiophen-2-yl

Scheme 1. Synthetic pathway of compound 1.



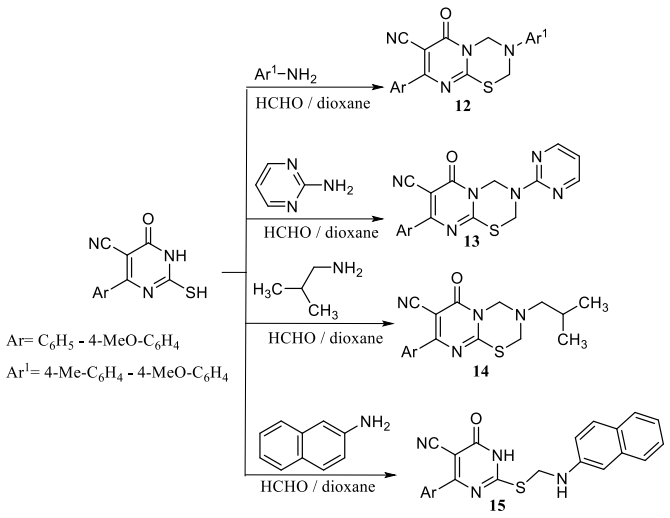
Ar= C_6H_5, 4-MeO-C_6H_4

Scheme 2. Synthetic pathways of compounds 3-5.

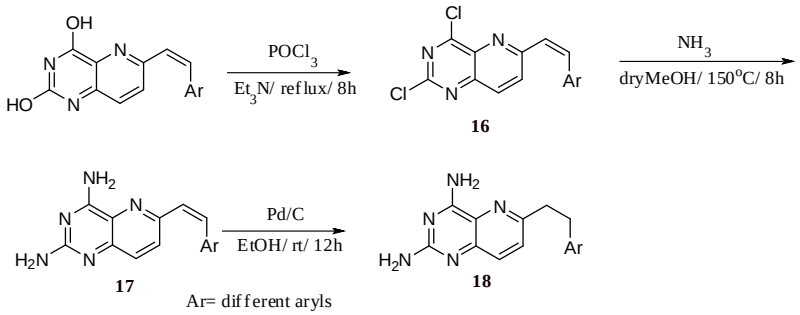


Ar= C_6H_5, 4-MeO-C_6H_4

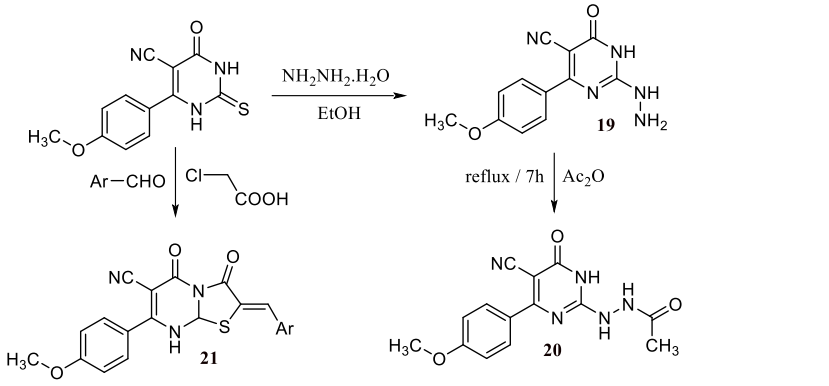
Scheme 3. Synthetic pathways of compounds 6-11.



Scheme 4. Synthetic pathways of compounds 12-15.

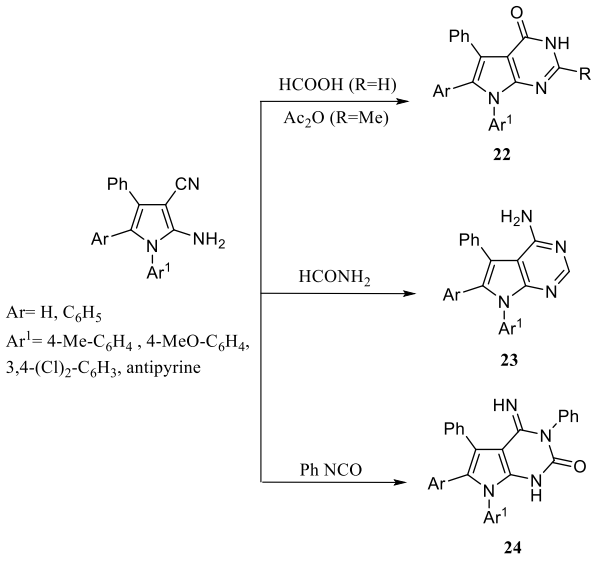


Scheme 5. Synthetic pathway of compounds 16-18.



Ar= C_6H_5, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 3,4-$(Cl)_2$-C_6H_3, 2-OH-C_6H_4, thiophen-2-yl, 3,4-$(MeO)_2$-C_6H_3, 4-NO_2-C_6H_4

Scheme 6. Synthetic pathway of compounds 19-21.



Scheme 7. Synthetic pathways of compounds 22-24.

and **39** respectively (Scheme 12). Using erlotinib as a reference (IC_{50} = 0.387 µM), compound **39** showed a comparable cytotoxicity on epidermal growth factor receptor (EGFR) enzyme with IC_{50} = 0.560 µM.

The mechanism of formation of compound **39** involved replacing the chloro group by mercapto group followed by addition of water and elimination of ammonia as illustrated in scheme 13.

One year later, L.K. Golani *et al*. designed and synthesized[47] antitumor agents **40** and **41** *via* the reaction of aminopyrimidines with *α*-bromo methyl ketones and refluxing the product with L- glutamate diethyl ester (Scheme 14). The antitumor agents **40** and **41** recorded anticancer activity by inhibition of DHFR using reference standards methotrexate (MTX) and pemetrexed (PMX).

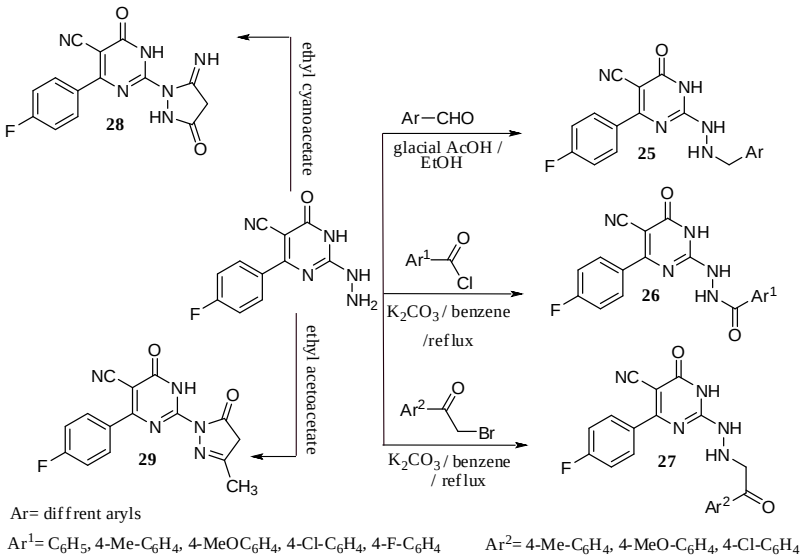
In continuation to their work[42], A.A. Helwa and co-author prepared[48] anticancer agents **42** and **43** *via* replacing the oxygen moiety of substituted pyrimidinone by morpholine moiety and performed the same reactions as scheme 8 (Scheme 15). Compound **43** (IC_{50} = 6.15 µM) compared to erlotinib (IC_{50} = 22.33 µM) showed higher potency and lower cytotoxic activity on normal cell.

Z. Kilic-Kurt *et al.*, in 2020, reported[49] the synthesis of pyrimidine derivatives with apoptotic activity **44**-**46** *via* Suzuki coupling of chloro pyrimidine and reacted the product with phenyl isocyanate derivatives or *via* reacting the chloro pyrimidine with phenyl isocyanate derivatives and then reacting the produced compound with amines (Scheme 16). Compound **45** exhibited the highest cytotoxic activity against SW480 cancer cell line with IC_{50} value of 11.08 µM using normal cell as a control.

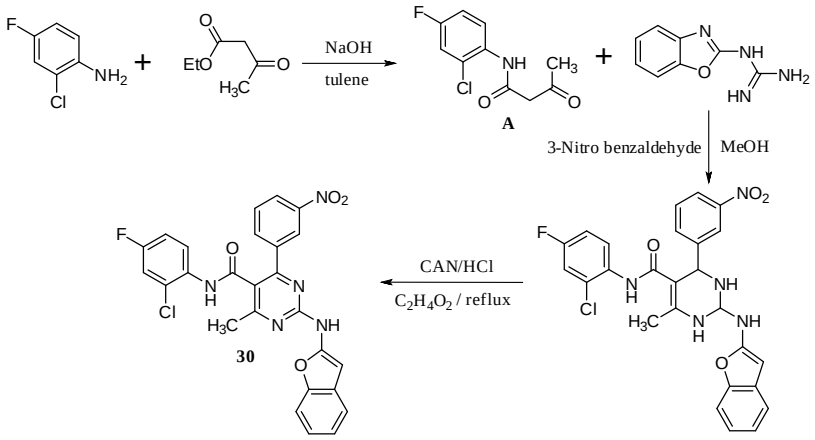
One year later, we prepared[50] fused pyrimidine analogues **47** and **48** and assigned their anticancer activity against nine types of cancer on approximate sixty cell lines *via* the reaction of 2-amino-3-cyanochromenes with either formic acid or formamide (Scheme 17).

Also, during 2021, V.N Madia *et al*.,[51] synthesized new antitumor agents **49** and **50**, against breast cancer, colon cancer and glioblastoma, through several steps. These steps involved refluxing 2,6-dichloropyrimidine-4-amines with different anilines in 2-methoxyethanol and the produced compounds were further reacted with appropriate amines by microwave reaction to afford compounds **49**. Finally, compounds **49** were alkylated by refluxing them with *p*-fluorobenzyl bromide in DMF to obtain compounds **50** (Scheme 18). Compared to the reference standard, N^4-(4-chlorophenyl)-N^2-[3-(diethylamino)propyl]pyrimidine-2,4,6-triamine (RDS 3422), the synthesized compounds recorded the highest potency with EC_{50} ranging from 4 to 8 µM, 4-13 times more active of hit.

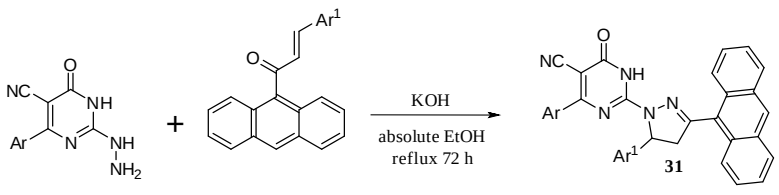
Recently, Abdelrehim and El-Sayed reported[52] the synthesis of pyrimidine thione derivatives **51** *via* the reaction of chalcones with thiourea in basic media. They also heated the product with ethylchloro acetate to produce the S-alkylated products **52**. To provide pyrimidine-3-ones **53**, they refluxed **52** in alkaline media using ammonia. For building up benzylidene thiazolopyrimidine-3-ones **54**, compounds **53** were heated under reflux with benzaldehyde in presence of freshly prepared sodium acetate as a catalyst. Iso-oxazolo derivatives **55** were obtained *via* heating **54** under reflux with hydroxyl amine. HCl in presence of freshly prepared sodium acetate as a catalyst (Scheme 19).



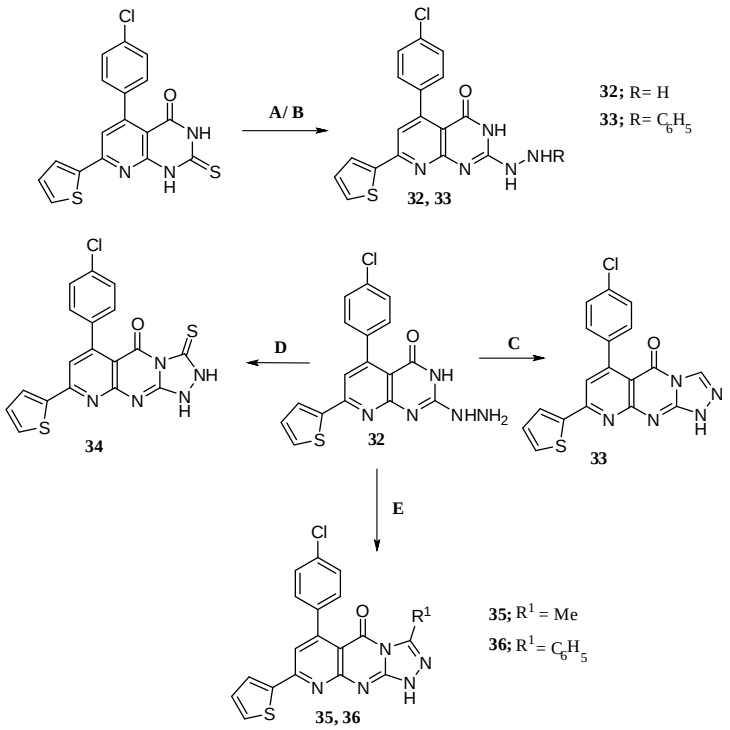
Scheme 8. Synthetic pathways of compounds 25-29.



Scheme 9. Synthetic pathway of compound 30.



Scheme 10. Synthetic pathway of compound 31.



(A) $NH_2NH_2.H_2O$, n-butanol, reflux 15 h **(B)** phenylhydrazine, absolute EtOH, reflux 15 h
(C) N, N-dimethyl formamide, reflux 3h **(D)** CS_2, KOH, absolute EtOH, reflux 5 h
(E) acetyl and/or benzoyl chloride, dry pyridine, reflux 20 h

Scheme 11. Synthetic pathways of compounds 32-36.

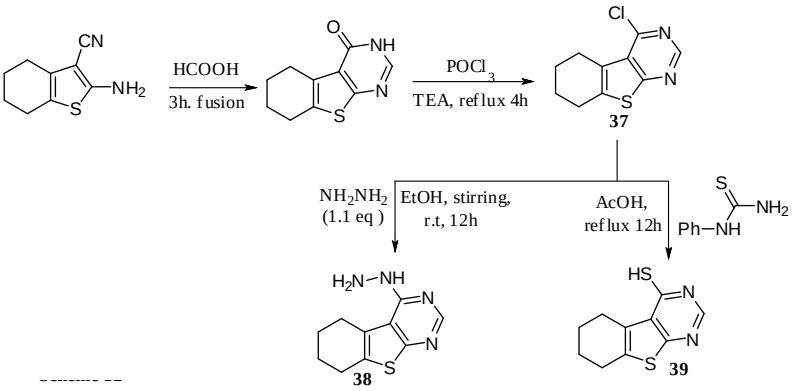
In addition to the anticancer compounds **51-55**, other compounds like **56-58** with antitumor activity against both hepatocellular and colon carcinoma were also produced. Among these compounds, compound **56** exhibited the highest activity on both HCT-116 and HepG-2 cell lines with (IC_{50} = 14.27 and 19.85 µM) compared to the reference standard Vinblastine (IC_{50} = 12.98 and 15.12 µM) respectively, the other compounds showed considerable activities.

Also, during 2022, M. Al-Anazi and coworkers synthesized[53] anticancer agents with EGFR inhibition **59** *via* cyclization of chalcones, through their reaction with thiourea using KOH as a basic catalyst and ethanol as a solvent (Scheme 20). The derivative in which R is a thiophene moiety and X is NH recorded the highest potency against MCF-7 cell line (IC_{50} 5.5 ± 0.07 µM) using tamoxifen as a reference (IC_{50} 26.95 ± 3 µM).

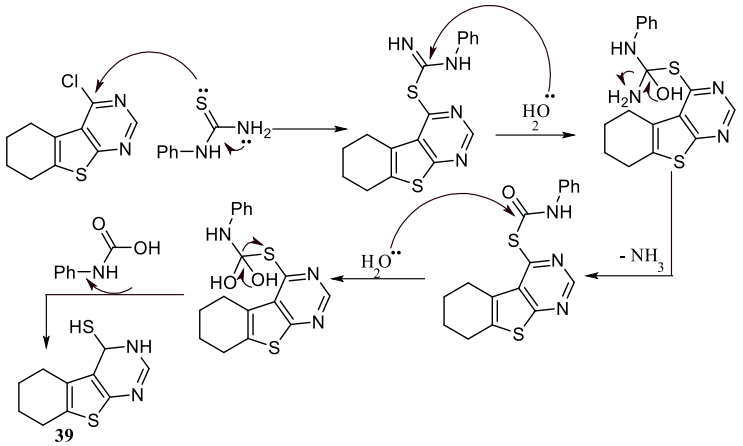
During the same year, some thiazolopyrimidines with antitumor activity **60** are produced *via* refluxing thiazole-carboxamide derivatives with trifluoroacetic anhydride. The synthesized compounds **60** then reacted with $POCl_3$ and /or PCl_5 and the products were reacted with different amine to obtain **61** and **62** respectively, these compounds showed potential activity against prostate, breast cancer and melanoma (Scheme 21).[54] All of these compounds are tested against nine types of cancer on sixty cell line and exhibited complete cell death on leukemia, ovarian, renal and CNS cancer with % growth ranged from -88.95 to -5.14.

Also, during 2022, P.S. Bhale *et al*., reported[55] the synthesis, anticancer and anti-inflammatory activity of 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles **(63)** *via* cycloaddition of 2-(1-methyl-1*H*-indol-3-carbonyl)-3,3-bis(methylthio) acrylonitriles with guanidine in alkaline media (Scheme 22). Compounds in which R=CN and R^1= NH_2, Me or phenyl recorded significant anti-breast cancer activity on MCF-7 cell line with GI_{50}= 2.0, 0.5 and 0.5 µM, respectively.

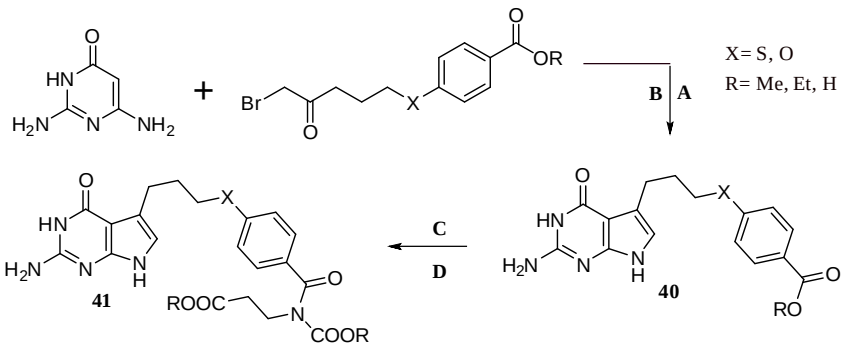
D.N. Bhogriddy and coauthors, synthesized[56] substituted isoxazole pyrazolo[1,5-a]pyrimidines **64** *via* Suzuki coupling of isoxazole derivatives with aryl boronic acid using DMF as a solvent and palladium chloride as a catalyst (Scheme 23). The preliminary anticancer activities of pyrimidine analogues **64** were tested against four human cancer cell lines, prostate cancer cell lines PC3 and DU-145, lung cancer cell line



Scheme 12: Synthetic pathways of compounds 37-39.

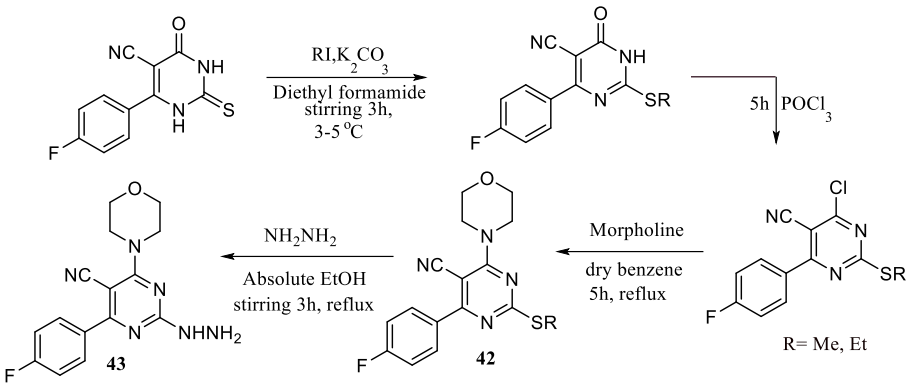


Scheme 13. Mechanism of formation of compound 39.

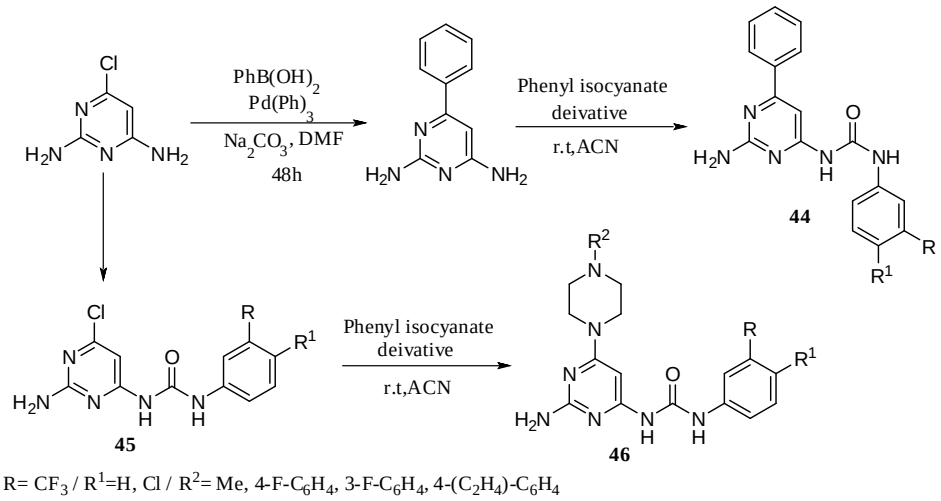


A= DMF, R.T, 3d **B**= NaOH **C**= *L*-glutamate diethyl ester, N-methyl morpholine-2-chloro-4,6-methoxy-1,3-triazine, DMF 12h **D**= NaOH 4h.

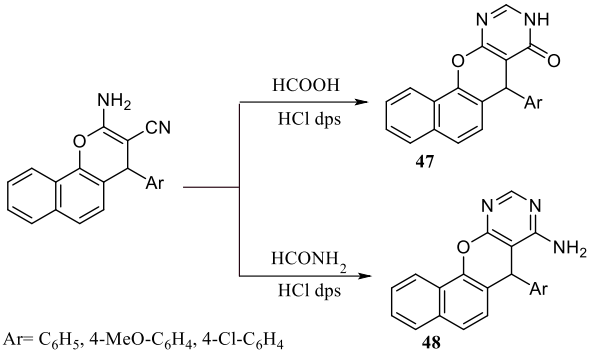
Scheme 14. Synthetic pathway of compounds 40 and 41.



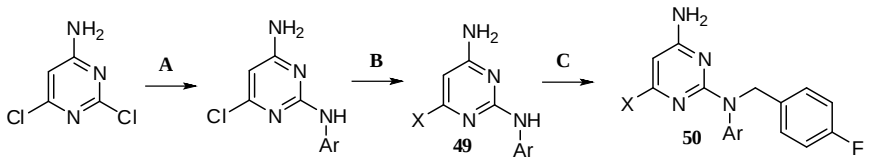
Scheme 15. Synthetic pathway of compounds 42 and 43.



Scheme 16. Synthetic pathways of compounds 44-46.



Scheme 17. Synthetic pathways of compounds 47 and 48.



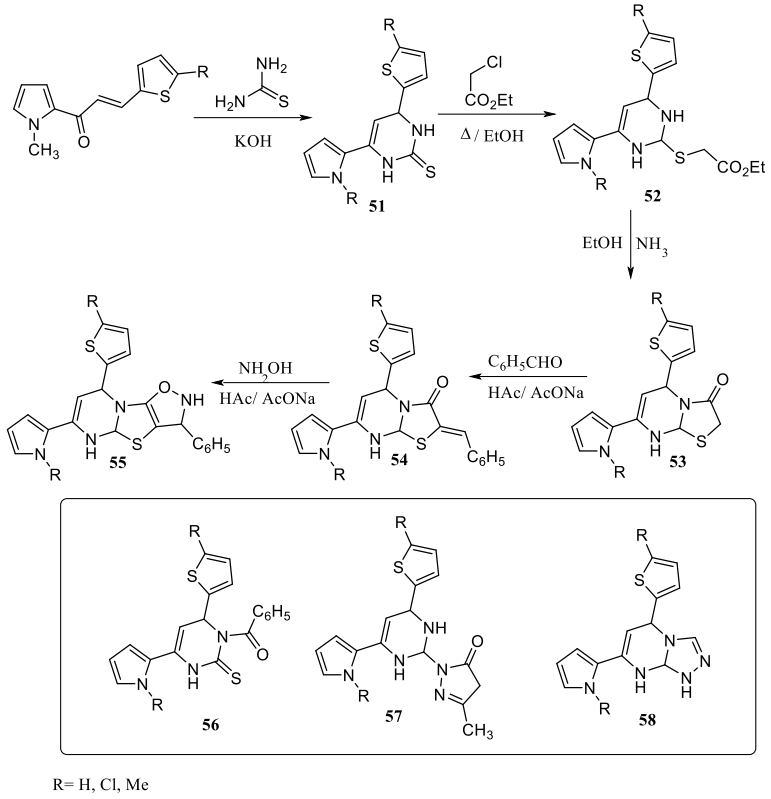
A= appropriate aniline, 2-methoxyethanol, reflux **B**= appropriate amine, N,N diethyl propane-1,3-diamine, K_2CO_3 dry, DMF dry

C= 4-Fluorobenzyl bromide, NaH, Cs_2CO_3

Ar= 3-F-C_6H_4, 4-F-C_6H_4, 3-MeO-C_6H_4, 3-NO_2-C_6H_4, 3-Cl-C_6H_4, 2-F-4-Cl-C_6H_3

X= 3-(diethylamino) propyl-amino, dipropylamino, 4-methyl-piperazine-1-yl

Scheme 18. Synthetic pathway of compounds 49 and 50.



R= H, Cl, Me

Scheme 19. Synthetic pathways of compounds 51-55 with examples of significant antitumor compounds.

A549 and breast cancer cell line MCF-7, compared with standard reference etoposide and the activities were promising.

Synthesis, anticancer evaluation and molecular docking of chalcone incorporated-indole-pyrimidine derivatives **65** as promising anticancer agents against breast, lung and prostate cancer were documented by R. Boddiboyena and coworkers[57]. The synthesis involved dissolving pyrimidine-2-carbaldehyde analogue in ethanol and then addition of certain ketones and heating the reaction mixture for 12 hours using few drops of pipridine as a catalyst (Scheme 24). Compounds **65** recorded remarkable antitumor activities against three types of cancer, breast, lung and prostate cancer, with IC_{50} ranged from 0.01 ± 0.005 µM to 14.6 ± 6.32 µM while the standard drug recorded IC_{50} 1.97 ± 0.45 to 3.08 ± 0.135 µM, respectively.

A. Casallas *et al.*, reacted[58] *β*-enaminones with aminopyrazoles under solvent and catalytic free conditions to produce pyrazolo[1,5-*a*] pyrimidines **66**

with promising activity against colorectal carcinoma (Scheme 25). The % cell viability of these compounds ranged from 62.0 to 70.1.

P.K.R. Cherukumalli and coauthors reported[59] the synthesis of urea derivatives of pyrimidine-pyrazoles **67** as tubulin binding protein inhibitors through the reaction of aminopyrazolo derivatives with aryl isocyanate using tetrahydrofuran as a solvent at room temperature for 12 hours (Scheme 26). Derivative **67** (Ar= 3,5-dinitrophenyl) recorded the highest potency with IC_{50} = 0.032, 0.01, 0.083 and 0.65 µM compared to etoposide (IC_{50} = 2.11, 3.08, 0.13 and 1.31 µM) on MCF-7, A549, Colo-205 and A2780 cell lines, respectively.

Synthesis of new pyrimidine analogues **68** with antitumor activity through inhibition of both EGFR and vascular endothelial growth factor (VEGF) was reported by A.M. El-Naggar *et al.*,[60] *via* the reaction of chalcones with either guanidine or thiourea in basic media. The products were further undergone alkylation through the reaction with different halo compounds to give series of active derivatives **69** (Scheme 27). Compound **69** (Ar= 4-Me-C_6H_4, X= N and R= NH_2) showed very strong antiproliferative effects towards all the five studied cell lines (HepG-2, MCF-7, MDA-231, HCT-116, and Caco-2) with IC_{50} values of 3.74, 7.81, 4.85, 2.96, and 9.27 µM, respectively. Also, it exhibited the highest inhibitory activities against both EGFR and VEGF (IC_{50} = 0.071 and 0.098 µM) compared to the two reference drugs, erlotinib ($IC5_0$ = 0.063 µM) and sorafenib (IC_{50} = 0.041 µM), respectively.

To obtain new thioxopyrimidines **70** and **71** as cyclin-dependent kinases (CDKs) A.A. El-Sayed and coauthors[61] refluxed either isothiocyanates with cyanoacetamide in dry acetonitrile or picolinic acid analogues with acetic anhydride respectively (Scheme 28). Compound **70** recorded a weak potency on HCT116 and MCF-7 cell lines with IC_{50} values 58.37 and 66.28 µM respectively, while compound **71** showed an excellent potency on the same cell lines with IC_{50} values 11.64 and 8.97µM respectively compared to doxorubicin (IC_{50} = 11.64 and 8.97µM, respectively).

1n 2022, B. Farag and coworkers[62] reported the synthesis of pyridopyrimidines **72** through the reaction of 4(6)-aminouracil with arylidinemalononitriles or ethyl arylidinecyanoacetate in acetic acid. On the other hand, changing the solvent to ethanol in presence of few drops of pipridine and reacting 4(6)-aminouracil with ethyl-4-nitrobenzylidinecyanoacetate compound **73** was obtained which was further reacted with 2^{ry} amines to afford **74** (Scheme 29). The tumor activity of all compounds was assessed towards the hepatic cancer (HepG-2), Colon Cancer (HCT-116) and human mammary carcinoma (MCF-7) cell lines and recorded a broad-spectrum activity compared to the standard drugs, 5-fluourcail, MTX and doxorubicin.

During the same year, F. Islam *et al.,* reacted[63] chlorothienopyrimidine with different aniline derivatives using toluene as a solvent to obtain thienopyrimidines **75** with anticancer activity *via* targeting microtubules (Scheme 30). These compounds were tested against nine types of cancer on approximate sixty cell lines and recorded significant activity. Some of these compounds showed higher potency than the lead compound paclitaxel and circumvented drug resistance mediated by Pgp and βIII-tubulin and could be candidates for preclinical studies.

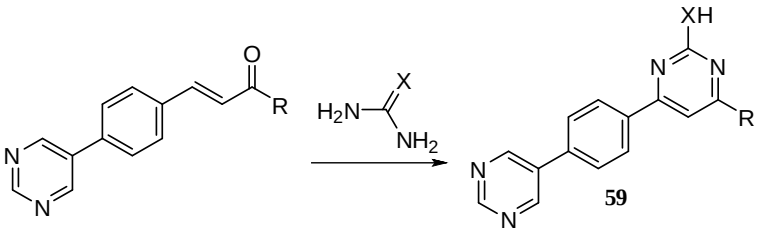
To obtain anticancer agents **76**, with less cytotoxicity on normal cells, P.A. Jose and coauthors[64] refluxed aminopyrimidine analogue with 2-hydroxy-5-nitrobenzaldehyde through Schiff's base reaction (Scheme 31). Compared to cisplatin, compound **76** recorded less anticancer activity. To destroy the cancer cells 33 mg/mL of compound **76** was needed, but for cisplatin only 8 mg/mL was needed. However, against normal NHDF cells, compound **76** compared to cisplatin ten times less toxicity was found.

Anti-breast cancer compounds **77**, were synthesized by S. Lin *et al.*,[65] *via* the reaction of chloro atom on pyrimidine nucleus with different amines using triethyl amine as a catalyst and tetrahydrofuran as a solvent. The reaction showed replacing the chloride atom with alkyl moiety (Scheme 32). Compound **77** (R= morpholine) recorded the highest inhibition activity against EGFR compared to the other compounds and the reference standard ola, where the % inhibition at 0.1 µM was 92.11% ± 2.24.

Also, during 2022, H.S. Mohamed and coauthors reported[66] the cyclo condensation of diamino triazoles with different chalcones using DMF as a solvent and KOH as a catalyst to afford the corresponding triazolo pyrimidines **78** which showed tubulin polymerization inhibitions (Scheme 33). Some derivatives of **78** exhibited higher potency than CA-4 with IC_{50} ranging from 0.53 to 6.55 µM, compared to 6.65 µM of CA-4 against colon cancer HCT-116 cell line. Other exhibited IC_{50} comparable to CA-4.

M.A. Mansour and coworkers, during the same year, refluxed[67]amino cyano-furan with formic acid in presence of acetic acid to obtain furopyrimidine analogue **79**. The acetyl furopyrimidine derivative **79** was further stirred with certain aldehydes to afford chalcone based pyrimidines **80** with potential anticancer activity (Scheme 34). Compounds **80** ((Ar= 4-chlorophenyl or Ar= 4-bromophenyl) demonstrated potent anti-proliferative activity against approximate sixty cell lines, with mean GI_{50} values of 2.41 µM and 1.23 µM, respectively. Also, both compounds recorded pronounced cytotoxic activity (1.20 ± 0.21 and 1.90 ± 0.32 µM, respectively) against MCF-7 cell line when compared to doxorubicin; 3.30 ± 0.18 µM.

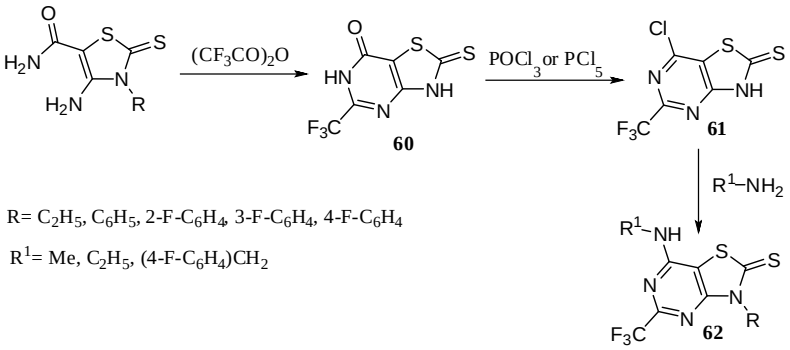
Also, during this year, A.S. Shaikh *et al.*, reported[68] the synthesis of pyrimidin-2-yl acetamide



R= C_6H_5, 4-MeO-C_6H_4, 4-F-C_6H_4, C_4H_4S

X= S, O, NH

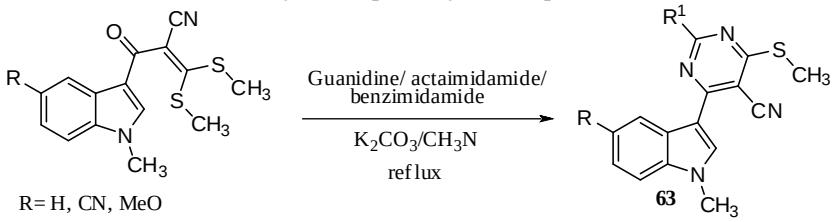
Scheme 20. Synthesis of compound 59.



R= C_2H_5, C_6H_5, 2-F-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4

R^1= Me, C_2H_5, (4-F-C_6H_4)CH_2

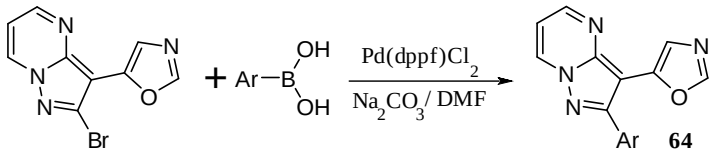
Scheme 21. Synthetic pathways of compounds 60-62.



R= H, CN, MeO

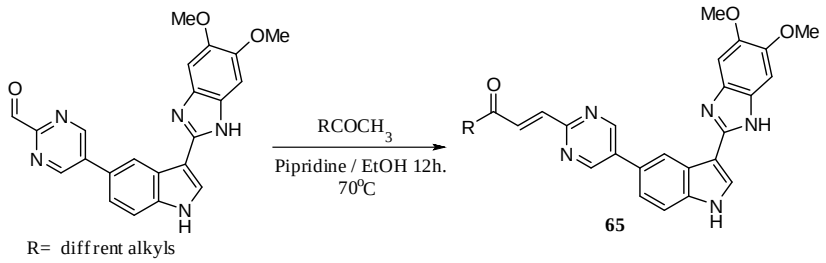
R^1= NH_2, Me, C_6H_5

Scheme 22. Synthetic pathway of compound 63.

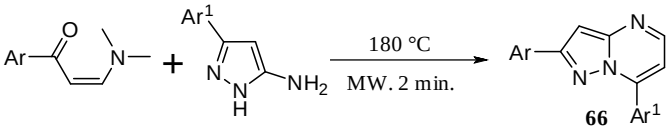


Ar= 4-MeO-C_6H_4, 4-CN-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 3,4,5-$(MeO)_3$-C_6H_2, 3,5-$(MeO)_2$-C_6H_3, 4-MeO-3,5-$(NO_2)_2$-C_6H_2

Scheme 23. Synthetic pathway of compound 64.

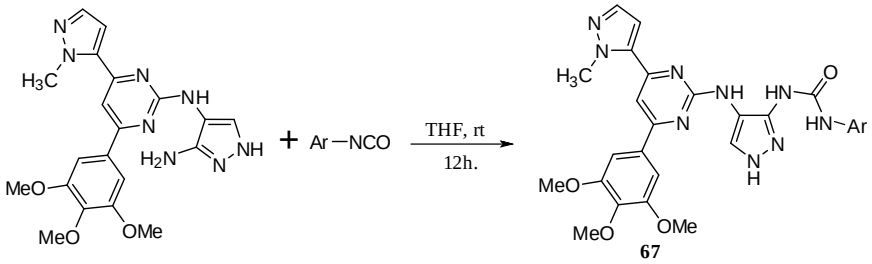


Scheme 24. Synthetic pathway of compound 65.



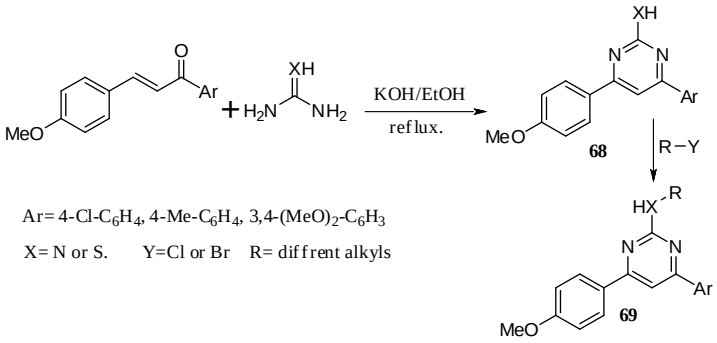
Ar, Ar^1= C_6H_5, 4-MeO-C_6H_4, 4-Cl-C_6H_4

Scheme 25. Synthetic pathway of compound 66.



Ar= C_6H_5, 4-MeO-C_6H_4, 4-CN-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 3,4,5-$(MeO)_3$-C_6H_2, 4-Me-C_6H_4, 3,5-$(MeO)_2$-C_6H_3, 3,5-$(NO_2)_2$-C_6H_3

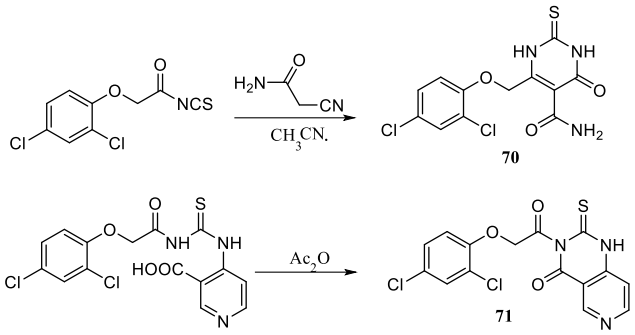
Scheme 26. Synthetic pathway of compound 67.



Ar= 4-Cl-C_6H_4, 4-Me-C_6H_4, 3,4-$(MeO)_2$-C_6H_3

X= N or S. Y=Cl or Br R= diffrent alkyls

Scheme 27. Synthetic pathway of compounds 68 and 69.



Scheme 28. Synthetic pathways of compounds 70 and 71.

analogues **81** were further coupled with oxadiazole derivatives to afford DNA intercalative topo II inhibitors **82** (Scheme 35). Compound **82** (Ar= phenyl and Ar^1= 4-fluorophenyl) among these compounds recorded the highest potency with IC_{50} values 0.02 and 0.02 µM on A549 and PC-3 cell lines, respectively compared to doxorubicin (IC_{50} = 1.79 and 1.24 µM).

To obtain anti-EGFRs **83** and **84**, T. Wang and coauthors[69] refluxed substituted chlorothieno-pyrimidines, separately, with different 2ry amines and /or phenols. The reaction involved replacing the chloro atom with either N alkyl or O aryl moiety (Scheme 36). Compounds **83** and **84** were tested for their cytotoxic activity against Hela and A549 cancer cell lines in which EGFR is highly expressed. Compounds **84** recorded excellent activity against Hela and A549 cancer cell lines compared to the lead drug olmutinib. The preliminary structure activity relationship revealed that the introduction of oxygen substituents was more favorable for anticancer activity.

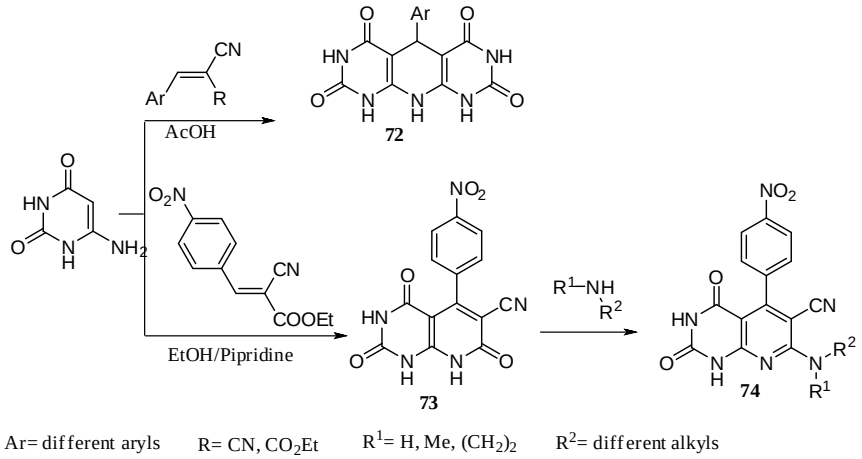
Finally, I. Zaki and coworkers[70], refluxed 4-(N, N dimethyl) benzaldehyde with thiourea and ethyl cyanoacetate to afford substituted mercapto-cyano-pyrimidinone **85**. The substituted mercapto-cyano-pyrimidinone 85 was treated with various reagents like, methyl iodide, methyl acrylate, ethyl chloroacetate, N-aryl-2-chloro acetamide and 2-(2-chloroactamido) carboxylic acid to give antitumor compounds **86-90**, respectively (Scheme 37). All compounds were assessed for their cytotoxic activity and from these compounds, derivative **88** (Ar=2-chlorophenyl) and compound **90** (n=ethyl benzene) recorded good cytotoxic activity against HepG2 cells compared with Sorafenib as a reference standard. Also, the two compounds showed potent inhibition of VEGFR-2 with IC_{50} value 0.067 and 0.44 µM.

Synthesis And Reactions of Pyrimidines with Antiviral Activity

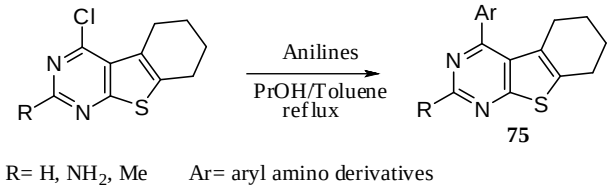
1n 2018, A. Abu-Hashem and co-authors prepared[71] fused pyrimidine analogues **91** with anti-herpes simplex virus-1 and human immune deficiency virus-1 *via* refluxing amino-cyano heterocyclic compound with carbon disulfide (CS_2) to obtain pyrimidine dithiones which were further treated with different reagents (Scheme 38). For anti-herpes simplex virus-1, the synthesized compounds exhibited comparable activities with IC_{50} values of 0.25, 0.24 and 0.23 µM respectively, compared to the reference aphidicolin (IC_{50} = 0.15 µM). Moreover, they showed higher potency against human immune deficiency virus-1 (IC_{50} = 20.2, 10.5 and 14.1 µM) than the reference standard AZT (IC_{50} = 33.8 µM)

During the same year, the synthesis of pyrazolo[2,3-*d*]pyrimidine derivatives **92** with antiviral activity against tobacco mosaic virus was reported[72] through several steps. The first step involved addition on the amino group and then the second step showed cyclo condensation and formation of aminopyrimidine analogues. Finally, the amino moiety was allowed to react with different aldehydes through Schiff's reaction (Scheme 39). Antiviral assay revealed that several of the derivatives showed significant activity against TMV. In particularly, the derivatives (R=R^1=H and Ar=pyridine) and (R=R^1=Me and Ar=thiophene) displayed excellent inhibitory activity against TMV, with EC_{50} values of 70.3 and 53.65 µg/mL, respectively, which were much better than that of ribavirin (150.45 µg/mL), and the second derivative was superior to ningnanmycin (EC_{50} = 55.35 µg/mL).

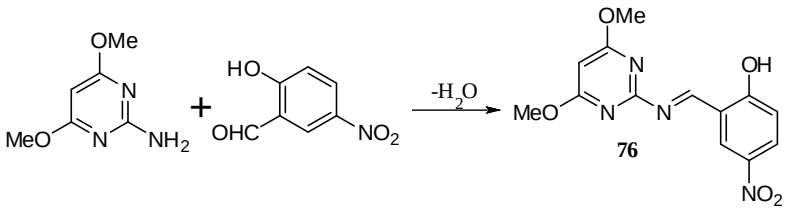
To obtain anti-influenza (H5N1) **93** and **94**, R.R. Khattab *et al.*, reacted[73] hydrazinyl thienopyrimidine derivative with certain aldehyde namely acetaldehyde and *p*-nitro benzaldehyde which were further reacted with $FeCl_3$ in presence of ethanol and few drops of acetic acid (Scheme 40). The mechanism of formation of compound **94** was illustrated in the following scheme (Scheme 41). From these compounds, derivative **93** (Ar= 4-nitrophenyl) exhibited the most effective activity against influenza (H5N1) virus with % inhibition up to 64%.



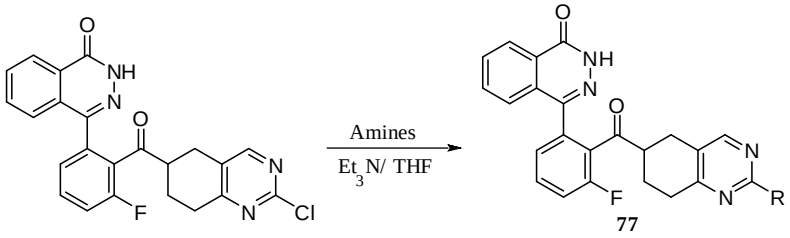
Scheme 29. Synthetic pathways of compounds 72-74.



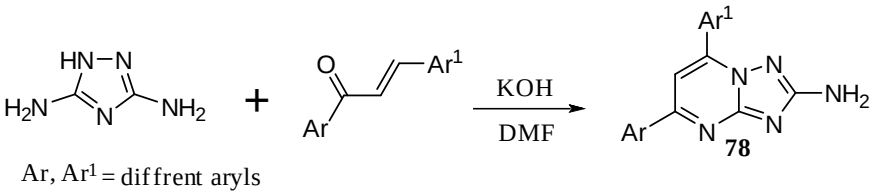
Scheme 30. Synthetic pathway of compound 75.



Scheme 31. Synthetic pathway of compound 76.

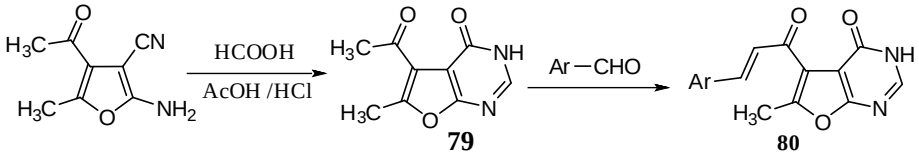


Scheme 32. Synthetic pathway of compound 77.



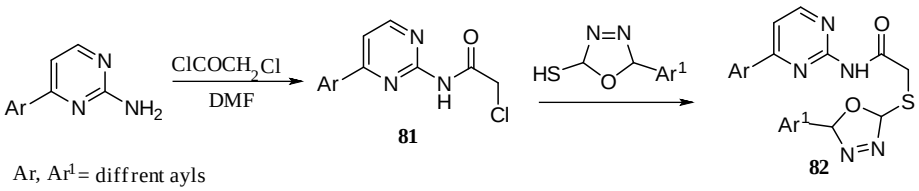
Ar, Ar^1 = diffrent aryls

Scheme 33. Synthetic pathway of compound 78.



Ar= C_6H_5, 4-F-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-MeO-C_6H_4, 4-N(Me)$_2$-C_6H_4, 2,4-$(Cl)_2$-C_6H_3, 2,4,5-$(MeO)_3$-C_6H_2, 2-MeO-4-OH-C_6H_3

Scheme 34. Synthetic pathway of compounds 79 and 80



Ar, Ar^1 = diffrent ayls

Scheme 35. Synthetic pathway of compounds 81 and 82.

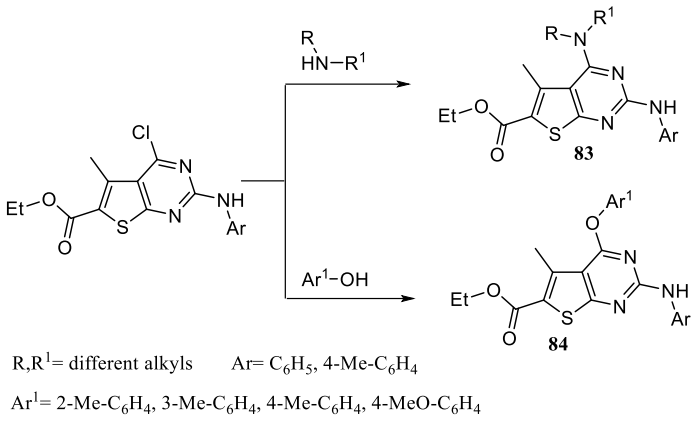
Also, during 2019, anti-gastroenteric viruses especially *Rotavirus* and *Coxsackievirus* was reported[74] by our co-authors *via* synthesis of pyrrolopyrimidine derivatives **95** and reaction of the product with $POCl_3$ and the produced compounds were further refluxed with different amine to afford **96** and **97** respectively (Scheme 42). Compounds **95-97** were tested for their antiviral activity against the two previously mentioned viruses and their results revealed that their activity were good as the % inhibition ranged from 56.7 to 88.2 % against *Rotavirus* and from 63 to 90% for *Coxsackievirus*.

After one year, J. Moesslacher *et al*., reacted[75] chloropyrimidine analogue with either tatrahydroquinoxaline or with tetrabutyle-1,4-diazepane carboxylate then refluxed the product with fluorobenzenesulfonyl chloride to get anti *chikungunya virus* compounds **98 (**Scheme 43). The two derivatives exhibited comparable antiviral activity with EC_{50} values of 77 ± 5 and 16 ± 1 µM and CC_{50} values of 202 ± 18 and 106 ± 69 µM, respectively with the reference standard *N*-ethyl-6-methyl-2-(4-(4-fluorophenylsulfonyl)piperazine-1-yl)pyrimidine-4-amine (EC_{50} = 8.7 ± 1 µM and CC_{50} = 122 ± 24 µM.

Also, during 2020, new pyrimidine derivatives with antiviral activity **99** were synthesized[76] by R.A. Azzam and coauthors *via* refluxing benzothiazole analogue with N,N-dimethylformamide dimethyl acetate and N-aryl sulfonated guanidine in multistep reaction then the produced aminopyrimidine sulfonamides **99** were further reacted with either bromo-4-substituted acetophenone or chloro diketons to obtain **100** and **101** respectively, (Scheme 44).

Compounds **99-101** recorded their antiviral activity against herpes simplex virus. In particularly, compounds **100** presented inhibitory activity against the Hsp90α protein with IC_{50} in the range of 4.87−10.47 µg/mL. Combination of compounds **100** with acyclovir showed IC_{50} values lower than that of acyclovir alone.

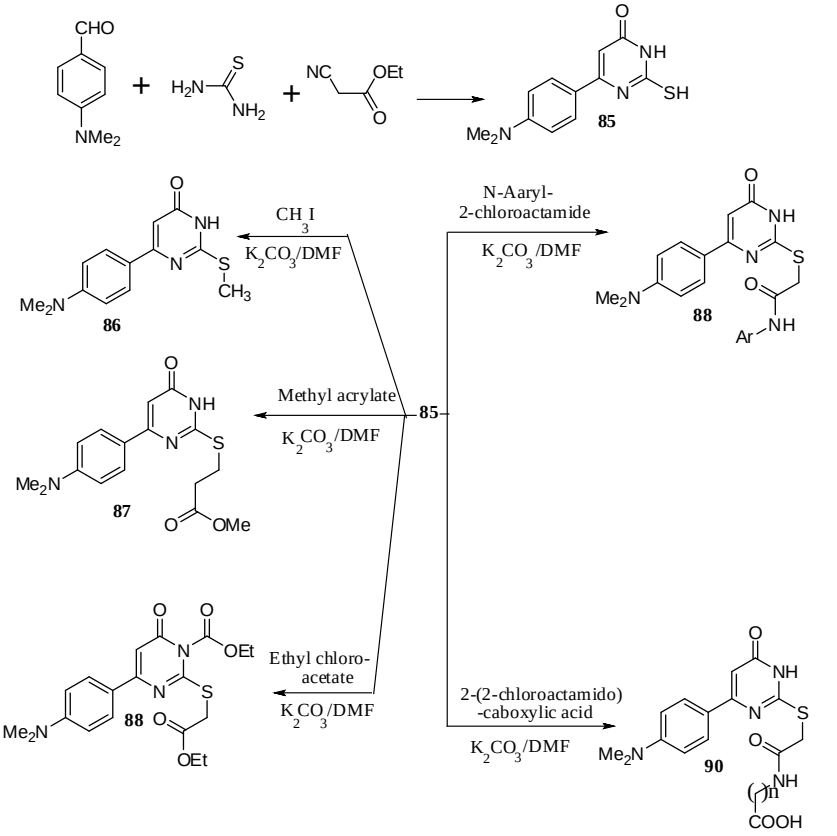
To obtain antivirals especially anti-herpes simplex virus, S.M. Hassan *et al.*, during the same year refluxed[77] thiopyrimidinone derivatives with thionly dichloride and the produced chloro-analogues reacted with different amine to get thiopyrimidinone analogues **102** then resulted compounds were further refluxed with different reagent in different condition and afforded **103-109** (Scheme 45). These compounds exhibited potent



R,R^1= different alkyls Ar= C_6H_5, 4-Me-C_6H_4

Ar^1= 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4

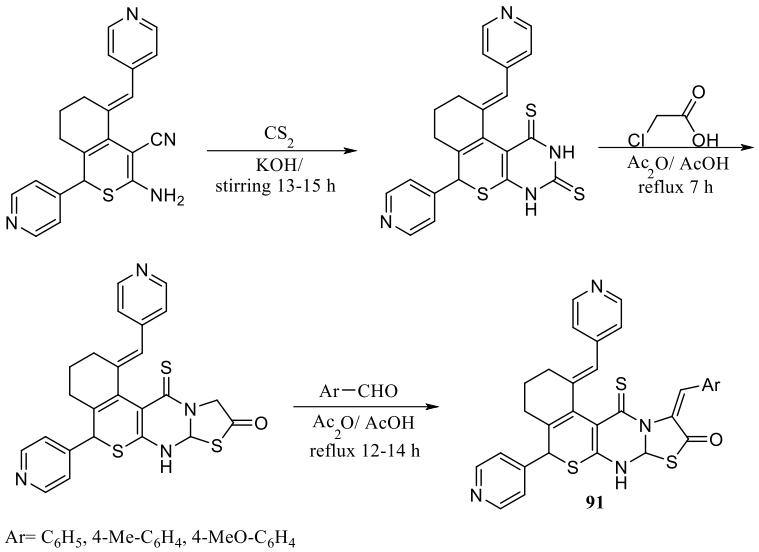
Scheme 36. Synthetic pathways of compounds 83 and 84.



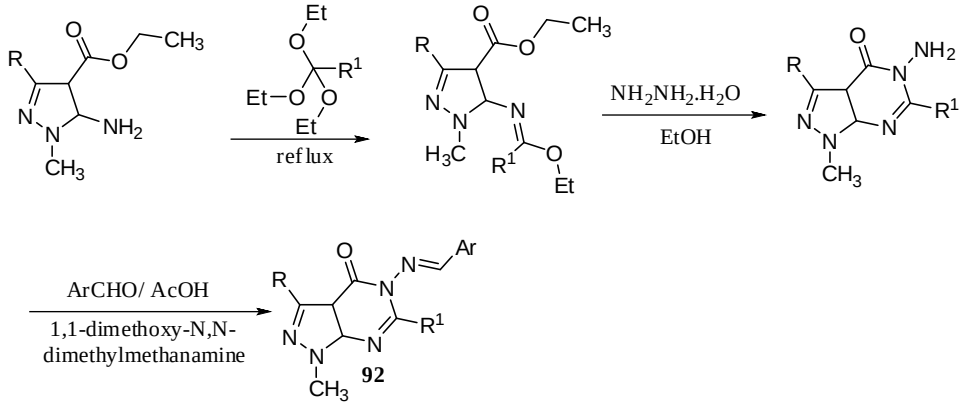
Ar= 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4,4-Me-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 3,5-$(Me)_2$-C_6H_3, 4-COMe-C_6H_4

n= CH_2, CH_2CH_2, -CHMe, -$CHCH_2$Ph

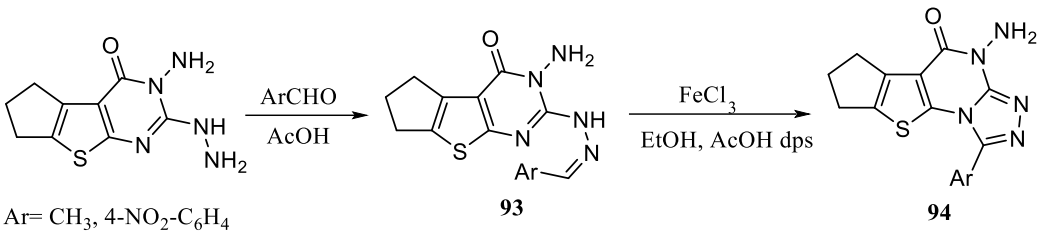
Scheme 37. Synthetic pathways of compounds 85-90.



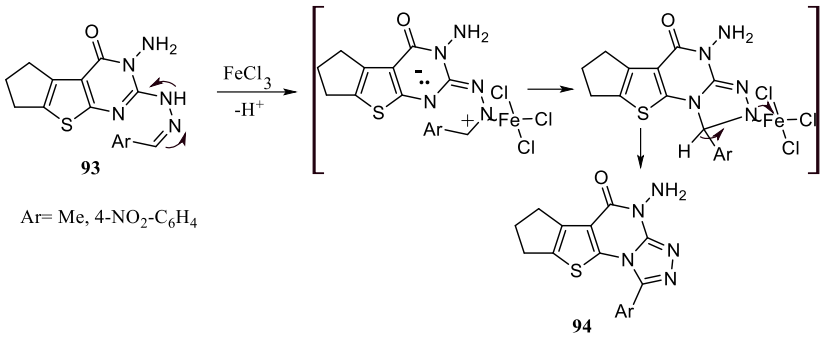
Scheme 38. Synthetic pathway of compounds 91.



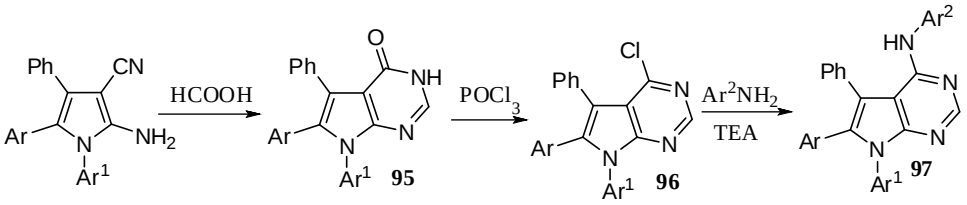
Scheme 39. Synthetic pathway of compound 92.



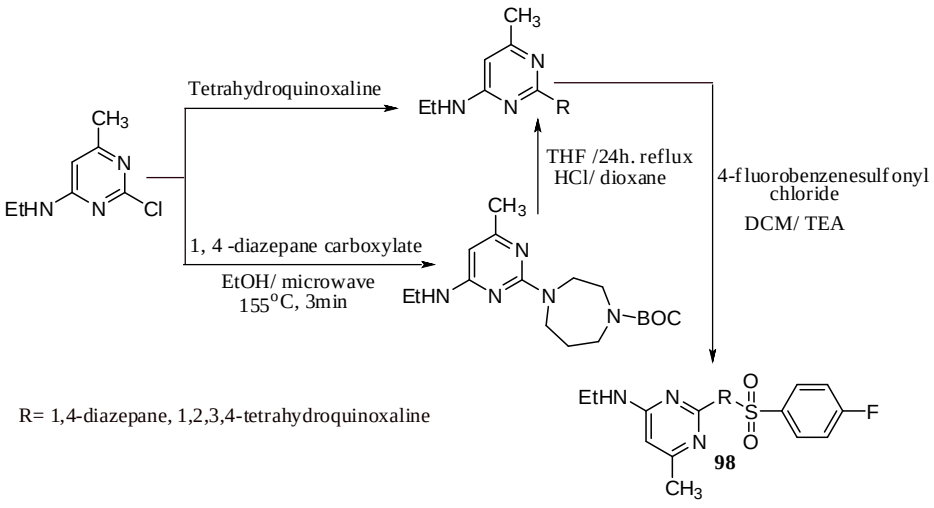
Scheme 40. Synthetic pathways of compounds 93 and 94.



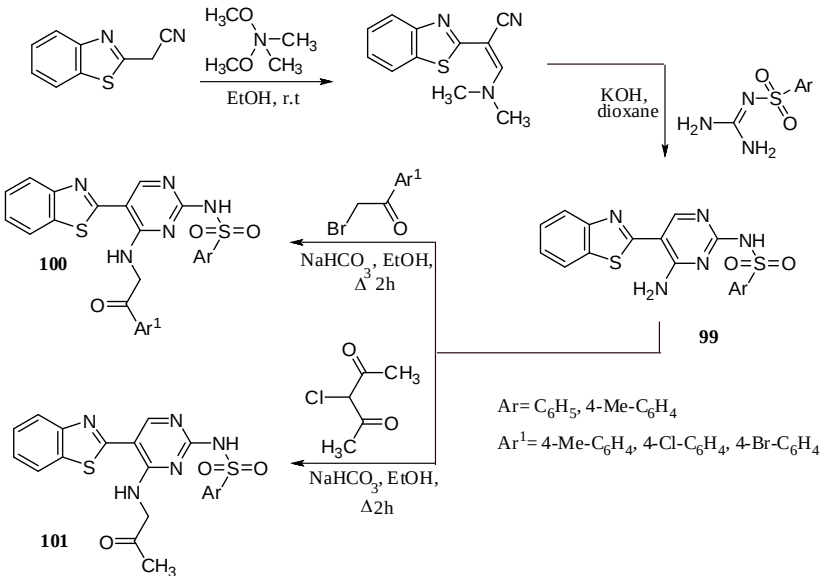
Scheme 41. Mechanism of formation of compound 94.



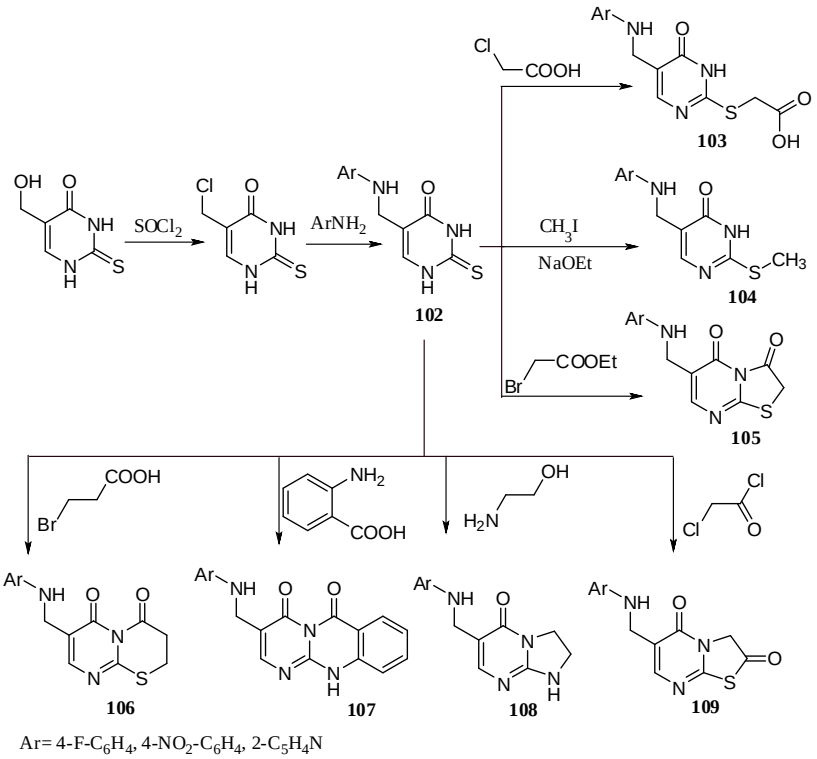
Scheme 42. Synthetic pathways of compounds 95-97.



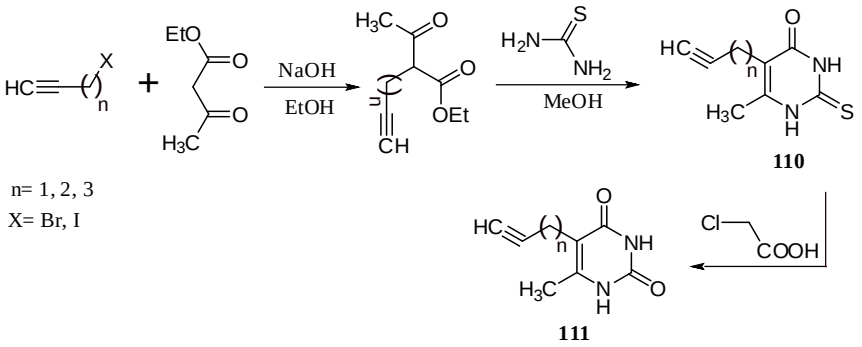
Scheme 43. Synthetic pathways of compound 98.



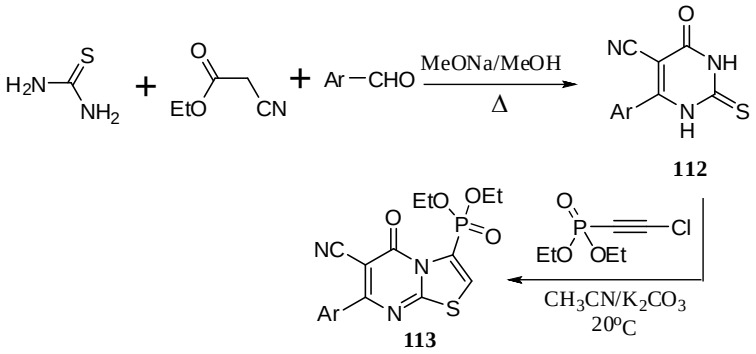
Scheme 44. Synthetic pathways of compounds 99-101.



Scheme 45. Synthetic pathways of compounds 102-109.

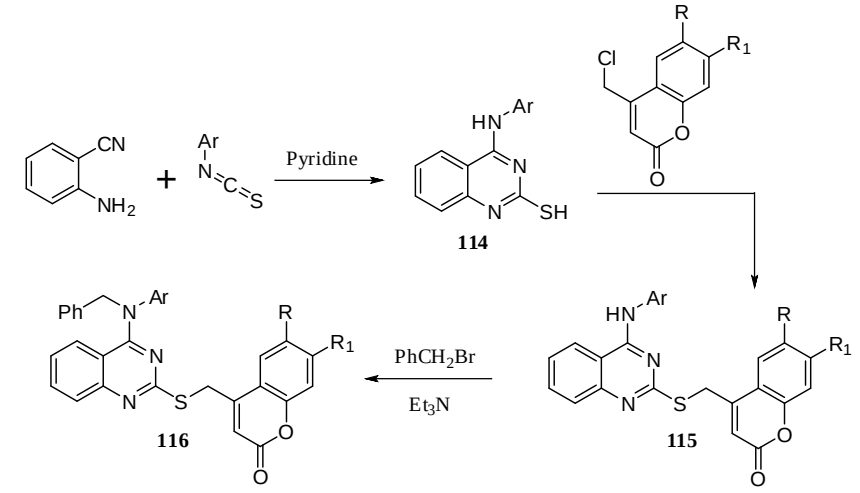


Scheme 46. Synthetic pathways of compounds 110 and 111.



Ar= 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-MeOCO-C_6H_4

Scheme 47. Synthetic pathways of compounds 112 and 113.



Ar= different aryls R= H, Me, t.Bu, OMe R^1 = H,OH, OMe

Scheme 48. Synthetic pathways of compounds 114 - 116.

activity especially, compound **102** (Ar= pyridinyl) and compound **103** (Ar= 4-flourophenyl) with EC_{50} values of 27.68 and 23.67 µg/mL respectively, compared with acyclovir (EC_{50} = 17.42 µg/mL).

One year later, O.V. Andreeva *et.al*, reported[78] the synthesis of alkyne thiopyrimidine derivatives **110** through the reaction of halo alkynes with ethylacetoacetate and thiourea in a multistep procedure then the produced thiopyrimidines were refluxed with chloroacetic acid to afford pyrimidinone derivatives **111** (Scheme 46). These compounds recorded potent antiviral activity against both H1N1 and *coxsackievirus* B3 especially derivative **110** (n= butenyl) with IC_{50} values of 34 and 15 µM, respectively compared to the reference standards rimantadine, ribavirin and oseltamivir carboxylate for H1N1 also, ribavirin and pleconaril for coxsackievirus B3.

Recently, A.A. Babushkina and coauthors reported[79] the synthesis and anti-influenza A virus (H1N1) of 6-aryl-5-cyano-2-thiouracil **(112)** *via* one pot three components addition of thiourea, ethyl cyanoacetate and aldehydes. The products were undergone phosphonylation by the reaction with diethyl chloroethynylphosphonate to afford **113** (Scheme 47). These compounds exhibited promising antiviral activity (IC_{50} ranged from 77 to 300 µM) with low cytotoxicity (CC_{50} > 1000 µM) in some derivatives.

To obtain antiviral compounds **114-116** with broad spectrum activity against both hepatitis C (HCV) and chikungunya (CHIKV) viruses, J.R. Hwu *et.al.*, designed[80] quinazoline-4-amines derivatives and then coupled them with coumarins *via* a S-CH_2 linkers. The products were further treated with benzyl bromide (Scheme 48). The antiviral testing revealed that five derivatives inhibited chikungunya virus with EC_{50} values as potent as 1.96 mM and two conjugates inhibited hepatitis C virus with EC_{50} values as low as 16.6 mM. These conjugates possess a xylene substituent at the C-4 amino group of quinazoline and a t-butyl substituent at the C-6 position of coumarin.

CONCLUSION

This review highlights the various strategies and pathways for the synthesis of pyrimidines and their fused analogues. Also, it discusses the anticancer value and antiviral activity of pyrimidine moiety bearing compounds.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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