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Review Article

Synthetic Methodologies of Anticancer Active Pyrimidines: Update From 2015-Till Date

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Abstract

Pyrimidine and its analogues possess a significant role in medicinal chemistry due to exhibiting pharmacological relevance. Cancer is among the most costly and deadly healthcare burdens globally, and investigation on synthesis of new anticancer agents is an important subject of the current research all over the world. In this mini-review, the authors updated the research literature pertaining to the synthetic methodologies of various pyrimidine derivatives exhibiting anticancer activity. The mini-review is a collection of significant contributions done during Mid 2015-December 2022.

Keywords

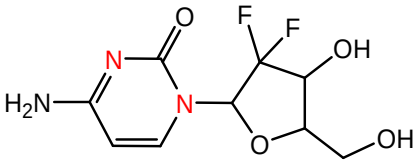
Pyrimidines; Pharmacological activity; Synthesis; Anti-tumor.

Introduction

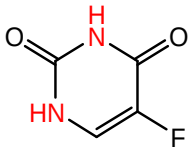
Pyrimidine and its analogues possess a significant role in medicinal chemistry due to exhibiting pharmacological relevance i.e. plant growth regulatory, herbicidal, antihypertensive, anticancer, antimicrobial, anti-inflammatory, and antioxidant activity.[1-9] Pyrimidines are the building blocks of many natural compounds such as vitamins, liposaccharides, and antibiotics.[10-15] This obviously inculcates researchers who wish to further explore synthesis and pharmacological evaluation of pyrimidine derivatives. Some important pyrimidine derived drugs which already exist in market having various biological activities were shown in Figure 1. Pyrimidine is the major component of nucleic acid chemistry and its derivatives were used in thyroid drug production and in the treatment of leukemia.[16-17] For the last five to six decades, this scaffold has been much explored by medicinal chemists for various pharmacological purposes such as anti-inflammatory,[18] anti-microbial[19-22] etc.

Anticancer activity

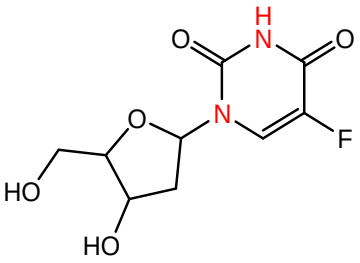
One of his areas is of great importance because it provides improved treatments for diseases such as cancer. Cancer is among the most costly and deadly healthcare burdens globally, and the International Agency for Research on Cancer has estimated that by the year 2030, the number of existing cancer cases will increase to 21.7 million globally. The number of annual global cancer deaths is also projectedto increase to 13 million by 2030 based on rates of population growth and aging. It isimportant to identify novel potent target molecules for the effectivetreatment of cancer. In recent years, many substituted pyrimidinederivatives possessinganticancer activity have been reported by various research groups including us.[23-29, 47]



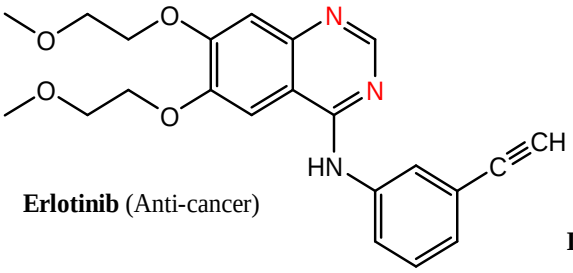
Gemcitabine (Anti-cancer)



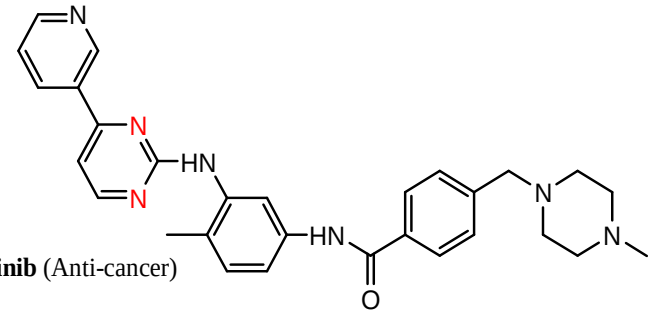
5-Flurouracil (Anti-cancer)



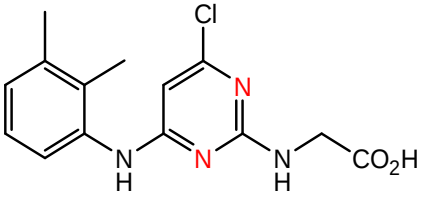
Floxuridine (Anti-cancer)



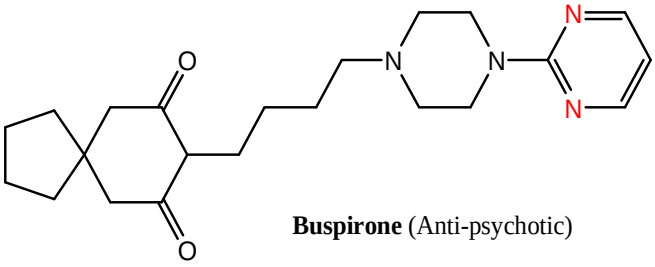
Erlotinib (Anti-cancer)



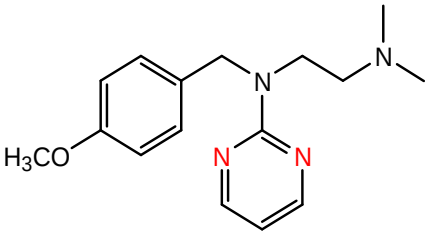
Imatinib (Anti-cancer)



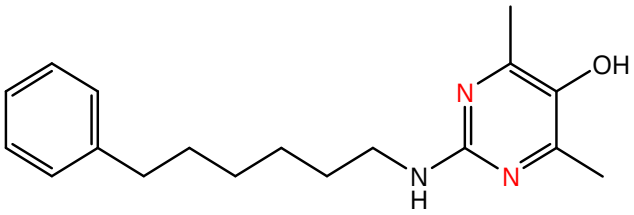
Aronixil (Anti-hyperlipidemic)



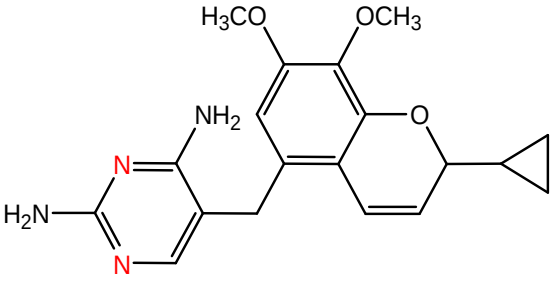
Buspirone (Anti-psychotic)



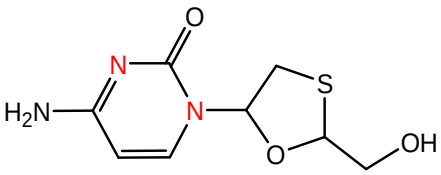
Thonzylamine (Anti-histaminic)



Enazadrem (Anti-psoriatic)



Iclaprim (Antibiotic)



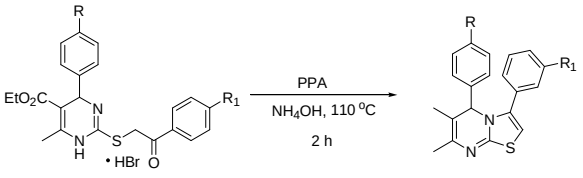
Lamivudine (Anti-HIV)

Figure 1: Marketed drugs having pyrimidine scaffold

Synthetic approaches of Pyrimidine scaffolds

Therefore, on the basis of previously above-mentioned biological activities exhibited by pyrimidines, many synthetic methodologies have been developed in an effort in the design and synthesis of new anticancer agents.[28-33]

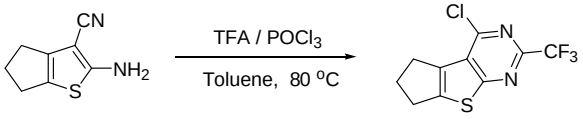
In recent years, thiazolopyrimidines have been of interest due to their vital role in many biological activities.Compound **5** was cyclodehydrated into the corresponding thiazolo[3,2-a]pyrimidine compound **6** by heating with freshly prepared polyphosphoric acid (PPA) followed by treating with ammonia solution (Scheme 1).[34] Structural modification of various thiazolo[3,2-a]pyrimidine analogues and their biological activity was studied. These compounds were found to possess antimicrobial, analgesic anti-inflammatory and anti-tumor activities.



5 6

Scheme 1: Synthetic route for compound 6

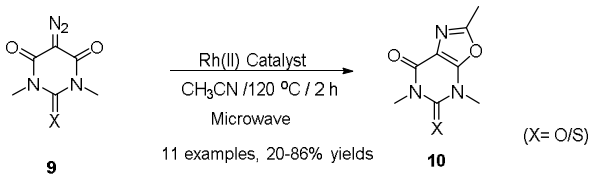
Trifluromethylthieno[2,3-d]pyrimidine Substituted 2-aminothiophene-3-carbonitrile **7** was converted into the corresponding trifluromethylthieno[2,3-d]pyrimidine scaffold **8** in excellent yield in the optimized reaction conditions (Scheme 2).[35]*In vitro* antitumor activity of the target compound resulted from treating ((*R*)/(S)--1-phenyl Ethanamine with compound **8**, against HepG2 (human hepatocellular liver carcinoma cell line) and MCF-7 (human breast cancer cell line) was evaluated by the standard MTT assay was evaluated in this protocol and Gefitinib was used as a positive control. In this (R)-enantiomer exhibited good antitumor property whereas (S)-enantiomer did not.



7 8

Scheme 2: Synthesis of trifluoromethyl thieno[2,3-d]pyrimidines

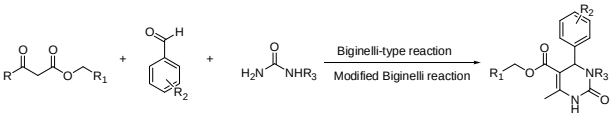
Oxazolo[5,4-d]pyrimidine-5,7-diones have attracted Krasavin and group' attention owing to possessing a wide range of pharmacological activities. They investigated treating 5-diazo-barbituric acids **9** with nitriles, resulting in the synthesis of oxazolo[5,4-*d*]pyrimidine-5,7-diones **10** by using Rh^{II}-catalyzed cycloaddition under microwave conditions (Scheme 3).[36] Sulfonyl-azide-free (SAFE) diazo transfer and $Rh_2(esp)_2$-catalyzed cycloaddition were the key features of this methodology.



9 10

Scheme 3: **Cycloaddition of 9 with acetonitrile**

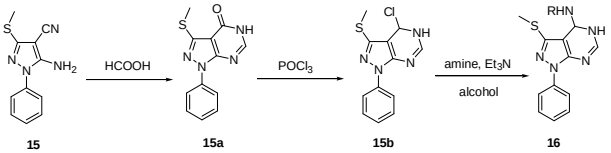
Heravi et al. reviewed recent advances in Biginelli-type reactions, particularly, for the synthesis of poly-functionalized pyrimidines using multicomponent reactions (MCRs) involving formation of dihydropyrimidine 14, from urea and its derivatives 13, β-keto esters 11, and aryl aldehyde 12(Scheme 4).[37] And also, have glimpses of the biological activity exhibited by products emerging from Biginelli-Type Reactions (BTRs) or modified Biginelli reactions (MBRs).



11 12 13 14

Scheme 4: Synthetic routes for pyrimidine and its analogues

A new series of 3-(methylthio)-1-phenyl-*1H*-pyrazolo[3,4-d]pyrimidine derivatives (**16**) was synthesized sequentially from compound **15** (Scheme 5) by Hamada and his group.[38] All these compounds (twenty nine) were evaluated for antitumor activity against human breast adenocarcinoma cell line MCF7. Among 29 compounds tested, 10 were shown to possess mild to moderate activity compared with doxorubicin as a reference drug.

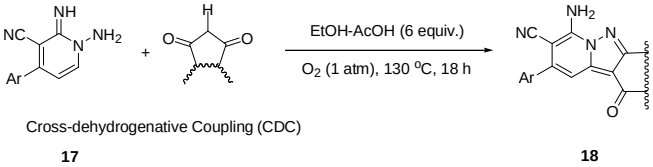


15 15a 15b 16

Scheme 5: Synthetic routes for substitute pyrazolo[3,4-d]pyrimidine derivatives

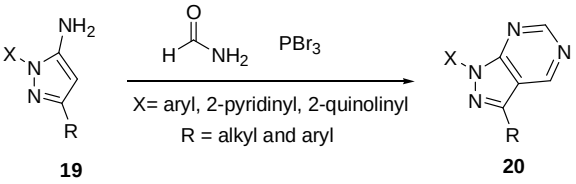
Among fused *N*-heteroaromatic substances, ring system containing pyrazolo[1,5-a]pyridine is medicinally important owing to their varying biological activities.*N*-Amino-2-imino pyridines **17**

upon treatment with 1,3-dicarbonyl compounds produce pharmacologically relevant pyrazolo[1,5-a]pyridine-3-carbonitrile **18** under cross-dehydrogenative coupling strategy, wherein, acetic acid acts as Bronsted acid catalyst and molecular oxygen as the oxidant (Scheme 6).[39] This protocol has several advantages such as high atom economy, wide substrate scope, use of eco-friendly reagents and purification simplicity.



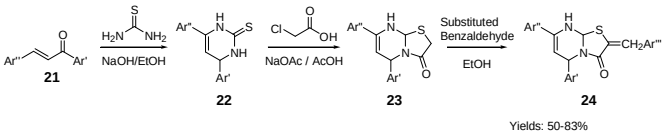
Scheme 6: Synthetic routes for substituted pyrazolo[1,5-a]pyrimidine-3-carbonitrile

5-Aminopyrazole was employed as precursor in design and synthesis of several fused pyrazoloazines. Pyrazolo[3,4-d]pyrimidines**20** were synthesized from treatment of 5-aminopyrazoles **19** with formamide in presence of PBr_3 as the coupling agent and they were subjected to anti-proliferative activity against various cancer cell lines such as lung carcinoma (NCI-H226), nasopharyngeal (NPC-TW01) and T-cell Leukemia (Jurkat) cancer cells using MTT assay (Scheme 7).[40]



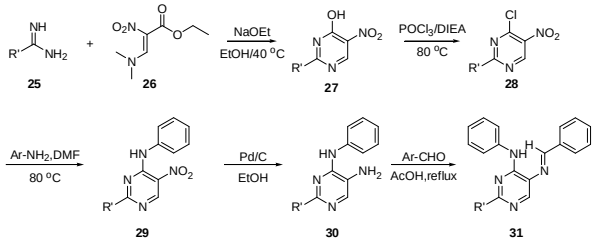
Scheme 7: Synthetic routes for substituted pyrazolo[3,4-d]pyrimidine derivatives

Thiourea was reacted with chalcone derivatives **21** in presence of anhydrous sodium hydroxide in absolute ethanol to yield thiodihydropyrimidine**22** and it was further reacted with chloroacetic acid to obtain thiazolo[3,2-*a*]pyrimidine derivatives **23**. Compound **23** was proceeded for further reaction with aryl aldehyde in ethanol at reflux condition to isolated compounds is thiazolo[3,2-a]pyrimidin-3(2*H*)-one **24** (Scheme 8).[41] The target compounds were tested for their anti-cancer activity on HepG2, PC-3 and HCT-116 cell lines and they showed moderate activity against reference drug Doxorubicin.



Scheme 8. Synthetic routes for dihydropyrimidine, thiazolo[3,2-*a*]pyrimidine and thiazolo[3,2- a]pyrimidin-3(2*H*)-one

Pyrimidine nucleus **27** was constructing with aryl formimide **25** and ethyl3-(dimethylamino)-2-nitroacrylate **26** in presences of sodium ethoxide base and ethanol as a solvent. The chlorination of compound **27** by using $POCl_3$ to obtain **28** and it was further reacted with aryl amines followed hydrogenation with Pd/C to isolate corresponding compound **30**. Further, it was reacted with substituted aromatic aldehyde in glacial acetic acid containing anhydrous sodium acetate to yield substituted desired compound **31** (Scheme 9).[42]



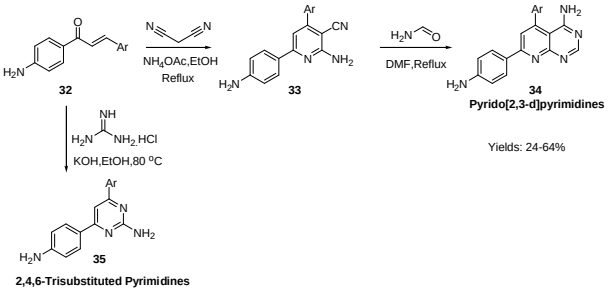
Scheme 9: Synthetic routes for substituted benzylidene pyrimidine-2,4,5-triamine/ pyrimidine-4,5-diamine

The target compounds were tested for their anti-cancer activity on HeLa cell line and they showed moderate activity against reference drug Cisplatin.

Atla *et al* reported the synthesis of 2,4,6-trisubstituted pyrimidines and pyrido[2,3-d]pyrimidines and studied of their anti-tumour activity. Substituted 4-aminochalcones **32** were reacted with malononitrile in presence of NH_4OAc in EtOH at reflux condition to obtain substituted 2-amino-3-cyanopyridines **33** and it was further reacted with formamide to give pyrido [2,3-d] pyrimidines **34**. If substituted 4-aminochalcones **32** were reacted with guanidine hydrochloride in presence of KOH in EtOH at 80 °C to yield 2,4,6-trisubstituted pyrimidines **35** (Scheme 10).[43]

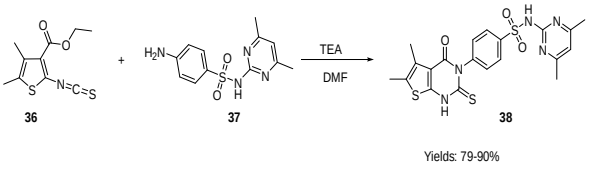
All the 2,4,6-trisubstituted pyrimidines and pyrido [2,3-d] pyrimidines have been evaluated for their anticancer activity on various human cancer cell lines *i.e*Hos (bone cancer), HT29 (colon cancer), G361 (human skin cancer), A549 (lung cancer), DU145 (prostate cancer) and they showed moderate

activity against reference drug Doxorubicin and Methotrexate.



Scheme 10: Synthetic routes for 2,4,6-trisubstituted pyrimidines and pyrido [2,3-d] pyrimidines

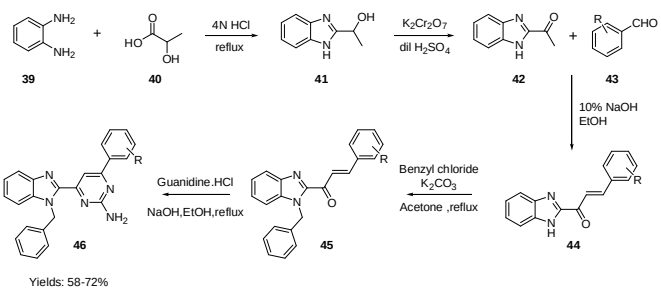
The thieno [2,3-d] pyrimidine derivatives **38** was synthesized from treating compound **36** with sulfa-drugs **37** in presence of triethyl amine base (Scheme 11).[44]



Scheme 11: Synthetic routes for thieno [2,3-d] pyrimidine derivatives

The *in vitro* anticancer screening of the synthesized thieno[2,3-d] pyrimidine derivatives **38** against human breast cancer cell line (MCF-7). IC50 values were found the nearly as active as doxorubicin as positive control drug.

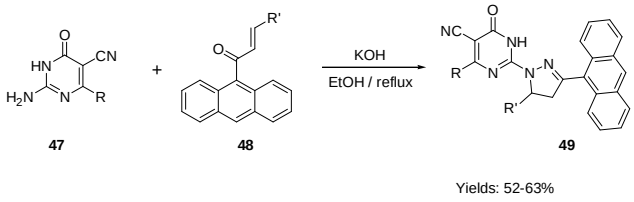
2-Hydroxyethylbenzimidazole **41** was obtained by condensation of *o*-phenylenediamine **39** with lactic acid **40** under acidic condition. Oxidation of the **41** followed by neutralization with ammonia gave 2-acetylbenzimidazole **42**. The required chalcones **43** were obtained by Claisen-Schmidt condensation of 2-acetylbenzimidazole **42** with substituted aromatic aldehydes **43** in presence of NaOH (Scheme 12).[45]



Scheme 12:Synthetic routes for N-Benzyl benzimidazole linked pyrimidine derivatives

N-Benzyl substituted benzimidazole chalocones**45** were obtained by nucleophilic substitution reactions of 1*H*-Benzimidazole chalcones **44** with benzyl chloride. Condensation of the *N*-benzyl benzimidazole chalcones **45** with guanidine hydrochloride resulted in novel *N*-benzyl benzimidazole linked pyrimidine derivatives **46**. The *in vitro* anticancer activities (cell viability assay) of compounds were evaluated by SRB assay against human breast cancer cell line MDA-MB-231.

Compounds exhibited weak activity when compared to standard drug Adriamycin. Mixture of compound **47**, the appropriate propenone**48** were allowed to react to yield novel substituted pyrimidine pyrazoline derivatives **49** (**Scheme 13**).[46]



Scheme 13:Synthetic routes for substituted pyrimidine pyrazoline derivatives

All compounds were tested for their *in vitro* anti-HCC activity against HepG2, Huh-7 cell lines, and normal fibroblast cells and the outcome resulted in exhibiting moderate to good anti-proliferative activities against the chosen cell lines compared to doxorubicin standard drug.

Conclusions

In conclusion, antiviral properties of pyrimidine derivatives are briefly summarized along with significant synthetic procedures during mid 2015- December 2022. The preparatory methodologies of some of the divergent pyrimidine analogues discussed in this mini-review consist the construction of the pyrimidine moiety starting with various organic reagents of them where indicated. The synthetic protocols deployed by various research groups presented, involve readily accessible, eco-friendly and cost-effective reagents and reaction parameters. Hope this will be a valuable addition for the researchers to develop divergent biologically relevant heterocyclic compounds possessing pyrimidine scaffold in the field of medicinal chemistry.

Acknowledgements

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