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RECENT ADVANCES IN THIENOPYRIMIDINE CHEMISTRY: SYNTHESIS AND THERAPEUTIC EXPLORATION OF THEIR DERIVATIVES (2018-2025)

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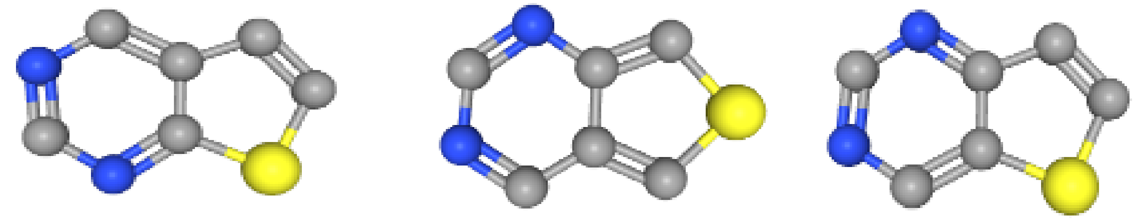
ABSTRACT

Thienopyrimidines are fused bicyclic heterocyclic ring systems composed of a 6-membered Pyrimidine ring and a 5-membered thiophene ring, respectively. They possess substantial therapeutic relevance in the realm of drug discovery. The thienopyrimidine scaffold has served as a starting point for the development of a multitude of clinically validated or under investigation drugs, such as Relugolix (TAK-385), Sufugolix (TAK-013), Pictilisib (GDC-0941), Olmutinib (IKo), Apitolisib, DDP-225, SNS-314, PF-03758309, PRX-08066, GNE-490, GNE-493, Fimepinostat, and Tepotinib. Due to the extensive therapeutic applications, thienopyrimidine and its derivatives are currently a major focus in drug discovery research. The current review highlights the latest developments in bioactive thienopyrimidine hybrids from 2018 to 2025, underscoring the significant advantages of incorporating thienopyrimidines into drug development. Also, this review presents an in-depth exploration of recent progress in the synthesis and therapeutic potential of thienopyrimidines, serving as a key reference for researchers and professionals in the dynamic field of medicinal chemistry.

KEYWORDS: Drug development, Heterocyclic system, Synthesis, Therapeutic applications, Thienopyrimidine Scaffold.

1. INTRODUCTION

We are living in an exciting era when research is being turned into real-world improvements in diagnosis, prevention, and therapy.[1] Pyrimidines and fused pyrimidines have a significant role in heterocyclic chemistry due to their versatility and pharmaceutical interests.[2] Recent studies have shifted their focus to heterocyclic compounds, especially those containing a thienopyrimidine core.[3] They are bio-isosteres to purine with a thiophene ring intertwined with pyrimidine. This platform has become an exciting basic component in the development of pharmaceutical agents due to its broad variety of applications. Thienopyrimidines have been innovated as compounds with many interesting activities, including antioxidants, anticancer agents, and tyrosine kinase inhibitors.[1]



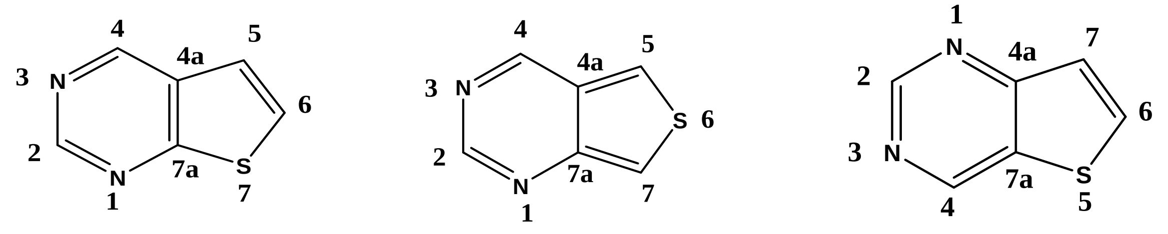
Thieno[2,3-d] pyrimidine **Thieno[3,4-d] pyrimidine** **Thieno[3,2-d] pyrimidine**

Fig. 1- 3-Dimensional structures of different thienopyrimidine isomers.

The thienopyrimidine scaffold has emerged as a frequently utilized chemical framework in drug development. Compounds containing thienopyrimidine exhibit structural and isoelectronic characteristics similar to purines, making them attractive in the production of pharmaceutical drugs and have demonstrated significant pharmacological properties, including antibacterial, antiviral, anti-inflammatory, antiprotozoal, and anticancer activities.[4] In addition, pyrimidines and their fused derivatives can be considered as the main constituents in different materials applications such as herbicides, dyes, pesticides, and fluorescent brighteners.[2]

1.1 Isomers and Chemistry of Thienopyrimidines

The thienopyrimidine scaffold is a bicyclic ring system composed of a thiophene ring fused with a pyrimidine ring, exhibiting structural similarity to purines like adenine. It involves the three basic systems (thieno[2,3-d] pyrimidine, thieno[3,2-d] pyrimidine, and thieno[3,4-d] pyrimidine), which are among those fused pyrimidines that are proven to have a variety of biological activities.[2] They have been shown to possess antimicrobial, antiviral, and anti-inflammatory properties, serve as 3-adrenoceptor agonists, exhibit anti-tuberculosis properties, antiprotozoal activity, and kinase inhibition, act as antioxidants, and possess anticancer activity.[3]



Thieno[2,3-d] pyrimidine **Thieno[3,4-d] pyrimidine** **Thieno[3,2-d] pyrimidine**

Fig. 2. Structures and IUPAC names of different thienopyrimidine isomers.

1.2 Characteristics of Thienopyrimidine

Table 1: Primary Characteristics of Thienopyrimidine.

Molecular formula	**$C_6H_4N_2S$**
IUPAC name	Thieno[2,3-d]pyrimidine Thieno[3,4-d]pyrimidine Thieno[3,2-d]pyrimidine
Molecular weight	136.18 g/mol

Although several reviews have described the thienopyrimidine synthesis and biological activities for decades. However, this review focused on published research regarding the synthesis and biological activities of thienopyrimidine derivatives, covering the period from 2018-2025.

2. SYNTHETIC APPROACHES TO THIENOPYRIMIDINES

In 1914, **Wilhelm Steinkopf** made a foundational contribution to heterocyclic chemistry by reporting the first synthesis of a thienopyrimidine, thereby laying the groundwork for future developments in this class of compounds.

The synthesis of thienopyrimidines has primarily been accomplished through two strategic methodologies.

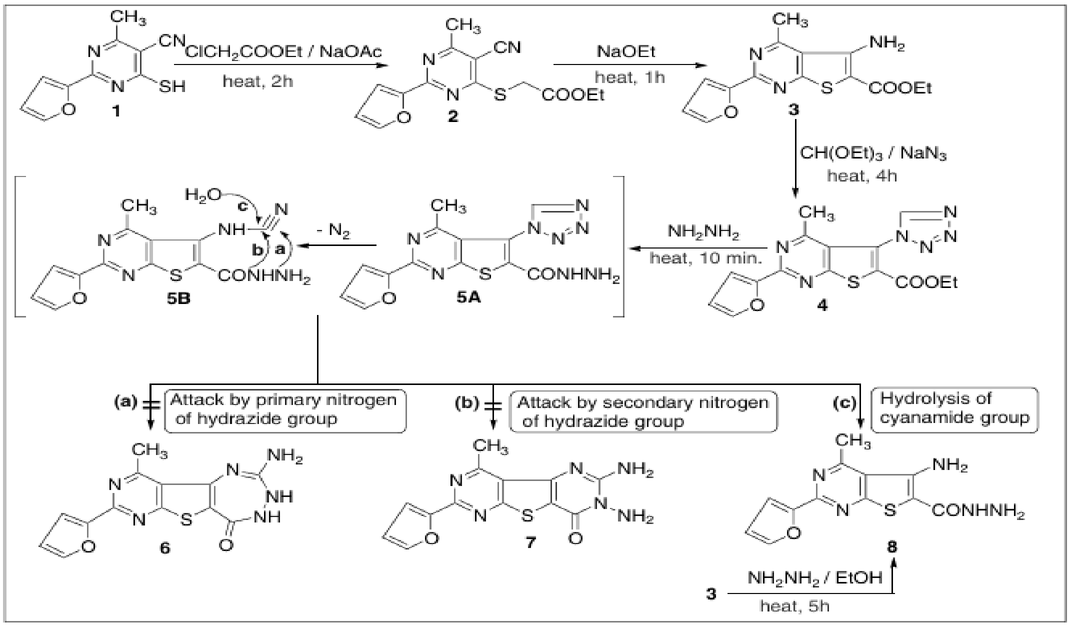
(i) annulation of the pyrimidine ring onto a thiophene scaffold.

(ii) incorporation of a thiophene moiety onto a preconstructed pyrimidine core.

In recent years, numerous synthetic methodologies have been developed for the efficient preparation of thienopyridine derivatives. This review focuses on consolidating recent advances reported in the literature concerning their synthesis. These synthetic strategies are generally classified into two principal approaches, based on the sequence in which the heterocyclic rings are constructed.

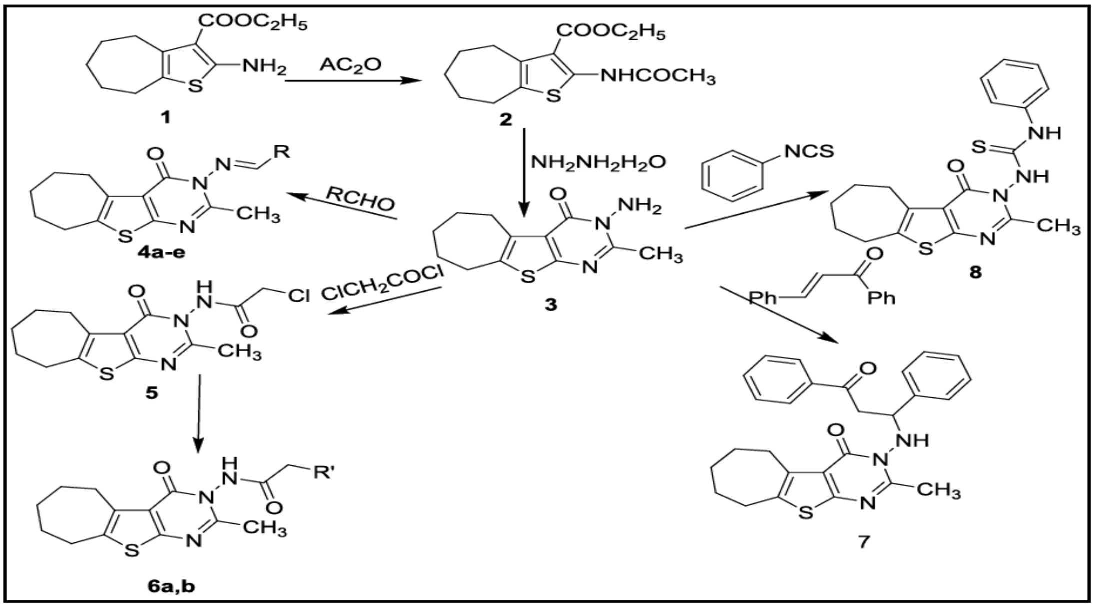
2.1 General synthesis of thieno[2,3-d] pyrimidine

(i) M. Abdel *et al.* reported the synthesis of a thieno[2,3-d]pyrimidine derivative (3) via a two-step sequence. First, 2-(furan-2-yl)-4-mercapto-6-methylpyrimidine-5-carbonitrile (1) was S-alkylated with ethyl chloroacetate using sodium acetate as a mild base, yielding intermediate (2). This was cyclized under reflux with sodium ethoxide via the Thorpe–Ziegler method to afford the fused thienopyrimidine (3). Treatment of compound 3 with triethyl orthoformate and sodium azide in acetic acid under reflux produced the tetrazolyl-substituted derivative (4). Subsequent reaction with hydrazine cleaved the tetrazole ring, typically generating a cyanamide. Hydrazinolysis targeting both the tetrazole and ester groups in compound 4 was expected to yield fused heterocycles (6 or 7), but only one product—acid hydrazide (8)—was obtained. Its formation is proposed to involve ester hydrazinolysis yielding hydrazide (5A), followed by tetrazole ring cleavage to cyanamide (5B), and final hydrolysis to compound 8. (**Scheme 1**).[5]



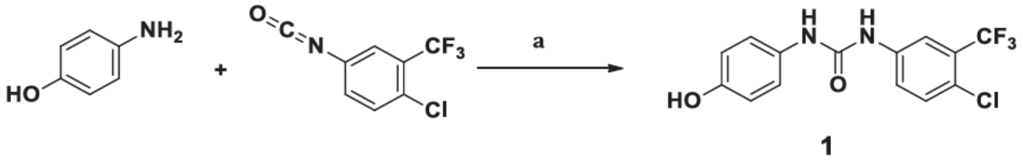
Scheme 1. Synthesis of thienopyrimidines 3, 4, and 8.

(ii) Elmongy *et al.* developed an efficient synthetic route for thienopyrimidine derivatives. The key intermediate, aminothiophene ester (1), was synthesized via the Gewald reaction using cycloheptanone, ethyl cyanoacetate, elemental sulfur, and a secondary amine. Acetylation with acetic anhydride yielded compound (2), which upon reflux with hydrazine hydrate in ethanol produced 3-amino-2-methylthieno[2,3-d]pyrimidine (3), a central intermediate. Condensation of compound 3 with various aromatic aldehydes (e.g., p-chlorobenzaldehyde, 3,4,5-trimethoxybenzaldehyde) in ethanol and glacial acetic acid gave Schiff bases (4a–e). Reaction of the chloroacetamido derivative (5) with morpholine and 2,6-dimethoxyaniline in dry benzene with triethylamine afforded amide derivatives (6a, 6b). Compound 3 also condensed with benzalacetophenone in DMF to yield the 3-oxo-1,3-diphenylpropylamino derivative (7), while reaction with phenyl isothiocyanate in ethanol and triethylamine gave the thiourea derivative (8) (**Scheme 2**).[6]

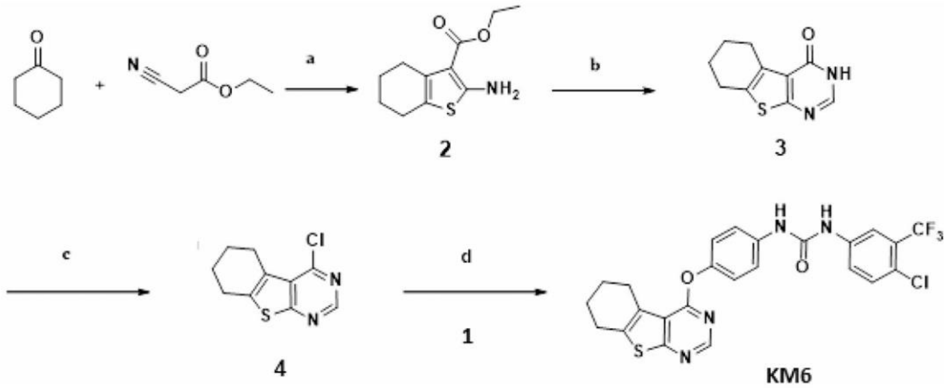


Scheme 2. Synthesis of thienopyrimidine derivatives 3, 4, 5,6, 7, and 8.

(iii) M. Sharaky *et al.*, described the synthesis of KM6 through a convergent approach involving the condensation of a diaryl urea intermediate (1) with a 4-chloro-5,6,7,8-tetrahydrobenzo [4,5] thieno[2,3-d] pyrimidine derivative (4). The diaryl urea compound (1) was synthesized by the reaction of *p*-aminophenol with 4-chloro-3-(trifluoromethyl) phenyl isocyanate in anhydrous 1,4-dioxane (A). The synthesis of intermediate (4) was achieved via a three-step sequence. Initially, a Gewald reaction involving cyclohexanone, ethyl cyanoacetate, and elemental sulfur in the presence of piperidine yielded the 2-amino-tetrahydrobenzothiophene derivative (2). Subsequent cyclization of compound (2) with formamide produced the tetrahydrobenzo[4,5]thieno[2,3-d] pyrimidine derivative (3), which was then subjected to chlorination to furnish compound (4) (**Scheme 3**).[7]



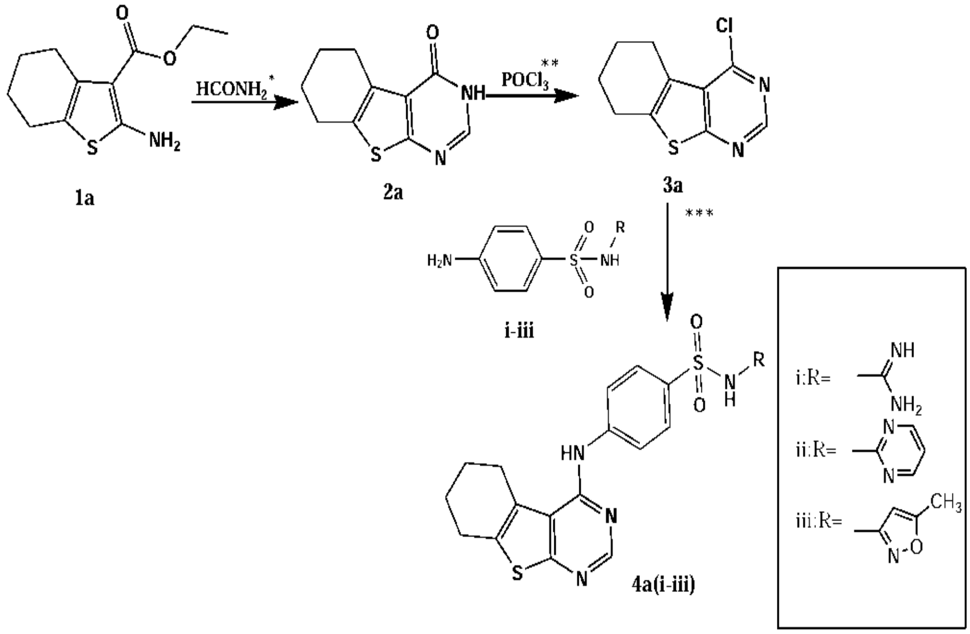
(ii) Preparation of diaryl urea derivative: Reagents and conditions: (a) 1,4-dioxane, room temperature, 1h, 75%.



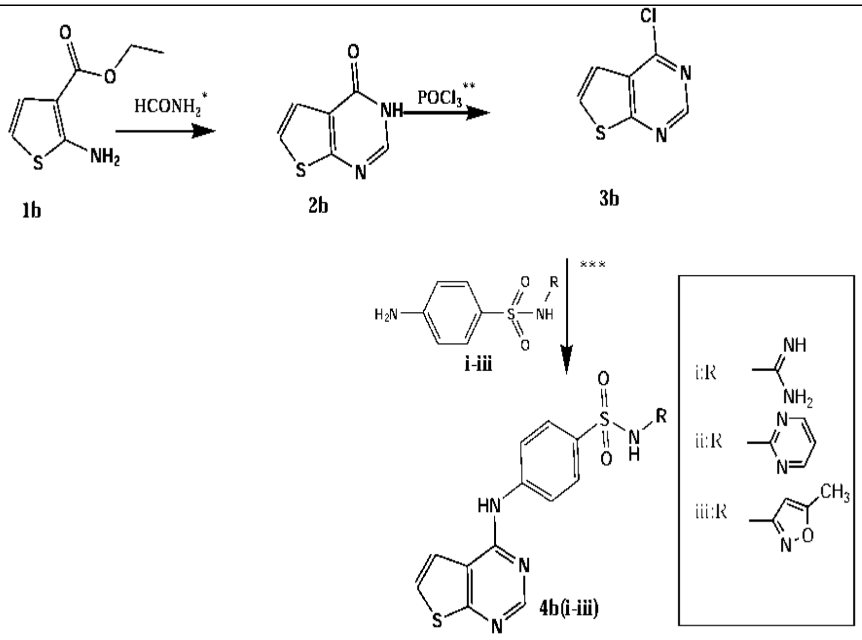
(iii) Reagents and conditions: (a) S, piperidine, water bath at 50–60 C, 16h,70% (b) HCONH2, reflux, 3h, 81% (c) POCl3, reflux, 3h, 76% (d) Acetonitrile, urea derivative (1), Cs2CO3,60 C, 6h, 66%.

Scheme 3. Synthesis of thienopyrimidine derivative KM6.

(iv) Elmongy *et al.* synthesized a series of thienopyrimidine derivatives via a multistep approach. Intermediates 1a and 1b were prepared through the Gewald reaction using elemental sulfur, ethyl cyanoacetate, morpholine, and either a cycloketone or ethyl acetoacetate. Refluxing these with excess formamide yielded cycloheptathieno[2,3-d]pyrimidin-4(3H)-ones (2a, 2b), which were then chlorinated using phosphorus oxychloride to afford derivatives 3a and 3b. Subsequent reaction with sulfaguanidine in glacial acetic acid gave sulfonamide derivatives 4ai and 4bi. To assess the effect of structural rigidity, 3a and 3b were also reacted with sulfadiazine, producing analogues 4aii and 4bii with N-(pyrimidin-2-yl)sulfamoyl groups. Additionally, treatment with sulfamethoxazole yielded compounds 4aiii and 4biii bearing N-(5-methylisoxazol-3-yl)sulfamoyl functionalities. (**Scheme 4 and 5**).[8]

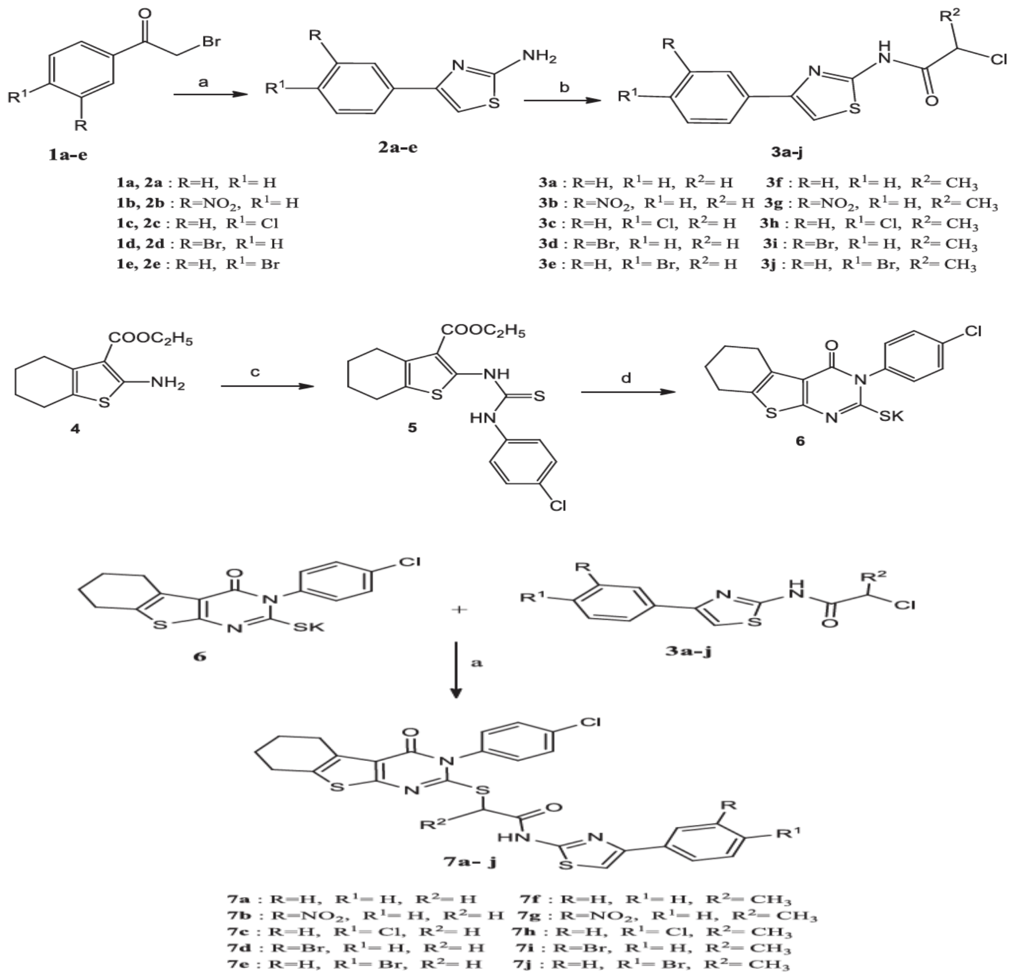


Scheme 4. Reagents and reaction conditions: * reflux, 110 °C, 6 h; ** gentle reflux, 90 °C, 8 h; * reflux 110 °C,12–15 h. Scheme 1. Reagents and reaction conditions: * reflux, 110 °C, 6 h; ** gentle reflux 90 °C, 8 h; *** reflux 110 °C, 12–15 h.**



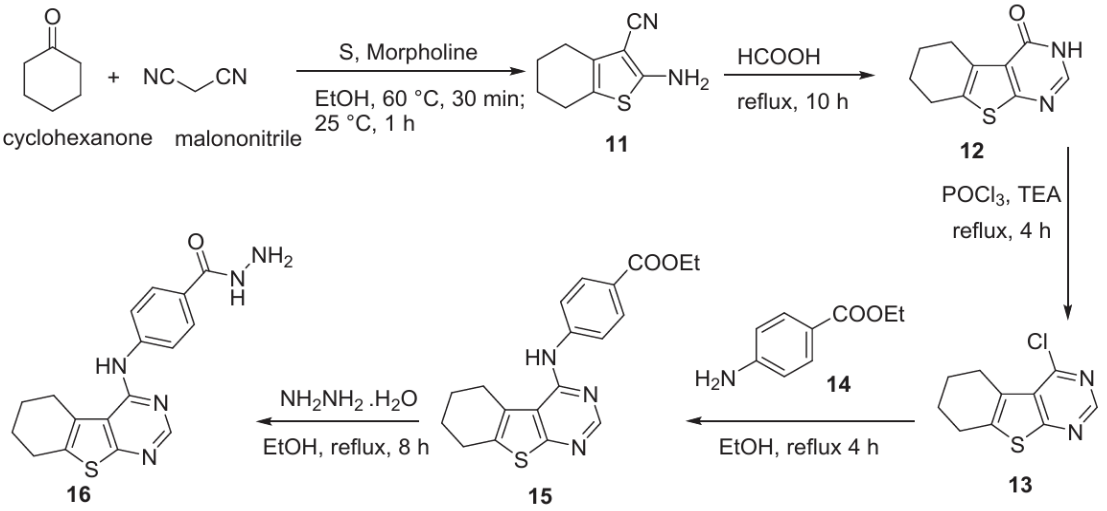
Scheme 5. Reagents and reaction conditions: * reflux, 110 °C, 24 h; ** gentle reflux, 90 °C, 10 h; * reflux, 110 °C, 12–15 h.**

(v) **Y. El-Dash *et al.*** synthesized a series of hexahydrobenzo[4,5]thieno[2,3-d]pyrimidine derivatives (7a–j). Substituted 2-aminothiazoles (2a–e) were first prepared by reacting aryl bromoethanones (1a–e) with thiourea. These were then alkylated with chloroacetyl chloride or 2-chloropropionyl chloride in dry CH_2Cl_2 using triethylamine to yield acetamide (3a–e) and propanamide (3f–j) derivatives. The core scaffold, ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4), was obtained via the Gewald reaction and reacted with 4-chlorophenyl isothiocyanate to form thioureido derivative (5). Treatment with KOH in ethanol gave the thiolate salt (6), which was condensed with intermediates 3a–j in acetone and K_2CO_3 to yield final products 7a–j in good to excellent yields. **(Scheme 6).**[9]

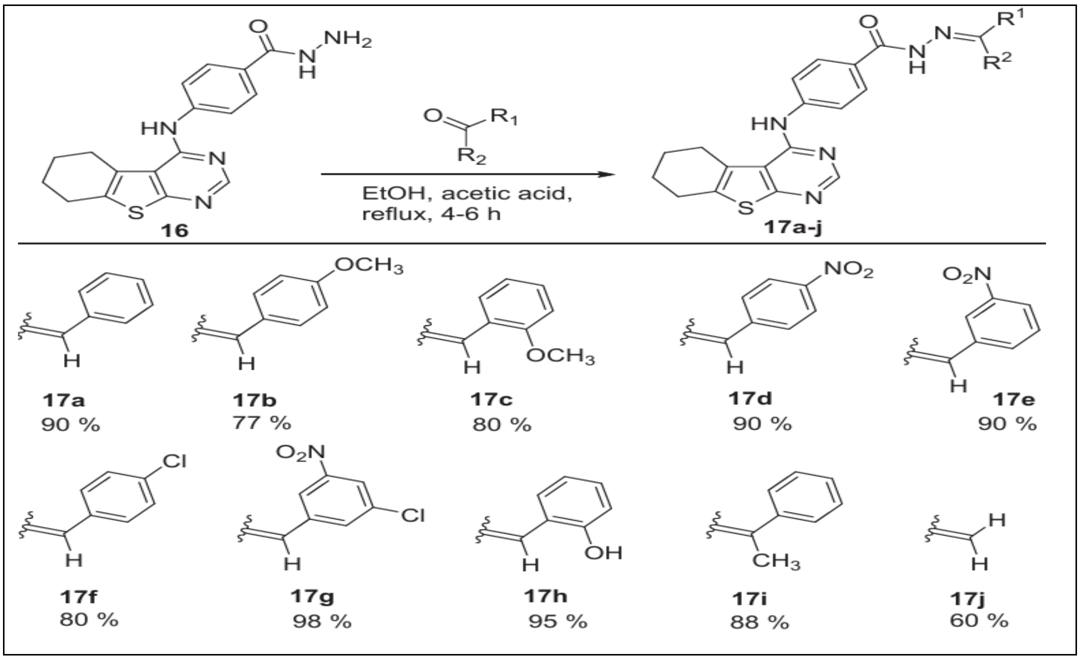


Scheme 6: Synthesis of aryl thiazole derivatives 3a-j and intermediates 4,5, and 6. Reagents and conditions: a) Thiourea, ethanol anhydrous Na acetate, R.T, 4h; b) Chloroacetyl chloride or 2-chloropropionylchloride CH_2 Cl_2, TEA, R.T, 4h; c) 4-Chlorophenyl isothicyanate, ethanol, reflux 9h; d) KOH, ethanol, reflux 6h.

(vi) S.A. El-Metwally *et al.* reported the synthesis of target compounds starting with 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (11), prepared via the Gewald reaction from cyclohexanone, malononitrile, and sulfur in morpholine. Refluxing 11 with formic acid gave compound 12, which was chlorinated using $POCl_3$ and TEA to yield compound 13. A nucleophilic substitution with ethyl 4-aminobenzoate (14) in ethanol produced compound 15, followed by hydrazinolysis to afford hydrazide intermediate 16 (85% yield). Condensation of 16 with various aromatic aldehydes in ethanol/DMF gave Schiff base derivatives 17a–h. Additionally, reactions with acetophenone and formaldehyde produced 17i and 17j, respectively (**Schemes 7 and 8**).[10]

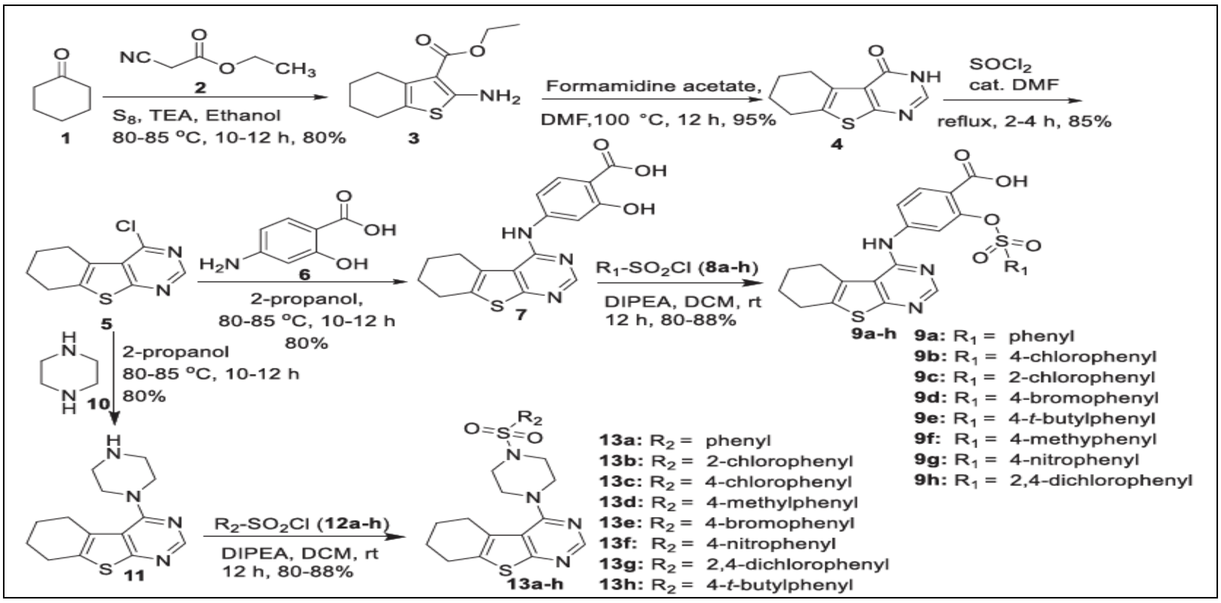


Scheme 7: Synthesis of the target compounds 15 and 16.

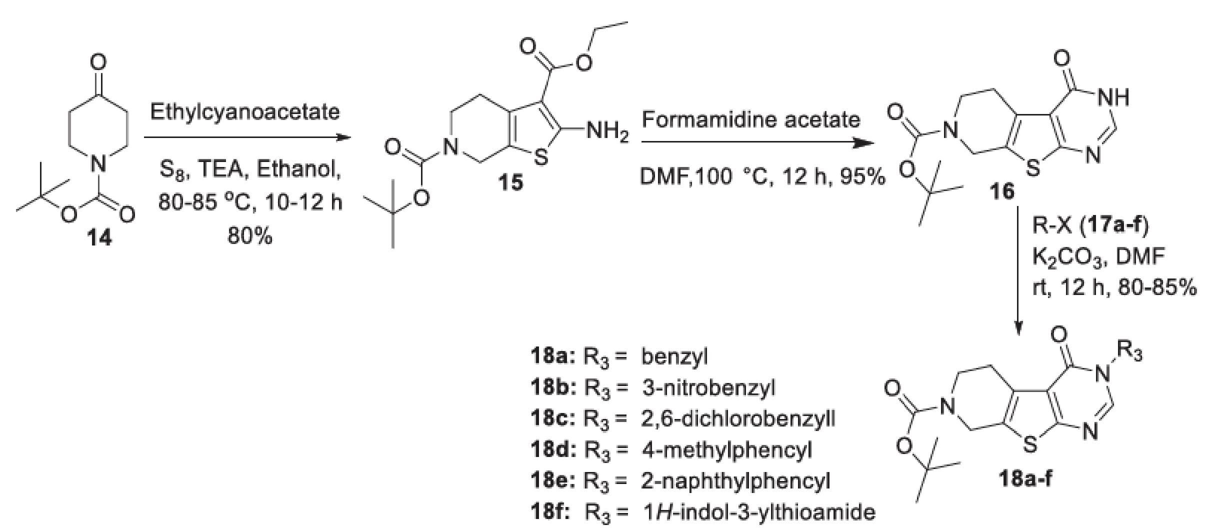


Scheme 8: Synthesis of the target compounds 17a-j.

(vii) S. Malasala *et al.* synthesized a series of novel thienopyrimidine derivatives. Cyclohexanone (1) or N-Boc-piperidone (13) was reacted with ethyl cyanoacetate (2) via the Gewald reaction to yield thiophene intermediates 3 and 14. Cyclization with formamidine acetate afforded thienopyrimidines 4 and 15. Intermediate 4 was chlorinated with thionyl chloride/DMF to obtain compound 5, which underwent nucleophilic substitution with p-aminobenzoic acid (6) and piperazine (10) to give compounds 7 and 11, respectively. These were further reacted with substituted aryl sulfonyl chlorides and triethylamine to yield sulfonyl esters (9a–h) and sulfonamides (13a–h). Meanwhile, intermediate 16 was N-alkylated with benzyl halides (17a–f) to produce N-benzylated products (18a–f) in moderate to good yields **(Scheme 9 and 10).**[11]

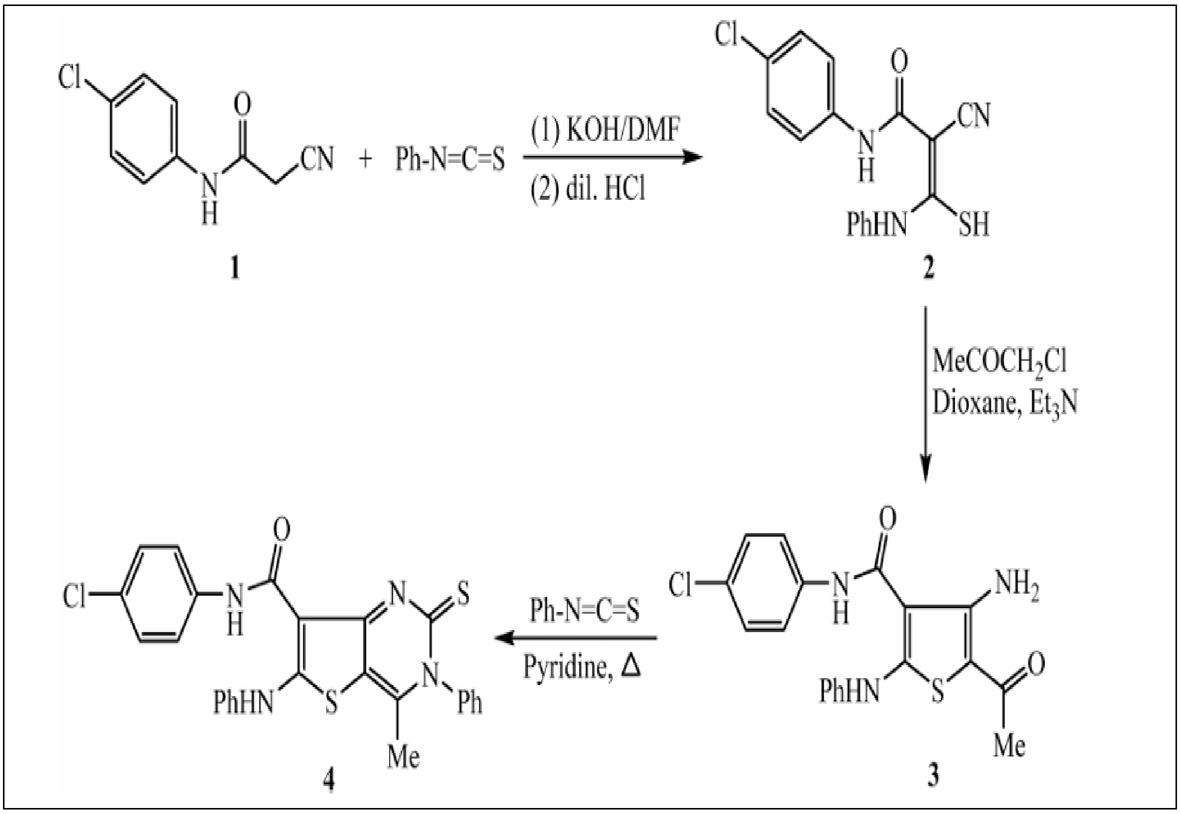


Scheme 9: Synthesis of 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine sulphonyl esters 9a-h and sulphonamides 13a-h.

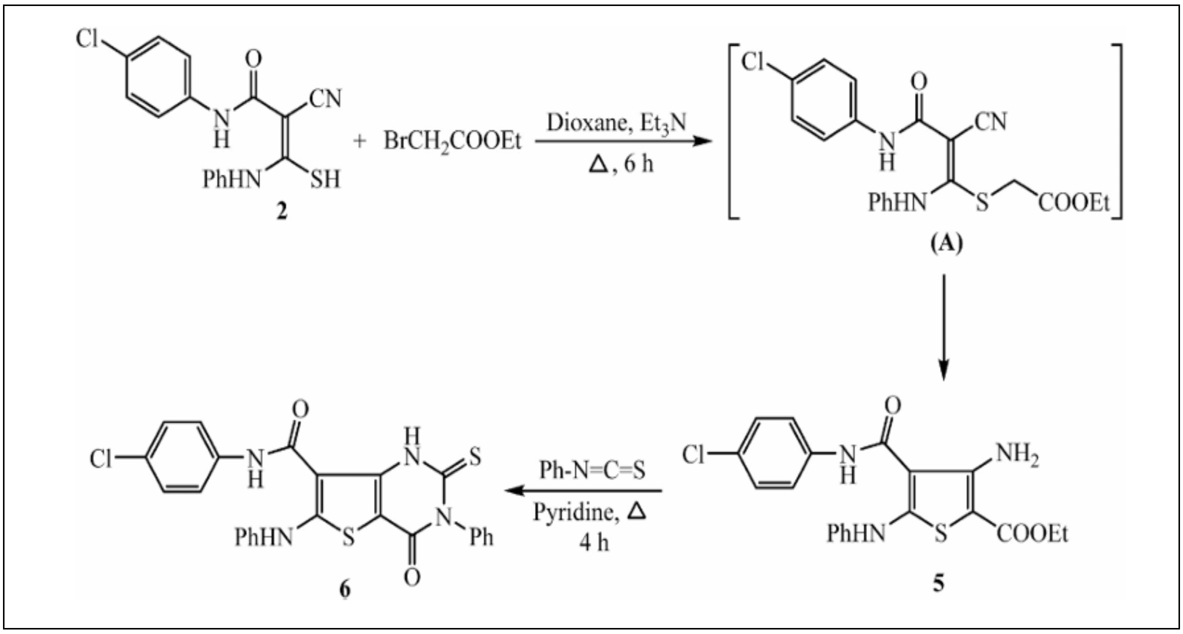


Scheme 10. Synthesis of tert-butyl 4-oxo-3,5,6,8-tetrahydropyrido[4 ,3 :4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate derivatives 18a-f.

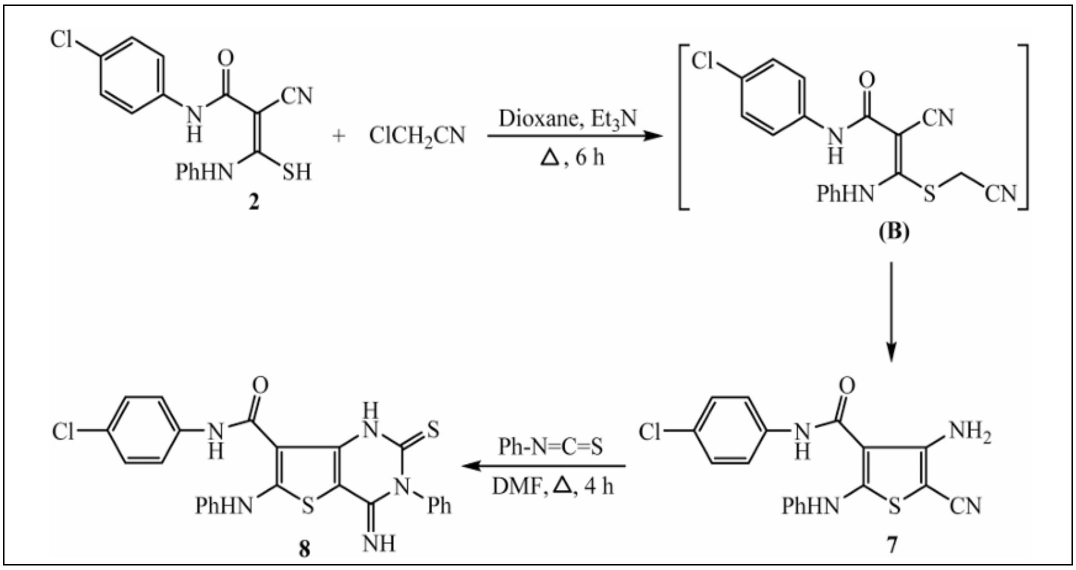
(viii) A. Hossan *et al*. reported a synthetic approach to 4-aminothiophene derivatives from N-(4-chlorophenyl)-2-cyano-3-mercapto-3-(phenylamino)acrylamide (2). Cyclization with chloroacetone in dioxane and triethylamine yielded compound 3, which upon treatment with phenyl isothiocyanate in refluxing pyridine afforded thieno[3,2-d]pyrimidine derivative 4. In a parallel route, reaction of compound 2 with ethyl bromoacetate produced aminothiophene derivative 5 via nucleophilic substitution and intramolecular cyclization; further reaction with phenyl isothiocyanate gave bicyclic compound 6. Additionally, reaction with chloroacetonitrile led to cyanothiophene 7, which underwent cyclization with phenyl isothiocyanate in DMF to yield 4-imino-thieno[3,2-d]pyrimidine derivative 8. All structures were confirmed by spectral and elemental analysis **(Scheme 11,12, and 13).**[12]



Scheme 11: Synthesis of 5-acetyl-4-aminothiophene analogue 3 and its congruous theino[3,2-d]pyrimidine derivative 4.

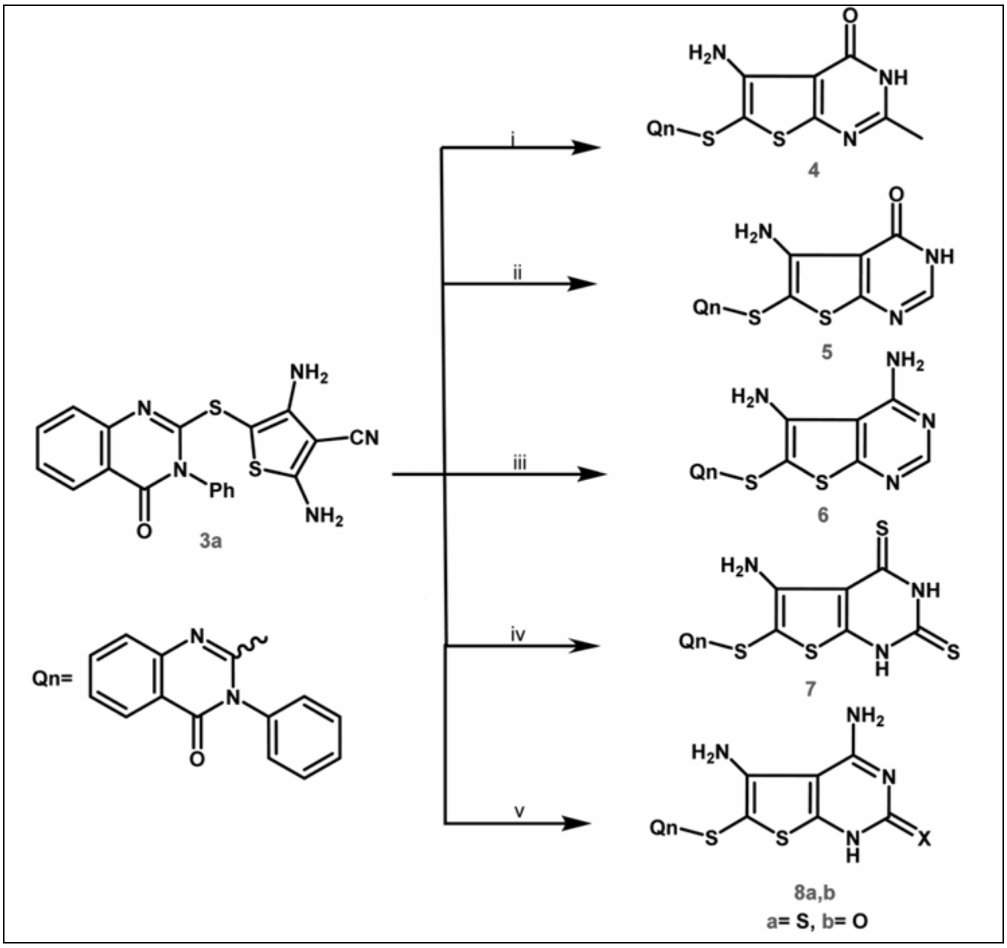


Scheme 12: Synthesis of 4-amino-5-ethoxycarbonyl-thiophene analogue 5 and its congruous theino[3,2-d]pyrimidine derivative 6.



Scheme 13: Synthesis of 4-amino-5-cyanothiophene analogue 7 and its congruous theino[3,2-d]pyrimidine derivative 8.

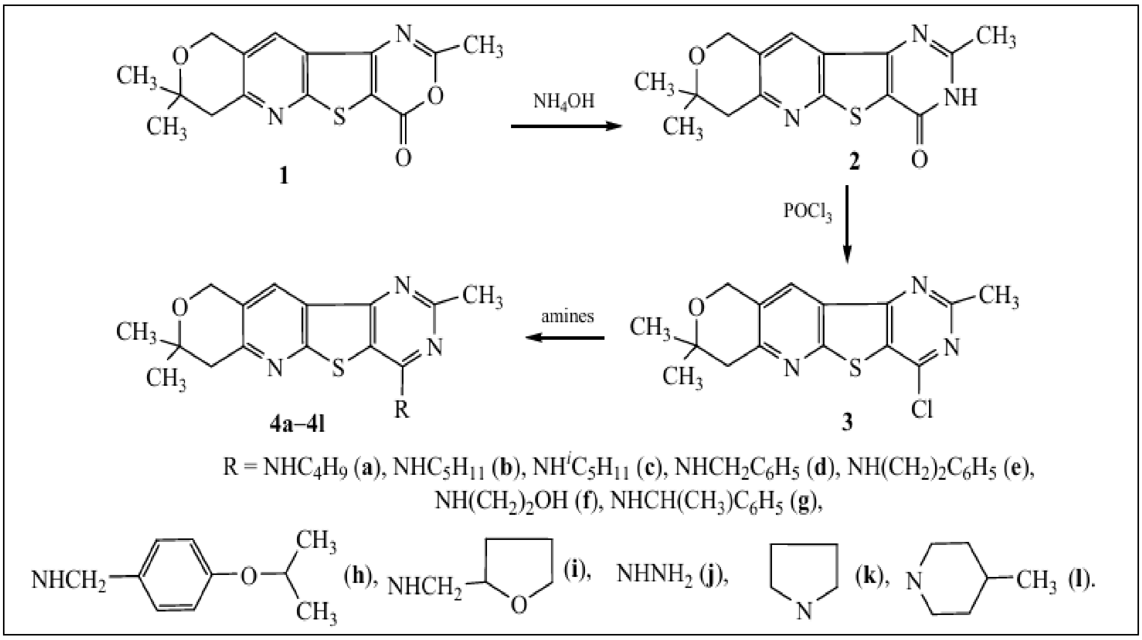
(ix) **Aisha A. Alsfouk *et al.*,** reported the synthesis of thienopyrimidine derivatives 4 and 5. In this procedure, a solution of aminothiophene-3-carbonitrile derivative 3a (10 mmol) in either acetic anhydride or formic acid (20 mL) was refluxed for 24 hours. After completion of the reaction, the mixture was allowed to cool and was subsequently poured into ice water under continuous stirring, leading to the precipitation of the cyclized products. The resulting solid was isolated by filtration and purified through recrystallization from methanol, affording the corresponding thienopyrimidines 4,5,6,7, and 8 respectively (**Scheme 14**).[13]



Scheme 14: Synthetic pathway for synthesis of different substituted thienopyrimidines 4–8a, b. Reagents and conditions: (iandii) aceticanhydride and/or formic acid, reflux for 24 h;(iii) formamide, reflux for 12 h; (iv) carbondisulphide, pyridine, reflux on water bath for 10 h; (v) thiourea and/or urea, ethanolic sodium ethoxide, reflux for 9 h.

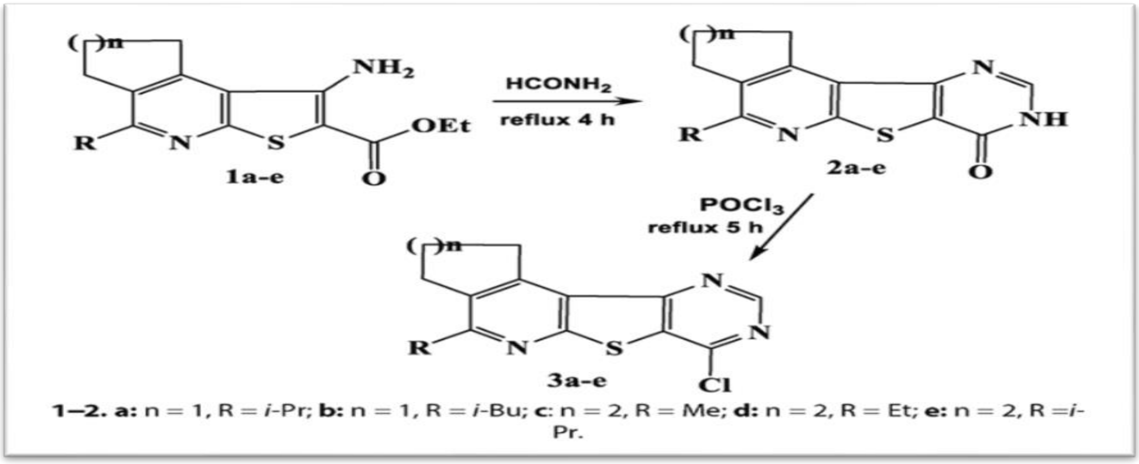
2.2 General synthesis of thieno[3,2-d] pyrimidine

(i) **V. V. Dabaeva *et al.*,** reported the synthesis of a pyrimidin-4-one derivative (2) based on the heterocyclic scaffold 2,8,8-trimethyl-7,10-dihydro-4H,8H-pyrano [3",4":5,6] pyrido[3',2':4,5]thieno[3,2-d][1,3]oxazin-4-one (1). Chlorination of compound 2 using phosphorus oxychloride afforded the corresponding 4-chloropyrimidine derivative (3). The presence of diethylamine was found to significantly enhance the reaction yield. Subsequent nucleophilic substitution of the chlorine atom in compound 3 with various amines proceeded efficiently, furnishing the corresponding substituted amine derivatives (4a–4l) in high yields (**Scheme 15**).[14]

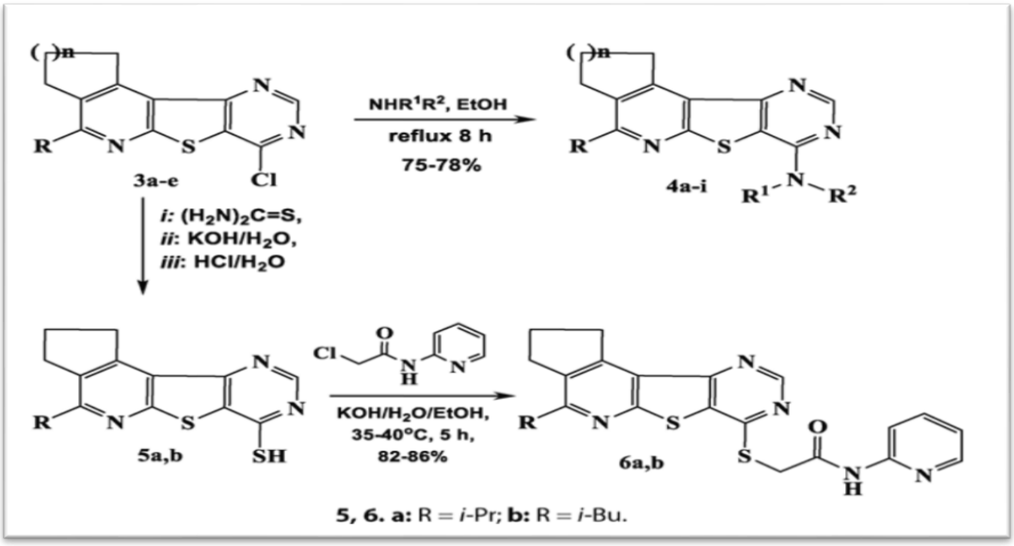


Scheme 15. Synthetic pathway for synthesis of different substituted thienopyrimidines 4a-4l.

(ii) Samvel N. Sirakanyan *et al.* synthesized a series of thieno[3,2-d]pyrimidine derivatives using ethyl 5-alkyl-1-amino-cyclopentathienopyridine (1a, 1b) and tetrahydrothienoisoquinoline carboxylates (1c–1e) as starting materials. These intermediates, containing two reactive sites, were condensed with various reagents (2a–2e) to yield pyrido[3’,2’:4,5]thieno[3,2-d]pyrimidin-7(8)-ones. Chlorination with $POCl_3$ afforded 4-chloro derivatives (3a–3e), which underwent nucleophilic substitution with amines and hydrazine hydrate in ethanol to furnish 7(8)-amino and hydrazino-substituted derivatives (4a–4i) in high yields (**Scheme 16 and 17**).[15]

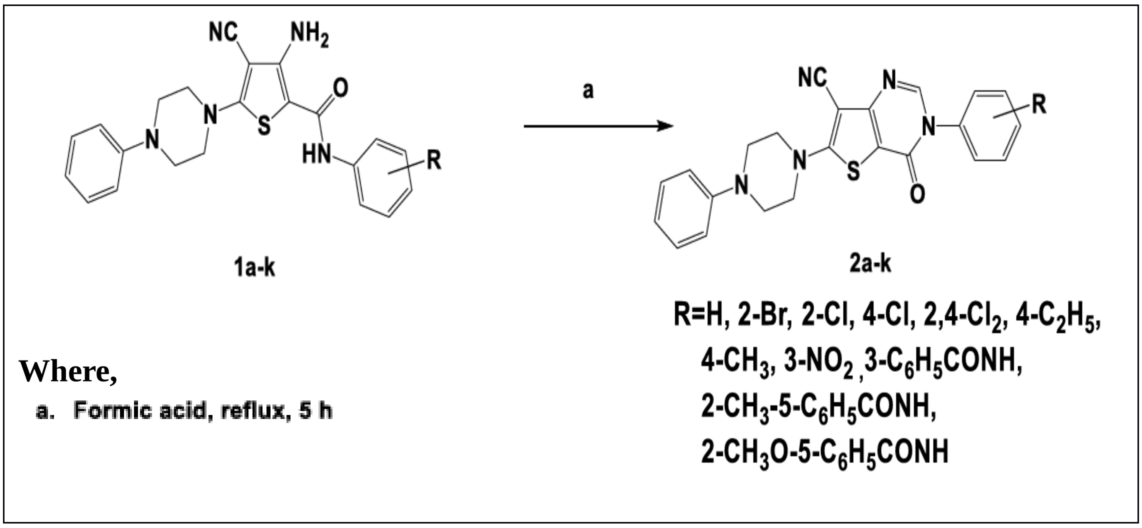


Scheme 16: Synthesis of 7(8)-chloro derivatives of pyridothieno[3,2 d]pyrimidines 3.



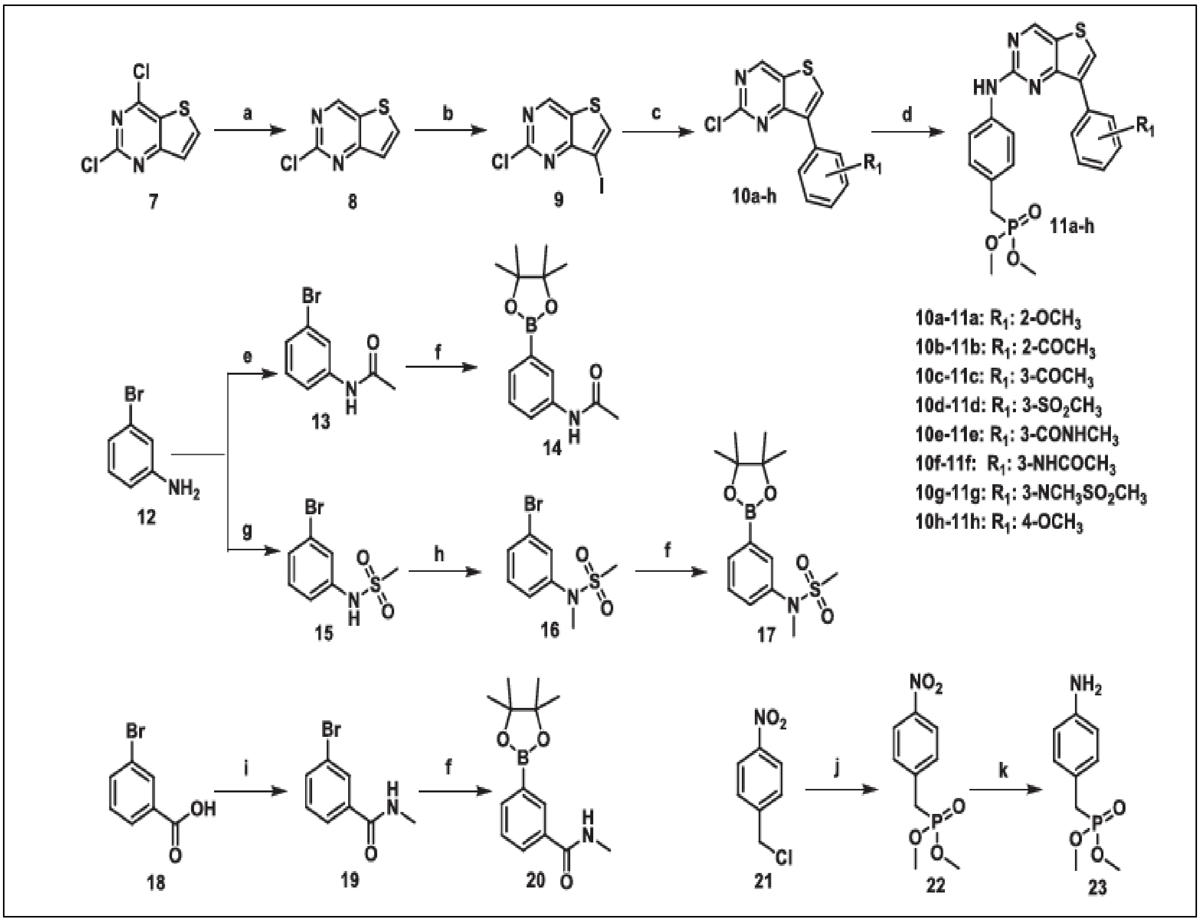
Scheme 17: Synthesis of N- and S-substituted pyridothieno[3,2-d]pyrimidines 4–6.

(iii) E. M. El-Meligie *et al.*, reported novel synthetic approaches for the preparation of thieno[3,2-*d*]pyrimidine derivatives. A suspension of thiophene-2-carboxamide derivatives 1a–k (2 mmol) in formic acid (15 mL) was heated under reflux with continuous stirring for 5 hours. Upon completion, the reaction mixture was allowed to cool to room temperature and then poured onto ice-cold water (100 mL). The resulting suspension was stirred for an additional 30 minutes. The precipitated solid was collected by filtration, thoroughly washed with distilled water (2 × 20 mL) followed by ethanol (2 × 20 mL), and subsequently dried in an oven to constant weight. Final purification was achieved by recrystallization from an appropriate solvent, affording the desired thieno[3,2-*d*]pyrimidine derivatives in good purity (**Scheme 18**).[16]



Scheme 18: Synthesis of thieno[3,2-*d*]pyrimidine derivatives 2a-k.

(iv) R. Wang *et al.* synthesized thieno[3,2-d]pyrimidine derivatives (11a–h) via a multistep route. Regioselective dechlorination of 2,4-dichlorothieno[3,2-d]pyrimidine (7) using Na_2CO_3 afforded compound 8, followed by iodination with NIS to yield intermediate 9. Suzuki–Miyaura coupling of 9 with various boronic acids/esters produced arylated derivatives 10a–h, which underwent Buchwald–Hartwig amination with dimethyl(4-aminobenzyl)phosphonate to form final compounds 11a–h. Parallel routes included: acetylation of 3-bromoaniline (12) and Suzuki coupling to obtain intermediate 14; sulfonylation and methylation of 12 followed by borylation to form coupling partner 17; synthesis of amide 19 from 3-bromobenzoic acid (18) and methylamine, leading to intermediate 20 via Suzuki coupling; and reduction of dimethyl (4-nitrobenzyl)phosphonate (22), prepared from 1-(chloromethyl)-4-nitrobenzene (21), to yield aniline intermediate 23. (**Scheme 19**).[17]



Scheme 19: Synthesis of compounds 11a-h and intermediates 14, 17, 20 and 23. Reagents and conditions: (a) Pd/C, H2,Na2CO3, EtOH, 30 C; (b) NIS, CH3COOH, 80 C; (c) corre sponding boric acid or borate, Pd(dppf)Cl2,K2CO3, 1,4-dioxane/H2O, 90 C; (d) dimethyl (4-aminobenzyl)phosphonate, Pd(AcO)2, X-phos, Cs2CO3, dioxane, 90

C; (e) acetic an hydride, TEA, CH2Cl2, rt; (f) Bis(pinacolato)diboron, Pd(dppf)Cl2, AcOK, dioxane, 80 C; (g) methanesulfonyl chloride, pyridine, CH2Cl2,0 C; (h) CH3I, K2CO3, DMF, rt; (i) I) oxalyl chloride, DMF, CH2Cl2, 60 C; II)CH3NH2$HCl, TEA, CH2Cl2, rt; (j) trimethyl phosphite, 120 C; and (k) Pd/C, H2, EtOH, 40 C.

3. BIOLOGICAL ACTIVITY OF THIENOPYRIMIDINE DERIVATIVES

Thienopyrimidine derivatives have attracted significant attention since their initial discovery due to their broad spectrum of biological activities. Their therapeutic effectiveness has been well-documented over the years, establishing them as valuable structures in the field of medicinal chemistry. These compounds have found applications in various pharmacological areas, notably as anticancer, antimicrobial, anti-tubercular activity, antioxidant, neuro-protective, and anti-inflammatory activity and the following sections highlight the major biological roles in which thienopyrimidine -based compounds have demonstrated considerable potential.

3.1 Anti-microbial activity

A. Hossan *et al.* reported that a series of 4-amino-5-substituted-thiophene derivatives 3, 4, 6, and 8 designated acceptable activity towards (+ve and −ve) Gram strains compared to standard drugs, Chloramphenicol and Cephalothin. DFT calculations were utilized to determine frontier orbital energies. The data showed that the compounds have low HOMO and LUMO energies, where 4-methylthienopyrimidine 4 and 5 have the lowest values. According to results of antibacterial activity against two distinct strains of Gram-positive and negative bacteria through two different concentrations (0.5 and 1.0 mg/mL). Compounds 6 and 8 show (IC50 = 43.53±3.26, 45.64±3.42 and 39.72±2.98, 42.57±3.19 mg/mL) good action toward S. aureus compared to chloramphenicol.[12]

3.2 Anti-proliferative activity

El-Metwally *et al.* reported that new thieno[2,3-d] pyrimidine-derived compounds possessing potential anticancer activities were designed and synthesized to target VEGFR-2. The thieno[2,3-d] pyrimidine derivatives were tested in vitro for their abilities to inhibit VEGFR-2 and to prevent cancer cell growth in two types of cancer cells, MCF-7 and HepG2. Compound 18 exhibited the strongest anti-VEGFR-2 potential with an IC50 value of 0.084 mM. Additionally, it displayed excellent proliferative effects against MCF-7 and HepG2 cancer cell lines, with IC50 values of 10.17 mM and 24.47mM, respectively.[10]

3.3 Anti-tubercular activity

Harrison *et al.* reported that the study successfully identified a 4-amino-thieno[2,3-d] pyrimidine derivative (**CB37)**, that inhibited the growth of *Mycobacterium smegmatis*. Recognizing that the carboxylate group on CB37 may have limited its cellular penetration, a series of structurally related analogs lacking this group were evaluated. Among these, **CB81** demonstrated enhanced growth-inhibitory activity and was subsequently resynthesized and designated as **CWHM-728**. This compound emerged as a promising lead, indicating that structural optimization of thieno[2,3-d]pyrimidines could improve their antimicrobial potential against mycobacterial species.[18]

3.4 Anti-oxidant Activity (Free radical scavenging activity)

Elshaymaa I. Elmongy *et al.*, reported the biological evaluation and synthetic approach for a new series of thiophene/pentahydrocycloheptathieno[2,3-d]pyrimidine derivatives. As part of the study, six of the top-ranked synthesized compounds were selected for assessment of their antioxidant activity using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay, with ascorbic acid serving as the reference standard. Notably, three compounds (**4c,5a and 6b**) demonstrated 100% free radical scavenging activity, indicating excellent antioxidant potential.[19]

3.5 Anti-inflammatory activity

Sara Elsayed *et al.*, have successfully designed and synthesized a series of tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine monomers and a heterodimer with the aim of developing dual-action anti-inflammatory agents. The compounds were evaluated for their COX-2 and 15-LOX inhibitory activities, as well as antioxidant potential. Among the monomers, compound **5k** demonstrated the highest COX-2 inhibition with notable selectivity, while compound **5i** showed superior activity against 15-LOX. The heterodimer **compound 11** outperformed the monomeric series, exhibiting the most potent and selective dual inhibitory activity against both COX-2 and 15-LOX enzymes. These findings underscored the potential of the synthesized thienopyrimidine-based scaffolds as promising leads for multi-target anti-inflammatory drug development.[20]

3.6 Neuroprotective activity

Triloknadh Settypalli *et al.*, reported the design and synthesis of a series of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole-incorporated thieno[2,3-d]pyrimidine derivatives (10a–l) with the aim of identifying novel neuroprotective and antimicrobial agents. The synthesized compounds were evaluated for their neuroprotective, neurotoxic activities. Among the tested derivatives, **compound 10a** (bearing a 4-methylphenyl group) and **compound 10c** (bearing a 4-nitrophenyl group) exhibited notable neuroprotective activity against H_2O_2-induced cytotoxicity in PC12 cells, with EC_{50} values of 10.44 µg/mL and 14.12 µg/mL, respectively. In contrast, **compounds 10b** and **10k** demonstrated comparatively higher neurotoxic effects, with CC_{50} values of 100.16 µg/mL and 120 µg/mL, respectively.[21]

3.7 Anti-Viral Activity

Zhang H. *et al.* reported the design and synthesis of novel influenza polymerase PB2 inhibitors aimed at the treatment of influenza A infection. Among the synthesized compounds, two thienopyrimidine derivatives, namely **16a** and **16b**, exhibited potent anti-influenza A activity, with efficacy observed in the single-digit nanomolar range in cell-based assays. Furthermore, molecular modeling studies elucidated the binding interactions of these compounds within the PB2 pocket of the influenza polymerase, providing insights into their mechanism of action.[22]

4. CONCLUSION

Thienopyrimidines have established themselves as a vital class of synthetic heterocyclic compounds, owing to their broad spectrum of biological activities and notable contributions to therapeutic drug development. Extensive research has been devoted to the design of efficient and sustainable synthetic methodologies, encompassing both traditional and green chemistry approaches, each with its respective merits and limitations. This review provided a comprehensive overview of these strategies while highlighting the wide-ranging pharmacological properties of thienopyrimidine derivatives, including anticancer, anti-inflammatory, antimicrobial, anti-oxidant, neuro-protective, and anti-tubercular activities.

In particular, fused thienopyrimidines demonstrated promise not only as anticancer agents but also in the management of neurodegenerative disorders such as Alzheimer’s disease. As the field continued to evolve, the integration of rational drug design with innovative synthetic strategies was expected to further elevate the importance of thienopyrimidines in modern medicinal chemistry. Collectively, the insights presented in this review underscore their significance and encourage further exploration within this promising domain of heterocyclic drug discovery.

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6. CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

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