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REVIEW ARTICLE

Pyrimidine-fused Derivatives: Synthetic Strategies and Medicinal Attributes

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Abstract: Pyrimidine-fused derivatives traits the inextricable part of DNA and RNA, exhibit indispensable role in numerous biological processes, possessing momentous chemical and biological importance. Pyrimidine-condensed derivatives as the pharmacophore exhibit broad spectrum of biological activities encompassing antitubercular, antibacterial, antifungal, antiviral, anti-inflammatory, antimalarial, anticancer and anti-HIV. Several retrosynthetic approaches, are available for the synthesis of pyrimidine-fused analogues which offers enormous scope in the field of medicinal chemistry. Ring fused pyrimidine and their innumerable derivatives continue to hold the attention of chemists since their presence in the biologically active resources have been known to elicit additive effects on the bio-efficacy of the molecules. The present review is a concerted effort to congregate information mainly focusing on the comprehensive categorization of pyrimidine ring based on their fusion with five, six, seven and eight-membered ring(s). Moreover, it also puts forward their systematic nomenclature, synthetic strategies, and bioactivities including SAR studies. This review is being put forwarded with an incentive to provide researchers with a comprehensive and updated literature. In addition, the manuscript also brings to light the various pharmacophore designs based on fused-pyrimidine ring system, delving deeper into synthesis and the subsequent generation of new libraries of pyrimidine-fused derivatives including their biological assessments.

Keywords: Ring-fused pyrimidines, Synthetic strategies, Medicinal attributes, Patents, Marketed drugs.

1. INTRODUCTION

In the recent years, pyrimidine-fused heterocycles[1] have constituted an indispensable class owing to the numerous characteristics, chemo-diversity and larger biodiversity.[2] They are known to significantly alter the drug properties such as potency, selectivity, lipophilicity, polarity and aqueous solubility, thus contributing crucially to the design of therapeutic molecules.[3] Recent developments in the field of drug design and discovery have highlighted pyrimidine (Fig. **1**), a six-membered diazine, and its fused derivatives to exhibit broad spectrum of activities. Pyrimidines are classified as six membered nitrogen containing heterocycles, with the nitrogen present at 1 and 3 position of the ring.[4] Pyrimidine derived compounds are acclaimed to be biologically significant owing to their presence in uracil, thiamine and cytosine, which make up the main framework of the nucleic acids. In addition, their fused scaffold also forms a part of essential vitamins such as thiamine, riboflavin, folic acid, etc.[5] The presence of pyrimidines in compounds of biological significance, has escalated their importance, thus, prompting the researchers to design and synthesize pyrimidine-based compounds (Fig. **2**; path A) utilizing 1,2- and 3,4- bond coupling reactions (path B); 3,4- and 4,5-coupling reactions (path C); 4,5- and 1,6-bond coupling reactions (path D); 2,3- and 4,5-bond coupling reactions (path E); Pinner pyrimidine synthesis and Biginelli condensation (3,4- and 1,6-bond forming reactions (path F).[6] Moreover majority of pyrimidines derivatives are synthesized by the "Principal Synthesis" that involves cyclization of beta-dicarbonyl compounds with N-C-N compounds (path G).[7] Regardless of many methods being accessible for the synthesis of pyrimidine derivatives, their broad utility has accentuated the need to develop new synthetic routes for novel pyrimidine compounds. Pyrimidines have been observed to lend their characteristics modulation of various activities (Fig. **3**) such as anticancer[8], antifungal[9], antiinflammatory[10], analgesic[11], antihypertensive[12], antihistaminic[13] and CNS depressant activity.[14] This review is a strenuous effort to highlight design, synthetic strategies as well as *in vitro* and *in vivo* biological activities of various classes of pyrimidine fused derivatives. This review seeks to congregate five, six and seven membered fused pyrimidines from 2012-15 and the eight-membered heterocycles fused pyrimidines from 2010 – till date.

It also covers patents filed for the fused pyrimidines in the time frame of 2012-2015. The marketed drugs especially pertaining to fused pyrimidines have also been incorporated.

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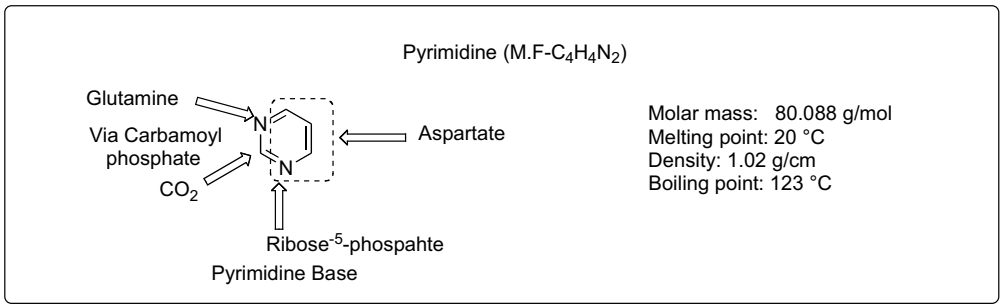


Fig. (1). Synthetic precursors and physical properties of pyrimidine.

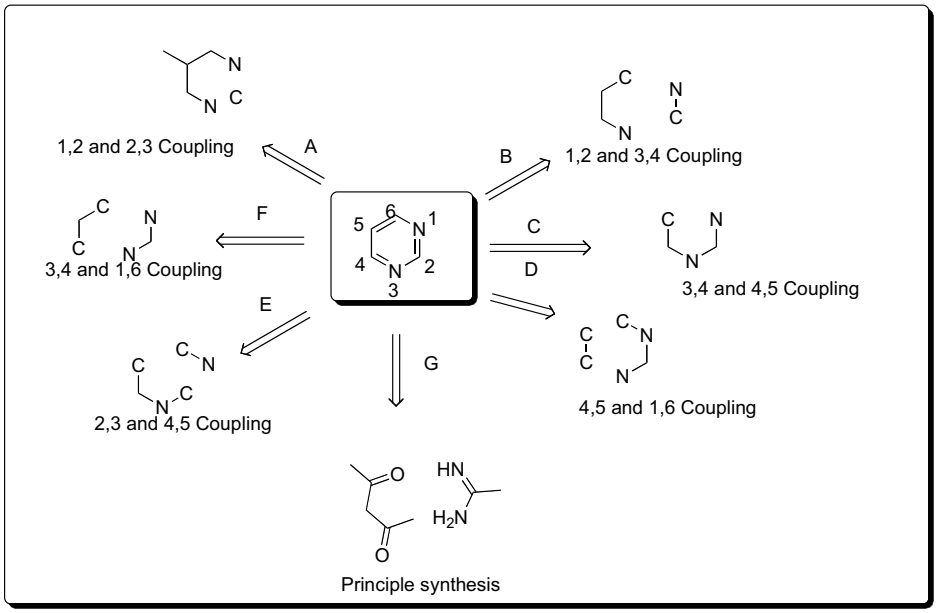


Fig. (2). Retrosynthesis route of pyrimidines.

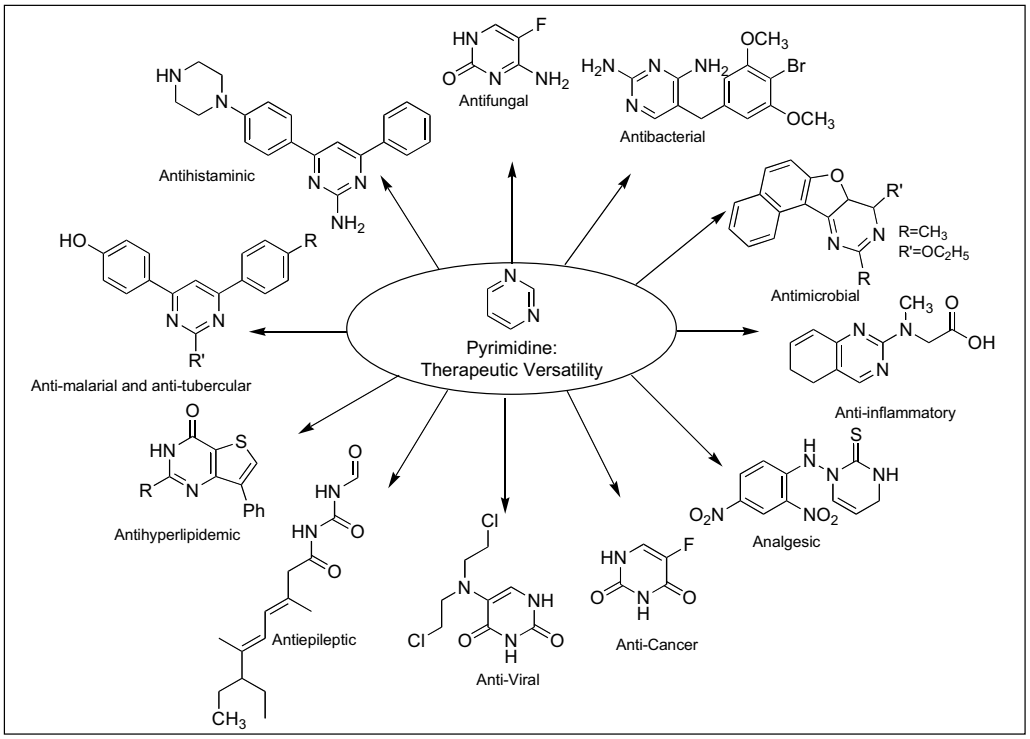


Fig. (3). Some of the pyrimidines derived compounds and their biological attributes.

2. CLASSIFICATION

We have categorized various pyrimidine-condensed heterocycles by ring size of a heterocycle fused with a pyrimidine. These classes have been discussed and elaborated in subsequent sections.

2.1. Five-Membered Heterocycle Fused-Pyrimidines

Pyrimidine can be fused with various five-membered heterocycle in a variety of permutation and combinations as shown in Fig. (**4**). However, a few are reported and explored, and many are yet to be synthesized. We shall be discussing the synthetic strategies and biological activities of reported ring fused heterocycles in next sections.

2.1.1. Synthetic Strategies

Research over the years has led to the development and designing of different schemes for the efficient synthesis of various five membered-fused pyrimidines, some of which have been represented in Fig. **(5)**. Most of the reactions involve multi-step synthetic routes. Kumar *et al.*[15] carried out the one-pot three-component synthesis (route a) of pyrazolo[1,5-*a*]pyrimidines (**1**) from an aromatic aldehyde, terminal alkyne and a reactant containing the –C=C(NH_2)–NH– moiety, (**2**). Trifluoromethane sulfonic acid as the catalyst and air in acetic acid as the suitable solvent at an elevated temperature produced the appropriate five-member fused pyrimidine as the only product in a yield of 85%. Al-Issa [16] synthesized pyrimido[3,2-*b*]-1,2,4-triazole in 50% yield by refluxing (**3**) with the excess of potassium-tertbutoxide and one equivalent of *p*-cyano acetophenone in *t*-butanol for 48 h as outlined in reaction (route b**)**. In the reaction, (**2**) was directly converted into the corresponding pyrimido[3,2-*b*]-1,2,4-triazole. Khalafi-Nezhad[17] and the team gave the synthesis of new heterocyclic adenine analogs (**4**) under tungstophosphoric acid (mol 2.5%) catalysis (route c**)**. Balakumar *et al.*[18] carried out the microwave–assisted synthesis (route d) of new pyrimido[2,1-*b*] benzothiazoles. The intermediates (**5**) were prepared by passing a stream of nitrogen gas and converted to the desired 2, 3- disubstituted benzothiazole fused heterocycles **1**. In comparison to the conventional technique, microwave based reaction considerably shortened the reaction time from 10 to 15 min. The reaction yield obtained for different substitutions ranged from 70-82 %. Kandeel and his research group (route b)[19] synthesized pyrazolo[3,4-*d*]pyrimidines[20] by refluxing pyrazole intermediate **6** with phosphorus oxychloride and formamide for a time duration of 3h.

2.1.2. Pyrazolo[3,4-d]pyrimidine

We have recently reported a critical review on pyrazolo[3,4-d]pyrimidnes and their bioactivities in 2013[20]. We herein present the medicinal activities, which have not been covered so far.

2.1.2.1. Anticancer Activity

Hai-Yun and his research group[21] carried out the synthesis and the subsequent cell-based screening of novel pyrazolo[3,4-*d*]pyrimidine derivatives. Among compounds **7**, **8** and **9**, **7** portrayed promising inhibitory activity against four different types of tumor cell lines inclusive of A549, MCF-7, HepG2 and PC-3 (Table **1**). The biological assays performed for 2- methyl thioether-substituted pyrazolo[3,4-*d*]pyrimidine derivatives revealed that the prototype compound **7** ex-

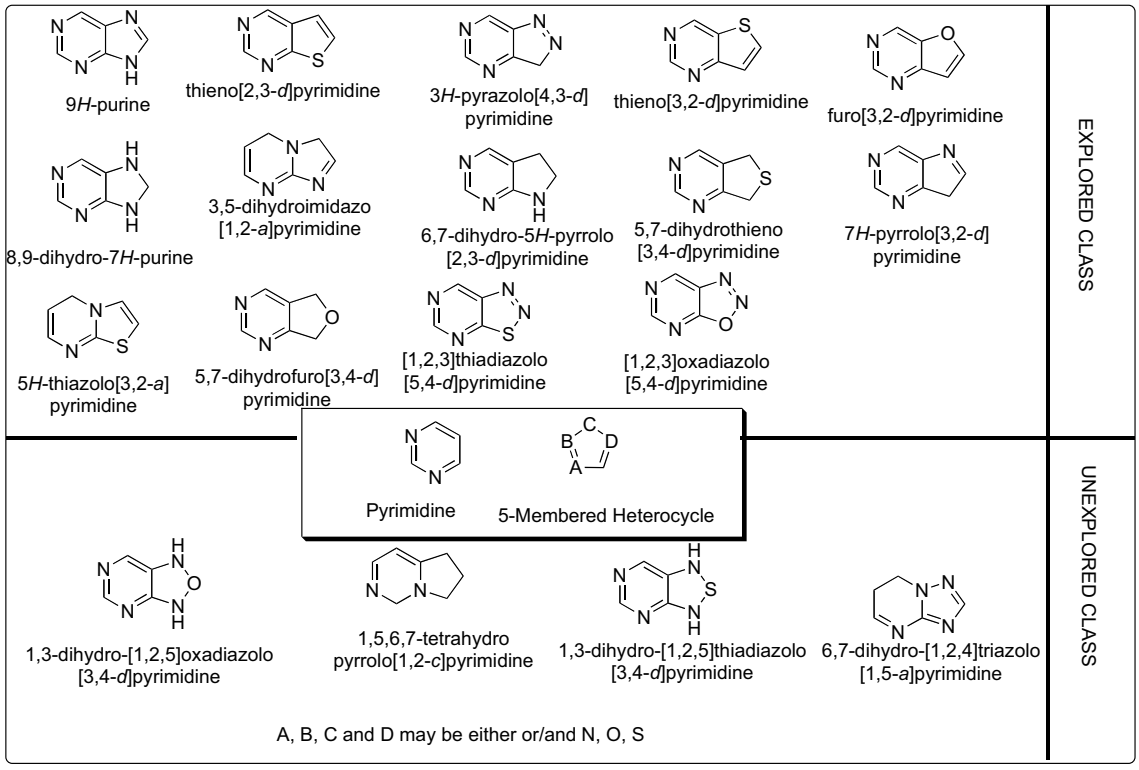


Fig. (4). Possible fused heterocycles obtained from fusion of pyrimidine with various five-membered heterocycle.

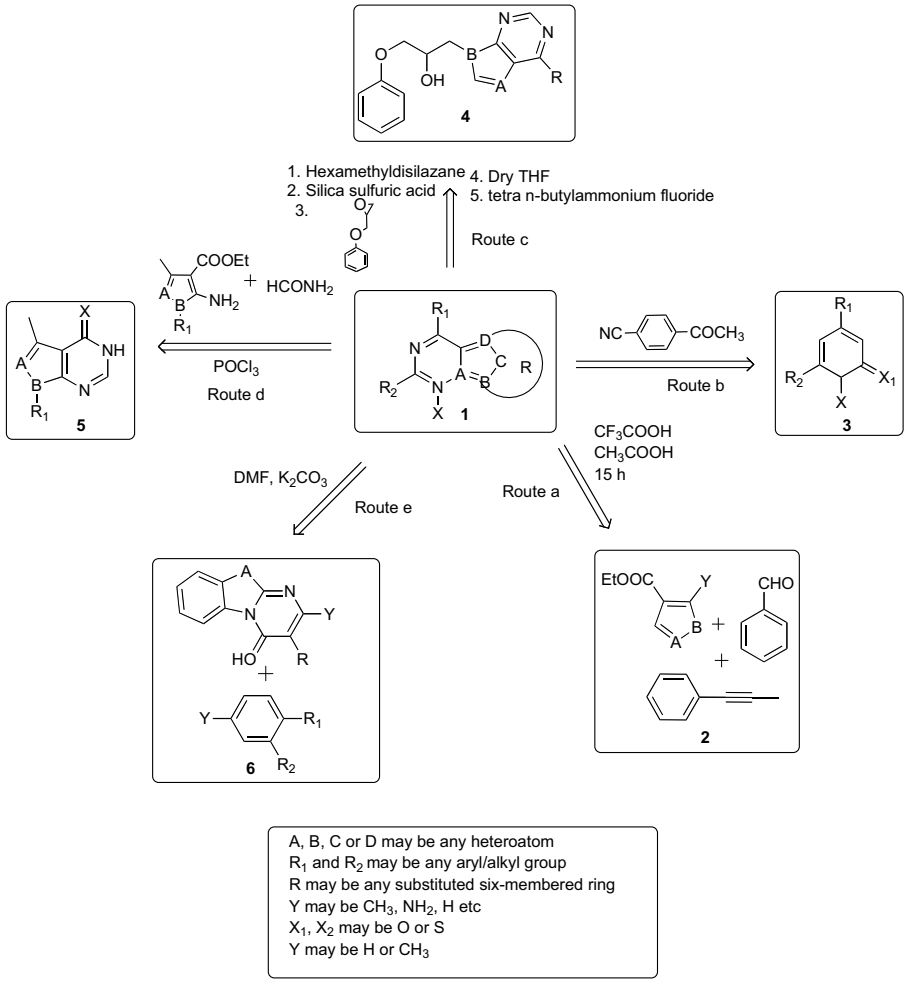
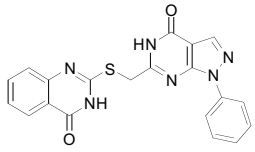
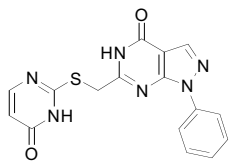
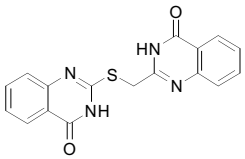


Fig. (5). Retrosynthetic routes for five-membered ring fused pyrimidines

Table 1. Antiproliferative activity of compounds 7, 8, and 9 against various cancer cell lines.

Compound	Structure	IC_{50} (μM)			
		HepG-2 (Liver Cancer cell line)	MCF-7 (Breast Cancer cell line)	A-549 (Lung Cancer cell line)	PC-3 (Prostate Cancer cell line)
7		13.9	42.3	2.24	26.6
8		25.2	1.74	5.20	>100
9		>100	>100	47.0	>100
Doxorubicin		0.54	0.75	9.20	0.60

hibited an IC_{50} of 2.24 μM against A549 as compared with doxorubicin (9.20 μM). The structural activity relationship (SAR) study performed by the group revealed that substitution of the pyrazole ring[22] (**7** and **8**) with phenyl ring (**9**) decreased the activity substantially, highlighting the importance of the core pyrazolo[3,4-*d*]pyrimidine scaffold. Also, the replacement of the quinazoline ring with the pyrimidone ring specifically enhanced the potency towards the MCF-7 cell line. An effort to understand the death pathway indicated that compound **7** significantly induced apoptosis in A549 cells *in vitro* at low micromolar concentrations. This was summarized from the percentage of cells in the sub-G1phase found to be 25.1%–41.0% for compound **7** (2.0–4.0 μM) as compared to 5.1% for control.

Kandeel *et al.*[19] designed, synthesized and evaluated a series of pyrazolo[3,4-*d*]pyrimidines for their *in vitro* antitumor activity against 60 different cell lines including leukemia, colon cancer, renal cancer, ovarian cancer, prostate cancer (Table **2**). Compounds **10**, **11**, **12**, and **13,** were found to have the highest inhibitory potential in most of the cell lines tested. This activity was attributed to the presence of electron releasing phenol group in **12** as compared to the presence of electron withdrawing nitro group as in compound **13**.

2.1.3. Pyrrolo[1,2-c]pyrimidines

2.1.3.1. Anticancer Activity

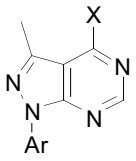
Ream and group[23]synthesized a series of pyrrolo[1,2-*c*]pyrimidines derivatives and evaluated the synthetics for their anticancer potential. The data obtained from the biological studies (Table **3**) revealed that the compounds **14**, **15** and **16** possessed significant inhibitory activity against MCF-7 breast cancer cell line showing IC_{50} values of 19.8, 14.2 and 16.6μg/mL, respectively. This increment of activity was attributed to the greater lipophilicity of the thioxo (**15** and **16**) as compared to (**14** and **17**). Furthermore, in respect to **3A**, the introduction of an imidazoline rings in **18** exhibited significant increase in the growth inhibitory activity with an IC_{50} of 10.8μg/ml. On the contrary, increase was seen in IC_{50} (18.6μg/mL) with the introduction of the imidazoline-2, 5-dione side chain (compound **19**) as compared to **14** (19.8 μg/mL).

2.1.4. Pyrrolo[2,3-d]pyrimidines, pyrrolo[3,2-d]pyrimidines, thieno[2,3-d]pyrimidines, thieno[3,2-d]pyrimidines and furo[3,2-d]pyrimidines

2.1.4.1. Inhibitors of Hedgehog Pathway

Liandi and group[24] synthesized a series of novel five-membered heteroaromatic ring fused pyrimidine derivatives, based on 4-(2-pyrimidinylamino) benzamide as the core scaffold, comprising of purines, pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, thieno[2,3-*d*]pyrimidines, thieno [3,2-*d*]pyrimidines and furo[3,2-*d*]pyrimidines. The research group also assessed the compounds for their ability to hamper the hedgehog (Hh) signaling pathway *via* Gli-luciferase reporter assay in NIH3T3 cell carrying a stably transfected Gli-reporter construct (Gli-luciferase reporter cell lines) with GDC-0449 (0449: 7.17 nM) as the active control (Table **4**). Compound **20** exhibited higher inhibition as compared to **21** with an IC_{50} of 1.6 nM than the latter showing IC_{50} of 5.2 nM, which was over three-fold. In comparison to pyrrolo [2,1-*f*][1,2,4]triazines, **22**, **23** and **24** with basic amine side chains showed promising inhibitory potential at IC_{50} of 0.69 nM, 0.90 nM and 2.98 nM, respectively. Compounds **25** (6.85 nM) and **26** (6.04 nM) showed only moderate inhibitory potential. Whereas **27** with *N*-methyl group showed a three-fold increase (2.58 nM)about GDC-0449. Also, pyrrolo[3,2-*d*]pyrimidine derivatives bearing the methyl (**28**) showed better potency than those with no methyl group (**29**). Moreover, it was also noted that on isosteric replacement of

Table 2. Antitumor activity of 10, 11, 12, and 13 against various cell line.



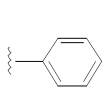
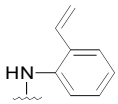
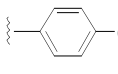
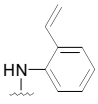
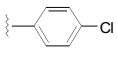
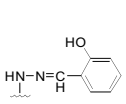
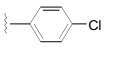
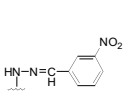
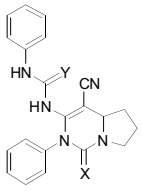
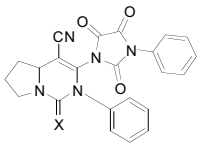
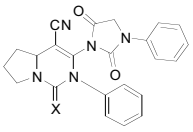
Compound	10		11		12		13	
	Ar	X	Ar	X	Ar	X	Ar	X
								
Cell Line	**Percent inhibition of the tested compounds (Conc 10^{-5} M)**							
K-562	**65.57**		**76.32**		**81.45**		**82.62**	
UACC-62	**10.31**		**14.27**		**86.54**		**-**	
HT29	**5.24**		**4.20**		**79.92**		**9.36**	
PC-3	**1.59**		**22.41**		**58.41**		**61.01**	
T-47D	**12.42**		**2.13**		**86.73**		**-**	

Table 3. Anticancer activity of pyrrolo[1,2-*c*]pyrimidines against various MCF-7.

Compound				IC_{50} (μg/mL)
		**X**	**Y**	
14		**O**	**O**	**19.8±0.3**
15		**S**	**O**	**14.2±0.3**
16		**O**	**S**	**16.6±0.4**
17		**S**	**S**	**20.8±0.6**
18		-		**10.8±0.3**
19		-		**18.6±0.2**

N-atom of five carbon ring adjacent to the ring junction with S or O atom as in thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines and furo[3,2-*d*]pyrimidines portrayed commendable Hh signaling inhibitory activity where IC_{50} ranged from 0.60 nM to 9.39 nM. The data obtained further revealed that the thieno[2,3-*d*]pyrimidine (**31**; IC_{50}=3.36 nM) was more potent than thieno[3,2-*d*]pyrimidine one (**30**; IC_{50}= 9.39 nM). Similar behaviour was observed when R_2 was un-substituted as in compounds **32** and **33** (IC_{50}: 3.61 nM vs. 0.60 nM). The data disclosed that furo[3,2-*d*]pyrimidine (**34**) was having three times increase in inhibitory potential with an IC_{50} of 1.78 nM as compared to thieno[3,2-*d*]pyrimidine (IC_{50} = 3.61 nM). The morpholine derivatives **35** and **36** showed low nanomolar Hh inhibitory activity with IC_{50} of 1.75 nM and 1.13 nM, respectively.

2.1.5. Pyrazolo[1,5-a]pyrimidines,triazolo[1,5-a]pyrimidines and pyrimido[1,2-a]benzimidazoles

2.1.5.1. Aurora Kinase Inhibitors and Colon Anticancer Agents

Mohammed *et al.*[25] carried out an efficient and time-conserving one pot three-component procedure for the synthesis of pyrazolo[1,5-*a*]pyrimidines (**37-42**), pyrimido[1,2-*a*]benzimidazoles (**42-44**) and triazolo[1,5-*a*]pyrimidines (**45-46**). These were assessed for their Aurora-A kinase inhibitory activity and cytotoxic potential against HCT116 colon tumor cell line. Doxorubicin was used as a reference drug. SAR studies indicated (Table **5**) that compounds with chloro-substituted phenyl ring (**37** and **38**) were less active than a unsubstituted/bromo-substituted phenyl (**39, 40,** and **41**) ring. The second series (**42-44**) was devoid of any activity displaying low inhibitory potential. Whereas, the third series showed better activity with the unsubstituted (**45**) ring as compared to chloro-substituted (**46**) against both Aurora A kinase as well as HCT 116 cell line (Table **5**).

2.1.6. Pyrazolothienopyrimidine

2.1.6.1. Antiparkinson, Hypoglycemic and Anti-Microbial Activity

Al-Harbiand and his team[26] synthesized a series of pyrazolo-thieno pyrimidine derivatives and evaluated them for their antiparkinsonism, hypoglycemic, and antimicrobial activity. The biological data obtained (Table **6**) highlighted mainly compound **48** bearing cyano substitution importance in Parkinsonism, hypoglycemia as well as in bacterial and fungal diseases. **47** was also observed to exhibit potential bioactivities.

2.1.7. Thiazolo[3,2-a]pyrimidines

2.1.7.1. Analgesic and Anti-inflammatory Activity

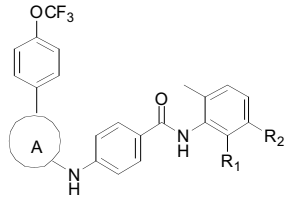
Khalifa research group[27] synthesized and investigated the novel bicyclic thiazolopyrimidine derivatives for their analgesic and anti-inflammatory activity (Table **7**). The anti-inflammatory effects were tested in a rat model of carrageenan-induced paw edema and the central and peripheral analgesic activity in hot plate test and writhing test, respectively. Compounds **50**, **51**, and **52** showed comparable anti-inflammatory as well as analgesic potency as compared to the standard drug. The increased activity in case of compound **51** may be attributed to the presence of electron releasing methoxy group.

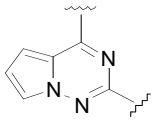
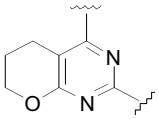
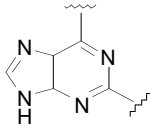
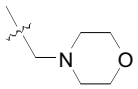
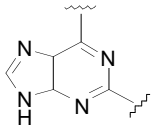
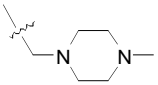
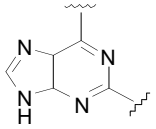
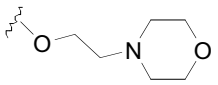
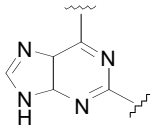
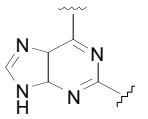
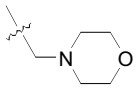
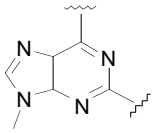
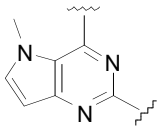
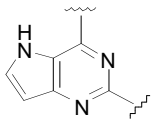
2.1.8. Thiazolo[4,5-d]pyrimidines

2.1.8.1. Corticotropin Releasing Factor Modulators.

Fahmy *et al.*[28] disclosed the synthesis of Corticotropin Releasing Factor (CRF) Modulators which are a category of neurohormone that plays a crucial role in integrating the body's overall response to stress. CRF are released in response to various triggers among which chronic stress is a major reason. Thus the research group based on pharma-

Table 4. Gli-luciferase reporter assay of various pyrimidine-fused moieties in NIH3T3 cell.



Compound	A-ring	R1	R2	Gli-luc reporter IC_{50} (nM)
20			-	**1.6**
21			-	**5.2**
22		**H**		**0.69**
23		**H**		**0.90**
24		**H**		**2.98**
25		**Me**	**H**	**6.85**
26		**H**		**6.04**
27		**Me**	**H**	**2.58**
28		**Me**	**H**	**1.17**
29		**Me**	**H**	**12.84**

(Table 4) contd….

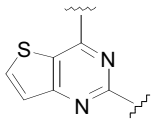
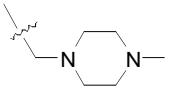
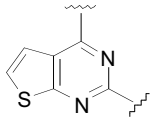
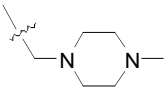
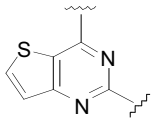
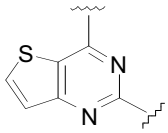
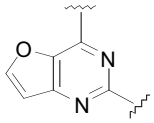
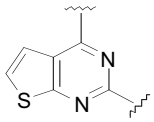
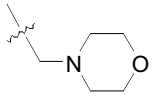
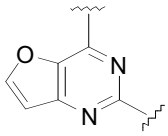
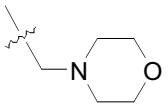
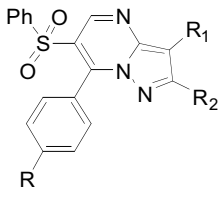
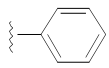
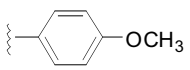
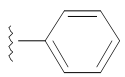
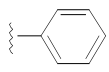
Compound	A-ring	R1	R2	Gli-luc reporter IC_{50} (nM)
30		**H**		**9.39**
31		**H**		**3.36**
32		**Me**	**H**	**3.61**
33		**Me**	**H**	**0.60**
34		**Me**	**H**	**1.78**
35		**H**		**1.75**
36		**H**		**1.13**
GDC-0449				**7.17**

Table 5. Structural Modifications altering the biological activities of pyrazolo[1,5-*a*]pyrimidines, triazolo[1,5-*a*]pyrimidines and pyrimido[1,2-*a*]benzimidazoles.

Compound	Structure	R	R1	R2	Biological Activity	
					Cytotoxic Activity against HCT-116 (μg/mL)	Aurora-A inhibition activity (μM)
37		**Cl**	**H**		**>25**	**NA**
38		**Cl**	**H**		**>25**	**NA**
39		**H**	**H**		**1.27**	**0.051**
40		**H**	**Br**		**1.34**	**0.039**

(Table 5) contd….

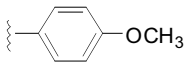
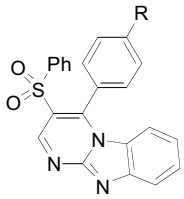
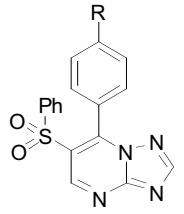
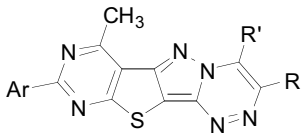
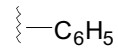
Compound	Structure	R	R1	R2	Biological Activity	
					Cytotoxic Activity against HCT-116 (µg/mL)	Aurora-A inhibition activity (µM)
41		**H**	**H**		**1.28**	**0.025**
42		**H**	**-**	**-**	**>25**	**NA**
43		**Cl**	**-**	**-**	**>25**	**NA**
44		**Br**	**-**	**-**	**16.3**	**NA**
45		**H**	**-**	**-**	**1.97**	**0.104**
46		**Cl**	**-**	**-**	**2.15**	**9.328**
Doxorubicin					**1.30**	**0.040**

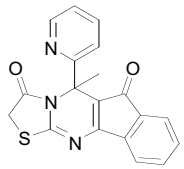
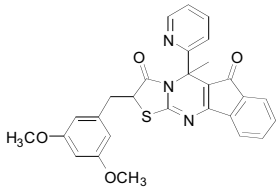
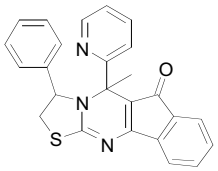
Table 6. Biological activity of pyrazolothienopyrimidine.



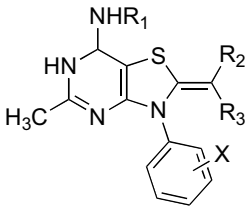
Compound	Structure		Hypoglycemic (% age blood lowering activity ± SEM in SLM model)		Anti-Parkinsonism (Relative potency to Benzotropene)	Anti-microbial (MIC µg/mL)	
						P. mirabilis	*C. albicans*
	R'	**R**	**1h**	**3h**			
47			**108.4 ± 5.4**	**117.6 ± 5.7**	**0.75 ± 0.03**	**15**	**16**
48			**112.2 ± 5.7**	**118.1 ± 5.6**	**0.86 ± 0.04**	**22**	**13**
49			**83.5 ± 3.8**	**87.2 ± 4.3**	**0.25 ± 0.01**	**13**	**12**
Pioglitazone			**100.0 ± 5.1**	**100.0 ± 5.1**	**-**	**-**	**-**
Benztropine			**-**		**1.00 ± 0.04**	**-**	**-**
Ciprofloxacin			**-**		**-**	**20**	**-**
Amphotericin			**-**		**-**	**-**	**19**

cophore of the CRF1 receptor antagonists, synthesized a new series of thiazolo[4,5-*d*] pyrimidines as CRF receptor modulators and the synthetics were found to produce optimum binding affinity to CRF receptors. These compounds were further evaluated for their CRF1 receptor binding affinity in HEK 293 cell lines and two compounds **53** and **54** showed approximately 25% binding affinity to CRF1 receptors. Compounds **55** was selected as the representative compound for the gene expression studies associated with depression and anxiety disorders., among all compound **55,** showed a significant effect on gene expression at 2.5µM and 25µM concentration (Fig.**6**).

Table 7. Analgesic and anti-inflammatory activity of thiazolo[3,2-*a*]pyrimidines.

Compound	Structure	Anti-inflammatory Activity (at 4h) (Edema%)	Analgesic Activity	
			Central (at 90 min) (reaction time(s))	Peripheral No. of writhes/ 20 min
50		**36.0 ± 3.01**	**20.5 ± 0.63**	**39.6 ± 3.14**
51		**47.8 ± 4.22**	**28.8 ± 2.58**	**38.8 ± 1.77**
52		**45.5 ± 2.51**	**24.6 ± 2.18**	**26.4 ± 2.46**
Indomethacin		**52.4 ± 4.34**	-	-
Acetyl salicylic acid		-	-	**17.4 ± 1.57**
Tramadol			**± 2.28**	

Values represent the mean ± S.E. of five mice for each group



53: $R_1=C_2H_4OCH_3$; R_2=CN; $R_3=CO_2C_2H_5$; X=Br^{-4}-isopropyl

54: R_1= CH_2C-Pr; R_2= C_3H_7; $R_3=CO_2C_2H_5$; X=Br^{-4}-isopropyl

55: R_1= C_3H_7; R_2=CN; $R_3=CO_2C_2H_5$; X=2,4,6-trimethyl

Fig.(6). Thiazolo[4,5-*d*]pyrimidines derivatives.

2.1.9. Fused-Pyrimidine Derivatives as a Series of Novel GPCR119 Agonists

Ohta *et al.*[29] disclosed the synthesis of a series of fused-pyrimidine derivatives (Fig.**7**) that were claimed as potent and orally active GPCR (G- Protein Coupled Receptor 119) agonists. A combination of the cyclopentane ring fused-pyrimidine structure and 4-chloro-2,5-difluorophenyl group provided a potent GPCR119 agonist 4-chloro-2-(4-chloro-2,5-difluorophenyl)-5,7-dihydrothieno[3,4-*d*]pyrimidine 6,6-dioxide **56** with an original scaffold. Optimization of the fused-pyrimidine moiety in compound led to formation of 2-(4-chloro-2,5-difluorophenyl)-4-morpholino-5,7-dihydrothieno[3,4-*d*]pyrimidine6,6-dioxide **57,** which further led to the identification of the 5,7 -dihydrothieno[3,4-*d*]pyrimidine 6,6-dioxide derivative **58** with an approximately 10-fold improvement in GPCR119 agonistic activity. Subsequent replacement of the amino group at the 4-position in the pyrimidine ring was done to improve activity and water solubility that led to the identification of 2,1-[2-(4-chloro-2,5-difluorophenyl)-6,6-dioxido-5,7-dihydrothieno[3,4-*d*] pyrimidin-4-yl]piperidin-4-yl]acetamide **59** as an advanced analog. Among all the analogs synthesized compound **68** was found to have extremely potent agonistic activity, with an EC value of 8.3 nM, and to improve glucose tolerance at 0.1 mg/kg po in mice. Also, a docking study of **59** to the GPCR119 homology model suggested that **59** exerts its GPR119 agonistic activity by effectively utilizing some dif-

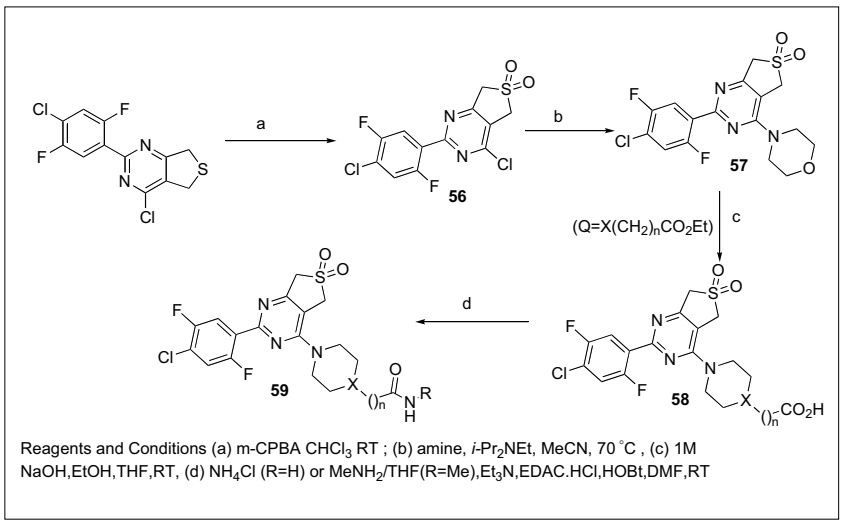


Fig. (7). Synthesis of fused pyrimidine derivatives as a series of novel GPR119 agonists

ferent interactions. Thus, the compound **59** and its analogs have shown the simple utility in exploring the practicality of GPR119 agonists as potential therapeutic agents for the treatment of diabetes (Table **8**).

2.1.10. Thieno[2,3-d][1,2,4]triazolo[3,4,-b]pyrimidin-5-on derivatives as Fused Pyrimidine Heterocycles

S. A. AL-ISSA synthesized fused pyrimidine derivatives (**9A-9H**) utilizing microwave irradiation **(**Fig. **8**). The compounds were synthesized with the aim to evaluate them for their antibacterial or antifungal agents against *Candida albicans* (ATCC No. 10231), *Staphylococcus aureus* (ATCC No. 6538), *Escherichia coli* (ATCC No. 8739), *Proteus mirabilis* (ATCC No. 29906) and showed promising biological activities (Table **9**) [30].

2.1.11. Synthesis of New pyrido[4',3':4,5]thieno[2,3-d]pyrimidines and Related Heterocycles

Vanelle *et al.* disclosed the synthesis of pyrimidine-based fused heterocycles. The thiourea derivative **78** on treatment with concentrated sulfuric acid produced a thiazinone derivative **79.** On further reaction with hydrazine hydrate, the sulfur atom was removed, thus, yielded 3-amino-7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno [2,3-*d*]pyrimidin-4-one **80** [31] which was further explored for the synthesis of various derivatives as summarized in Fig.**9**.

2.2. Six-Membered Heterocycle Fused-Pyrimidines

We have summarized possibilities of structures emerged from the fusion of pyrimidine with various six-membered rings (Fig. **10**). Of these classes, only four are not explored until today.

2.2.1. Synthetic Strategies

Most of the routes devised for synthesis involved muti-component and microwave based reactions (Fig. **11**).Verma and group[32] performed a simple, time-preserving and high yielding one-pot clean synthesis (route a and b**)** of diverse six-membered fused pyrimidines (**82**) following domino coupling uracil of derivative, aldehydes, and cyclic 1,3-diketones (**83** or **84**) in water as a solvent and *p*-toluene sulfonic acid. The reaction was carried out at 90 °C for 2.5 h and resulted in 90-94% yield. Khurana and his research team[33] utilized water as solvent and indium trichloride as a promoter for the three-component combinatorial synthesis (**85;** route c) of **82**. Jiang *et al.* [34] synthesized thiopyrano[4,3-*d*]pyrimidine derivatives through an inexpensive, time-saving and green multicomponent reaction **(**route d**)** of aromatic aldehydes, tetrahydrothiopyran-4-one(tetrahydropyran-4-one), and aryl amidines (**86**). The reaction was carried out under microwave conditions in the presence of potassium tert-butoxide as a base and butanol as the solvent at 140 °C for 15-17 min yielded 79-90% product. Panahi *et al.* [35] carried out the synthesis (route e), of **1** through multi-component reaction of **87** (barbituric acid), aldehyde, amine, and tungstophosphoric acid in ethanol, at 90˚C. The yields obtained for the synthetics ranged from 81-91%.

2.2.1. Thiopyrano[3,2-d]Pyrimidine Derivatives

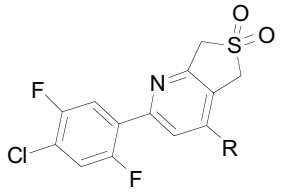
2.2.1.1. Phosphodiesterases-4 (PDE-4) Inhibitory Activity

Goto and his research group[36] synthesized thieno[3,4-*d*]pyrimidine **88** (a 5 membered ring fused with pyrimidine) and thiopyrano[3,2-*d*]pyrimidine derivatives and evaluated them for their inhibitory potential against human phosphodiesterases-4 (PDE-4) and TNF-α in mouse splenocytes **(**Table **10)**. Among the synthetics, **88** was observed to display moderate PDE4B inhibitory activity (IC_{50} = 150 nM). Replacing the thieno group with thiopyran **(89)** enhanced the inhibitory potential significantly to an IC_{50} of 25 nM. Further enhancement of activity was seen with the conversion of the acid group to amide moiety **(90)** where the IC_{50} was increased to 7.5 nM (PDE4B) and 9.8 nM for TNF-α inhibition (Table **10**).

2.2.1.2. HCV Inhibitory Activity

Hepatitis C virus (HCV), a (+)-strand RNA virus of the *Flaviviridae*, is the primary causative organism for several disease states such as cirrhosis, hepatocellular carcinoma (HCC) as well as liver failure. Six major genotype classes,

Table 8. Fused-pyrimidine derivatives as a series of novel GPR119 agonists.



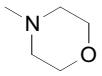
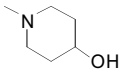
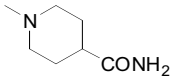
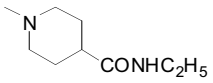
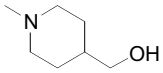
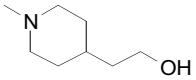
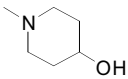
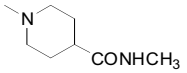
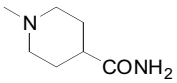
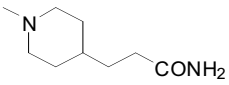
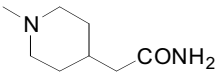
Compound	R	GPR119/pCRE	
		EC (nM)	IA (%)
60		28	668
61		14	575
62		21	294
63		350	292
64		3.9	501
65		2.8	506
66		560	528
67		21	294
68		8.3	483
69		18	627
70		44	737

Table 9. Antimicrobial activity of the synthetics against bacteria and fungi.

Test organisms	76	77	74
Candida albicans	-	+	-
Staphylococcus aureus	-	+	+
Eschierichia Coli	-	+	+
Proteus mirabilis	-	-	-

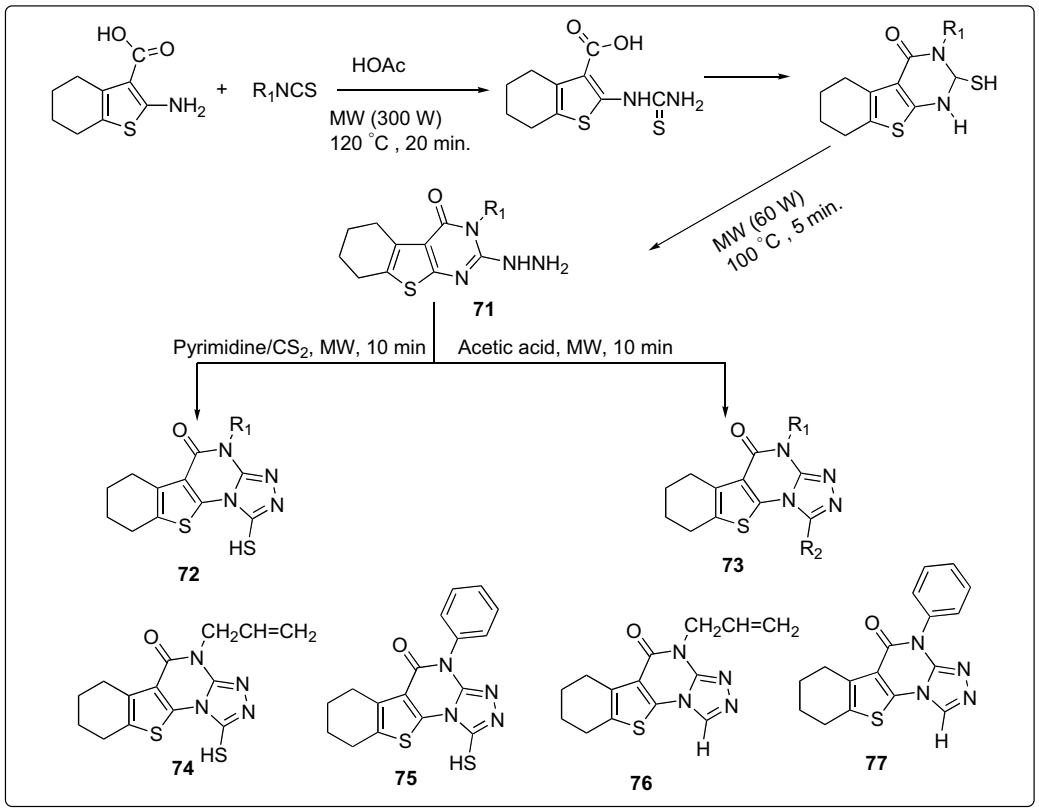


Fig. (8). Synthesis of thieno[2,3-*d*][1,2,4]triazolo[3,4,-*b*]pyrimidin-5-on derivatives

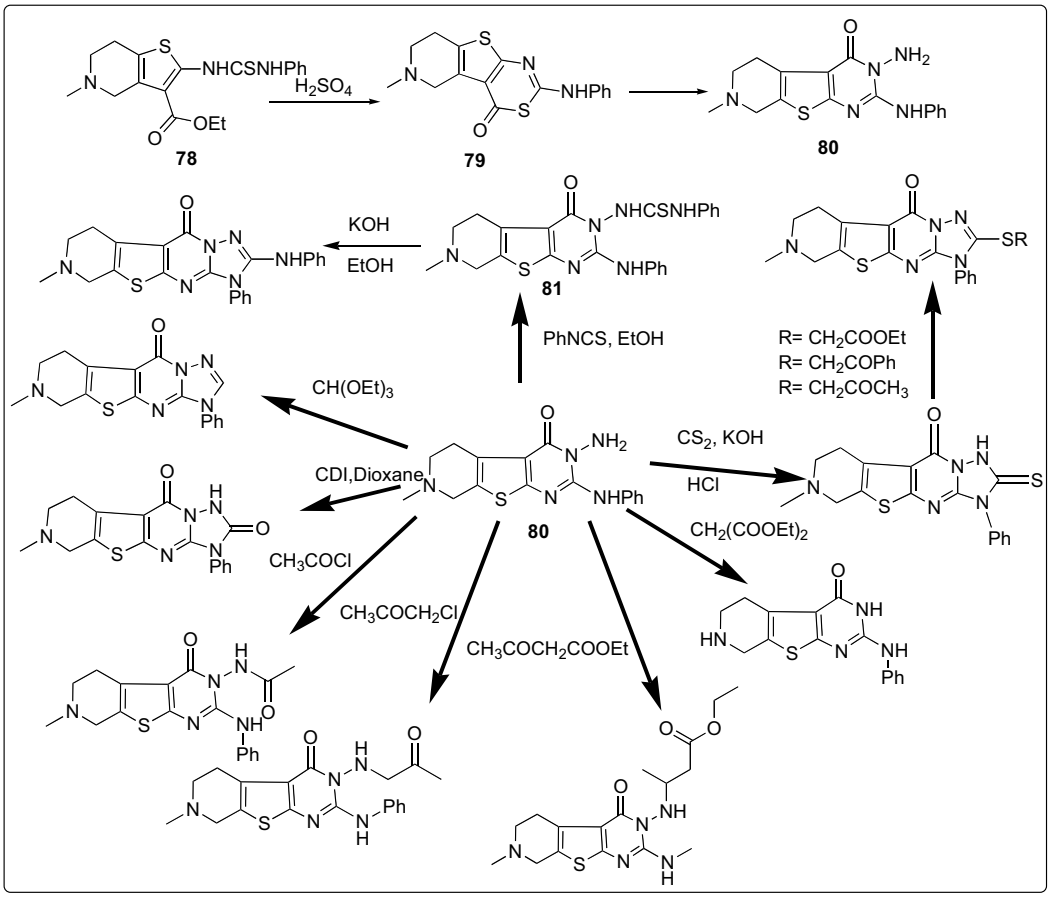


Fig. (9). Synthesis of New pyrido [4',3':4,5]thieno[2,3-*d*]pyrimidines and related heterocycles

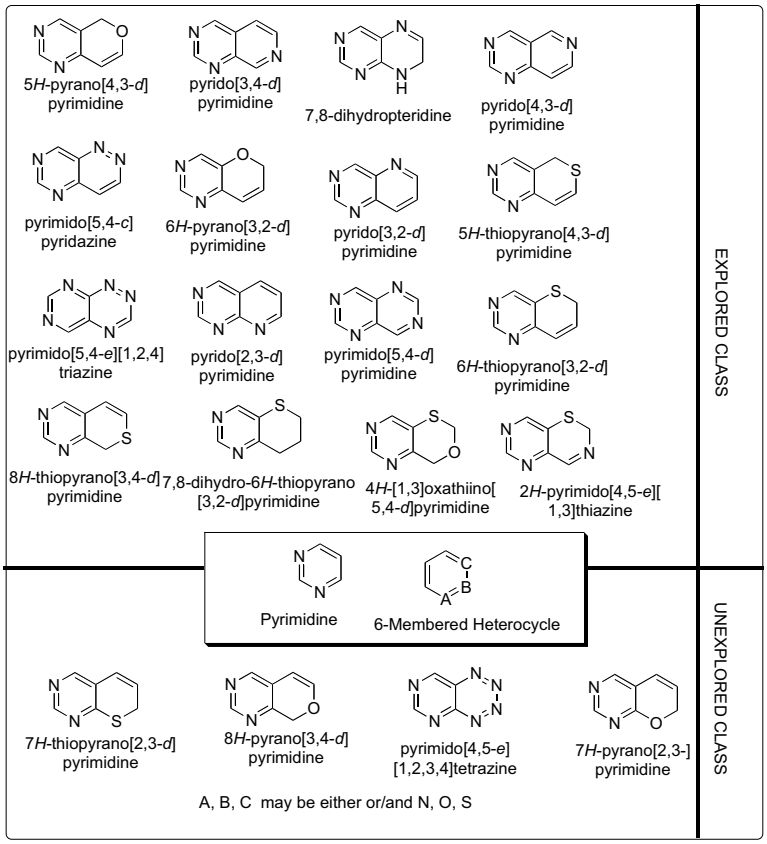


Fig. (10). Possible fused heterocycles obtained from fusion of pyrimidine with various six-membered heterocycles.

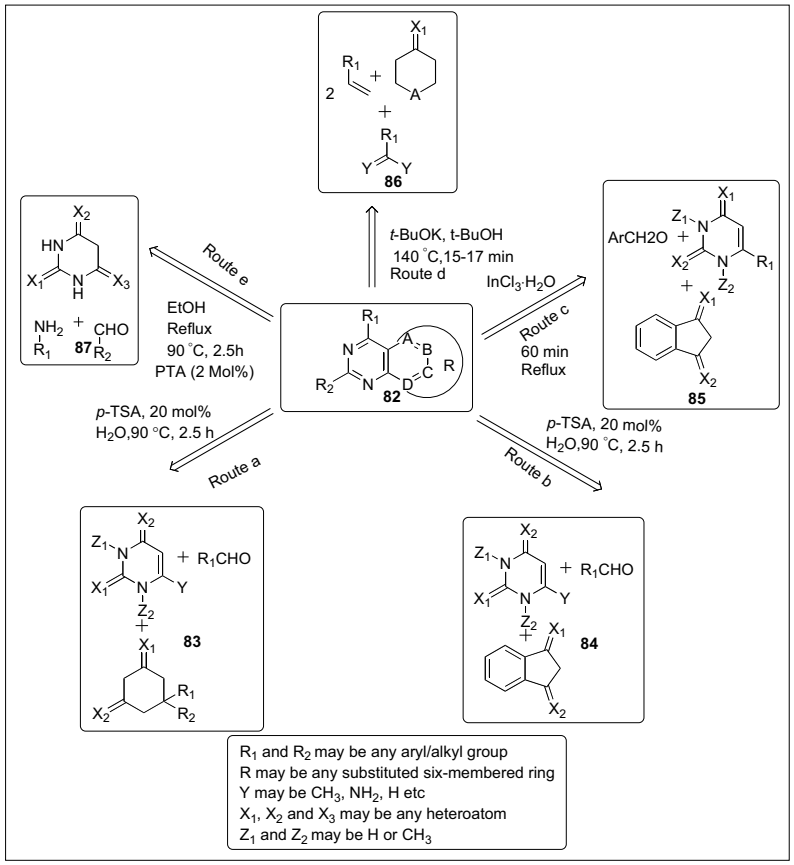
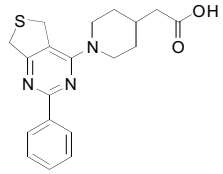
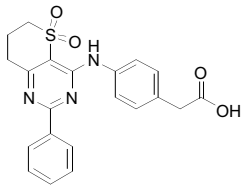
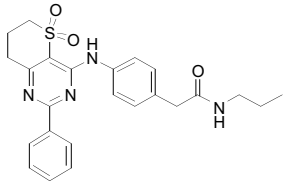


Fig. (11). Reterosynthesis of pyridine ring fused with six-membered heterocycle.

Table 10. PDE-4 and TNF-α inhibitory activity of thieno[3,4-*d*]pyrimidine and thiopyrano[3,2-*d*]pyrimidine.

Compound	Structure	Inhibitory Activity (IC_{50} nM)	
		hPDE-4B	mTNF-α
88		**150**	**190**
89		**25**	**390**
90		**7.5**	**9.8**

HCV with genotypes 1 and 2 have been found to be the most prevalent across United States, Europe, and Japan. Krueger *et al.*[37] designed and evaluated series of pyrido[2,3-*d*]pyrimidine and pyrimido[4,5-*d*]pyrimidine analogs for their inhibitory potency against genotypes 1a and 1b HCV replicon assays **(**Table **11)**. The SAR study carried out highlighted the hydroxyl derivatives to display a more potent EC_{50} as in the case of **91**, **92,** and **93,** which showed submicromolar potency against both the genotypes. However, any modifications, other than the hydroxyl group, resulted in several-fold decrease in inhibitory potential as in **94** and **95**.

2.2.3. Coumarino[4,3-d]-pyrimidine

2.2.3.1. Anticancer Activity

Sherif and Yossef[38] designed and synthesized coumarino[4,3-*d*]pyrimidine derivatives and on evaluating them for their anticancer activity found compound **96** and **97** with IC_{50} of 18.80 µg and 36 µg, respectively, to be potent against Hep G2 cell line. This may be due to the presence of electron releasing methoxy group at the phenyl ring **(**Table **12)**.

2.2.4. Pyrrido-pyrimidine: α-glucosidase (α-Gls) Inhibitors

Mehraban and his research group[35] designed and synthesized novel, pyrimidine-fused heterocycles (PFHs), assessed to be potent inhibitors of α-glucosidase (α-Gls), an important enzyme targeted by drugs employed in the treatment of type-II diabetes and HIV/AIDS infection. To facilitate the efficient delivery of these compounds to the small intestine, β-lactoglobulin (β-LG) is required as a carrier. Therefore, the group studied the extent of interaction of the pyrimidine-fused heterocycles with β -LG by spectroscopic methods such as fluorescence, circular dichroism (CD) and UV–Vis spectroscopy, at various temperatures of 298, 304, 310 K. The results obtained **(**Table **13)**, represented by mean of values, and highlighted these derivatives to be useful in controlling postprandial hyperglycemia (PPHG) in type-II diabetes as well as in treatment of HIV/AIDS infection. The research team, thus, concluded **99** having methylene moiety as the linker to have the least binding affinity as compared to **98** and **100**.

2.2.5. Chromeno[2,3-d]pyrimidinone and pyrano[2,3-d]pyrimidine

2.2.5.1. Antimicrobial Agent

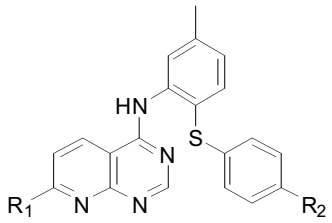
Aly *et al.* [39] synthesized a series of novel chromeno [2,3-*d*]pyrimidinone and pyrano[2,3-*d*]pyrimidines. They assessed the synthetics for their antimicrobial activity, by the disc diffusion method, against a panel of bacterial and fungal organisms including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus flavus* and *Candida albicans*. The standard drugs used were tetracyclin (antibacterial) and amphotericin B (antifungal). The activity was measured by as minimum inhibitory concentration (MIC) of the biologically active compounds. The data obtained **(**Table **14)** from the study revealed compound **101** possessing pyranose ring bearing an amine group to be an excellent antibacterial among the series. Replacing the pyrano group with thiopyran group also showed potent antimicrobial activity **102**). On the contrary, chromene bearing compound (**103**) showed poor antimicrobial activity.

2.2.6. Pyrimido[1,6-a]pyrimidine

2.2.6.1. Antidiabetic and Antioxidant Activities

Ahmed *et al.*[40] disclosed the synthesis of some novel pyrimido[1,6-*a*]pyrimidine derivatives (Fig. **12**). **105**, **113,** and **114** via the respective reactions of sodium salts of formyl ketones via 6-aminothiouracil. The characterization of the synthetics was confirmed by elemental analysis and

Table 11. HCV inhibitory activity of pyrido[2,3-*d*]pyrimidine and pyrimido[4,5-*d*]pyrimidine.



Compound	Structure		EC_{50} (μM)		MTT (Ctotoxic assay)
	R_1	R_2	Replicon 1a	Replicon 1b	
91	i-Propyl	OH	0.17	0.016	22.9
92	tert-Butyl	OH	4.6	0.47	7.1
93	Cyclohexyl	OH	2.7	0.88	>3.12
94	Methyl	NHAc	>50	>50	>50
95	iso-Butyl	NHAc	27.4	3.3	38.5

Table 12. Coumarino[4,3-*d*]pyrimidine derivatives and their evaluation against HepG2 cell lines.

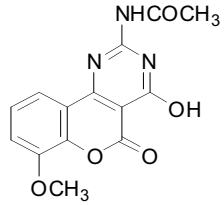
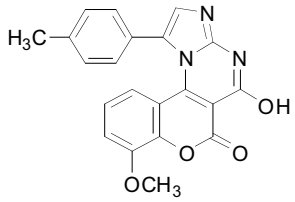
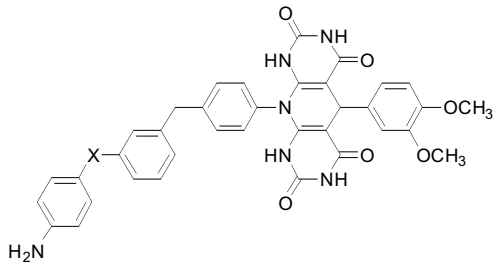
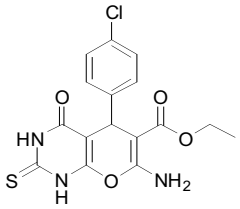
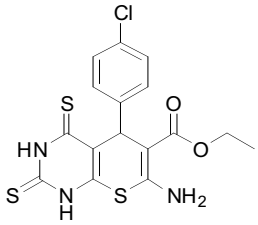
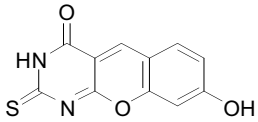
Compound	Structure	IC_{50} against HepG2 (μgm)
96		18.80
97		36

Table 13. α-glucosidase (α-Gls) inhibitory activity of Pyrrido-pyrimidine.



Compound	X	Binding Parameter (a) measured using UV-vis (nM)
98	O	7.9×10^3
99	CH_2	2.5×10^3
100	CO	3.2×10^3

Table 14. Antimicrobial activities of chromeno[2,3-*d*]pyrimidinone and pyrano[2,3-*d*]pyrimidine.

Compound	Structure	Zone Inhibition Diameter (mm)			
		Antibacterial		Antifungal	
		Pseudomonas aeruginosa	*Staphylococcus aureus*	*Aspergillus flavus*	*Candida albicans*
101		**19**	**16**	**0**	**13**
102		**18**	**16**	**14**	**14**
103		**13**	**13**	**0**	**12**
Tetracycline		**28**	**26**		
Amphotericin B				**16**	**19**

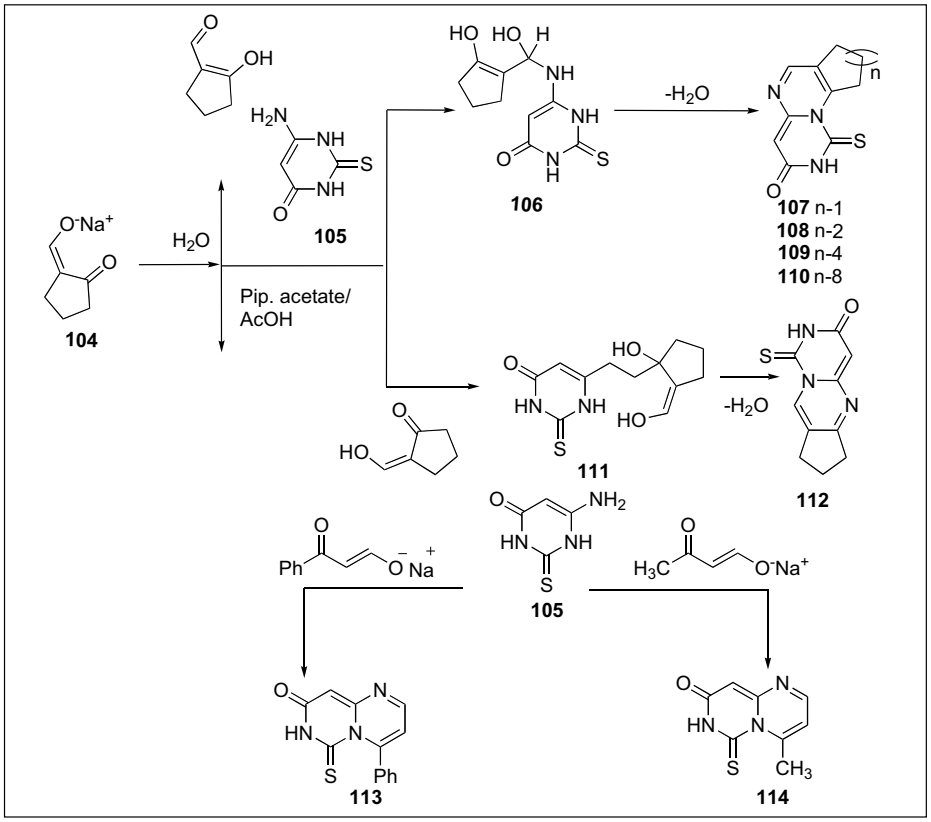


Fig. (12). Synthesis of pyrimido[1,6-*a*]pyrimidine derivatives

Table 15. Effect of pyrimido[1,6-*a*]quinazoline derivative 108 on serum insulin and C-peptide levels at fasting state and after 2 h of oral glucose loading in streptozocin-induced type 2 diabetic male rats[1]

Group(Parameters)	Insulin (µLU/mL) (Fasting)	Insulin (µLU/mL) (2 h)	C-peptide (pmol/mL) (Fasting)	C-peptide (pmol/mL) (2 hours)
Normal Control	25.23±1.83	36.43±2.26	160.67±6.41	147.65±5.74
Diabetic Control	10.01±0.76	10.80±0.54	58.05±13.85	64.05±12.33
Diabetic treated with 108	31.36±3.30	36.88±6.64	141.97±2.04	194.14±23.23
F-probability	P<0.001	-	P<0.001	-
LSD at the 5% level	9.46	-	36.56	-
LSD at the 1% level	12.74	-	49.24	-

[1]Data are expressed as mean ± standard error and number of animal in each group is 8.-If the difference between two means is higher than LSD at 5%, the effect will be significant (p<0.05).-If the difference between two means is higher than LSD at 1%; the effect will be significant (p<0.01).

Table 16. Effect of pyrimido[1,6-*a*]quinazoline derivative 108 on serum insulin and C-peptide levels at the fasting state and after 2 h of oral glucose loading in streptozocin-induced type 2 diabetic female rats.

Group(Parameters)	Insulin (µLU/mL) (Fasting)	Insulin (µLU/mL) (2 h)	C-peptide (pmol/mL)(Fasting)	C-peptide (pmol/mL) (2 h)
Normal Control	30.73±4.83	41.91±0.64	158.60±6.26	209.23±5.74
Diabetic Control	13.66±1.54	14.40±1.79	47.85±3.46	58.74±3.95
Diabetic treated with 108	29.90±5.25	34.41±5.60	65.19±3.40	172.17±10.03
F-probability	P<0.001	-	P<0.001	-
LSD at the 5% level	11.07	-	29.91	-
LSD at the 1% level	14.91	-	40.29	-

spectral data. One of these derivatives (**108**), 1-thioxo-hexahydro-3*H*-pyrimido[1,6-*a*]quinazolin-3-one, was tested using sublethal dose level and was found to have potent anti-hyperglycemic, antihyperlipidemic and antioxidant properties in neonatal streptozotocin-induced diabetic male and female *albino* rats (Table **15** & **16**). In this research work, the researcher reported the synthetic strategy that starts from the easy and commercially available compound, 6-aminothiouracil and the sodium salts of formyl ketones, which further led to the direct construction of the novel fused pyrimido[1,6-*a*] pyrimidine nucleus (**113-114**). Thus, a fusion of 6-aminothiouracil with the formyl salts (1) in piperidine acetate and acetic acid afforded the cyclo condensed pyrimido [1,6-*a*]pyrimidines **106-112** as summarized in (Fig. **12**).

2.3. Seven-Membered Heterocyclic Fused-Pyrimidines

Seven-membered rings fused with pyrimidine are being further divided into twelve classes, out of these, eight are still unexplored and offer the researchers to work upon this chemotype (Fig. **13**). Ring-closing metathesis (RCM) is a highly favorable reaction in the synthesis of heterocycle-fused azepine and azepinone derivatives.

2.3.1. Pyrimido[4',5':4,5]pyrimido[1,6-a]Azepines

2.3.1.1. Anticancer Activity

Sayed and research group[23] designed, synthesized and evaluated novel fused seven-membered tricyclic- pyrimido [4',5':4,5]pyrimido[1,6-*a*]azepines for their potential as anti-cancer agents. The representative compounds were evaluated for their cytotoxic potential against MCF-7 breast cancer cell line and kinase inhibitory activity against non-receptor (c-Src) and receptor (VEGFR) tyrosine kinases **(**Table **17)**. In comparison to the pyrrolo derivatives synthesized by the same group, their counterparts, pyrimido [4',5':4,5] pyrimido[1,6-*a*]azepines derivatives proved to exhibit slightly better growth inhibitory activity. With compound **115**, c-Src activity was observed to be reduced by 81%. Additionally, the data obtained by the group also indicated tricyclic pyrimidines with pyrimido[4',5':4,5]pyrimido[1,6-*a*]azepine scaffold as potential building blocks for antiproliferative agents with multi-kinase inhibitory properties.

2.3.2. Synthesis of N-aryl Amines Based Pyrimidine Derivatives

Oble *et al.* disclosed a new four-component coupling (4-CC) involving Ugi-Smiles coupling reaction followed by ring closure metathesis for the synthesis of *N*-aryl amines. By their results, authors reciprocated the role of *N*-allyl amines and allyl-substituted phenols to synthesize benzo-fused azepines based upon Multi-component reactions (MCR) strategy in which three or more reactants were coupled together in a one-pot procedure (Fig. **14**), suitable for the preparation of a large collection of molecules. Authors further disclosed that among all the post-Ugi modifications, olefin RCM provides a convergent pathway for the synthesis of macrocyclic lactams **116**[41].

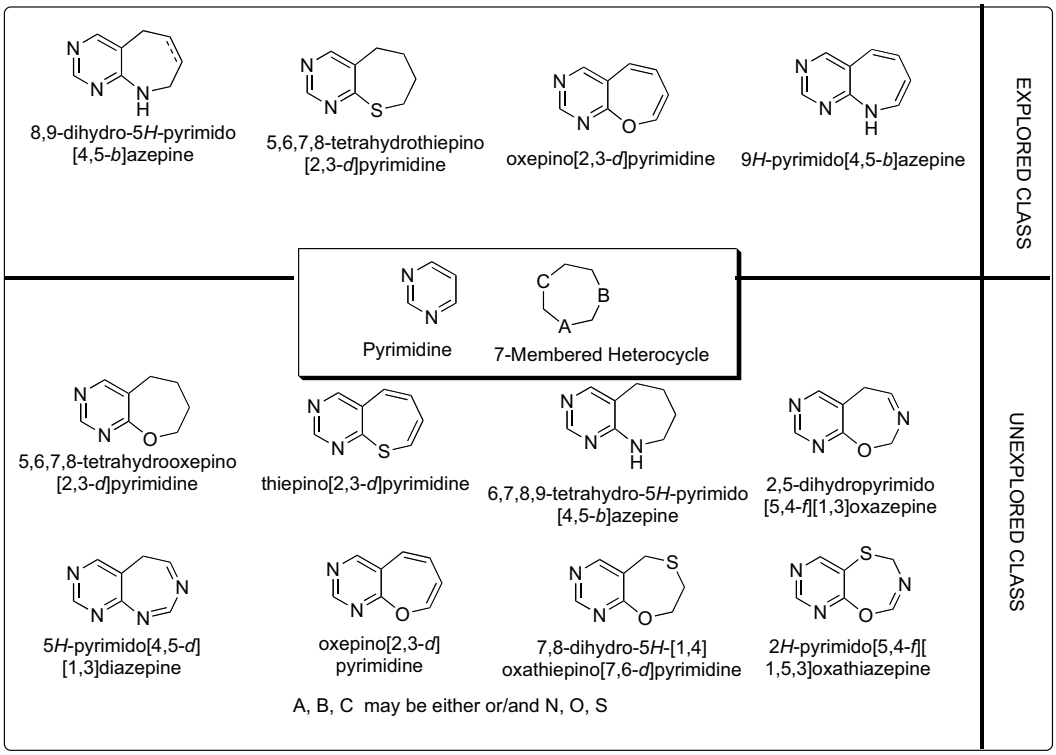
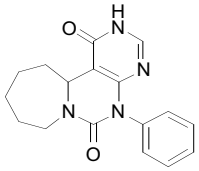


Fig. (13). Possible fused heterocycles obtained from fusion of pyrimidine with various seven-membered heterocycle.

Table 17. IC_{50} and % activity inhibition for compound 115.

Compound	Structure	IC_{50} (μg/mL) in MCF-7 cell line	% inhibition	
			c-Src	VEGFR
115		**11.2 ± 0.3**	**81**	**3**

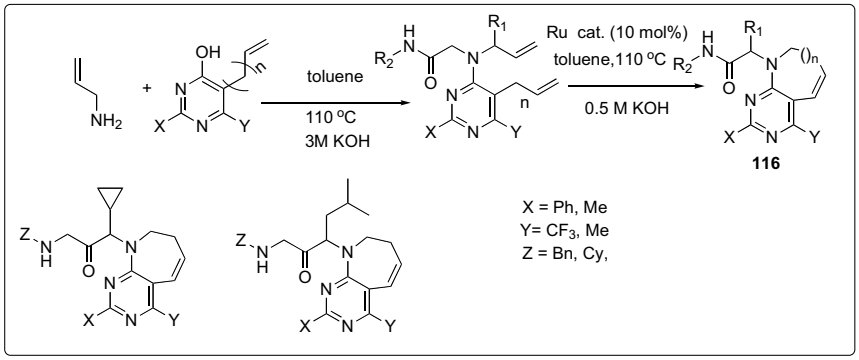


Fig. (14). Aryl-amine derivatives synthesized on the principle of RCM.

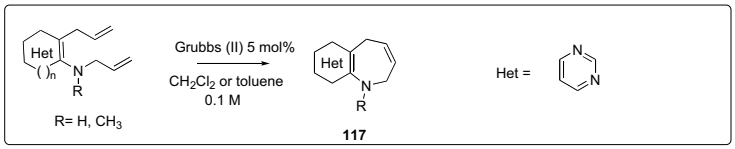


Fig. (15). Synthesis of pyrimidine-fused azepines.

2.3.4. Benzo-Fused Azepines

Thomas A. Moss and his team outlined the synthesis of benzo-fused azepines by treating the unprotected pyrimidine with 5 mol % Grubbs (II) catalyst in a solution of either dichloromethane or toluene which resulted in trace amount of the RCM azepine product **117** (Fig. **15**) [42]

2.4. Eight-Membered Heterocycle Fused-Pyrimidines

There are not many reports under this category. Eight-membered heteroaromatic ring fused pyrimidines (Fig. **16**) includes pyrimidines merged with eight membered heterocyclic ring systems**.**

2.4.1. Tricyclic Pyrimidine-Fused Eight-Membered Diazocines

Che *et al.* group synthesized novel tricyclic pyrimidine-fused with eight-membered heterocycles that were prepared by cyclization of an iminium ion using pyrimidine diamine systems with electron-rich aromatic rings (Fig. **17**). This was a new method developed for the effective preparation of novel tricyclic pyrimidine-fused eight-membered diazocines. The group also synthesized two types of diazocines pyrimidine-fused benzodiazepines **118** and indole diazocines **119** and **120** under mild reaction conditions [43].

2.4.2. Eight-Membered Rings (Azocine)

Ghosh and team synthesized eight-membered rings (azocine) **121** as preventives of urinary disturbances, AChE inhibitors, 5 and 17-β-hydroxysteroid dehydrogenase inhibitors. These were synthesized by the reaction of thiophenol-mediated radical cyclization that were prepared in 90–93% yields by the reaction with propargyl bromide in the presence of anhydrous K_2CO_3 in refluxing acetone for 4–5 h.[44] The synthetic route for the preparation of precursors is depicted in Fig. **18**.

2.5. Miscellaneous

2.5.1. Steroidal Pyrimidines

Heterosteroids emerged as an important area of research, and enormous efforts have been made for their synthesis because of their inherent biological activities. The enormous attention has been prearranged to annelate steroidal moiety with pyrazole, pyridine, isoxazole, pyrrole, tetrazole, isothiazole rings using various synthetic strategies. Due to emerging interests of pyrimidine derivatives as potential drugs, the synthesis of annelated steroidal pyrimidine ring system has become a subject of great concern [45]. Earlier, compounds with steroidal D-ring merged with pyrimidine were synthesized by Wang *et al.,* using the multi-component reaction of steroid-17-ones, urea, and aromatic aldehydes.[46] Recently, Sakia *et al.,* developed a versatile new method for synthesis of pyrimidine annelated steroids **122** by the MCR involving 16-DPA and benzamidine hydrochloride as substrates in the basic conditions of the microwave irradiation (Fig. **19**) [46].

2.5.2. Synthesis of Fused Steroidal Pyrimidines from β-halo-α,β-Unsaturated Aldehydes

Boruah *et al.* designed and synthesized Pd-catalyzed protocol for the synthesis of fused steroidal pyrimidines **123-133** from β-halo-α,β-unsaturated aldehydes under microwave irradiation. The β-halo-α,β-unsaturated aldehydes were synthesized from corresponding ketones using Vilsmeier formylation reaction (Fig. **20**).[45]

2.5.3. Pyrimidine-fused Steroidal scaffolds as anti-Alzheimer

Sabrye *et al.* synthesized heterocyclic pyrimidine and thiopyrimidine derivatives fused with steroidal structure (Fig. **21**). The modifications were carried out on the structures **134** and **159** that afforded different pyrimidine derivatives with a variety of biological activity. For illustration, a fusion of heterocyclic ring system containing two hetero atoms into ring D of **134** and **159** gave the corresponding pyrimidones **135-138**, pyrimidothiones **139-143,** pyrimidine imines **144-146** and N-cyanoiminopyrimidine, respectively. Similarly, the corresponding pyrimidone **152A** (X=O), pyrimidothione **152B** (X=S) pyrimidine imine **152C**(X=NH) were obtained from fusion with ring D of **147** and **134**, respectively. These compounds displayed a different functionalization at the pyrimidine ring that has displayed moderate to high activity. The best results were found with N-cyanoimino pyrimidine **147** derivatives, particularly compound **147**, that was found to possess the highest activity with IC_{50} value of 3.28 nM. This study confirmed that functionalization of pyrimidine ring is necessary for healthy interaction with β and γ secretases receptor, which could further suggest the facilitation in the formation of hydrogen bonding thus resulting in reduced β-amyloid formation that were screened for their anti-Alzheimer potential [47] which is an age-related neurodegenerative disease[48]. Flurbiprofen was used as the reference for the measurement of the activity of the synthetics. Besides this some of their synthetics also exhibited noteworthy activity in lowering the β -amyloid, which is the principle component of amyloid deposits found in the plaques that is widely alleged to initiate the pathogenesis of Alzheimer and to trigger a cascade of events such as neurotoxicity, oxidative injury, and inflammatory response that contribute to the progression of Alzheimer.

2.5.4. Antidiabetic α-glucosidase and α-amylase inhibitors based on pyrimidine-fused heterocycles

Nezhad *et al.* synthesized pyrimidine-fused heterocycles involving a MCR of barbituric acid, aldehyde, and amine in a single-step process, offering easy access to the formation of pyrimidine combined derivatives **153** (Fig. **22**). These derivatives were further explored for their α-amylase and α-glucosidase inhibitory action (Table **18**). These enzymes are known to play a pivotal role in the reduction of postprandial hyperglycemia in diabetic patients. The synthetics were evaluated against acarbose that showed 82% inhibition. The synthetic compounds revealed either weak inhibitory action as in **153** and **154** or moderate inhibitory properties viz. **155, 156, 157** which was assessed to be desirable as they exhibited low susceptibility for any development of the gastrointestinal side effects. Thus, the research group concluded that pyrimidine-fused heterocycles may make up an important structural element that could be used in the construction of efficacious antidiabetic α-glucosidase inhibitors [49].

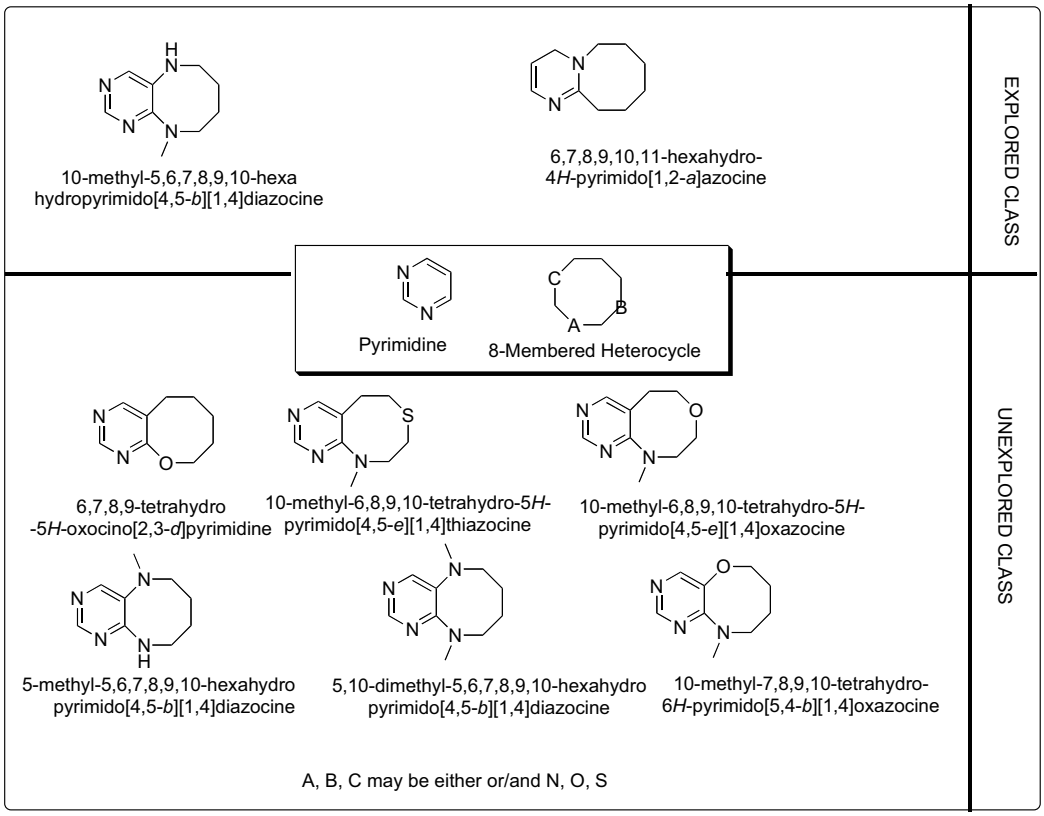


Fig. (16). Possible fused heterocycles obtained from fusion of pyrimidine with various eight-membered heterocycles

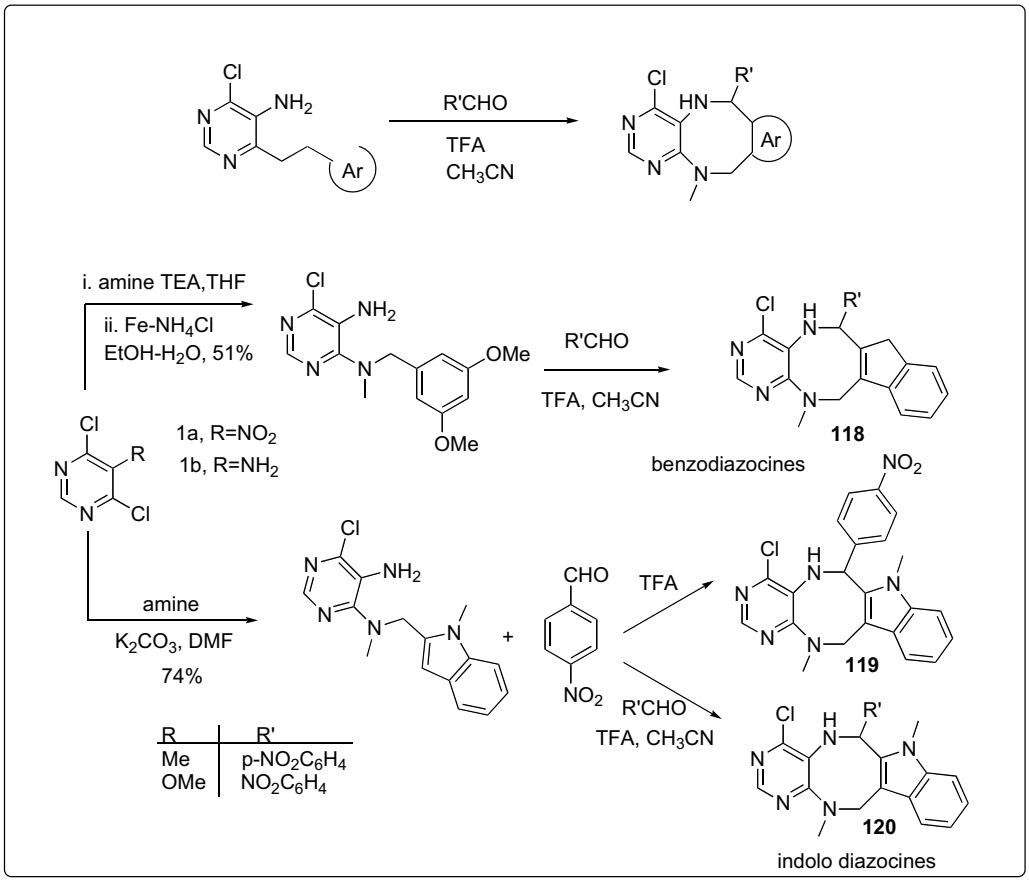


Fig. (17): Synthesis of Tricyclic pyrimidine-fused eight-membered diazocines

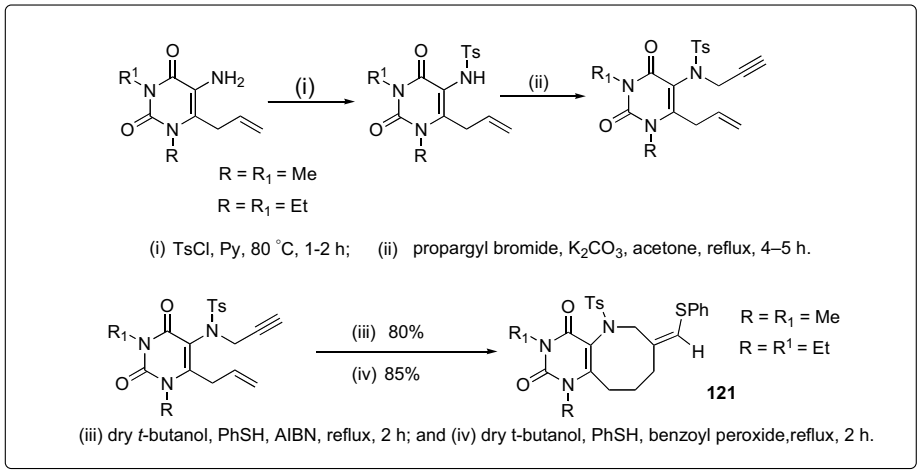


Fig. (18). Synthesis of Pyrimidine containing azocine derivative.

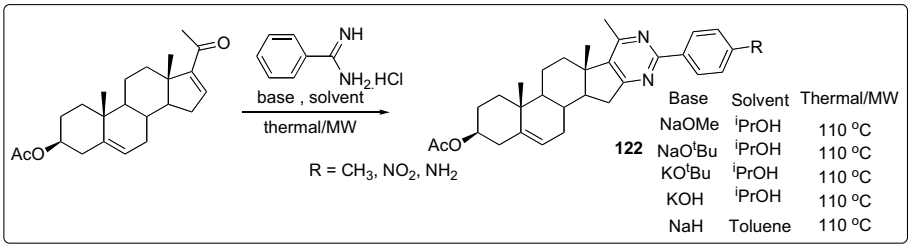


Fig. (19). Synthesis of pyrimidine annelated steroids.

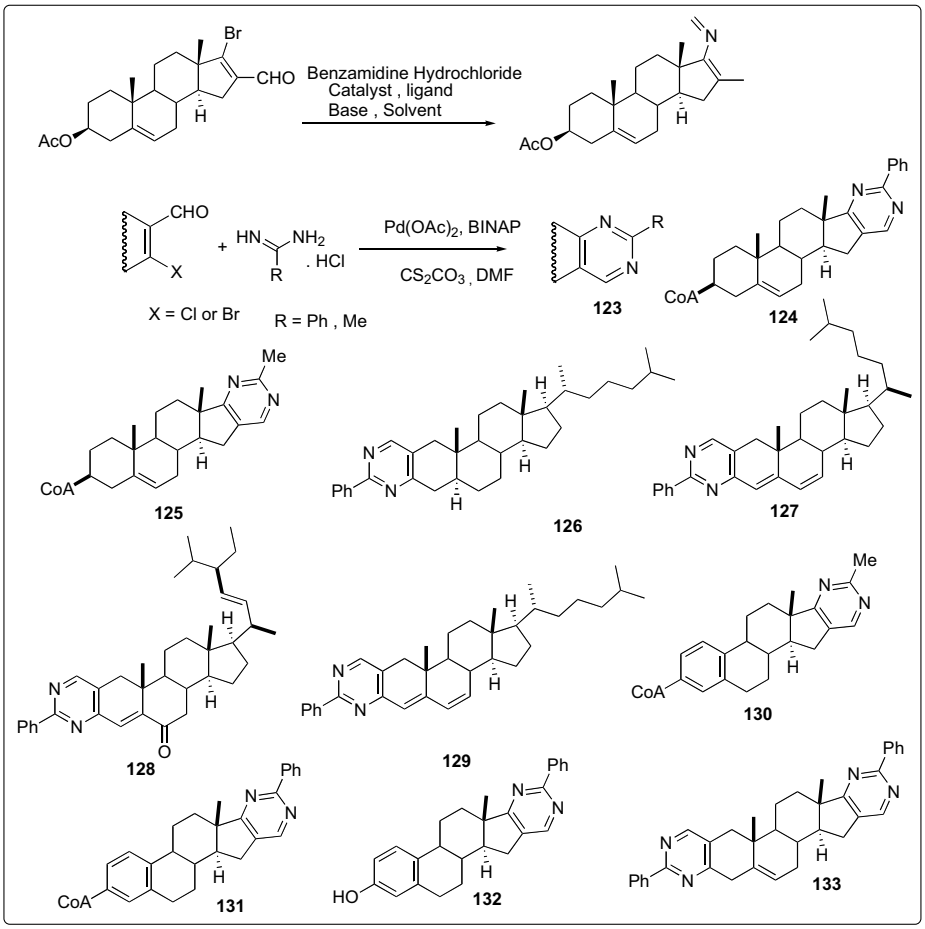


Fig. (20). Synthesis of fused steroidal pyrimidines from β-halo-αβ- unsaturated aldehydes.

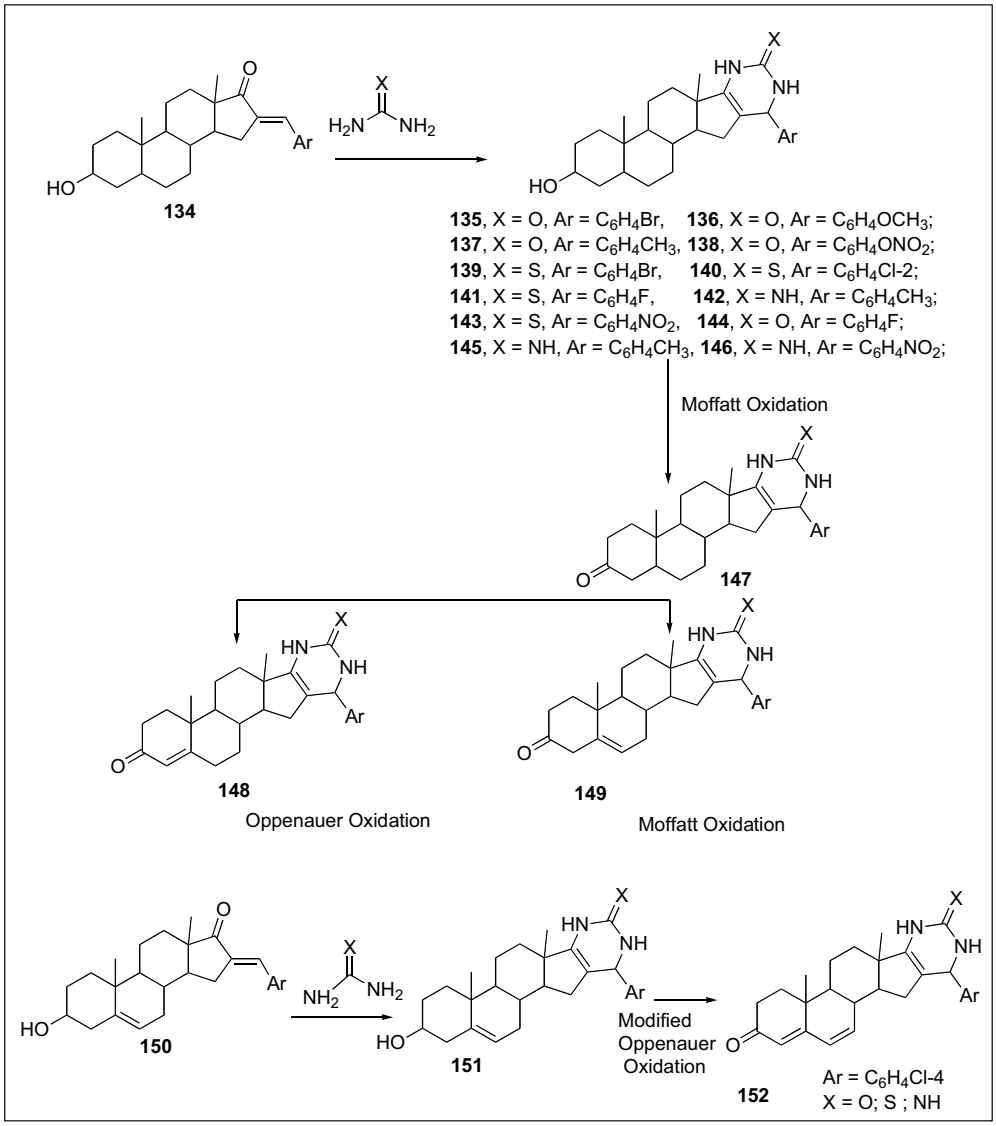


Fig. (**21**): Synthesis of fused steroidal based pyrimidine scaffolds.

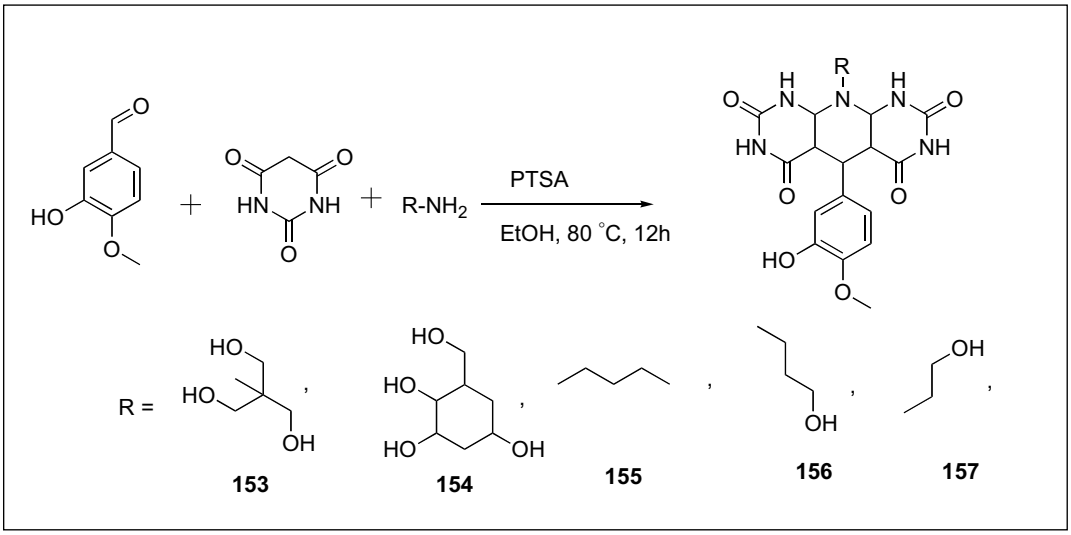


Fig. (22). Synthesis of chemical structures as α-glucosidase inhibitors

Table 18. Inhibitory activity of synthetic compounds against porcine pancreatic α-Amylase. The inhibitory properties of synthetic compounds against α -Amylase were measured in 20 mM sodium phosphate buffer (pH 6.9), containing 6 mM sodium chloride.

Compound	α- amylase inhibition (%)
Acarbose	82.88
153	19.8
154	24.25
155	26.21
156	2.7
157	2.7

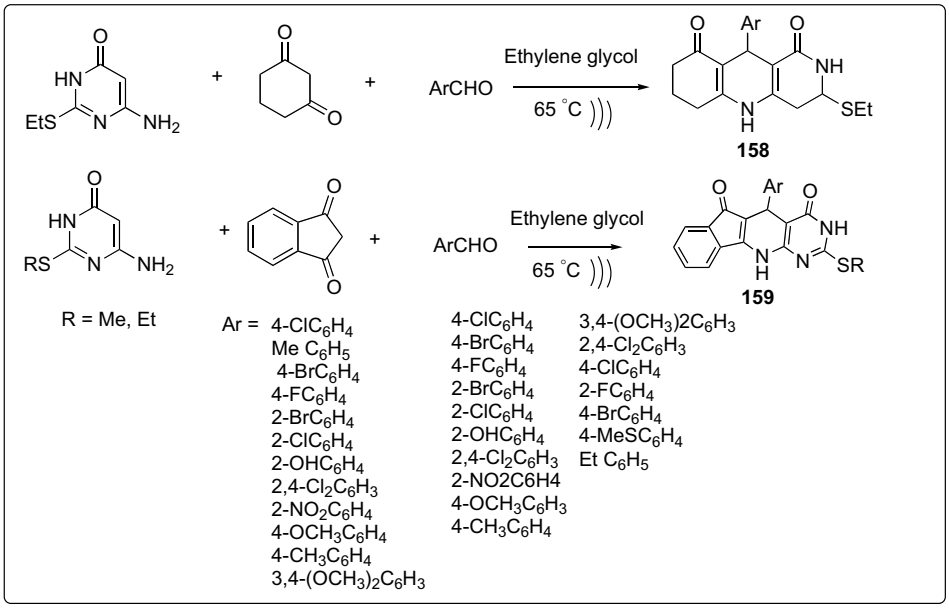


Fig. (23). Synthesis of indenopyrido[2,3-*d*]pyrimidine **23a** and pyrimido[4,5-*b*]quinolone **23b** derivatives.

2.5.5. Indenopyrido[2,3-d]pyrimidine and pyrimido[4,5-b]quinoline derivatives

Nia *et al*. synthesized indenopyrido[2,3-*d*]pyrimidine **158** and pyrimido[4,5-*b*]quinolone **159** derivatives (Fig.**22**) via one-pot three-component reaction of 6-amino-2-(alkylthio)-pyrimidin-4(3*H*)one, 1,3-indanedione, or 1,3-cyclohexadione and arylaldehyde under ultrasonic irradiation in ethylene glycol as solvent at 65 °C. The reaction carried out within small time duration of 10-33 min gave excellent yields of 82-97% (Fig. **23**). This effortless work for the synthesis of the products, without the use of catalyst, mild reaction condition yielded high to excellent amount of products in very short reaction times [50].

2.5.6. Pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-ones

Hamid and co-workers gave the synthesis of 7-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-5-phenyl-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one **162,** by reaction of 1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one **160** with 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **161** using ethanol as a solvent. Structure **162** was elucidated by elemental analysis, spectral data and chemical transformation methods. Further when compound **162** was reacted with **163** in chloroform under reflux afforded product as 3-acetyl-8-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1,6-diphenylpyrido[2,3-*d*][1,2,4]triazolo[4,3-a]pyrimidin-5(1*H*)-one **164** and **165** respectively (Fig. **24**).The synthetics were further explored for their cytotoxic potential in HepG2 and MCF-7 cell lines using doxorubicin as reference for the same (Table **19**).[51]

2.5.7. Novel Heterocyclic-Fused Pyrimidine Derivatives: Synthesis, and Pharmacological Screening

Sayed and his group synthesized novel heterocyclic-fused pyrimidines derivatives via various MCR as depicted in different schemes in Fig. (**25**). In scheme1,pyrimido[5,4-*e*]pyrrolo[1,2-*c*]pyrimidine derivatives with different substituents on the tricyclic backbone were obtained, this was achieved by sodium ethoxide-catalyzed intramolecular cyclization of the ureido derivative **167 (**also cyclised to give **169**) that reacted to give pyrimido[5,4-*e*]pyrrolo[1,2-

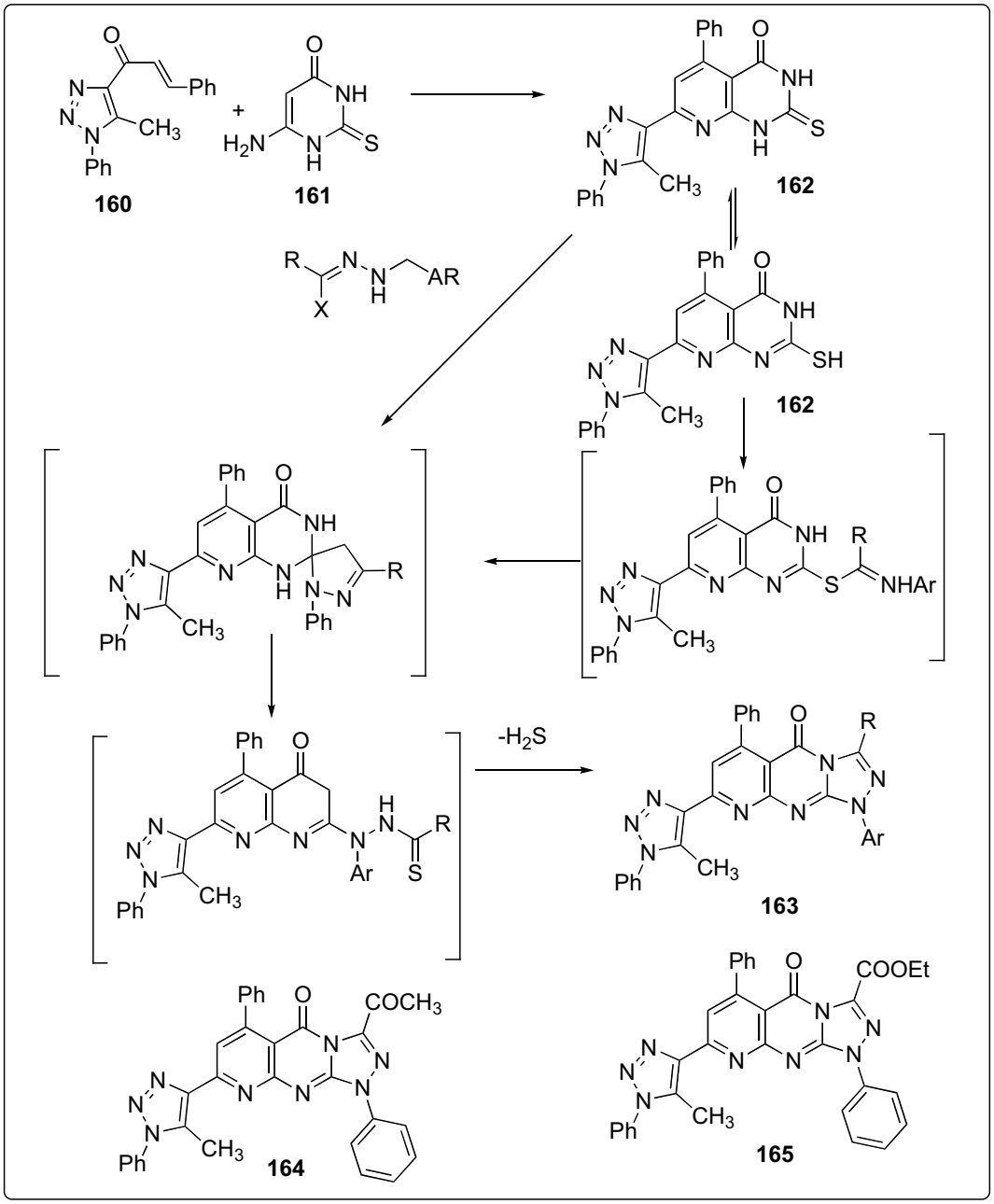


Fig. (24). Synthesis of pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)- ones

Table 19. The *in vitro* inhibitory activity of tested compounds against tumor cell lines expressed as IC_{50}values (μM) ± standard deviation from six replicates.

Compound	Human breast carcinoma cell line (MCF-7)	Human hepatocellular carcinoma (HepG2)
Doxorubicin	0.46±0.21	0.42±0.22
164	37.7±0.11	27.94±0.07
165	39.9±0.07	43.62±0.14

c]pyrimidine **168**. in addition, fusion of the key intermediates **166** with thiourea resulted in nucleophilic substitution reaction that was followed by cyclization onto the cyano function that yielded the tricyclic compounds **170**, **168,** further reacted with *p*-chloro- benzaldehyde to provide **171**. Also, the treatment of the **166** with formic acid resulted in the formation of tricyclic derivatives **169**. Further treatment of **172** with phosphorus oxychloride in the presence of

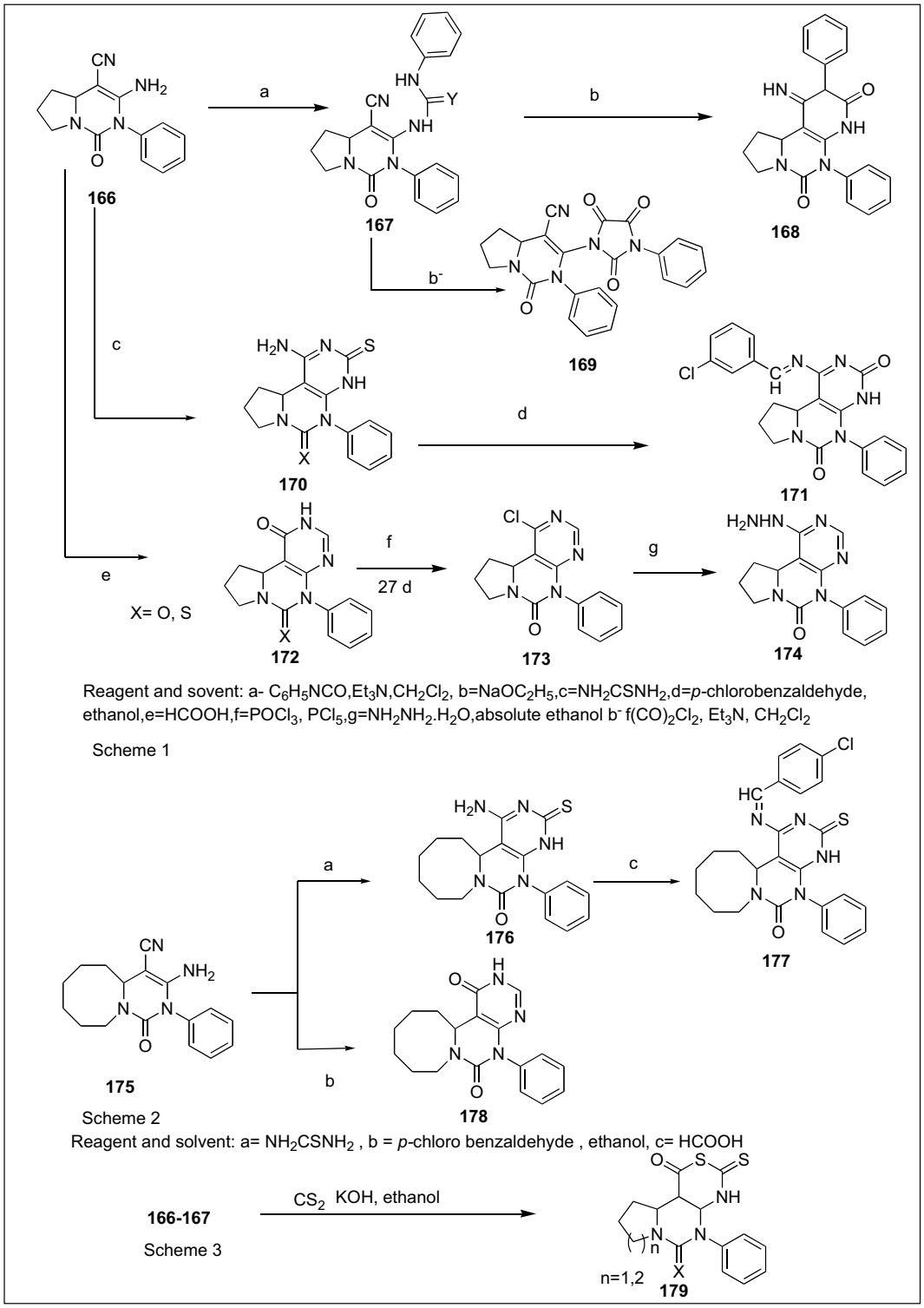


Fig. (25). Synthesis of Novel heterocyclic-fused pyrimidine derivatives

a catalytic amount of phosphorus pentachloride produced the more stable aromatic chloro derivative **173** that reacted with hydrazine hydrate affording the tricyclic hydrazine derivative **174**. The azepine analogs were synthesized using key intermediate enamino-nitrile **171**. Fusion of **175** with thiourea produced the 1-aminopyrimido [4',5':4,5]pyrimido [1,6-*a*]azepine **176** that was then condensed with p-chlorobenzaldehyde forming Schiff's base **177**. On the other hand, reacting **175** with formic acid afforded the tricyclicpyrimido [4',5':4,5]pyrimido[1,6-a]azepine **178**. Finally, the scheme 3 was concerned with the reaction of the five-membered enaminonitriles **166** or the seven-membered analog **171** with carbon disulfide that afforded the target pyrrolopyrimidothiazines **179**. All the structures were

Table 20. Antiproliferative activity of the synthesized fused pyrimidine derivatives against MCF-7 cell line.

Compound	IC_{50} µg/mL
Doxorubicin	**14.01±0.3**
171	**9.6±0.2**
170A (X=O)	**13.6±0.4**
170B (X=S)	**22.8±0.2**
172	**12.4±0.2**
173	**14.8±0.3**
174	**20±0.5**
176	**11±0.4**
177	**10.8±0.2**
178	**10.6±0.2**
179A (X=O, n=1)	**17±0.4**
179B (X=S, n=1)	**18.8±0.3**
179C (X=O, n=2)	**14±0.2**

supported by spectral and elemental analysis data. The synthetics were further evaluated for their anticancer properties. In this investigation, all the newly synthesized compounds were subjected to cytotoxic screening against MCF-7 breast cancer cell line (Table **20**). Moreover, kinase inhibitory assay was done for compound adjacent to the non-receptor and receptor tyrosine kinases c-Src and VEGFR, respectively. The tested compounds were more compelling against c-Src than VEGFR, and the highest activity was observed for **178** depicting 81% c-Src activity inhibition [23].

2.5.8. Pyrimido[5,4-e]pyrrolo[1,2-c]pyrimidine

2.5.8.1. Anticancer Activity

Ream *et al.* [23] synthesized and assessed tricyclic-pyrimido[5,4-*e*]pyrrolo[1,2-*c*]pyrimidine derivatives for their potency to act as anticancer agents. The derivatives were evaluated against MCF-7 breast cancer cell line, wherein, the cell growth inhibitory activity was measured *in vitro* using the SulfoRhodamine-B-stain (SRB) assay method. The data obtained from the biological studies was co-related with the inhibitory potential **(**Table **21)**. It was noticed that substitution of a phenyl group on the *N* atom of one of the pyrimidine ring (**180**) resulted in improved activity with an IC_{50} of 9.6µg/mL, and which was superior as compared to that of standard, doxorubicin. This indicates that bulkiness on the pyrimidine ring is well tolerated and confers higher lipophilicity, which might be thought to contribute towards molecular uptake by the cells or ligand-receptor interaction or both. Among these compounds, oxo compounds **181** and **183** exhibited better inhibitory potential in comparison to thioxo analogs **182** and **184**, which highlighted the fact that with an increase in hydrophilicity, activity increases. Cytotoxic activity was further augmented when the carbonyl group of **183** (14.8µg/mL) was replaced with hydrazine **185** (11 µg/mL).

2.5.9. 3-Amino2-mercapto5,6,7,8-tetrahydro-benzo(b) thieno-[2,3-d]pyrimidine-4-(3H)-ones Derivatives

Sirisha *et al.* attempted a successful synthesis utilizing the perception of bioisosterism for the synthesis of 3-Amino2-mercapto5,6,7,8-tetrahydro-benzo(b)thieno-[2,3-*d*]-pyrimidine-4-(3*H*)-ones **186** that were further treated with acetyl chloride, urea, carbondisulphide, chloroacetic acid, benzoin to affords novel fused thiadiazole, thiadiazole compounds **187-191** (Fig. **26**). These formed synthetics were further explored for their anti-microbial studies (Table **21**) on gram-positive, gram-negative and fungal organisms. The standard drug used for antimicrobial activity was ampicillin and ketoconazole was used for antifungal activity (Table **22**); additionally the compounds were also tested for their anti-proliferative potential in cancer cell lines by MTT assay method. Compound **191** showed promising antiproliferative activity. The tested compounds thereby exhibited noteworthy antimicrobial and anticancer activity.[52]

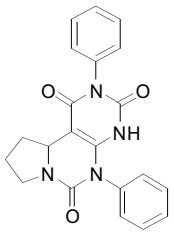
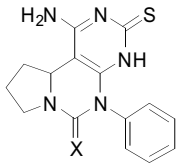
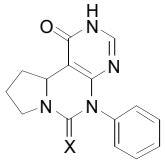
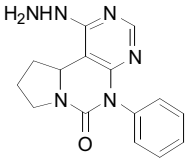
3. FUSED PYRIMIDINE MARKETED DRUGS

In Table **23** we have listed pyrimidines fused drugs which are in the market.[53]

4. LATEST PATENTS FILED FOR PYRIMIDINES FUSED DERIVATIVES

During the last two decades, several pyrimidine derivatives[64]have been developed as potent chemotherapeutic agents and have found acceptable clinical applications. We have compiled a list of fused pyrimidine-based compounds, which were patented after 2012 as summarized in Table **24**. A significant number of patents published during 2012-2015 confirm that the pyrimidine scaffold has received much attention from both the industry and academic researchers.

Table 21. Antiproliferative activity of pyrimido[5,4-*e*]pyrrolo[1,2-*c*]pyrimidine derivatives against MCF-7 cell line.

Compound	Structure	X	IC_{50} (µg/mL)
180		-	9.6 ± 0.2
181		O	13.6 ± 0.4
182		S	22.8 ± 0.2
183		O	14.8 ± 0.3
184		S	20 ± 0.5
185		-	11 ± 0.4
Doxorubicin			14.1 ±.3

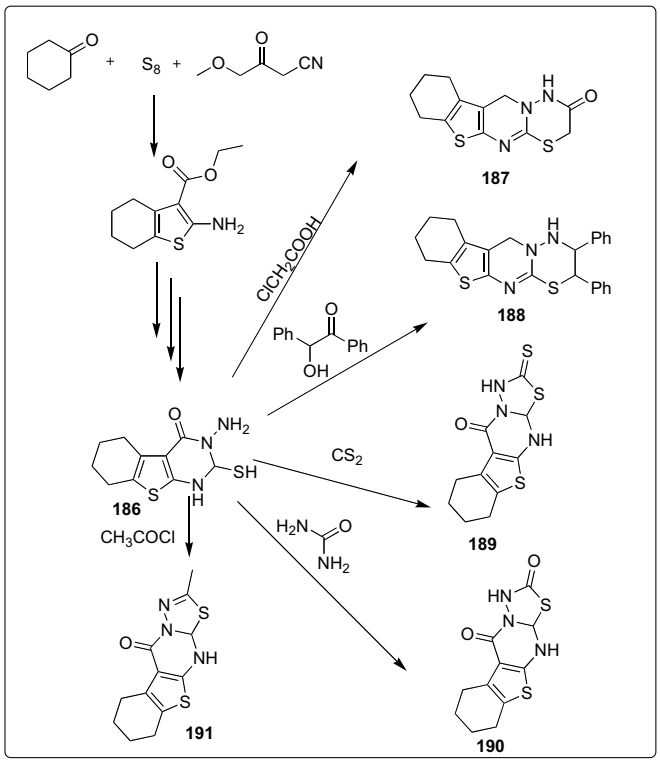


Fig. (26). Synthesis of 3-amino2-mercapto-5,6,7,8-tetrahydro- benzo(b)thieno-(2,3-*d*)-pyrimidine-4-(3*H*)-ones derivatives.

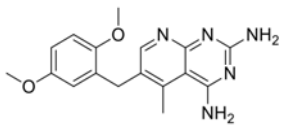
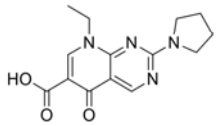
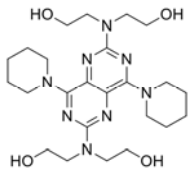
Table 21. Antimicrobial activity data of the synthetics (187-191).

Compound	Antimicrobial Activity (zone of inhibition in mm)											
	Staphylococcus aureus (conc in µg/ml)			*Staphylococcus epidermidis* (conc in µg/ml)			*Micrococcus luteus* (conc in µg/ml)			*Escherichia coli* mutant(conc in µg/ml)		
	25	50	100	25	50	100	25	50	100	25	50	100
187	5	12	14	5	12	14	4	10	13	6	9	13
188	5	13	14	4	11	13	5	10	14	4	10	13
189	6	12	13	5	12	14	4	10	13	4	10	13
190	5	10	12	4	12	13	5	11	14	4	11	14
191	4	11	13	5	11	12	5	10	13	5	10	13
Ampicillin (10 µg/ml)	17	17	17	18	18	18	17	17	17	18	18	18

Table 22. Antifungal activity data of the synthetics.

Compound	Antifungal Activity (zone of inhibition in mm)					
	Candida albicans (conc in µg/ml)			*Aspergillus aniger* (conc in µg/ml)		
	25	50	100	25	50	100
187	8	12	16	8	14	18
188	9	12	17	9	13	19
189	9	13	17	8	14	18
190	9	12	16	8	11	19
191	9	12	16	8	11	19
Ketoconazole (10 µg/ml)	16	18	18	20	19	20

Table 23. Fused Pyrimidines based marketed drugs

Drug Name	Chemical Name	Indication	Mechanism of Action	Chemical structure
Piritrexim Isetionate[54]	2,4-Diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*]pyrimidine mono(2-hydroxyethanesulphonate)	Antineoplastic	Folic acid Antagonist	
Piromidic Acid[55]	8-Ethyl-5,8-dihydro-5-oxo-2- (pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid	Antibacterial	Inhibits Topoisomerase II	
Dipyridamole[56]	2,2',2'',2'''-[(4,8-Dipiperidino-pyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol	Vasodilator	Phosphodieterase inhibitor	

(Table 23) contd…

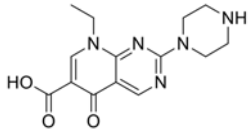
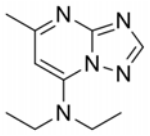
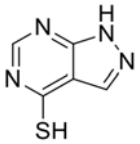
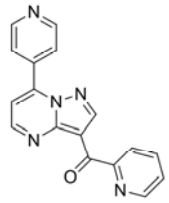
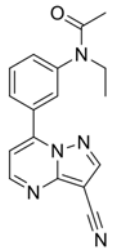
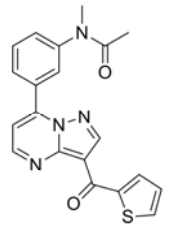
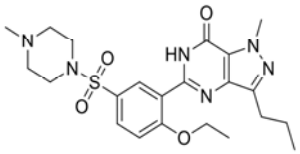
Drug Name	Chemical Name	Indication	Mechanism of Action	Chemical structure
Pipemidic acid[57]	8-Ethyl-5,8-dihydro-5-oxo-2- (piperazin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid	Urinary tract infections	Nucleic acid inhibitor	
Trapidil[58]	7-Diethylamino-5-methyl-1,2,4- triazolo[1,5-*a*]pyrimidine	Vasodilator	Nitric oxide donor	
Tisopurine[59]	1H-Pyrazolo[3,4-*d*]pyrimidine- 4-thiol	Disorders associated with hyperuricaemia	Rac1 activation	
Ocinaplon[60]	pyridin-2-yl-(7-pyridin-4-ylpyrazolo[1,5-*a*]pyrimidin-3-yl)methanone	Anxiolytic	enhances the action of the inhibitory neuro-transmitter GABA,	
Zaleplon[61]	N-(3-(3-cyanopyrazolo[1,5-*a*] pyrimidin-7-yl)phenyl)-N-ethylacetamide	Hypnotic and Sedative	enhances the action of the inhibitory neuro-transmitter GABA,	
Indiplon[62]	N-methyl-N-[3-[3-(thiophene-2-carbonyl) pyrazolo[5,1-*b*]pyrimidin-7-yl]phenyl]acetamide	Hypnotic and Sedative	enhances the action of the inhibitory neuro-transmitter GABA,	
Sildenafil[63]	1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl) phenylsulfonyl]-4-methylpiperazine	erectile dysfunc-tion and pulmonary arterial hypertension	inhibit cGMP-specific phosphodiesterase type 5 (PDE5)	

Table 24. Summary of patent filed in the field of pyrimidine-fused derivatives.

S.No.	Year	Patent No.	Title	Field of Patent	References
1	2012	US 8153639 B2	Substituted thieno- and Furano- fused pyrimidines as PI3K inhibitors	The present invention relates to pyrimidine derivatives and their use as inhibitors of phosphatidylinositol 3-kinase (PI3K).	[65]

(Table 24) contd….

S.No.	Year	Patent No.	Title	Field of Patent	References
2	2012	WO 2012137089 A1	Pyrrolo [2, 3 -*d*] pyrimidine derivatives as inhibitors of tropo-myosin- related kinases	The invention described herein relates to certain pyrrolo[2,3-d]pyrimidine compounds and the pharmaceutically acceptable salts of such compounds. The invention also relates to the processes for the preparation of the compounds, compositions containing the compounds, and the uses of such compounds and salts in treating diseases or conditions associated with tropomyosin-related kinase (Trk)..	[66]
3	2012	US 20120232073 A1	Fused bicyclic pyrimidine derivatives and methods of use thereof	The present invention relates to Fused Bicyclic Pyrimidine Derivatives and methods of using the Fused Bicyclic Pyrimidine Derivatives for treating or preventing obesity, diabetes, a diabetic complication.	[67]
4	2012	US 8129397 B2	Substituted thieno[2,3-*d*]pyrimidines as AMPA modulators	The present invention relates to heterocyclic derivatives, to pharmaceutical compositions comprising these compounds and to their use in therapy, in particular to their use for the manufacture of a medicament for the treatment or prevention of psychiatric diseases where an enhancement of synaptic responses mediated by AMPA receptors is required, such as schizophrenia, depression and learning and memory disorders.	[68]
5	2012	EP 2480550 A1	Methods for preparing pyrimidine derivatives useful as protein kinase inhibitors	Invention of Methods and synthesis of pyrimidine derivatives useful as protein kinase inhibitors.	[69]
6	2013	US 20130317021 A1	Heterocyclic pyrimidine carbonic acid derivatives that are useful in the treatment, amelioration or prevention of a viral disease	The present invention relates to a compound having the general formula ten optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, co-drug, co-crystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,	[70]
7	2013	US 8349847 B2	Pyrazolo [3,4-*d*] pyrimidine derivatives as anti-cancer agents	The invention relates to substituted pyrazolo[3,4-d]pyrimidine derivatives of the formula 11,	[71]
8	2013	US 20130190492 A1	Substituted Quinazoline and pyridopyrimidine derivatives	The present application provides novel substituted quinazoline and pyridopyrimidine compounds and pharmaceutically acceptable salts thereof. Also provided are methods for preparing these compounds. These compounds are useful in co-regulating PI3K and mTOR activity by administering a therapeutically effective amount of one or more of the compounds to a patient.	[72]
9	2013	WO 2013117615 A1	Piperidino-pyrimidine derivatives for the treatment of viral infections	This invention relates to piperdino-pyrimidine derivatives, processes for their preparation, pharmaceutical compositions, and their use in treating viral infections.	[73]
10	2013	EP 2543375 A1	Pyrrolo-pyrimidine analogs as inhibitors of Bruton's tyrosine kinase	The invention relates to irreversible kinase inhibitor compounds, methods for synthesizing such irreversible inhibitors, and methods for using such irreversible inhibitors in the treatment of diseases.	[74]
11	2013	US 8569314 B2	Triazole and tetrazolo pyrimidine derivatives as HNE inhibitors for treating COPD	The present invention relates to novel heterocyclically fused diaryl dihydro pyrimidine derivatives and their use alone or in their combination for the treatment and prevention of diseases and also to their use for preparing medicaments for the treatment and/or prevention of diseases particularly disorders of the lung and the cardiovascular system.	[75]

(Table 24) contd….

S.No.	Year	Patent No.	Title	Field of Patent	References
12	2013	EP 1939204 B1	Fused heterocyclic derivative, medicinal composition containing the same, and therapeutic use thereof	The present invention relates to fused heterocyclic derivatives that have an antagonistic activity against gonadotropin releasing hormone and can be used for the prevention or treatment of sex hormone-dependent disease such as, benign prostatic hypertrophy, hysteromyoma, etc	[76]
13	2014	US 8633193 B2	Pyrrolo-pyridine, pyrrole-pyrimidine, and related heterocyclic compounds	This invention generally relates to pyrrole-pyridine, pyrrole-pyrimidine and related heterocyclic compounds that act as modulators of natural complement C5a receptors.	[77]
14	2014	EP 2708538 A1	Process for preparing fused pyrimidinedione derivatives, useful as TRPA1 modulators	The present patent application relates to combined pyrimidinedione dione derivatives with transient receptor potential ankyrin1 (TRPA1) activity.	[78]
15	2014	US 8653091 B2	Pyrid-2yl fused heterocyclic compounds and compositions and uses thereof	The invention relates to fused heterocyclic compounds of the class tetrahydropyrido[4,3-d]pyrimidinesand pharmaceutical compositions comprising such compounds.	[79]
16	2014	WO 2014138562 A1	Thieno[3,2-*d*]pyrimidine-6-carboxamides and analogs as sirtuin modulators	The invention relates to novel substituted thieno[3,2-d]pyrimidine-6-carboxamide sirtuin inhibitors and methods of use thereof.	[80]
17	2014	US 20140179668 A1	Fused pyrimidine compounds and use thereof	The invention relates to fused pyrimidine compounds as kinase inhibitors, such as multi-kinase inhibitors, are provided as IGF-IR inhibitors are provided.	[81]
18	2014	WO 2014110000 A1	Pyrido- or pyrrole-fused pyrimidine derivatives as autotaxin inhibitors for treating pain	This invention relates to bicyclic pyrimidine compounds, or pharmaceutically acceptable salts thereof, and therapeutic use compounds as autotaxin inhibitors.	[82]
19	2014	US 20140249131 A1	Substituted 7-Oxo-Pyrido[2,3-*d*]Pyrimidines and Methods of Use	This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer.	[83]
20	2014	US 8748435 B2	Pyrazolopyrimidine derivatives	The present invention relates to pyrazolopyrimidine derivatives, to methods of preparing and their use in the treatment of diseases and disorders involving autoimmune diseases, angiogenesis, pain, and inflammatory diseases.	[84]
21	2014	US 8791123 B2	Substituted pyrazolo[1,5-*a*]pyrimidine compounds as Trk kinase inhibitors	The invention relates to certain substituted pyrazolo[1,5-a]pyrimidine compounds that exhibit Trk family protein tyrosine kinase inhibition, and which are useful in the treatment of pain, cancer, inflammation, neurodegenerative diseases and certain infectious diseases.	[85]
22	2014	US 8772272 B2	Pyrido-and pyrimidopyrimidine derivatives as antiproliferative agents	This invention relates to pyrimidopyrimidine derived macrocycles that have been found to possess anti-proliferative activity, such as anti-cancer activity.	[86]
23	2014	US 20140100184 A1	Selective inhibitors of histone methyltransferase dot1l	The invention generally relates to the design and synthesis of ribose and non-ribose containing selective inhibitors of histone methyltransferase.	[87]

(Table 24) contd….

S.No.	Year	Patent No.	Title	Field of Patent	References
24	2014	WO 2014056953 A1	Pyrrolo[3,2-*d*]pyrimidine derivatives for the treatment of viral infections and other diseases	This invention relates to pyrrolo[3,2-c/]pyrimidine derivatives, processes for their preparation, pharmaceutical compositions, and their use in treatment and therapy of diseases.	[88]
25	2014	WO 2014119752 A1	Condensed cyclic pyrimidine compound, and harmful organism control agent comprising same	The present invention relates to a pest control agent comprising a fused pyrimidine compound.	[89]
26	2015	US 20150045324 A1	Novel fused pyrimidine derivatives for inhibition of tyrosine kinase activity	The present invention relates to a novel fused pyrimidine derivative having an inhibitory activity of tyrosine kinases, and a pharmaceutical composition comprising same as an active ingredient.	[90]
27	2015	US 20150031881 A1	Pyrazolopyrimidine derivatives and methods of use thereof	This invention relates to pyrazolopyrimidine derivatives, including derivatives and analogs of inhibitors of short-chain dehydrogenase/reductase (SDR) family of NADPH-dependent oxidoreductases.	[91]
28	2015	US 8933067 B2	Pyrido and pyrimidopyrimidine derivatives as antiproliferative agents	This invention relates to pyrimidopyrimidine derived macrocycles that have been found to possess anti-proliferative activity, such as anti-cancer activity.	[92]
29	2015	US 8946237 B2	Pyrazolo[1,5-*a*]pyrimidines as MARK inhibitors	The invention relates to pyrazolo[1,5-a]pyrimidine derivatives that selectively inhibit microtubule affinity regulating kinase (MARK) and are therefore useful for the treatment or prevention of Alzheimer's disease.	[93]
30	2015	US 20150010518 A1	Nr2e1 mini-promoters	The invention relates to novel NR2E1 promoter compositions and related methods.	[94]
31	2015	EP 2694513 B1	Pyrazolo pyrimidine derivatives	The invention relates to pyrazolopyrimidine derivatives and involves in the treatment of autoimmune diseases, angiogenesis, pain, and inflammatory diseases.	[95]
32	2015	US 8933072 B2	Substituted 5-,6- and 7-membered heterocycles, medicaments containing such compounds, and their use	The present invention relates to compounds derived from the chemical scaffold that is structurally defined by the formula 40	[96]
33	2015	WO 2015028848 A1	Bicyclic heterocyclic compounds as multikinase inhibitors	The invention relates to bicyclic heterocyclic compounds processes for their preparation, pharmaceutical compositions and their use in the prevention and treatment of diseases or disorders associated with abnormal protein kinase activity such as proliferative diseases.	[97]
34	2015	US 20150038461 A1	Thiopyrimidinecarboxamides as CXCR1/2 modulators	The present disclosure provides pyrimidine carboxamides useful as pharmaceutical agents, synthesis processes, and pharmaceutical compositions that include pyrimidine carboxamide compounds. More specifically, the present disclosure provides CXCR1/2 inhibitor compounds that are helpful in treating a variety of inflammatory and neoplastic disorders.	[98]

CONCLUSION

Pyrimidine fused heterocyclics are rightly claimed to have made an inextricable contribution to the multifaceted activities projected by various such scaffolds. The broad spectrum of activities exhibited by scaffold bearing pyrimidine ring makes them indispensable for the synthesis of numerous pharmacologically active compounds. The review was put forward with an incentive to congregate such pyrimidine fused heterocyclics derivatives synthesized from 2010-till date and classifying them in a manner that would justify the activities portrayed by these derivatives. Retrosynthetic strategies for these derivatives have also been discussed. The compilation following various combination and permutation techniques helped in providing insight into different explored and unexplored classes of fused pyrimidines thereof, suggesting the classical approach to drug design. A plethora of information retrieved from the structure–activity relationship studies, IC_{50} values helped in highlighting the potential of inhibitory potential. The pyrimidine fused heterocyclics were observed to be potent against multiple bioactivities such as antibacterial, antifungal, antiviral, anti-inflammatory, antimalarial, anticancer, HIV infections, etc. Furthermore, the patents filed for the fused pyrimidines from 2012 to 2015 have also been discussed. To (or "intending to") provide information about the market status of such compounds, a list representing the marketed drugs has also been compiled. The unexplored classes of fused pyrimidines derivatives would provide researchers an opportunity to design, synthesize and generate libraries of fused pyrimidines.

LIST OF ABBREVIATIONS

DNA	=	Deoxyribonucleic acid
RNA	=	Ribonucleic acid
CNS	=	Central Nervous System
G1	=	Gap 1 phase
HCT	=	Human colorectal cancer cell line
A549	=	Human Lung cancer cell line
MCF-7	=	Human Breast cancer cell line
HepG2	=	Liver cancer cell line
PC-3	=	Prostate cancer cell line
EC_{50}	=	Effective Concentration
IC_{50}	=	Inhibitory Concentration
NIH3T3	=	Mouse embryo fibroblast cell line
SAR	=	Structure-Activity Relationship
PDE4	=	Phosphodiesterase
TNF-α	=	Tumor Necrosis Factor
VEGFR	=	Vascular Epidermal Growth Factor Receptor
ATCC	=	American Type Culture Collection
MTT	=	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
μM	=	Micromolar
nM	=	Nanomolar

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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