Recent Report on Thieno[2,3-*d*]pyrimidines. Their Preparation Including Microwave and Their Utilities in Fused Heterocycles Synthesis

Ashraf A Aly,[a,b,*] Esam A. Ishak,[a,c] Mohamed Ramadan,[d] Mousa O. Germoush,[e] Talaat I. El-Emary,[f] and Nayef S. Al-Muaikel[g]

[a]Chemistry Department, College of Science, Al-Jouf University, Sakaka, Kingdom of Saudi Arabia
[b]Chemistry Department, Faculty of Science, El-Minia University, 61519 El-Minia, Egypt
[c]Department of Chemistry, Faculty of Science, Al-Azhar University, Assuit, Egypt
[d]Department of Organic Chemistry, Faculty of Pharmacy, Al-Azhar University, Assuit, Egypt
[e]Biology Department, College of Science, Al-Jouf University, Sakaka, Kingdom of Saudi Arabia
[f]Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt
[g]College of Pharmacy, Al-Jouf University, Sakaka, Kingdom of Saudi Arabia
*E-mail: ashrafaly63@yahoo.com

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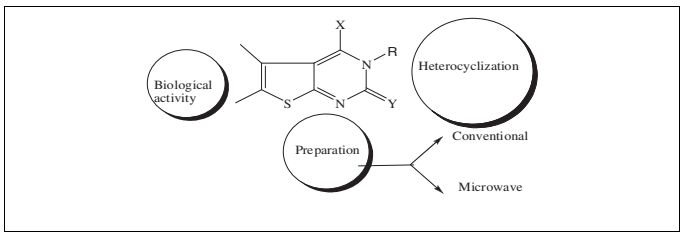

The review summarizes recent literatures dealing with the synthetic tools of thieno[2,3-*d*]pyrimidine derivatives including their biological activities and their applications in the synthesis of heterocycles.

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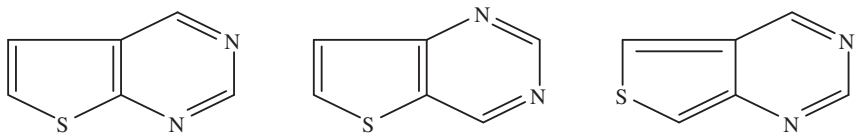
Contents

1. INTRODUCTION

It is well known that thieno[2,3-*d*]pyrimidine (**1**) has two regioisomers **2** and **3** (Fig. 1). In our work, we have dealt with the chemistry of compound **1** and their fused systems.

2. BIOLOGICAL AND PHARMACEUTICAL ACTIVITIES OF THIENO[2,3-*d*]PYRIMIDINES

Pyrimidine and thienopyrimidine derivatives (ring system) have attracted a great deal of interest owing to their medicinal activities; many thienopyrimidines have been evaluated pharmacologically as an active analgesics [1–5], antiinflammatory [2–7], antipyretic [3], antihypertensive agents [8,9], pesticides [10], herbicides [11,12], plant growth regulators [12], potential spasmolytic agents [13], gastric antisecretory [14], antihistaminic agents [15], antibacterial [16–19], antifungal agents [20,21], antimalarial,[22] anti-HIV-1 (Human Immunodeficiency Virus-1), anti-HSV-1 (Herpes Simplex Virus-1)[23] antitumor [24,25], selective 5-HT_3 receptor ligands (CNS: nausea and vomiting center in brain stem, anxiety, seizure propensity and/or PNS: neuronal excitation in autonomic, nociceptive neurons,



1 **2** **3**

Figure 1. Three structural isomers of thienopyrimidines.

and emesis) [26], and as hypnotics [27]. The importance of pyrimidine compounds is probably due to the fact that many compounds containing fused pyrimidones, such as guanosine, flavine uric acid, and folate play an important role in the biochemistry of living cells. Recent development of physiologically highly potent purine analogs with interesting antiviral, antiallergic, and specially anticancer activities has promoted a great current interest in facile and general routes to these molecules in synthetically useful yields [28]. The thienopyrimidone skeleton does not occur in nature but nevertheless attracts interest because of remarkable biological properties of its derivatives. For example, some 2-alkoxy-substituted or 2-alkyl-substituted thienopyrimidones showed significant antifungal and antibacterial activities [29a-d], whereas others exhibited good anticonvulsant and angiotensin II or H^1-receptor antagonistic activities [29a-h]. Among promising targeting therapies for cancer treatment, substituted thienopyrimidones have continued to retain attention of both academic institutions and pharmaceutical companies in the last few years [30–33]. Recently, it has been investigated the synthesis and biological activities of several thienopyrimidine derivatives **4–6** (Scheme 1) [34].

It was described on the design and synthesis of a series of potent thieno[2,3-*d*]pyrimidines **7** as $P2Y_{12}$ (i.e., the $P2Y_{12}$ protein is found mainly but not only on the surface of blood platelet cells and is an important regulator in blood clotting) inhibitors and the negative impact protein binding has on the inhibition of platelet aggregation [35]. The procedure described the mode of synthesis as shown in Scheme 2.

A series of highly potent and selective mGluR1 antagonists **8–10** having thieno[2,3-*d*]pyrimidine moiety has been discovered and demonstrated in the animal model for pain, which however, has been not proved [36]. The synthetic procedure is as outlined in Scheme 3.

Thieno[2,3-*d*]pyrimidine derivatives **11** and **12** (Scheme 4) are interesting compounds with diverse chemical properties and antiviral activities. These thienopyrimidines have also shown activity as anti-avian influenza virus (H5N1) [37].

3. THIOPHENE DERIVATIVES

3.1. Synthesis of *bi*-functional thiophene derivatives. The *bi*-functional 2-aminothiophene derivatives **15** have been found to be important intermediates in the chemistry of pyrimidines; it can be synthesized by the condensation of ketones, active methylene compounds, and elemental sulfur in the presence of base such as morpholine as a catalyst following the *Gewald* synthesis (Scheme 5) [38–41].

One variation of the Gewald reaction, an aminothiophene derivative of compounds **15**, was synthesized starting from a dithiane **16** (an adduct of sulfur and acetone) and the sodium salt of cyanoacetone, which in itself is very unstable (Scheme 6) [42].

4. SYNTHESIS OF THIENO[2,3-*d*]PYRIMIDINE DERIVATIVES (OR ITS FUSED SYSTEM)

4.1. From 2-aminothiophene-3-carboxylic esters. 2-Aminothiophene-3-carboxylic esters **15** are considered a good precursor for the preparation of thieno[2,3-*d*] pyrimidine derivatives, when they were heated with formamide, 4-hydroxy-thieno[2,3-*d*]pyrimidines **17** were obtained in a good yields (Scheme 7) [43–50].

2-Thioxothieno[2,3-*d*]pyrimidine-4-one (**22**) is prepared through the reaction of thieno[2,3-*d*]pyridine-3,6-dicarboxylate **18**[51] with ethoxycarbonyl isothiocyanate to give the open form **19**, followed by cyclization in refluxing sodium ethoxide solution (Scheme 8) [51]. Refluxing of compound **23** in ethanol led to the formation of **26**, which upon cyclization with hydrazine hydrate at room temperature, the reaction proceeded to give **28** (Scheme 5). Heating of either **28** or **26** with excess hydrazine hydrate produced compound **27** (Scheme 9) [52,53].

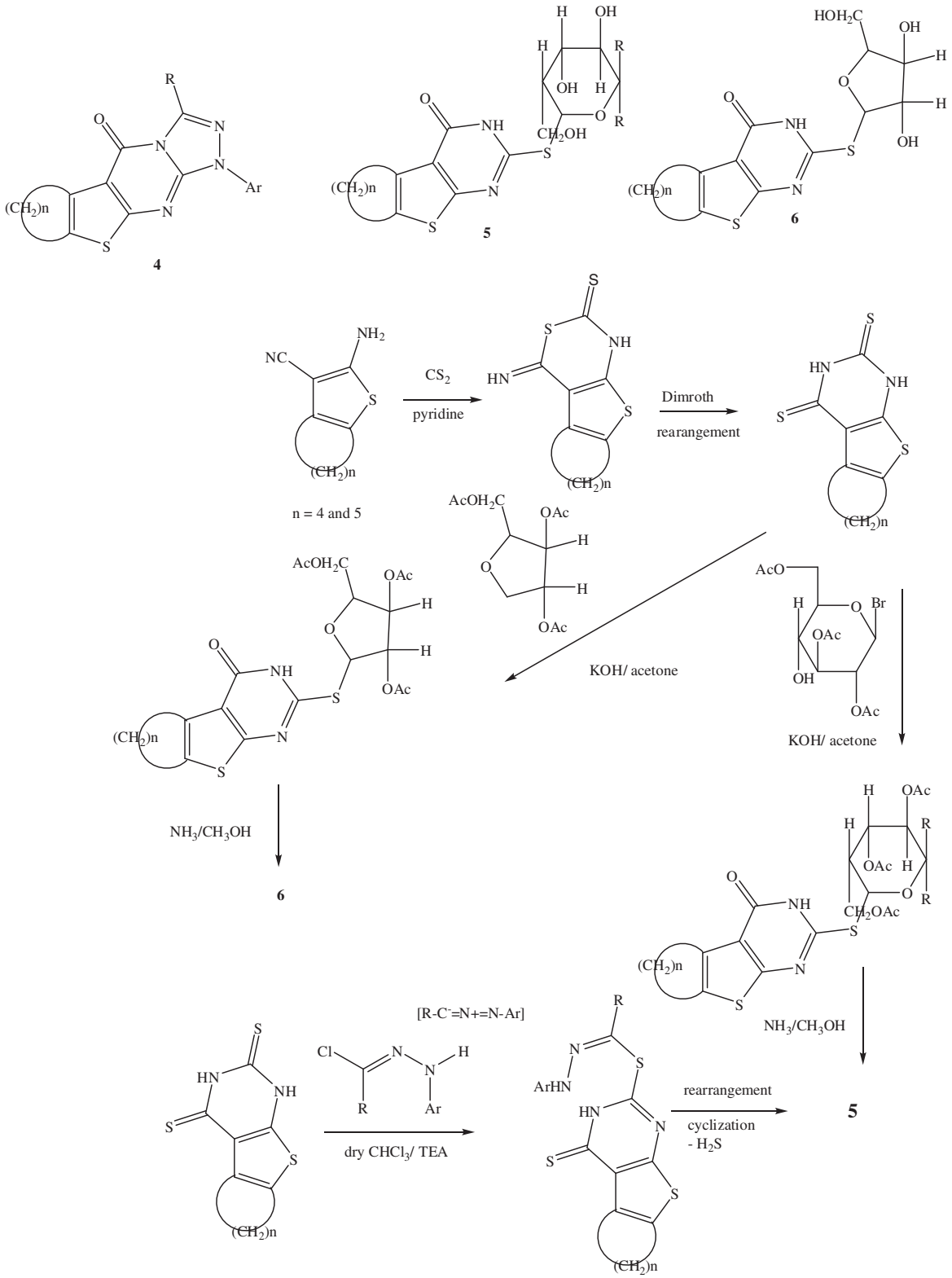
Analogously, by refluxing of thiophene derivatives **15** with an excess of hydrazine hydrate [54a] in benzene, the reaction performed to give 2-thioxo-3-aminothieno[2,3-*d*]-pyrimidine-4-one (**29**) (Scheme 10) [54b].

Compound **23** reacted with amino alcohols and allyl amine under mild conditions to provide the thiourido derivatives **30** and **31**, respectively, which upon heating in an ethanolic potassium hydroxide solution gave pyrido[4′,3′,4,5]thieno-[2,3-*d*]pyrimidine derivatives **32** and **33** (Scheme 11) [55].

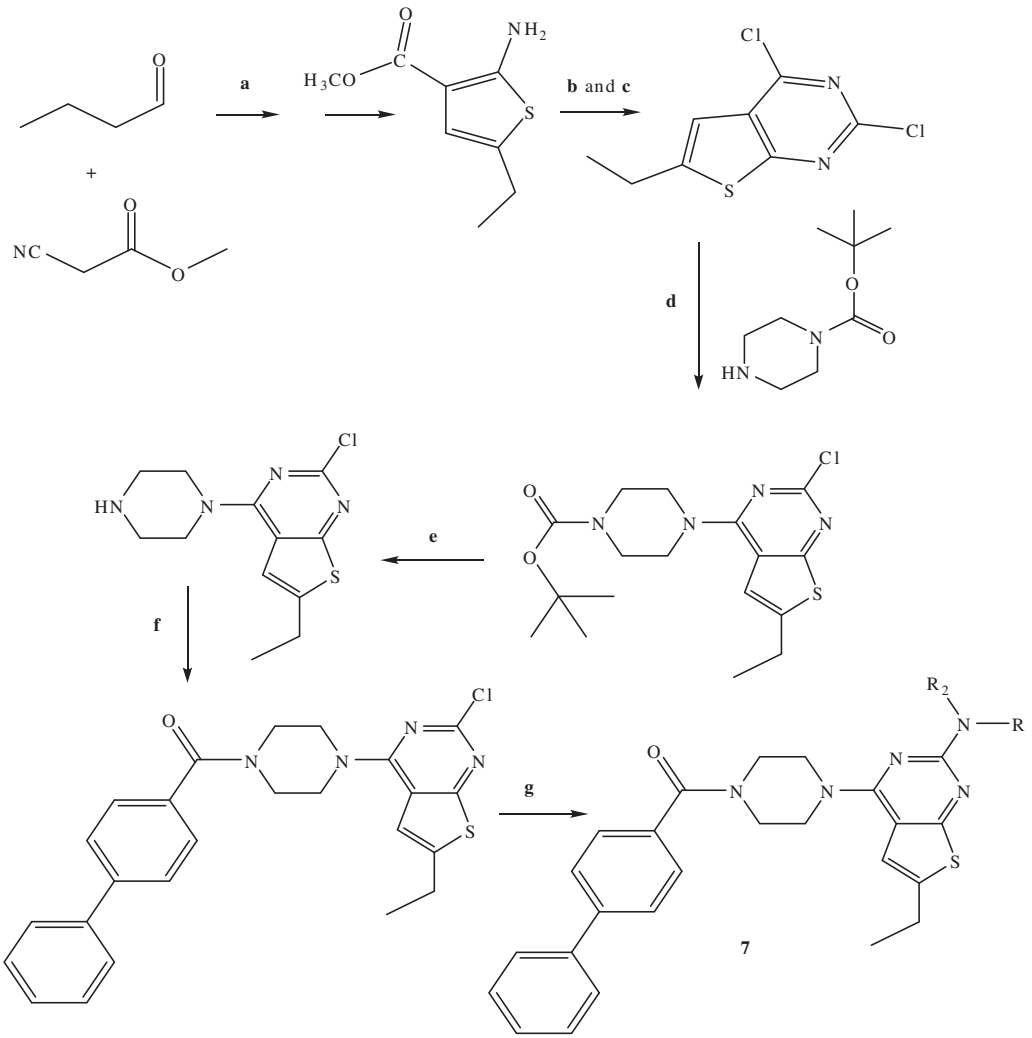
The strategy to synthesize the thienopyrimidines **35a–e** was established by the reaction of hydrazine hydrate with diethyl-2-[(arylamino)carbothioyl]amino-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylates **34a–e**, which was obtained from the reaction of isothiocyanate **23** with substituted aryl amines (Scheme 12) [56].

2-Substituted-4-chlorothieno[2,3-*d*]pyrimidines **37** have been prepared in a single pot reaction from ethyl 2-aminothiophene-3-carboxylate derivatives of **16** by using nitriles [57a] to give intermediates, 4-hydroxypyrimidines **36**. Thereafter, heating of **36** under reflux in phosphoryl

Scheme 1. The structure of thienopyrimidines **4–6**.



Scheme 2. Synthesis of the thienopyrimidine core **7**. Reagents and conditions: (a) sulfur, triethylamine, DMF, rt, 18 h (70%); (b) acetic acid, H_2O, KCN, rt, 18 h (64%); (c) phenylphosphonic dichloride, 150°C, 3 h (95%); (d) THF, DIEA, rt, 6 h (70–90%); (e) hydrochloric acid, methanol, rt, 3 h (quant); (f) THF, DIEA, rt, 6 h (70–90%); (g) DIEA, NMP, 130° C, 18 h (40–90%).



chloride afforded the target compound **37** in 40–60% yields (Scheme 13) [57b].

Synthesis of the thieno[2,3-*d*]pyrimidine-2,4-dione derivatives **39** was reported by the reaction of 2-aminothiophenes **38** with substituted isocyanates (Scheme 14) [57].

Sensfuss *et al*. [58] synthesized the thieno[2,3-*d*]pyrimidine **41** starting from 2-aminothiophene **40** through initial attack of the electrophile triethyl orthoformate [64] mainly upon the primary amino group but not on the piperidine N–H (Scheme 15) [58].

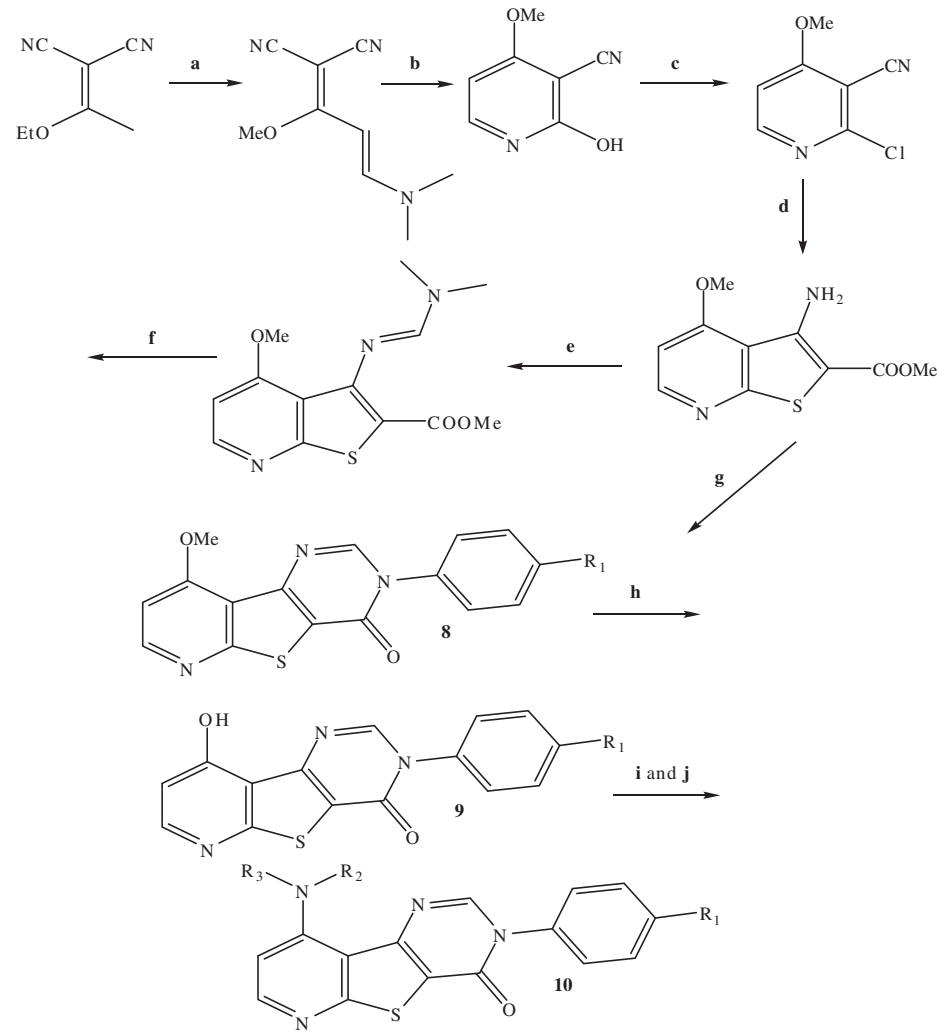
Treatment of 2-aminothiophene derivative **15** with α-chloroacetonitrile afforded the corresponding 2-chloromethyl-5-(substituted)-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **42** (Scheme 16) [59].

Briefly, thieno[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones were either obtained by heating methyl 2-aminothiophene-3-carboxylate derivatives **15** with urea 190–200°C or reacted with chlorosulfonyl isocyanate at 60°C. Chlorination of the thienopyrimidine compound with phosphoryl trichloride afforded compound **43** (Scheme 17) [60a]. Selective *N*-alkylation was performed to produce compounds **43** (Scheme 17) [60b].

The bis *N*-heteroaryl iminophosphorane **46** appeared to serve as a good building block for other heterocyles. It could be synthesized from diethyl 3,5-diaminodithieno [3,2-*e*,2,3-*b*]pyridine-2,6-dicarboxylate (**45**). Pentaheterocyclic compounds **49** were obtained in a one-pot reaction of the corresponding iminophosphoranes **46** with isocyanates, followed by heterocyclization on addition of amines in presence of sodium carbonate (Scheme 18) [61].

4.2. From 2-aminothiophene-3-carboxamides. Compound **50** reacted with triethyl orthoformate to afford benzo[*b*] thieno[2,3-*d*]-4-hydroxy-pyrimidine-4-ol derivative **51** and not the keto form (Scheme 19) [62]. Compound **50** reacted

Scheme 3. Reagent and conditions: (a) DMF–DMA, MeOH, 80°C; (b) HOAc (80%), 130°C; (c) $POCl_3$, Et_3N, 100°C; (d) $HSCH_2CO_2Me$, NaOMe, DMF, 80°C; (e) DMF–DMA, DMF, 100°C; (f) 4-Cl-aniline (R_1 = Cl), HOAc, toluene, 110°C; (g) 4-Cl-aniline (R_1 = Cl), HOAc, $CH(OEt)_3$, 160°C; (h) BBr_3, CH_2Cl_2; (i) $NPhTf_2$, CH_2Cl_2; (j) R_2R_3NH, DMSO.



with phenyl isothiocyanate in refluxing ethanol containing a catalytic amount of triethylamine to afford the 2-mercaptopyrimidine-4-one derivative **52** via ammonia liberation.[62] On the other hand, acid halides reacted with compound **50** to afford the acyl derivatives **53a,b**, which underwent cyclization in conc. H_2SO_4 at 160°C to give the corresponding benzothieno[2,3-*d*]pyrimidines **54a,b** (Scheme 19) [62].

Interestingly, reaction of compound **50** with equimolar amounts of ethylcyanoacetate and triethylamine yielded a product containing a methyleneamide moiety **57** instead of the expected ester moiety **56**. The reaction was preceded via formation of unstable ester intermediate **55**, which underwent cyclization followed by ammonolysis (Scheme 20) [62].

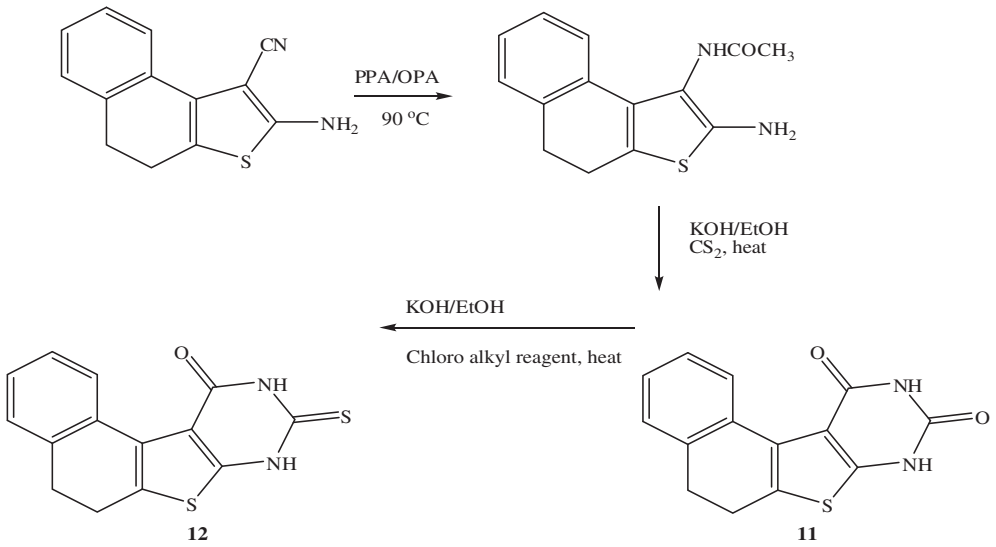
Manhas *et al*.[63] reported that the reaction of 2-aminothiophene-3-carboxamide derivative **15** with acetyl acetone yielded the corresponding 2-methylthieno[2,3-*d*] pyrimidines **58**. On the other hand, the reaction of **15** with cinnamaldehyde in the presence of HCl gas afforded the 2-styryl-thieno[2,3-*d*]pyrimidines **59** (Scheme 21) [63].

Treating the *spiro* compound **60**, obtained from *spiro* [5,5]undecane-3-one via Gewald reaction, with chloroacetyl chloride gave the open form **61**, which reacted with primary and secondary amines to give **62**, which was cyclized under basic conditions to build the pyrimidine moiety in compound **62** (Scheme 22) [64].

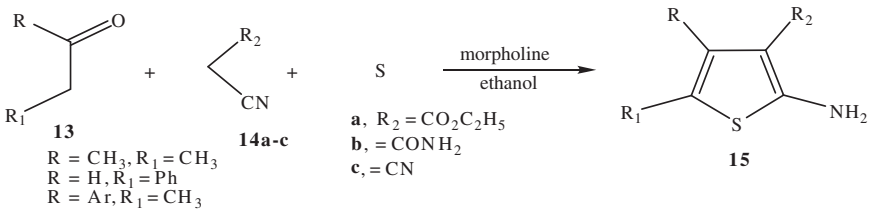
El-Sharief *et al*.[65] reported the synthesis of 2-thioxo-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4-(3*H*)one (**66**) or its possible isomer **64** via treatment of 2-aminothiophene-3-carboxamide **64** with carbon disulfide (Scheme 23) [65].

4.3. From 2-aminothiophene-3-carbonitriles. The thieno[2,3-*d*] pyrimidine **69** was synthesized from 2-aminothiophene-3-carbonitrile **67** through the action of triethyl orthoformate

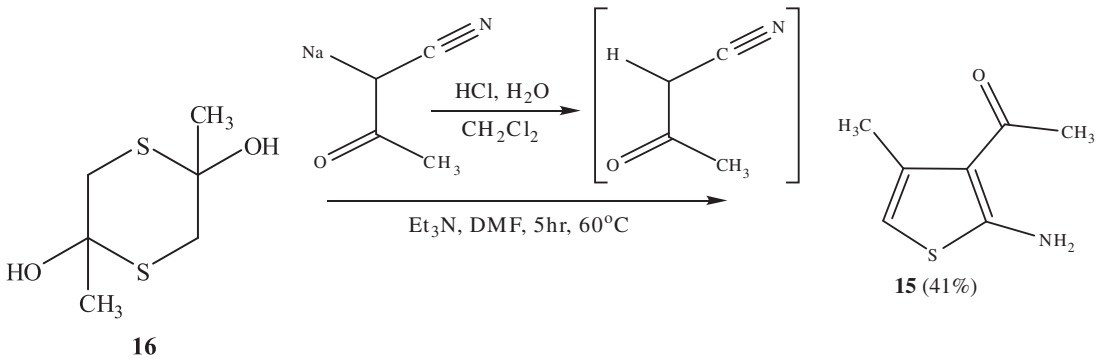
Scheme 4. Thieno[2,3-*d*]pyrimidine derivatives **11** and **12**.



Scheme 5. Synthesis of *bi*-functional 2-aminothiophene derivatives **15**.



Scheme 6. Synthesis of *bi*-functional thiophene derivative **15**.

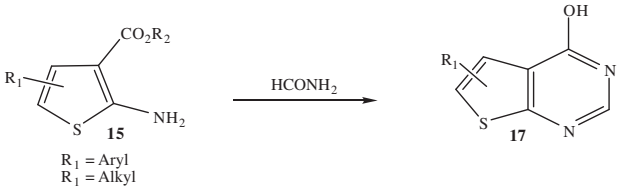


followed by cyclization of **68** by using sodium ethoxide (Scheme 24) [66].

The synthesis of the 5,6-disubstituted-3 *H*-thieno[2,3-*d*] pyrimidin-4-ones **70** was performed by the reaction between 2-amino-4,5-disubstituted-thiophene-3-carbonitrile derivative of **15** and formic acid (Scheme 25) [67]. The driving forces for the preferential attack at the NH_2 group are presumably the steric hindrance at the tetramethylpiperidine nitrogen as well as the thermodynamic stability of the products because the *N*-substituted double bond can be conjugated with the thiophene π-system (Scheme 25) [67].

4.4. From aminothiophenecarboxylic acids. Initially, 2-amino-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylic acid derivative **15** was tested with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazines (**71**) under mild thermal conditions; the desired thieno[2,3-*d*]pyrimidines **72** were obtained in moderate yield (Scheme 26) [68]. Screening of reaction conditions such as solvent and reaction temperature led to the identification of DMF–AcOH as an optimum solvent

Scheme 7. Synthesis of thieno[2,3-*d*]pyrimidine derivatives **17**.



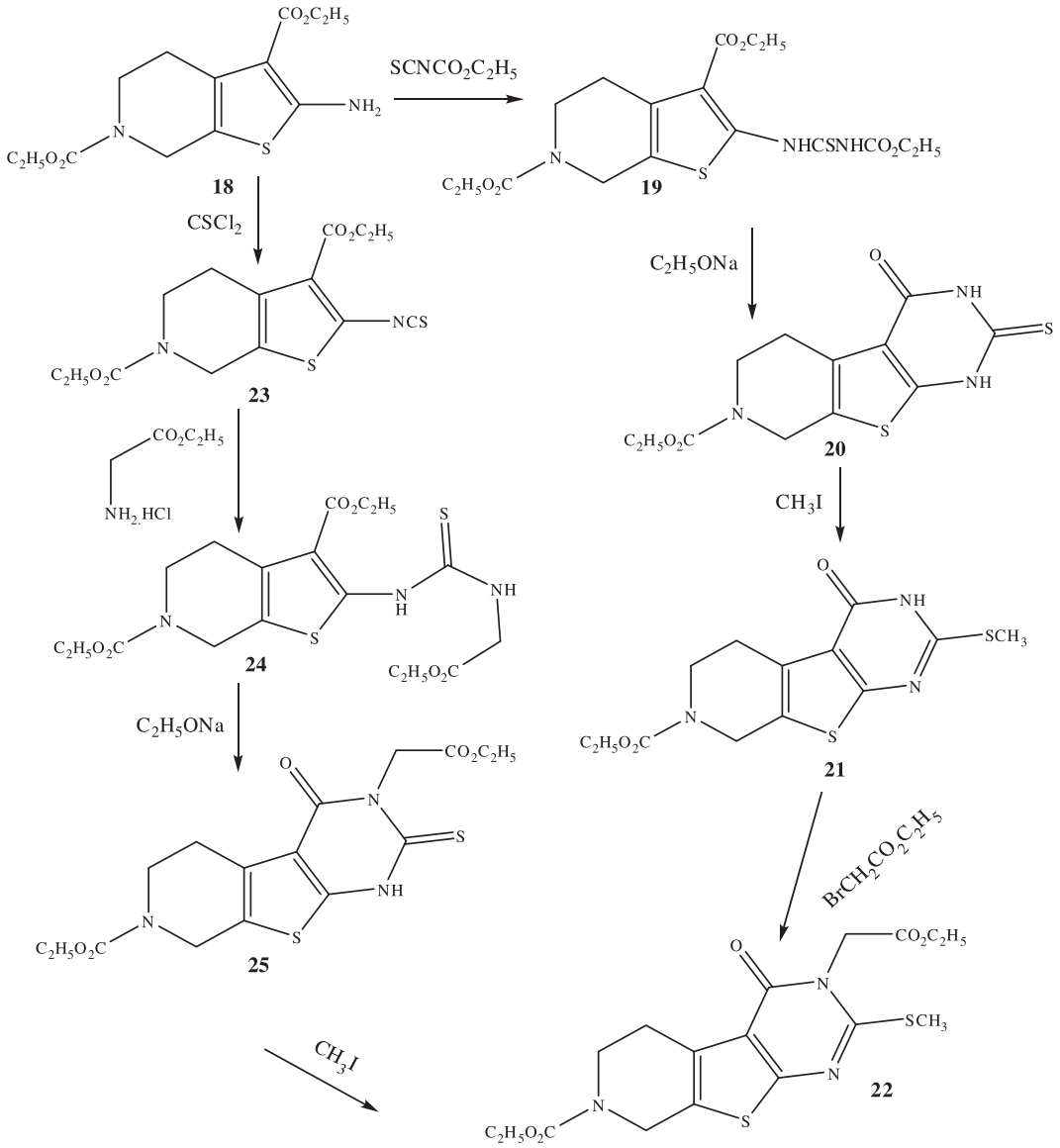
system, producing compound **72** from the starting compound **15**. The scope of this tandem decarboxylation inverse electron-demand Diels–Alder (IDA) reaction was explored using various 1,3,5-triazines **71** as the azadienes and thiophene **73** as the latent dienophile. The results indicated that the reaction proceeds via a tandem decarboxylation IDA reaction (Scheme 26) [68].

4.5. From 5-cyano-6-thioxopyrimidines. The reaction of 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine (**75**) with chloroacetone in DMF in the presence of excess anhydrous potassium carbonate at room temperature gave the 6-acetyl-5-amino-4-methyl-2-phenylthieno[2,3-*d*] pyrimidine (**76**) (Scheme 27) [69].

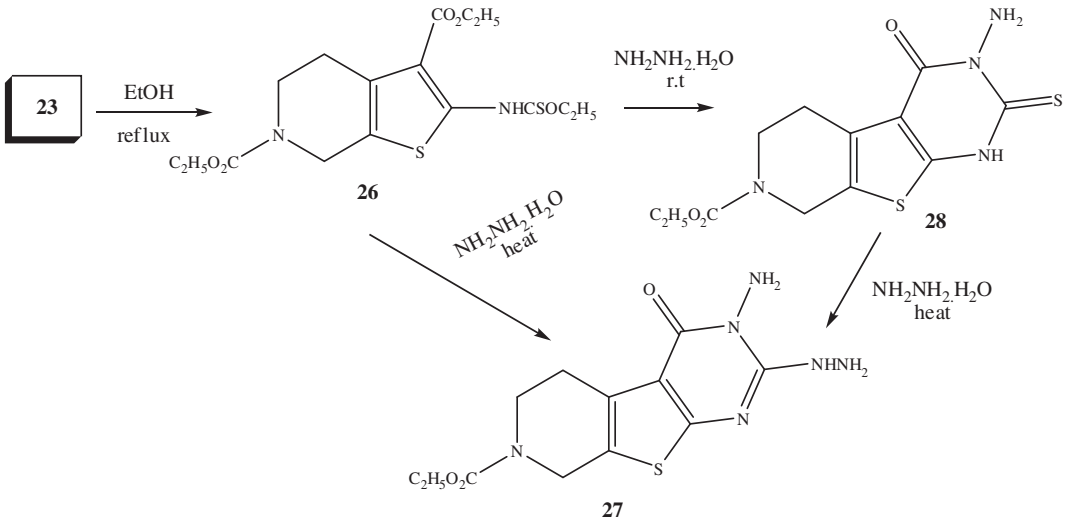
5. MICROWAVE-ENHANCED SYNTHESIS OF NOVEL THIENO[2,3-*d*] PYRIMIDINES

A series of 2-unsubstituted 4-(substituted)anilinothieno [2,3-*d*]pyrimidines is synthesized through the chlorination of the corresponding 2-unsubstituted-thieno[2,3-*d*]-pyrimidin-4-ones, followed by the nucleophilic displacement of the 4-Cl group with a variety of anilines. All four steps of this

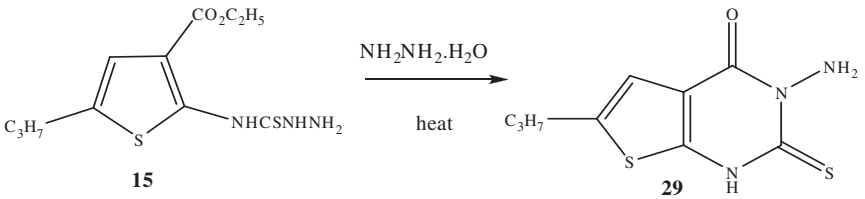
Scheme 8. Synthesis of thieno[2,3-*d*]pyrimidine derivative **22**.



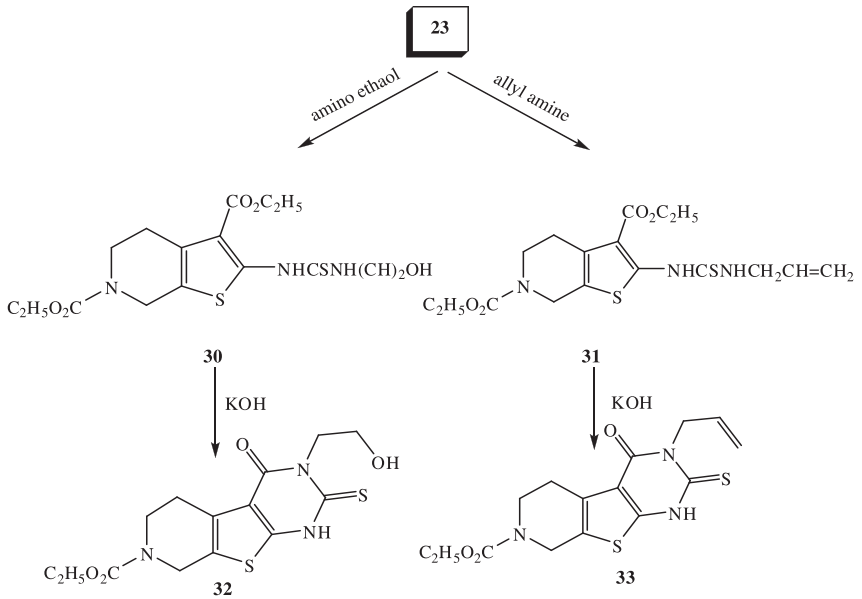
Scheme 9. Synthesis of thieno[2,3-*d*]pyrimidine derivatives **27** and **28**.



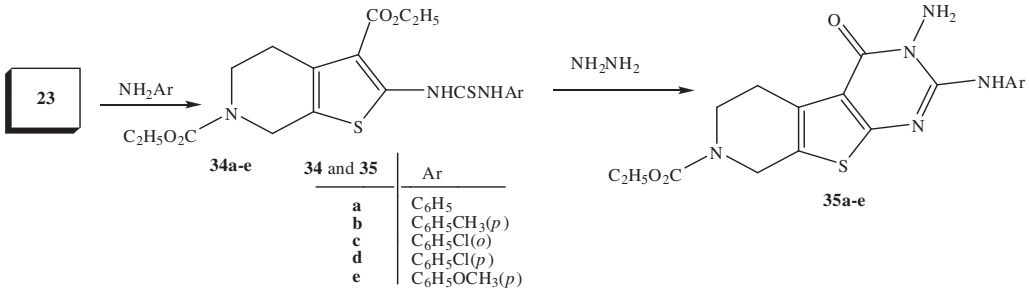
Scheme 10. Synthesis of 6-phenyl-2-thioxo-3-aminothieno-[2,3-*d*]pyrimidine-4-one (**29**).



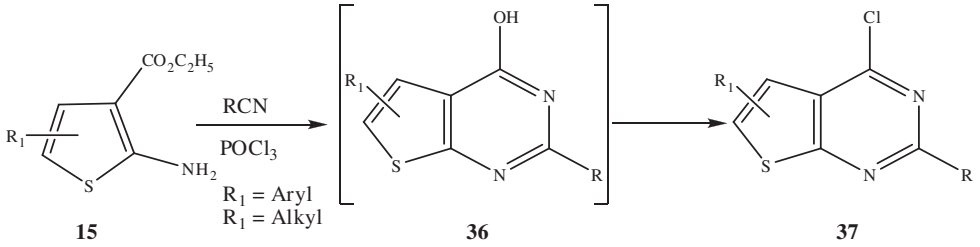
Scheme 11. Synthesis of pyrido[4′,3′,4,5]thieno[2,3-*d*]-pyrimidine derivatives **32** and **33**.



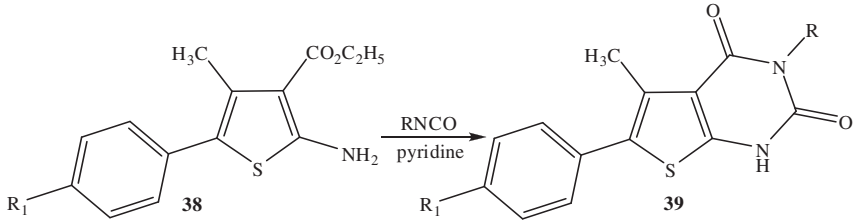
Scheme 12. Synthesis of thienopyrimidines **35a–e**.



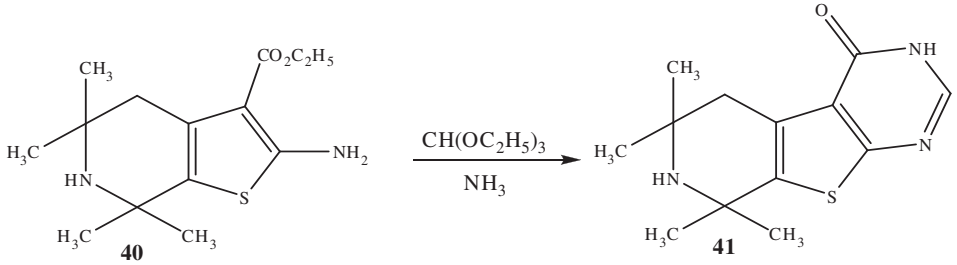
Scheme 13. Synthesis of 2-substituted-4-chlorothieno[2,3-*d*]pyrimidines **37**.



Scheme 14. Synthesis of the thieno[2,3-*d*]pyrimidine-2,4-diones **39**.



Scheme 15. Synthesis of tricyclic thieno[2,3-*d*]pyrimidine **41**.

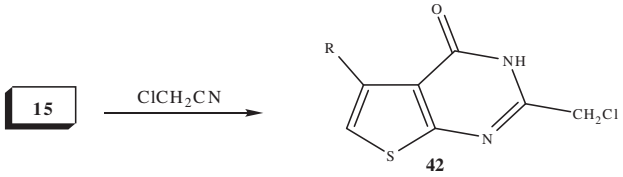


synthesis involve microwave irradiation, and the entire synthesis requires only 2 h (Scheme 28) [70].

A rapid microwave-assisted green chemical synthesis of condensed 2-substituted-pyrimidin-4(3 *H*)-ones involving the condensation of a variety of nitriles with *o*-aminoesters of thiophenes, benzene, dimethoxybenzene, and quinazolinone in the presence of catalytic amount of HCl alone or with the Lewis acid $AlCl_3$ under solvent-free conditions is described for the first time. This novel and clean one-pot methodology, which is characterized by very short reaction times and easy workup procedures, can be exploited to generate a diverse library of condensed pyrimidine heterocycles [71].

A series of novel small molecule FP-2 inhibitors (i.e., alcipain-2 and Plasmodial Cysteine Proteases) has been designed and synthesized on the basis of compound

Scheme 16. Synthesis of 2-chloromethyl-5-(substituted)-thieno[2,3-*d*]pyrimidin-4(3 *H*)-ones **42**.



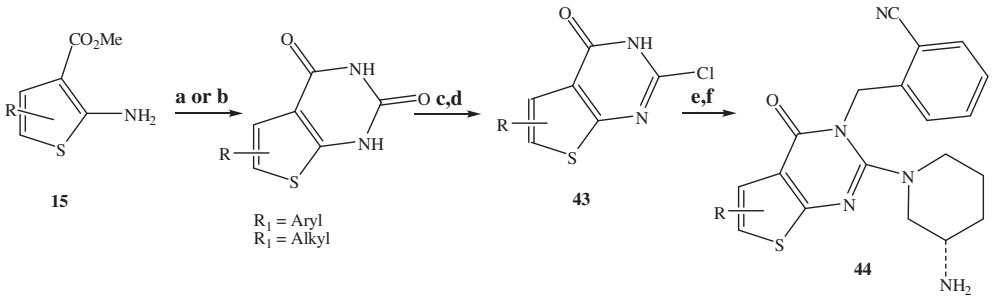
thieno[2,3-*d*]pyrimidines, which were identified by using structure-based virtual screening in conjunction with an enzyme inhibition assay. All compounds showed high inhibitory effect against FP-2 with IC50's of 1.46–11.38 μM. The preliminary-obtained SARs of these compounds should be helpful for future inhibitor design, and the novel scaffold presented here, with its potent inhibitory activity against FP-2, also has potential application in discovery of new antimalarial drugs [72]. Also, it is reported on the microwave-assisted synthesis of imidazopyrido and pyrimidopyrido [4′,3′:4,5]thieno[2,3-*d*]pyrimidines from 2-ethoxymethylene-amino-3-cyano-4,5,6,7-tetrahydrothieno[2,3-*c*]-pyridine-6-carboxylic acid ethyl ester and 4-chloro-pyridothieno[2,3-*d*]pyrimidine [73].

A simple and fast method for the isolation of intermediates in the synthesis of 3-arylthieno[2,3-*d*]pyrimidine-2,4 (1 *H*,3 *H*)-diones has been developed by microwave-assisted condensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate with aryl isocyanates. The intermediates, subsequently, underwent cyclization in *t*-butanol in the presence of potassium *t*-butoxide on heating to reflux to give the desired bicyclic products, 3-arylthieno[2,3-*d*]pyrimidine-2,4(1 *H*,3 *H*)-diones [74].

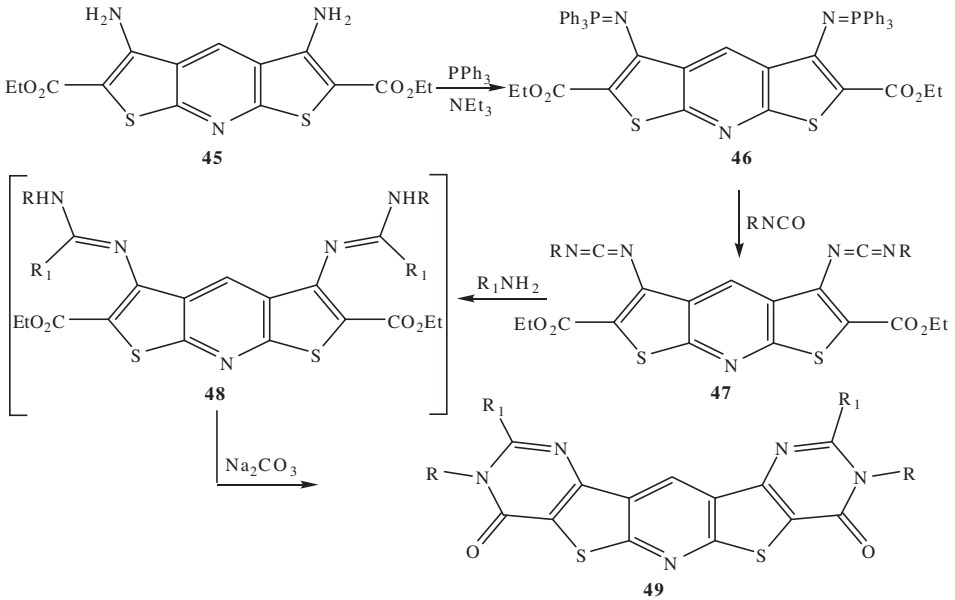
6. MICROWAVE-ENHANCED GEWALD

The reaction in combination with solid-support accelerated method was presented as an easy access to polysubstituted 2-aminothiophenes [75,76]. A variety of ketones was

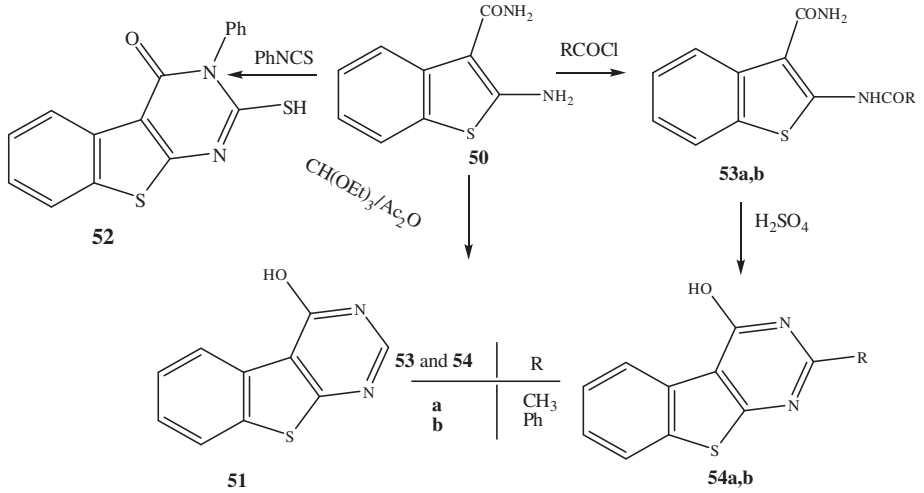
Scheme 17. Selective synthesis of thieno[2,3-*d*]pyrimidines **43** and **44**. Reaction conditions: (a) urea, 190-200 ° C; (b) $ClSO_2NCO$, CH_2Cl_2, -60 ° C; (c) $POCl_3$, DIEA, reflux; (d) 1 N NaOH; (e) 2-CNPhCH_2Br, NaH, LiBr; (f) 3-(R)-aminopiperidine, $NaHCO_3$, 150 ° C.



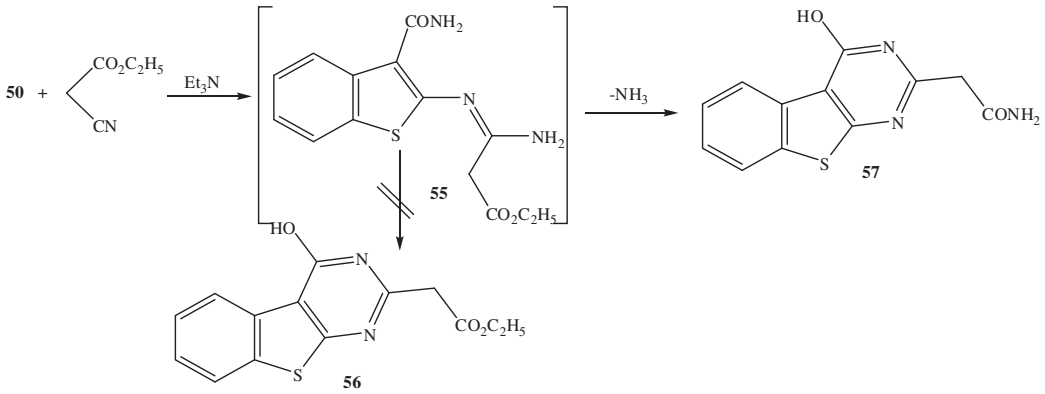
Scheme 18. Synthesis of pentaheterocyclic of thienopyrimidine derivatives **49**.



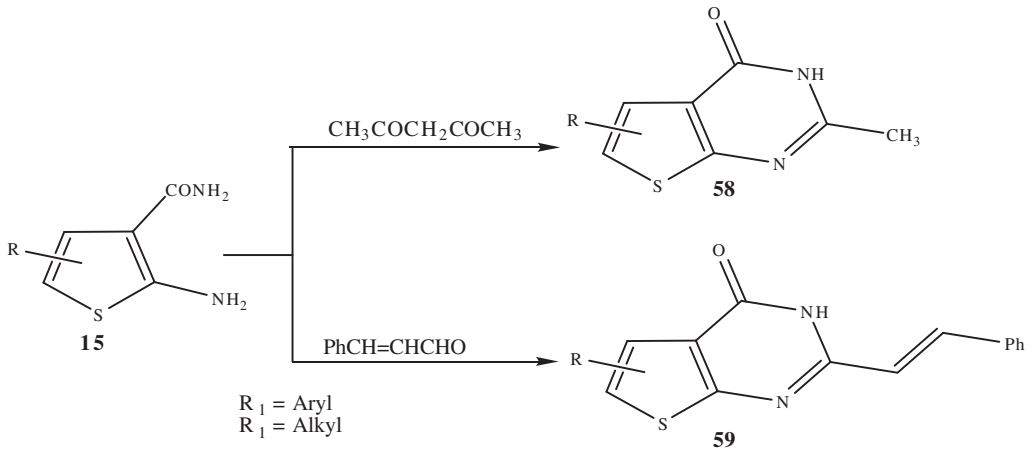
Scheme 19. Synthesis of thienopyrimidine derivatives **51** and **54**. A name could not be generated for this structure.



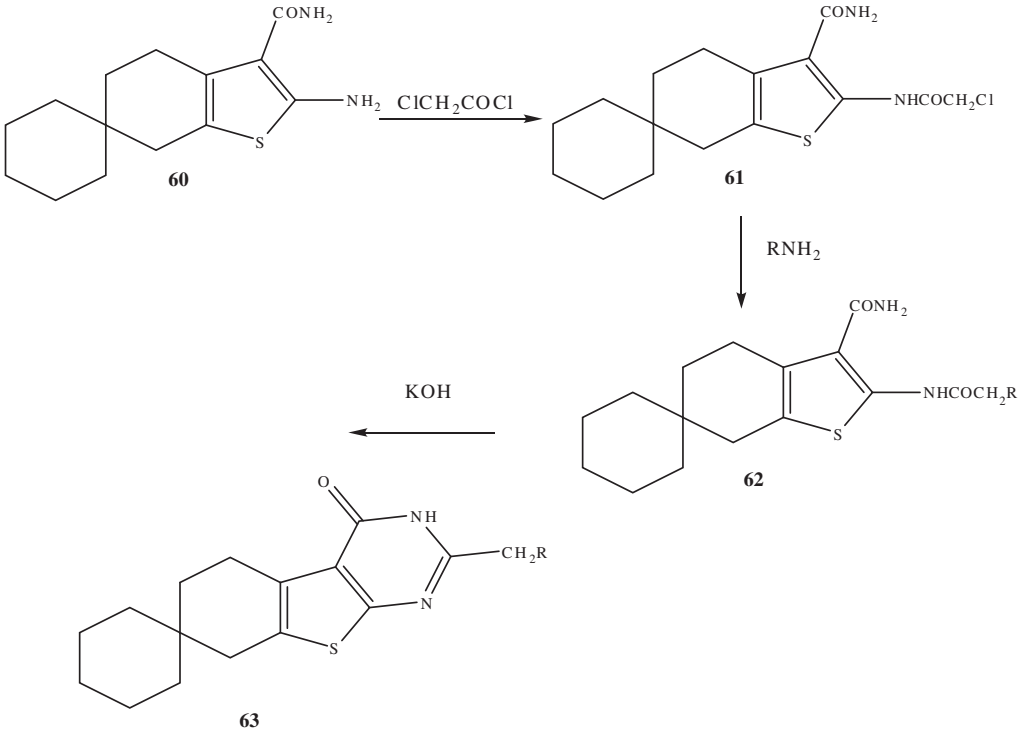
Scheme 20. Synthesis of thienopyrimidine **57**.



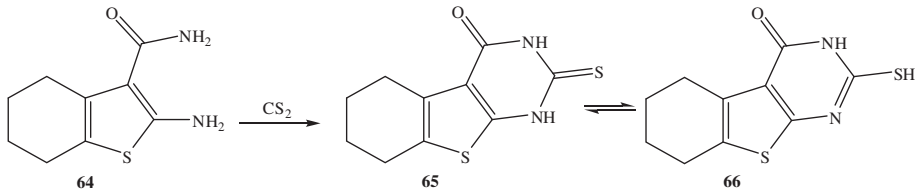
Scheme 21. Synthesis of thienopyrimidine **58** and **59**.



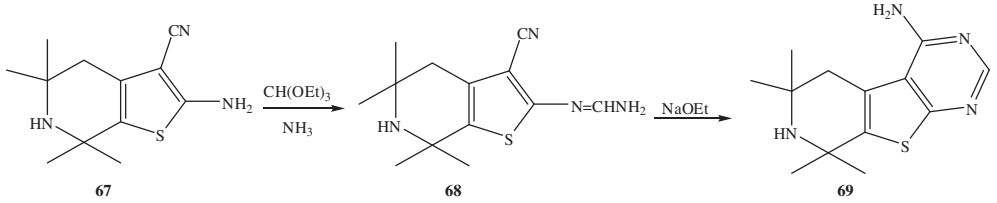
Scheme 22. Synthesis of thienopyrimidines **63**.



Scheme 23. Synthesis of thienopyrimidine **66**.

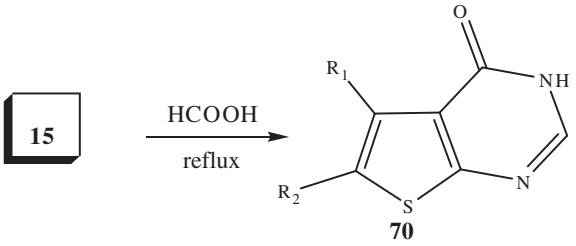


Scheme 24. Synthesis of thienopyrimidine **69**.



reacted with ethyl cyanoacetate or malononitrile, and sulfur in the presence of KF-alumina 89 KF immobilized on Al_2O_3 represents the heterogeneous catalyst with advantageous properties such as better selectivity and easier work upon its use. KF-alumina as a base used in Gewald synthesis proceeded well producing 2-aminothiophene derivatives in good yields. Using the microwave irradiation reaction was carried out in very short times, but alternatively, the reaction proceed well also under conventional heating (Scheme 29) [75,76].

Scheme 25. Synthesis of thienopyrimidines **70**.



7. REACTIONS OF THIENO[2,3-*d*]PYRIMIDINES

7.1. Substitution and condensation reactions. Panico *et al*. [77] have shown that a new class of antiinflammatory drugs **78a–c** and **80a–c** derived by thieno[2,3-*d*]pyrimidine (Scheme 30) is capable of *in vitro* preventing cartilage destruction in articular disease.

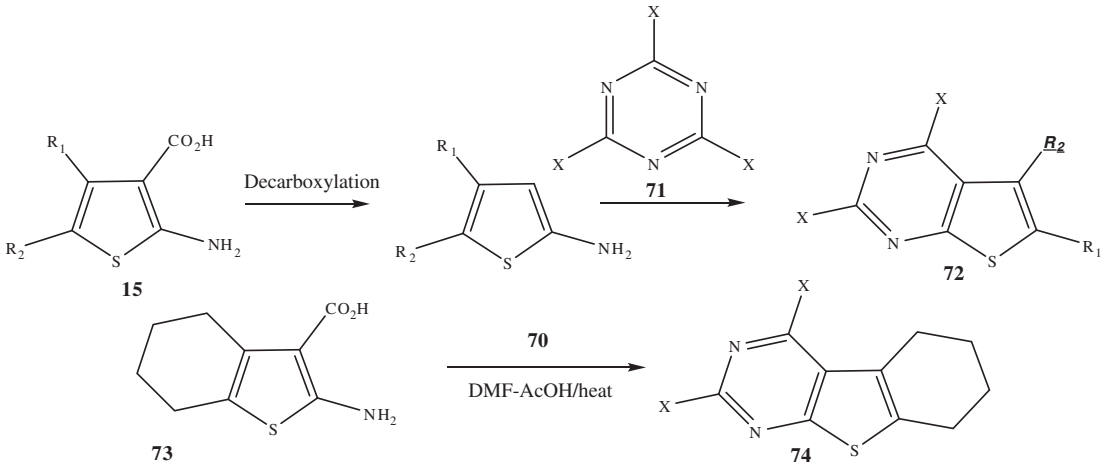
Thus, the acetic acid **78a**, propanoic acid **78b**, and phenyl acetic acid **78c** derivatives of 2-[(3-amino-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl) sulfanyl] and the corresponding methyl ester **80a–c** were synthesized (Scheme 30) [77].

Difflurobenzylation of thieno[2,3-*d*]pyrimidine-2,4-dione **81** at the 1-position, followed by radical bromination of the 5-methyl group in compound **82** with *N*-bromosuccinimide (NBS), furnished the bromomethyl **83**, which were converted to compound **84** by introduction of *N*-benzyl-methylamino moiety (Scheme 31) [78].

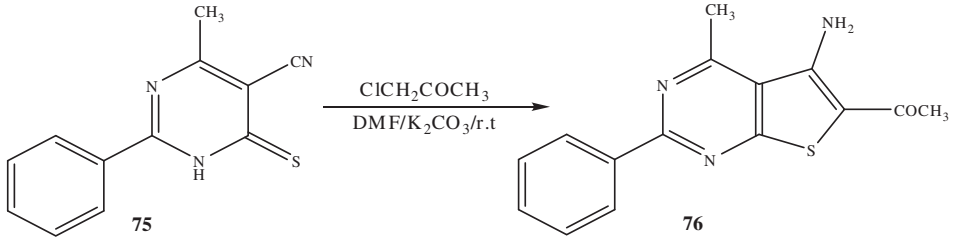
4,5-Disubstituted and 4-substituted alkyl 2-aminothiophene-3-carboxylates **85** react with triethyl orthoformate and sodium azide in acetic acid to yield 2-(1 *H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene derivates **86**. It was established that the reaction of these tetrazoles with hydrazine generates the insufficiently studied 2,3-diaminothieno [2,3-*d*]pyrimidin-4(3 *H*)-one system **87**. It is significant that the reaction mentioned earlier is the unique tetrazole ring cleavage under the action of hydrazine (Scheme 32) [79].

7.1.1. Glycosides of thieno[2,3-d]pyrimidines. A synthesis of a class of thioglycosides **92** by reactions of 5,6-disubstituted-thieno[2,3-*d*]pyrimidine-4-one-2-thiones **88** with 2,3,4, 6-tetra-*O*-acetyl-α-D-gluco-pyranosyl bromide or its α-D-galactopyranosyl isomer that may be used as anti-HIV was described in Scheme 33 [80].

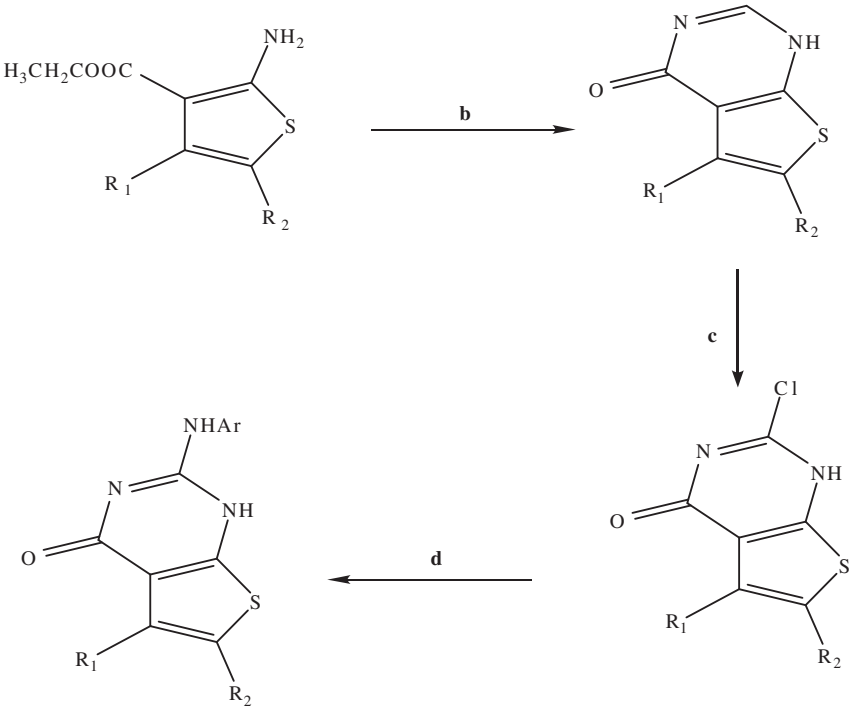
Scheme 26. A tandem decarboxylation and IDA reaction between aminothiophene carboxylic acid and 1,3,5-triazines.



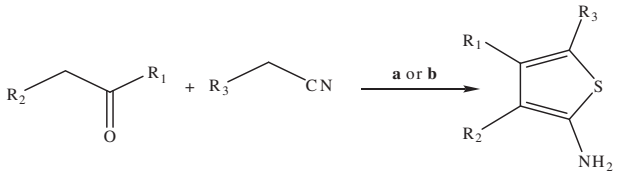
Scheme 27. Synthesis of thienopyrimidine **76**.



Scheme 28. Reaction conditions: (a) under microwave irradiation, 350 W, 2–5 min, (60–90%); (b) 350 W, 25–28 min, (87–92%); (c) 350 W, 10–12 min, (81–84%); (d) 350 W, 15–26 min, (68–98%).

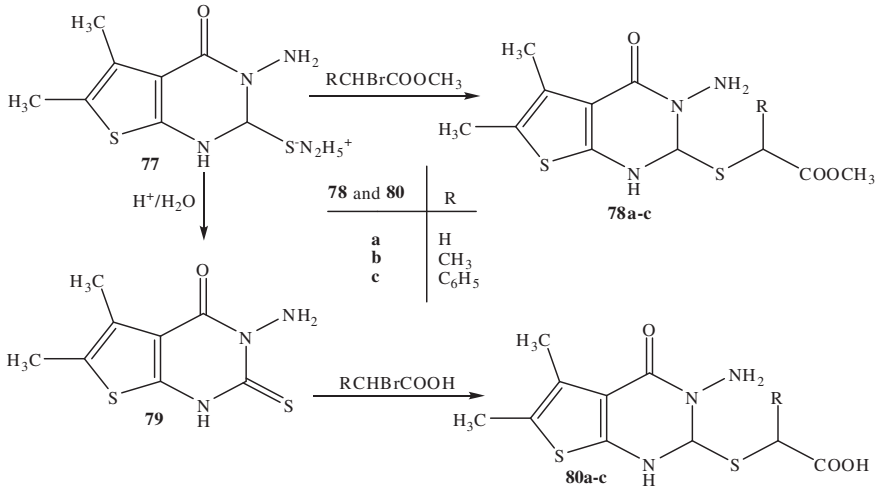


Scheme 29

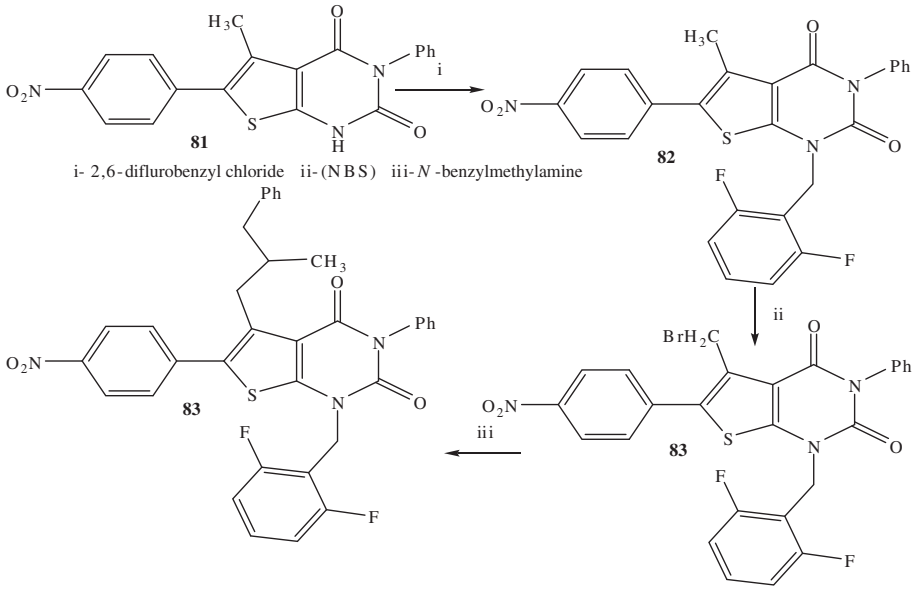


a: KF-alumina, microwave irradiation, 3.5 - 8 min.
b: KF-alumina, EtOH, 78 °C, 3.5 - 7 h.

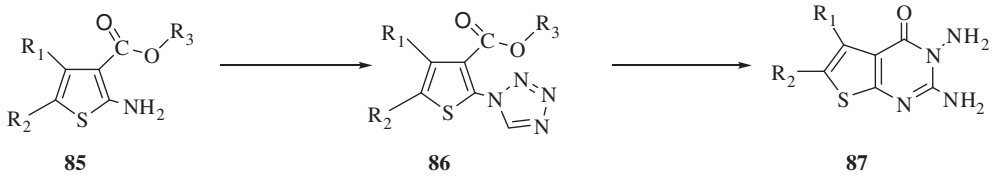
Scheme 30. Synthesis of antiinflammatory drugs of thienopyrimidines **78** and **80**.



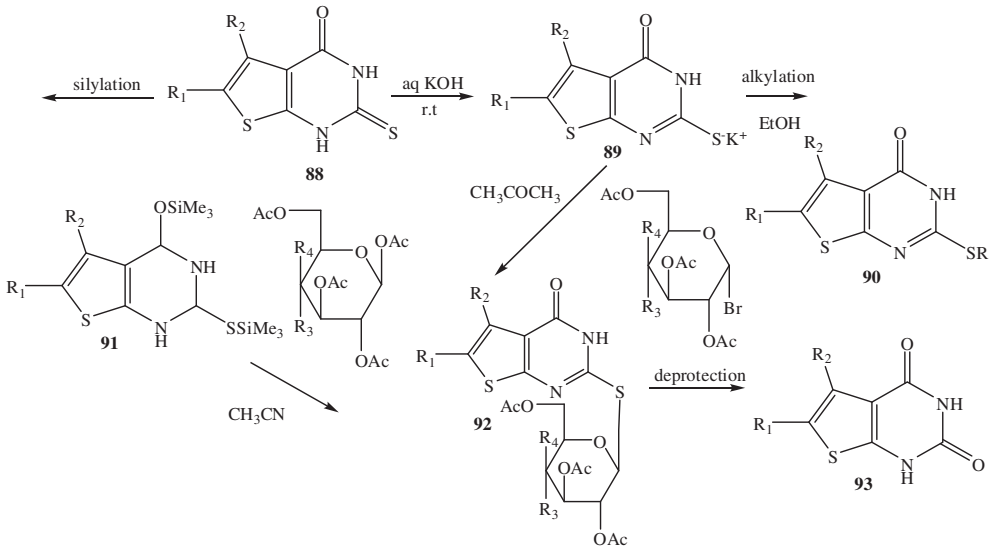
Scheme 31. Substitution reactions of thienopyrimidine **84**.



Scheme 32. Synthesis of 2,3-diaminothieno[2,3-*d*]pyrimidin-4(3*H*)-one system **87**.



Scheme 33. Substituted thioglycoside reactions of thienopyrimidines **88**.

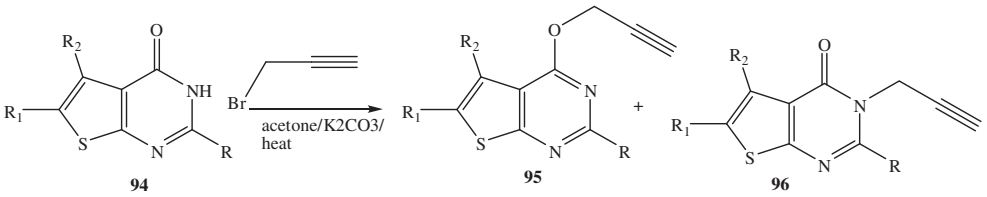


The same group reported on glycosides of another substituted thieno[2,3-*d*]pyrimidine derivatives as previously illustrated in Scheme 1 [34].

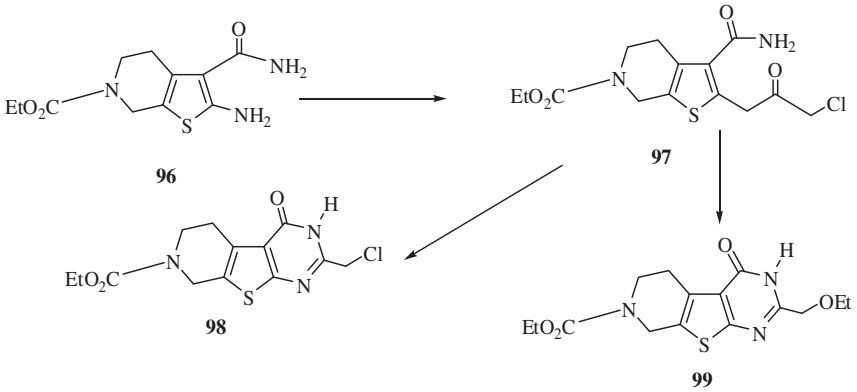
The thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **94** were reacted with propargyl bromide in acetone by using potassium carbonate as a base to yield two products, namely *O*-propargylated and *N*-propargylated thieno pyrimidines **95** and **95** in definite proportions as outlined in Scheme 34 [81]. The formation of each regioisomer depends on the bulkiness/electron-withdrawing or bulkiness/electron-donating nature of substituents present. The *O*-propargylated product **95** is formed in major when R is aromatic, whereas *N*-propargylated compound **96** is major when R is aliphatic (Scheme 34) [81].

Conjugation of tetrahydropyridothienopyrimidones **100** and carbohydrates or amino acids linked by 1,2,3-triazoles **102a–c** was synthesized as shown in Schemes 35 and 36. After establishing the tetrahydropyridothienopyrimidones ring system **100** by ring closure, propargyl groups were introduced by *N*-alkylation. Cu-catalyzed cycloaddition of the propargyl products with azido group containing hexoses or amino acids gives the corresponding 1,2,3-triazoles in high yields. This methodology also allowed attaching two carbohydrate molecules to the tetrahydropyridothienopyrimidone core. Interesting dependence of the regioselectivity of the *N*-propargylation of the pyrimidone ring on the exocyclic substituent found adjacent to the pyrimidine-*N*-atom was observed. A remarkable case of a noncatalyzed intramolecular [3 + 2]cycloaddition of an alkyne with an azide to a 1,2,3-triazole was observed, which occurred in the solid state at room temperature [81].

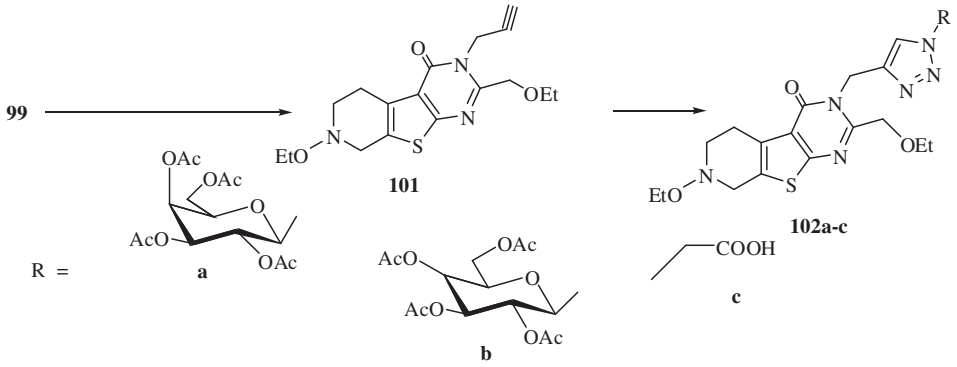
Scheme 34. Substituted *O*-propargylated and *N*-propargylated of thienopyrimidines **95** and **96**.



Scheme 35. Synthesis of thienopyrimidones **97**.



Scheme 36. Synthesis of glycosides of tetrahydropyridothienopyrimidones **102**.

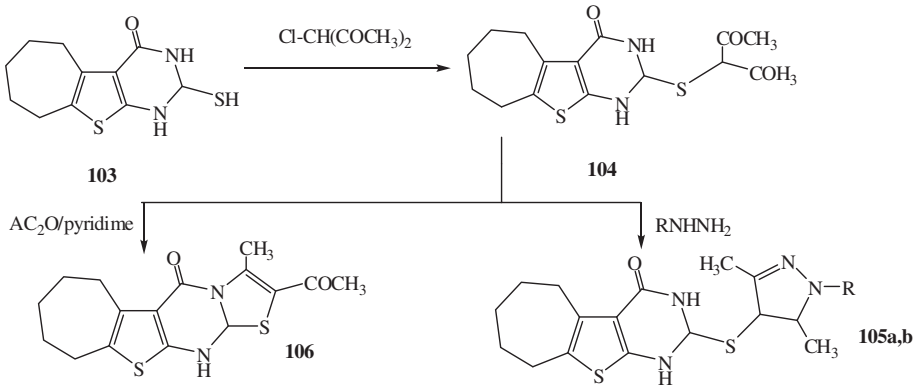


7.2. Cyclization reactions. Thieno[2,3-*d*]pyrimidine **103** reacted as 1,3-diketone with hydrazine hydrate and with phenyl hydrazine to afford the cyclized products **105a,b**. On the other hand, when compound **104** was heated in a mixture of acetic anhydride/pyridine mixture, the product was **106** (Scheme 37) [82].

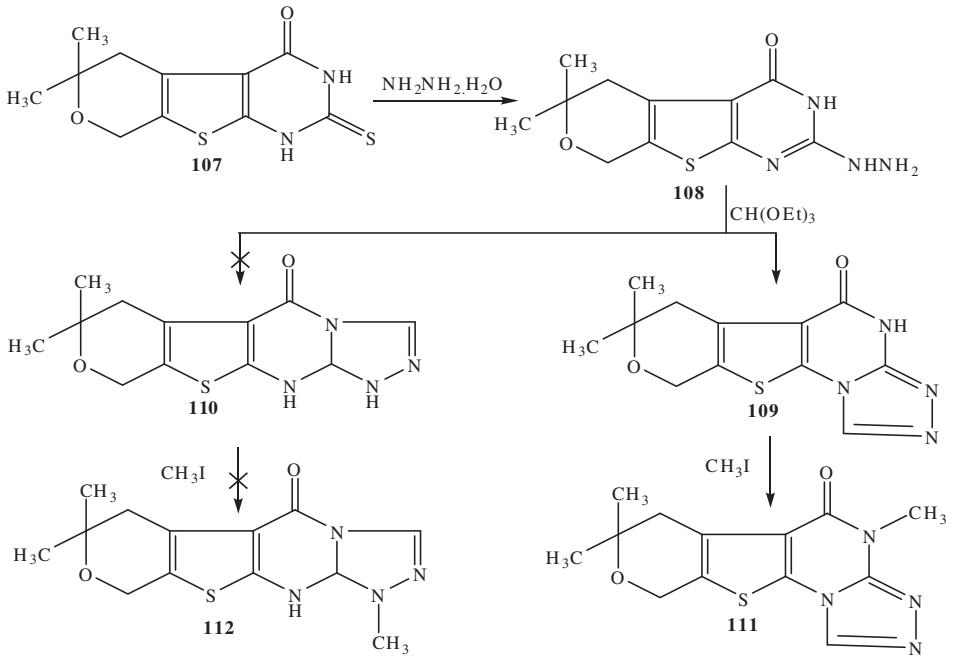
Condensation of 6,6-dimethyl-2-thioxo-5,6-dihydro-8*H*-pyrano[4′,3′:4,5]thieno-[2,3-*d*]pyrimidin-4-one (**107**) with concentrated hydrazine hydrate gave the corresponding 2-hydrazino-substituted compound **108**. The reaction of **108** with triethyl orthoformate gave a product that might be assigned the structure **109** or **110**. Alkylation of this product with methyl iodide gave an *N*-methyl derivative whose X-ray analysis proved that the structure corresponded to **111** and *not* **112** (Scheme 38) [83].

3-Amino-2-mercapto-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**113**) was condensed with aromatic and aliphatic carboxylic acids in the presence of phosphorous oxychloride to yield 2-(substituted phenyl)/alkyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-ones **114**. Treatment of compound **113** with carbon disulphide and alcoholic potassium hydroxide resulted in the formation of 2-mercapto[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo-(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**115**). Reaction of **113** with 2-chloroacetic acid in methanol and sodium

Scheme 37. Condensation reaction on thienopyrimidine **104**.



Scheme 38. Condensation reaction on thienopyrimidine **107**.

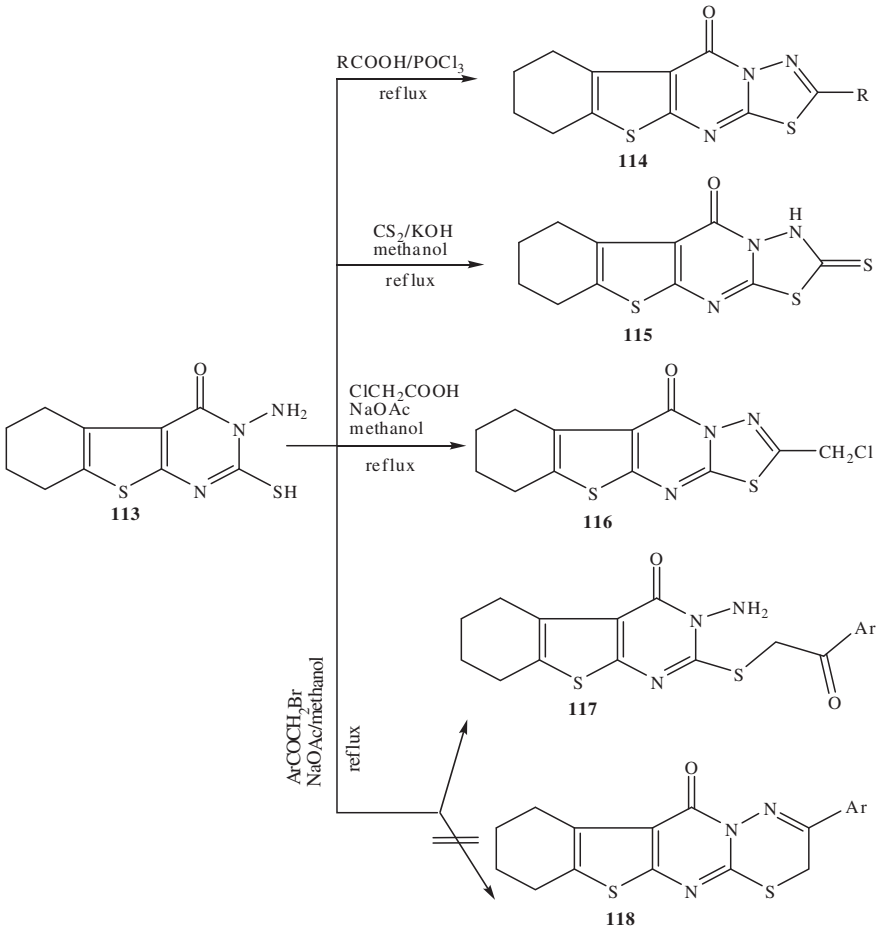


acetate resulted in the formation of the cyclised product 2-chloromethyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)-thieno[3,2-*e*]pyramidin-5(4 *H*)-one (**116**). Actual attempt was made to synthesize pyrimidothiadiazinone derivative **118** by the cyclocondensation of **113** with acyl bromides. However, the reaction ended in the formation of uncyclised **117**, which could be isolated in good yield and purity (Scheme 39) [84].

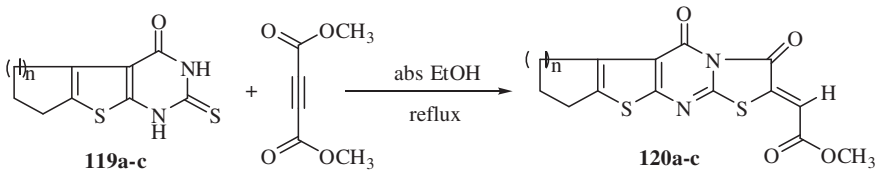
Aly *et al*. [85] reported that dimethyl acetylenedicarboxylate, ethyl propiolate, and *E*-dibenzoylethylene react with thienopyrimidines (cyclopentyl-**119a**, hexyl-**119b**, and heptyl-**119c** derivatives) to form (*Z*)-methyl (3,5-dioxo-cycloalka[4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-*b*][1,3] thiazol-2-ylidene)acetate derivatives (**120a–c**, Scheme 40), (*Z*)-ethyl 3′-((4-oxo-cycloalka[4,5]thieno[2,3-*d*]pyrimidin-2-yl)thio)acrylate derivatives (**121a–c**, Scheme 41), and 2-benzoyl-4-hydroxy-4-phenylcycloalka[4′,5′]thieno-[2′,3′:4,5] pyrimido[2,1-*b*][1,3]thiazin-6-one derivatives (**122a–c**, Scheme 42), respectively. Reaction proceeded via cyclization and thio-addition processes. Some derivatives of thienopyrimidines showed high inhibition of Hep-G2 cell growth compared with the growth of untreated control cells. Additionally, the heptyl derivative of thiazinothienopyrimidines indicates a promising specific antitumor agent against Hep-G2 cells because its IC_{50} is $<20\ \mu M$ [85].

Aly *et al*.[86] have also recently reported that diethyl azodicarboxylate and 3,4,5,6-tetrachloro-1,2-benzoquinone react with cyclopentano-fused and cycloheptano-fused thienopyrimidines **119a–c** to form the oxidative dimer of the starting materials **123a,c** via *S–S* bond formation (Scheme 43). Reaction of two equivalents of 2,2′-(cyclohexa-2′,5′-diene-1,4-diylidene)dimalononitrile with thienopyrimidines **119a–c** afforded 3-(4′,4′-dicyano-methylene-cycloalka [*a*]-2,5-dienyl)-4-oxo-6,7,8,9-tetrahydro-5 *H*-cyclo-hepta [4,5]-[1,3]thiazolo[3,2-*a*]-thieno-[2,3-*d*]pyrimidin-2-ylidene-2-dicarbonitriles **124a–c** (Scheme 43). The thioenopyrimidines **119a–c** react with 2-[1,3-dioxo-1 *H*-inden-2(3 *H*)-ylidene] malononitrile to produce 1,3,5′-trioxo-1,3,3′,5′-tetra-hydro-*spiro*-(indene-2,2′-thiazolo[2,3-*b*]-cycloalkyl[*b*]-thieno [2,3-*d*]pyrimidine)-3′carbonitriles **125a–c** (Scheme 43). However, the reaction of compounds **119a–c** with 2,3-dicyano-1,4-naphthoquinone proceeded to afford the fused

Scheme 39. Cylization reaction on thienopyrimidine **113**.

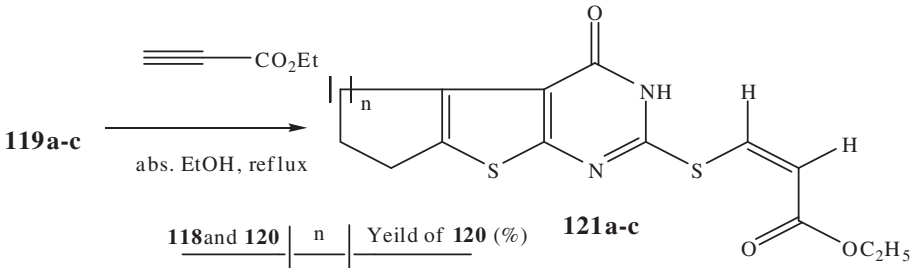


Scheme 40. Synthesis of thiazolo[3,2-*a*][2,3-*d*]pyrimidines **120a–c**.



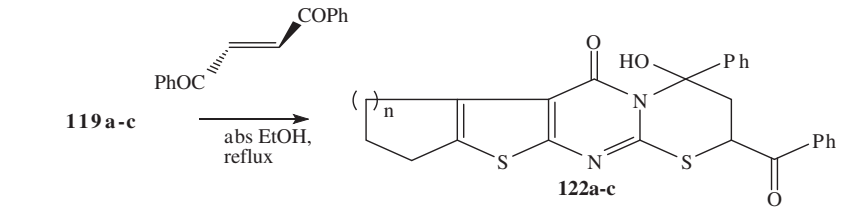
n	**119** and **120**	Yield of **120** (%)
1	**a**	84
2	**b**	86
3	**c**	82

Scheme 41. Synthesis of ethyl cycloalka-thieno[2,3-*d*]pyrimidin-2-ylthio)acrylaters **121a–c**.



118and **120**	n	Yeild of **120** (%)
a	1	81
b	2	85
c	3	80

Scheme 42. Synthesis of cycloalka-thiazino-[3,2-*a*]thieno[2,3-*d*]pyrimidine-5(4*H*)-ones **122a–c**.



119 and **122**	n	Yield of **122** (%)
a	1	74
b	2	76
c	3	72

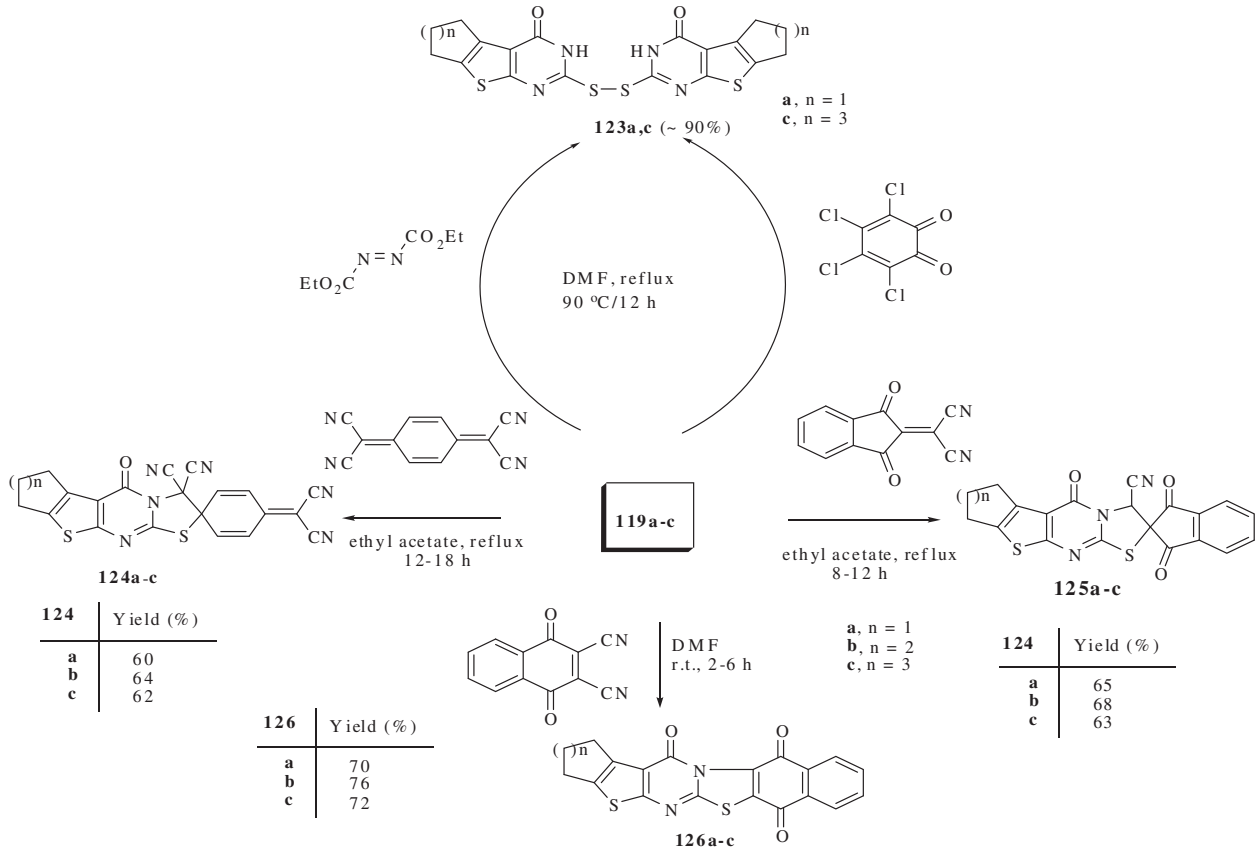
cycloalkylthieno form of naphtho[1,3]thiazolo[3,2-*a*]thieno [2,3-*d*]pyrimidin-6.7,12-triones **126a–c** (Scheme 43) [86].

Reaction of 2-hydrazino-5,6,7,8-tetrahydrobenzo-[*b*]-thieno[2,3-*d*]pyrimidine-4(1*H*)-one (**127**) with dimethyl acetylenedicarboxylate and ethyl propiolate, respectively, afforded cyclohexano-fused (*Z*)-dimethyl 2[(*E*)-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2(1*H*)-ylidene)-hydrazono]-succinate **128** and thienopyrimidinotriazine **129** (Scheme 44) [86].

Both oxidative dimers of thienopyrimidines showed high inhibition of Hep-G2 cell growth compared with the growth of untreated control cells. Moreover, the cycloheptano-fused thiazinothienopyrimidine indicates a promising specific antitumor agent against Hep-G2 cells because its IC_{50} is $<20\,\mu M$ [86].

Reaction of 2-hydrazino-3-methyl-3,4-dihydrothieno[2,3-*d*]pyrimidin-4-one derivatives **130** with nitrous acid yielded tetrazolothienopyrimidinone derivatives **131** and with carbon disulphide furnished 3-mercaptothienotriazolo-pyrimidinone derivatives **132**. Also, **130** reacted with aldehydes to afford the arylhydrazones **133**, which cyclized into thienotriazolopyrimidinone derivatives **134** (Scheme 45) [87].

Scheme 43. Reactions of thienopyrimidines **119a–c** with π-deficient compounds.

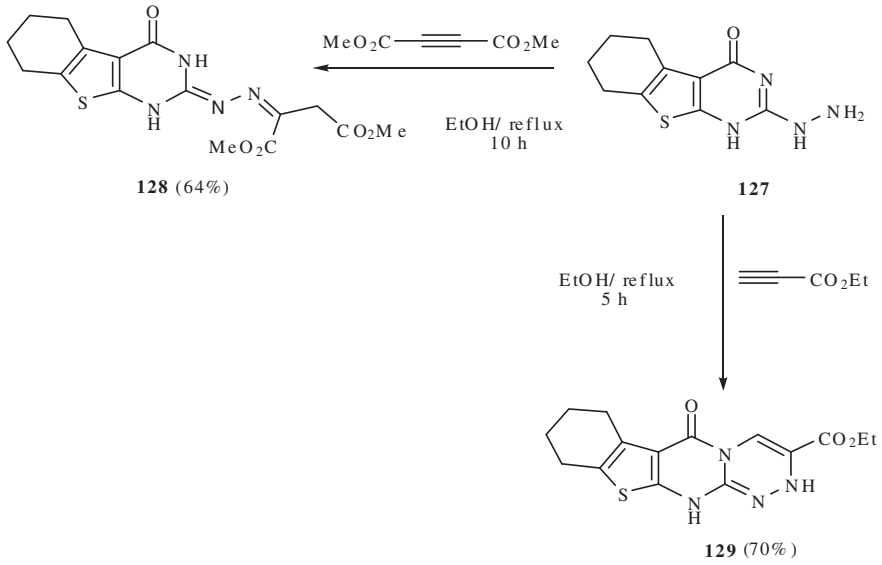


124	Yield (%)
a	60
b	64
c	62

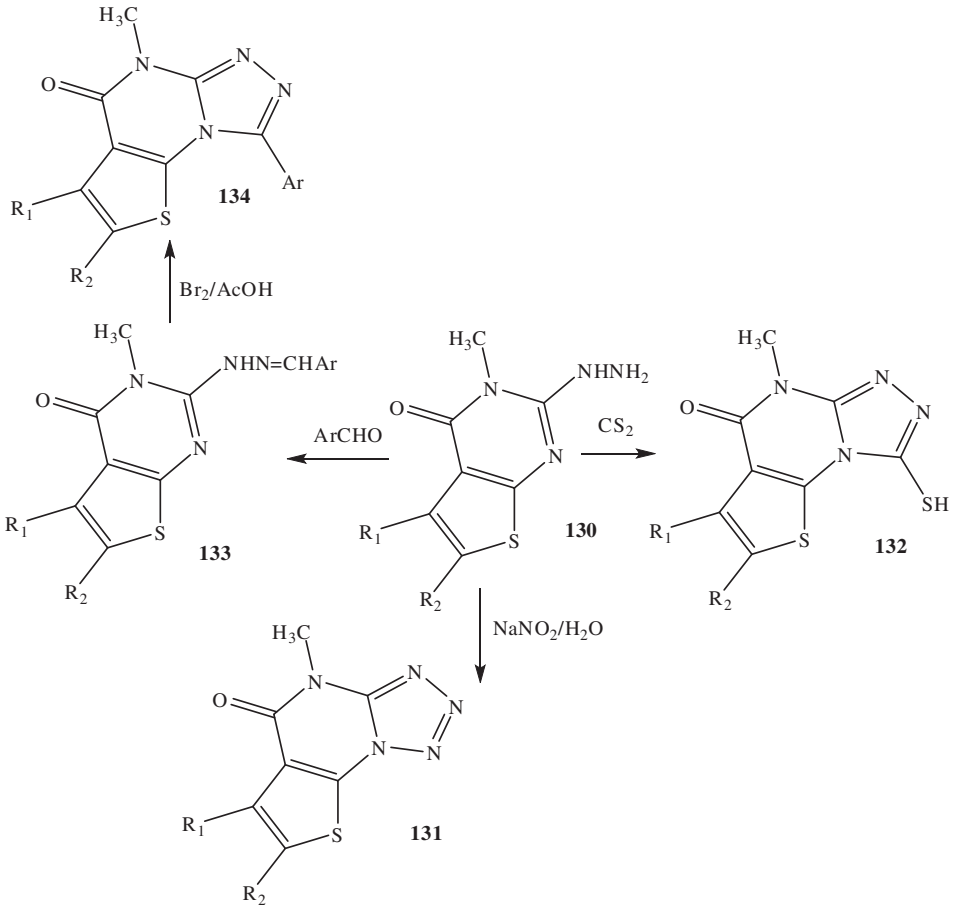
126	Yield (%)
a	70
b	76
c	72

124	Yield (%)
a	65
b	68
c	63

Scheme 44. Reactions of thienopyrimidine **127** with π-deficient acetylenic compounds.



Scheme 45



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