Chapter 1
CHAPTER 1

Applications of Gewald reaction: Syntheses of polysubstituted thiophene, fused thieno[3,2-e]pyridines, thieno[2,3-d]pyrimidines and thieno[2,3-d][1,3]oxazines

In this chapter we report syntheses of new category of fused polysubstituted thiophenes, thieno[3,2-e]pyridine, thieno[2,3-d]pyrimidine and thieno[2,3-d][1,3]oxazine derivate-ives from 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile and 2-5-amino-3-(4-chloro- phenyl)thiophene-2,4-dicarboxamide.

This chapter is incorporated two sections;

Section I: Synthesis of versatile scaffold 5-amino-3-(4-chlorophenyl)thiophene- 2,4-dicarbonitrile by multicomponent Gewald reaction.

Section II: Syntheses of fused thieno[3,2-e]pyridine and thieno[2,3-d]pyrimidines derivatives

1.1 Introduction

The importance of this type of heterocyclic chemistry gave impetus to the present study, where the synthesis, reactivity and applications of various substituted 2-aminothiophenes were systematized and analyzed. Chemistry of 2-aminothiophenes is debatably one of the most wide-ranging and dynamic field received much attention because their availability through versatile synthetic method developed by Gewald [1]. The reagent availability and its mild reaction conditions required made Gewald reaction most easy method for the synthesis of various thiophenes. The 2-amino-3-substituted thiophene derivatives are useful precursor in the dye industry and uses as intermediates
for the pharmaceuticals. Important thieno[2,3-\(d\)] pyrimidines [2, 3]. Previously, pharmacological studies of the thienopyridine and thienopyrimidine derivatives extensively showed variety of activities such as antibacterial [4, 5], antimicrobial [6], anxiolytic [7], pshycotropic [8]. These thienopyridines are also useful as potential class of VEGFR-2 kinase inhibitors [9], I\(\kappa\)B kinase inhibitors [10], gonadotropin releasing hormone antagonist [11-16] and anti-inflammatory agents, particularly for treating arthritis and bone resorption inhibiting agents [17]. Thieno[3,2-\(e\)] pyridine and thieno[2,3-\(d\)]pyrimidine derivatives are the lead molecules of pharmaceutical industries owing to their interesting biological activities displayed over a broad range of therapeutic classes. Consequently, thienopyridines and thienopyrimidines have become well sought privileged class of heterocyclic compound in drug discovery programs.

### 1.1 Literature updates of polysubstituted thiophene and their thienopyridine, thienopyrimidine derivatives

Thiophene nucleus has been established as the potential entity in largely growing chemical world of heterocyclic compounds possessing promising pharmacological characteristics. The similar compounds synthesized through different routes bear variable biological activities. The knowledge of various synthetic pathways and the diverse physicochemical parameters of these compounds draw our attention to produce combinatorial library. The present chapter provide a broad review of synthesis and properties of thiophene nucleus.

1) Literature support for the synthesis of intermediate \(\text{2}\) as the most promising precursor for synthesis of polysubstituted thiophene from 3-oxopropanenitriles. \(F. M. Abdelrazek et al.\) [18] has been successfully produced a Knoevenagel condensation product \(\text{2}\) along
with by-products by the condensation reaction of benzoylacetonitrile, 1 and malononitrile heated in pyridine. (Scheme-1)

\[
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{O} & \quad \text{Ph} \\
& \quad \text{CN}
\end{align*}
\]

\[
\text{malononitrile, } \Delta \rightarrow
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{O} & \quad \text{Ph} \\
& \quad \text{CN}
\end{align*}
\]

\[
\text{NH}_2
\]

Scheme 1

2) Kandeel et al. [19] obtained 5-amino-3-phenylthiophene-2,4-dicarbonitrile 4 in good yield by reaction of precursor 2 with elemental sulphur by refluxing in ethanol in the presence of catalytic amount of piperidine. This is a two step method; i.e. first-synthesis of ylidene intermediate 2, and then secondly base catalyzed cyclization in elemental sulphur. (Scheme-2)

\[
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{CN} & \quad \text{CN}
\end{align*}
\]

\[
\text{sulphur, EtOH, } \Delta \rightarrow
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{CN} & \quad \text{NH}_2
\end{align*}
\]

Scheme 2

3) The first report on the development and the use of substituted 2-aminothiophenes and the Gewald reaction was published by Z. Puterová et al. [20] by utilizing the \(\beta\)-aryl or \(\beta\)-heteroaryl substituted 3-oxopropanenitriles 5, morpholinepolysulfide (MPS) and substituted acetonitriles 6. (Scheme 3)

\[
\begin{align*}
\text{Ar} & \quad \text{CN} \\
\text{O} & \quad \text{CN}
\end{align*}
\]

\[
\text{NC} \rightarrow \text{R}^1
\]

\[
\text{MPS, MeOH, } \Delta \rightarrow
\begin{align*}
\text{Ar} & \quad \text{CN} \\
\text{NC} & \quad \text{NH}_2
\end{align*}
\]

\[
\text{R}^1= -\text{CO}_2\text{Me or } -\text{CN}
\]

Scheme 3
4) Wie Haung et al. [21] obtained 2-aminothiophenecarboxamides 11 under solvent free condition from ketone 8 and reactive methylene 9. Under solvent free microwave irradiation of cyanoacetamides 9 with ketone 8 afforded compound 10 under basic condition which on further treatment with sulphur in presence of catalytic amount of morpholine furnished 2-aminothiophene-3-carboxamide derivatives 11. (Scheme 4)

![Scheme 4]

5) Lee D. Jennings et al. [22] has revealed parallel synthesis and biological evaluation of 5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4(3H)-one 16 as a cytotoxic agent selective for p21-deficient cells. (Scheme 5)

![Scheme 5]

5) Recently, in our lab [23] the syntheses of 1,2,3,6-tetrahydro—8,9-dimethoxy-cyclopenta[b]indenol[1',2':4,5]thieno[3,2-e]pyridine-11-amine derivatives 19a-c were obtained by using Lewis acid catalyst and cyclic and/or acyclic ketones 18a-c under solvent less condition in moderate to good yields. (Scheme 6)
6) S. Ma et al. [24] has also revealed syntheses of 1,2-dihydro-4H-3,1-benzoxazine derivatives via various Lewis acid catalysts such as AlCl₃, CuCl₂, TiCl₄, ZnCl₂ and p-TSA out of which zinc chloride (ZnCl₂) catalyzed cyclocondensation reaction by using various ketones or aldehydes reacted with substituted o-aminobenzonitrile afforded moderate to good yield. (Scheme 7)

**Scheme 7**

**1.2 Present Work**

These literature reports, extensive trend in thiophene synthesis and consequently their fused cyclic derivatives prompted us to synthesize new class of fused polycyclic heterocyclic compounds such as thieno[3,2-e]pyridines, thieno[2,3-d]pyrimidines and thieno[2,3-d]-[1,3]oxazines.

**A retrosynthetic Approach**

**1.2.1 Synthesis of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile, 23**

Synthesis of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile 23 can be achieved by *in situ* condensation of 3-(4-chloro-phenyl)-3-oxo-propionitrile 24,
malononitrile 25 and elemental sulphur (S₈) as depicted in following retrosynthetic approach. (Scheme 8)

Syntheses of 4-amino-3-(4-chlorophenyl)-6,7-dihydro-5H-cycloalka[b]thieno [3,2-e] pyridine-2-carbonitrile, (26a, 27a) and 5'-(4-chlorophenyl)-4'-imino-1',4'-dihydropiropo-
[cycloalkane-1,2'-thieno[2,3-d][1,3]oxazine]-6'-carbonitrile, (26b, 27b) derivatives

Syntheses of 4-amino-3-(4-chlorophenyl)-6,7-dihydro-5H-cycloalka[b]thieno[3,2-e]-pyridine-2-carbonitrile, (26a, 27a) and 5'-(4-chlorophenyl)-4'-imino-1',4'-dihydropiropo-
[cycloalkane-1,2'-thieno[2,3-d][1,3]oxazine]-6'-carbonitrile, (26b, 27b) could be prepared by treatment of compound 23 with alicyclic ketones such as cyclohexanone and cyclopentanone. (Scheme 9)
1.2.2 Syntheses of 5-(4-chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-\(d\)]pyrimidine-6-carboxamide, 28 and \(N\)-(4-(4-chlorophenyl)-3,5-dicyanothiophen-2-yl)acetamide, 29 could be achieved by treatment of compound 23 with formic acid and acetic anhydride respectively. (Scheme 10)
1.2.3 Syntheses of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide, 30

Synthesis of dicarboxamide compound 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide 30 could be achieved by acid hydrolysis of compound 23. This could be another crucial precursor for syntheses of fused scaffolds. (Scheme 11)

1.2.4 Synthesis of 3-amino-5-(4-chlorophenyl)-4-imino-3,4-dihydrothieno[2,3-c]pyrimidine-6-carbonitrile, 29

Synthesis of new class of 3-amino-5-(4-chlorophenyl)-4-imino-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonitrile 32 could be achieved by treating N'-[4-(4-chloro-phenyl)-3,5-dicyano-thiophen-2-yl]-N,N-dimethyl-formamidine 31 with hydrazine monohydrate (N₂H₄.H₂O). This intermediate 31 can be obtained from compound 23 reacting with dimethylformamide dimethyl acetal (DMF-DMA). (Scheme 12)
1.2.5 Syntheses of 5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-(aryl)-4-oxothieno[2,3-d] pyrimidine-6-carboxamide, 33 and 5'-(4-chlorophenyl)-3',4'-dihydro-4'-oxo-1'H-spiro[cycloalkane-1,2'-thieno[2,3-d]pyrimidine]-6'-carboxamide, 34

Syntheses of new class of 5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-(aryl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 33 and 5'- (4-chlorophenyl)-3',4'-dihydro-4'-oxo-1'H-spiro[cycloalkane-1,2'-thieno[2,3-d]pyrimidine]-6'-carboxamide, 34 derivatives could be synthesized by cyclization of compound 30 with aromatic aldehydes and cyclic ketones respectively. (Scheme 13)

1.2.6 Syntheses of 5-(4-chlorophenyl)-3,4-dihydro-2-(aryl)-4-oxothio[2,3-d]pyrimidin-6-carboxamide, 35 and 5-(4-chlorophenyl)-3,4-dihydro-2-alkyl-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 36

Syntheses of 5-(4-chlorophenyl)-3,4-dihydro-2-(aryl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide 35 and 5-(4-chlorophenyl)-3,4-dihydro-2-alkyl-4-oxothieno[2,3-d] pyrimidine-6-carboxamide 36 derivatives could be achieved by treatment of compound 30 with aromatic aldehydes and acid chlorides respectively. (Scheme 14)
1.3 Results and discussion

We have utilized 4-chlorobenzoylacetonitrile 24 as an authentic precursor for the syntheses of polysubstituted thiophenes and its fused pyridine and pyrimidine derivatives. The closeness of two strongly electron withdrawing groups i.e. keto and cyano functionalities reflect the high acidity of protons adjacent to these two groups which eventually makes enhanced reactivity. The previous literature report [18, 19] on the synthesis of 5-amino-3-phenylthiophene-2,4-dicarbonitrile 4 was achieved in two steps i.e. Knovenagel condensation of benzoylacetonitrile 1 with malononitrile to obtain 3-dicyanomethylene-3-phenylpropionitrile 2 and then cyclization of this intermediate using sulphur (S₈) in ethanol in presence of catalytic amount of piperidine which gave average yield (Scheme 1 & Scheme 2). But in this report, [25] we have made an important modification i.e. electron withdrawing functionalities i.e. 4-chlorobenzoyl acetonitrile 24 and malononitrile, were utilized in-situ (i.e. multi-component reaction) using elemental sulphur (S₈) in pyridine to achieve directly 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile 23 in excellent yield in shorter time. Also, syntheses of thienopyridines, thieno-oxazines and thienopyrimidines were successfully prepared from two key intermediates i.e. 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile 23 and 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide 30.
1.3.1 Synthesis of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile, 23

The key precursor 23 was successfully prepared by one pot reaction of 3-(4-chlorophenyl)-3-oxo-propionitrile 24, malononitrile 25 and elemental sulphur (S₈) in pyridine at 55°C provided stochiometric yield i.e. 85% yield. *(Experiment No. 1, Page 28)* The structure of 23 was established by spectral and analytical data. Compound exhibited –NH₂ and –CN stretching frequencies at 3383, 3304 and 2198 cm⁻¹ respectively. The ¹H-NMR spectrum clearly showed broad singlet for NH₂ protons at δ 8.37. The ¹³C-NMR, elemental analysis & the mass spectrometric data i.e. m/z 259 (M⁺) is in full agreement with the proposed structure of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile 23 *(Spectrum No. 1, 2 & 3, Page 12 & 13).*
Spectrum No. 1: $^1$H NMR (DMSO-$d_6$) spectrum of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile, 23

Spectrum No. 2: $^{13}$C NMR (DMSO-$d_6$) spectrum of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile, 23

[Chemical structures and spectra images]
1.3.2 Green approach for the syntheses of 4-amino-3-(4-chlorophenyl)-6,7-dihydro-5H-cycloalka[b]thieno[3,2-e]pyridine-2-carbonitrile, 26a-b and 5′-(4-chlorophenyl)-4′-imino-1′,4′-dihydrosphiro[cycloalkane-1,2′-thieno[2,3-d][1,3]oxazine]-6′-carbonitrile, 27a-b

In this protocol, we planned the synthesis of fused thienopyridine derivatives by cyclocondensation of cyclopentanone with precursor 23 in presence of anhydrous ZnCl₂
(Lewis acid) under solvent free condition afforded mixture of compounds as acridines 26a-b and spiropyrazines 27a-b. These compounds were chromatographed on silica gel eluted with (chloroform-methanol, 9:1) to get acridine 26a-b in 20-25% while spiropyrazine 27a-b in 68-70% yields. (Experiment No. 2, Page 29) Structural assignment of these compounds were performed by IR, ^1H NMR, mass spectrometric and elemental analysis. The IR spectrum of this compound 26a showed absorption peaks at 3540, 3430 cm^{-1} for NH2, 2210 cm^{-1} for CN and 1626 cm^{-1} for Ar-C=CH functionals. The ^1H NMR in DMSO-d_6 showed six methylene protons as multiplet at δ 2.12-2.98, 5.92 assigned for two NH2 protons and 7.62-7.69 for aromatic doublets of doublet protons (Spectrum No. 4 and 5, Page No. 15). The mass spectral analysis showed the molecular ion peak at m/z = 325 and the elemental analysis was in agreement with the molecular formula C_{17}H_{12}ClN_3S. Also IR absorption of biproduct 27b exhibited 3168, 2935 cm^{-1} for two NH groups, 2205 cm^{-1} for CN group and 1620 cm^{-1} for Ar-C=CH group. The ^1H NMR in CDCl_3 showed multiplet at δ 2.04-2.87 for eight methylene protons, 4.93 for NH, 6.50 for imine NH and 7.48-7.60 for four aromatic protons (Spectrum No. 6, Page No. 16). The mass spectral analysis showed the molecular ion peak at m/z = 343 and the elemental analysis was in agreement with the molecular formula C_{17}H_{14}ClN_3OS.
Spectrum No. 4: $^1$H NMR (CDCl$_3$) spectrum of 4-amino-3-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carbonitrile, 26b

Spectrum No. 5: MS of 4-amino-3-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carbonitrile, 26b

Mol. Wt.: 339.84
1.3.3 Synthesis of 5-(4-chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 28

After successful condensation reactions with 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile, 23 we have extended our approach towards construction of fused thienopyrimidine cycle 28 by using formic acid. Thus, on refluxing compound 23 with 85% formic acid resulted pure compound 5-(4-chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-d] pyrimidine-6-carboxamide, 28 as pale yellow crystalline solid with
80% yield (Experiment No. 3, Page 31). This structure of 28 was established on the basis of IR, $^1$H NMR, $^{13}$C NMR, Mass spectrometric and elemental analysis. The IR spectrum of this compound 28 showed absorption peaks at 3400 cm$^{-1}$ for NH, 1668 cm$^{-1}$ for amide CO, 1641 cm$^{-1}$ for Ar-C=CH functionality and disappearance of CN absorption frequency. The $^1$H NMR in DMSO-d$_6$ showed two broad protons of amide at $\delta$ 6.40–6.56, 8.42 exhibited pyrimidine CH proton, broad peak at 11.41 for secondary amide NH and aromatic proton appeared at respective region i.e. $\delta$ 7.27–7.44. The mass spectral analysis showed the molecular ion peak at m/z = 305 and the elemental analysis was in agreement with the molecular formula C$_{13}$H$_8$ClN$_3$O$_2$S.

1.3.4 Synthesis of N-(4-(4-chlorophenyl)-3,5-dicyanothiophen-2-y)acetamide, 29

Treatment of compound 23 with acetic anhydride in presence of catalytic conc. H$_2$SO$_4$ at rt afforded N-(4-(4-chlorophenyl)-3,5-dicyanothiophen-2-y)acetamide 29 as an off-white solid with stochiometric yield of 90% (Experiment No. 4, Page 32). Here catalytic amount of conc. H$_2$SO$_4$ triggered the reaction to completion within an hour consequently giving excellent yield. The product obtained need not require any further purification and its structure was established on the basis of IR, $^1$H NMR, $^{13}$C NMR, Mass spectrometric and elemental analysis. Compound exhibited –NH and –CN stretching frequencies at 3267, 2216 cm$^{-1}$ and amide CO at 1703 cm$^{-1}$. The $^1$H-NMR in DMSO-d$_6$ clearly showed singlet at $\delta$ 2.31 for CH$_3$ protons and broad singlet for NH proton much downfield at $\delta$ 12.63. $^{13}$C-NMR spectrum showed carbons appeared at $\delta$
Mass spectrometric analysis of acetamide 29 showed the molecular ion peak at m/z = 301 and the elemental analysis was in agreement with the molecular formula C_{12}H_{8}ClN_{2}OS.

(Spectrum No. 7, Page No. 18).

**Spectrum No. 7: IR (KBr) spectrum of N-(4-(4-chlorophenyl)-3,5-dicyanothiophen-2-yl)acetamide, 29**

1.3.5 Synthesis of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide, 30

Another very important and versatile precursor 30 was easily synthesized by acid hydrolysis of dicayano compound 23 using Conc. H_{2}SO_{4} at ambient temperature to afford dicarboxamide 30 in excellent yield (Experiment No. 5, Page 33). This
important precursor was well characterized by IR, $^1$H NMR, $^{13}$C NMR, mass spectrometric and elemental analysis. Compound exhibited C2-amide NH$_2$ stretching frequencies at 3327, 3306, C4-amide stretching at 3252 and 3475, 3345 cm$^{-1}$ for free C5-NH$_2$, and amide CO at 1668, 1672 cm$^{-1}$. The $^1$H-NMR in DMSO-$d_6$ clearly showed broad singlets at $\delta$ 4.82 for C2-amide NH$_2$, 6.84 for C4-amide NH$_2$ protons and broad singlet for free C5-NH$_2$ proton at $\delta$ 7.69 and aromatic protons in their respective regions at $\delta$ 7.56-7.69. $^{13}$C-NMR spectrum showed carbons appeared at $\delta$ 109.3, 114.7, 129.2, 131.1, 133.6, 134.3, 139.0, 162.9, 163.0 and 166.8. Mass spectrometric analysis of dicarboxamide 30 showed the molecular ion peak at m/z = 295 and the elemental analysis was in agreement with the molecular formula C$_{12}$H$_{10}$ClN$_3$O$_2$S. (Spectrum No. 8, Page No. 20).

1.3.6 Synthesis of 3-amino-5-(4-chlorophenyl)-4-imino-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonitrile, 32 via intermediate precursor N’-(4-(4-chlorophenyl)-3,5-dicyanothiophen-2-yl)-N,N-dimethylformamidine, 31

![Scheme 20](image)

In this scheme, bisnucleophilic cyclization was accomplished successfully by simple reaction condition. The starting precursor 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile 23 was treated with DMF-DMA generated intermediate N,N-dimethylformamidine 31 in quantitative yield 90%. The intermediate N,N-dimethylformamidine
31 is an important skeletal having electron deficient nitrile and labile formamidine group. The reaction of hydrazine hydrate with this intermediate 31 gave substitution followed by addition which lead to cyclized product 3-amino-5-(4-chlorophenyl)-4-imino-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonitrile, 32 with 80% yield.

(Experiment No. 6, Page 34). Both of these structures were easily characterized on the basis of IR, $^1$H NMR, mass spectrometric and elemental analysis. IR frequency of compound 31 exhibited C=N and N-C stretching frequencies at 3312, 2950 cm$^{-1}$ and that for CN at 2208 cm$^{-1}$. The $^1$H-NMR in DMSO-$d_6$ clearly showed singlet at δ 3.21-3.23 for 2-CH$_3$ (6 protons) and singlet for imine CH proton downfield at δ 7.84 and δ 7.50-7.61 for four aromatic protons. Mass spectrometric analysis of intermediate 31 showed the molecular ion peak at m/z = 315 (M+1) and the elemental analysis was in agreement.
with the molecular formula C$_{15}$H$_{11}$ClN$_4$S. Further cyclized product 32, was also well elucidated on the basis of IR, $^1$H NMR, mass spectrometric and elemental analysis. IR frequency of 32 exhibited C=NH and NH$_2$ stretching frequencies at 3381, 3306, 3205 cm$^{-1}$ and that for CN at 2200 cm$^{-1}$. The $^1$H-NMR in DMSO-$d_6$ clearly showed broad singlet at $\delta$ 5.59 for NH$_2$ protons, broad singlet at $\delta$ 6.40 for C=NH proton, singlet for pyrimidine CH proton downfield at $\delta$ 8.42 and $\delta$ 7.45-7.51 for four aromatic protons. Mass spectrometric analysis of intermediate 32 showed the molecular ion peak at m/z = 301 and the elemental analysis was in agreement with the molecular formula C$_{15}$H$_{13}$ClN$_4$S.

1.3.7 Syntheses of 5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-(aryl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide (33a-c)

![Scheme 21](image)

<table>
<thead>
<tr>
<th>33</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-ClC$_6$H$_4$</td>
<td>52</td>
</tr>
<tr>
<td>b</td>
<td>2,4-diMeOC$_6$H$_3$</td>
<td>55</td>
</tr>
<tr>
<td>c</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>55</td>
</tr>
</tbody>
</table>

An interesting cyclization reaction was occurred when compound 30 was subjected to piperidine i.e. base catalyzed cyclization with equimolar amount of various aromatic aldehydes in a protic solvent provided tetrahydrothieno-oxopyrimidine derivatives 33a-c with moderate yields. **(Table 1)** We propose following possible mechanism for the formation of compound 33a-c;
Formation of this structure was established on the basis of IR, $^1$H-NMR, mass spectrometry and elemental analysis mentioned in the experimental section. (Experiment No. 7, Page 35) The IR spectrum of this compound showed absorption peaks at 3475, 3327, 3308 cm$^{-1}$ represented for 2° amide NH, 2° amine NH and 1° amide NH stretch respectively. Also 1689 cm$^{-1}$ for amide CO stretching. The $^1$H NMR in DMSO-d$_6$ showed $\delta$ 5.82 for 3°-CH proton, broad singlet at $\delta$ 6.31–6.48 for two 1° amide protons and two broad singlets at $\delta$ 8.40 and 12.76 for 2° amine and 2° amide NH protons respectively. The mass spectral analysis showed the molecular ion peak at m/z = 417 and the elemental analysis was in agreement with the molecular formula C$_{16}$H$_{13}$Cl$_2$N$_3$O$_2$S. (Spectrum No. 9, Page No. 23)

1.3.8 Green approach 5'-[(4-chlorophenyl)-3',4'-dihydro-4'-oxo-1'H-spiro[cycloalkane-1,2'-thieno[2,3-d]pyrimidine]-6'-carboxamide, 34a-b

This scheme represents an efficient and environmentally benign methodology for the synthesis of spiropyrimidines. In this reaction, 5-amino-3-(4-chlorophenyl)thiophene-
2,4-dicarboxamide 30 and little excess amount of alicyclic ketone/s furnished spiropyrimidine compounds 34a and 34b. (Experiment No. 8, Page 37) This is solvent free method for syntheses of oxospiro thienopyrimidines with excellent stoichiometric yield. Compound 5\'(4-chlorophenyl)-3',4'-dihydro-4'-oxo-1'H-spiro- [cyclohexane-1,2'-thieno[2,3-d]pyrimidine]-6'-carboxamide 34b established on the basis of IR, $^1$H NMR, $^{13}$C NMR, mass spectrometric and elemental analysis. The IR absorption frequency at 3381-3213 cm$^{-1}$ and 1654 cm$^{-1}$ clearly indicates presence of $-\text{NH}$ stretching for 2° amide and $-\text{C}=\text{O}$ stretching respectively. In addition 3288 cm$^{-1}$ for $-\text{NH}$ stretching for 1° amide group. $^1$H NMR in DMSO-$d_6$ supported presence of two broad singlets at $\delta$ 5.37 and 8.30 for two $\text{NH}$ protons and $^{13}$C NMR showed singlet for quaternary carbon at $\delta$
70.33 and secondary amide carbon at δ 163.09 as shown in spectrum. (Spectrum No.10, Page No. 24)

**Spectrum No. 10: ^1H NMR (DMSO-d$_6$) spectrum of 5'-{4-Chlorophenyl}-3',4'-dihydro-4'-oxo-1'H-spiro[cyclohexane-1,2'-thieno[2,3-d]-pyrimidine]-6'-carboxamide, 34b**

1.3.9 Syntheses of 5-(4-chlorophenyl)-3,4-dihydro-4-oxo-2-arylthieno[2,3-d]pyrimidine-6-carboxamide, 35a-c

Scheme 23

<table>
<thead>
<tr>
<th>35</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-ClC$_6$H$_4$</td>
<td>65</td>
</tr>
<tr>
<td>b</td>
<td>2,4-diMeOC$_6$H$_4$</td>
<td>68</td>
</tr>
<tr>
<td>c</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 2
Interestingly, slight excess amount of molecular iodine is also found to be a mild Lewis acid for cyclization of compound 30 with equimolar amount of various aromatic aldehydes in MeCN as an aprotic solvent provided dihydrothieno-oxopyrimidine derivatives 35a-c with good yields. (Table 2) The formation of this cyclized compound is well supported by following conceivable mechanism;

![Scheme: Possible mechanism](image)

Formation of this dihydrothieno-oxopyrimidine structure is best established on the basis of IR, $^1$H-NMR, mass spectrometry and elemental analysis mentioned in the experimental section. (Experiment No. 9, Page 39) The IR spectrum of compound 35a showed absorption peaks at 3470, 3330, 3308 cm$^{-1}$ represented for 2° amide NH and 1° amide NH stretch respectively. Also 1686 cm$^{-1}$ for amide CO stretching. The $^1$H NMR in DMSO-$d_6$ showed broad singlet at δ 6.40-6.50 for 1° amide NH$_2$, broad singlet at δ 11.98 for 2° amide NH proton and aromatic protons on pyrimidine ring appeared downfield at δ 7.53-8.02 for four protons with $J = 8.30$ Hz. The mass spectral analysis
showed the molecular ion peak at m/z = 415 and the elemental analysis was in agreement with the molecular formula C_{10}H_{11}Cl_{2}N_{3}O_{2}S. *(Spectrum No. 8, Page No. 23)*

1.3.10 5-(4-chlorophenyl)-3,4-dihydro-2-alkyl-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 36a-d

![Scheme 24](image)

<table>
<thead>
<tr>
<th>36</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH_{3}</td>
<td>65</td>
</tr>
<tr>
<td>b</td>
<td>C_{6}H_{5}</td>
<td>62</td>
</tr>
<tr>
<td>c</td>
<td>CH_{2}Cl</td>
<td>70</td>
</tr>
<tr>
<td>d</td>
<td>CH_{2}CH_{2}CH_{2}Cl</td>
<td>65</td>
</tr>
</tbody>
</table>

*Table 3*

Cyclization of precursor 30 with equimolar amounts of various acyl chloride in acetic acid at reflux temperature afforded dihydrothieno-oxopyrimidine derivatives 36a-d with good yields. *(Table 3)* These are new class of molecules and are well characterized by IR, ^1^H-NMR, mass spectrometry and elemental analysis mentioned in the experimental section. *(Experiment No. 10, Page 41)* The IR spectrum of compound 36c showed absorption peaks at 3489, 3468 cm\(^{-1}\) assigned for 2° amide NH and 1° amide NH stretching respectively, 1665 cm\(^{-1}\) for amide CO stretching and 1630 cm\(^{-1}\) for Ar-C=CH stretching. The ^1^H NMR in DMSO-\(d_6\) showed singlet at \(\delta\) 4.56 for two methylene protons on pyrimidine ring, broad singlet at \(\delta\) 6.58 for 1° amide NH_{2} protons and 2° amide proton appeared as broad singlet at \(\delta\) 12.04. ^1^C-NMR spectrum showed all carbon peaks at \(\delta\) 42.4, 120.2, 125.6, 128.9, 131.6, 133.1, 133.7, 136.8, 143.2, 163.4,
164.9 and 166.0. The mass spectral analysis showed the molecular ion peak at m/z = 353 (M+1)⁺ and the elemental analysis was in agreement with the molecular formula C₁₄H₉Cl₂N₃O₂S. *(Spectrum No. 11, Page No. 26)*

**Spectrum No. 11: **¹H NMR (DMSO-d₆) spectrum of 2-(chloromethyl)-5-(4-chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 36c

1.4 Conclusion:

In conclusion, a new versatile, multi-component reaction method was successfully developed for synthesis of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile, 23 and its simple acid hydrolysis furnished an extremely important precursor 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide, 30. The new synthons 23 and 30 are important scaffolds for bis-electrophilic and bis-nucleophilic substitution reactions, 27
treated with acids, various ketones, various aldehydes and various acid chlorides afforded fused thieno[3,2-e]pyridine, thieno[2,3-d] pyrimidine and thieno[2,3-d] [1,3]oxazine derivatives in moderate to excellent yields. All reactions reported here are clean with simple workup and require inexpensive chemicals and reagents. These compounds are new addition to heterocyclic compound library having future pharmaceutical activity and technical applications.

1.5 Experimental Section

Experiment No. 1

Synthesis of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile, 23

![Scheme 15]

Procedure

3-(4-Chloro-phenyl)-3-oxo-propionitrile 24 (1.79 g, 0.01 mol) and malononitrile 25 (0.66 g, 0.01 mol) and elemental sulphur (0.32 g, 0.012 mol) were heated together in pyridine (40 ml) at 70 °C for 8 h. After completion, excess pyridine was concentrated under reduced pressure and solid obtained was stirred in methanol (20 ml) for 0.5 h at room temperature. This solid was filtered and dried to obtain pale yellow amorphous solid;

Yield 2.20 g, (85 %); m.p.: 292-294 °C; IR (KBr): 3383, 3304, 2208, 2198, 1630, 1506, 1485, 1421 cm⁻¹; ¹H NMR (DMSO-d₆): δ 7.57 (d, J = 8.4 Hz, 2H, Ar-H), 7.62 (d, J =
8.4 Hz, 2H, Ar-H), 8.37 (bs, 2H, NH2); 13C NMR (DMSO-d6): δ 85.7, 85.8, 114.9, 115.0, 129.5, 130.5, 135.2, 150.9, 198.3; MS (70 eV) m/z = 259 (M+, 100%), 261 (M+2, 33%).

Analysis Calculated for C12H6ClN3S (259.00): Calcd: C, 55.50; H, 2.33; N, 16.18 %

Found: C, 55.38; H, 2.15; N, 16.32 %

Experiment No. 2

Syntheses of 4-aminio-3-(4-chlorophenyl)-6,7-dihydro-5H-cycloalka[b]thieno[3,2-e]pyridine-2-carbonitrile, 26a-b and 5'-(4-Chlorophenyl)-4'-imino-1',4'-dihydro-spiro[cycloalkane-1,2'-thieno[2,3-d][1,3]oxazine]-6'-carbonitrile, 27a-b

Procedure

A mixture of 23 (0.259 g, 0.001 mol) and cyclohexanone/ cyclopentanone (0.001 mol) was stirred at 130 °C in an oil bath in presence of anhydrous ZnCl2 (0.136 g, 0.001 mol) for 2-3 h (TLC check, chloroform: methanol, 9:1). The residue was dispersed in cold water. The pH of solution was adjusted to 12-13 by adding 20% NaOH (5 mL). The solid product separated was filtered, washed with water, dried and purified by column chromatography eluting with chloroform: methanol (9:1) gave 26a-b and 27a-b in 20-25% and 68-70% yield respectively.
4-Amino-3-(4-chlorophenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-\(\text{e}\)]pyridine-2-carbonitrile, 26a

This compound was obtained as faint brown amorphous solid; Yield 0.081 g (25%); m.p.: 249-251 °C; IR (KBr): 3540, 3430, 2210, 1626 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.12 (m, 2H, CH\(_2\)), 2.73-2.98 (m, 4H, 2 CH\(_2\)), 5.92 (bs, 2H, NH\(_2\)), 7.62 (d, \(J = 7.8\) Hz, 2H, Ar-H), 7.69 (d, \(J = 7.8\) Hz, 2H, Ar-H); MS (70 eV) \(m/z = 325\) (M\(^+\), 100%), 327 (M+2, 33%). Analysis Calculated for C\(_{17}\)H\(_{12}\)ClN\(_3\)S (325.04): Calcd: C, 62.67; H, 3.71; N, 12.90 %

\[\text{Found: C, 62.53; H, 3.60; N, 12.76 %}\]

4-Amino-3-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-\(\text{b}\)]quinoline-2-carbonitrile, 26b

This compound was obtained as an off white amorphous solid; Yield 0.068 g (20%); m.p.: 260-261 °C; IR (KBr): 3500, 3392, 2937, 2208, 1624 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.83-1.98 (m, 4H, 2 CH\(_2\)), 2.41 (t, \(J = 5.3\) Hz, 2H, CH\(_2\)), 2.95 (t, \(J = 5.3\) Hz, 2H, CH\(_2\)), 4.37 (bs, 2H, NH\(_2\)), 7.43 (d, \(J = 8.2\) Hz, 2H, Ar-H), 7.57 (d, \(J = 8.2\) Hz, 2H, Ar-H); \(^13\)C NMR (CDCl\(_3\)): \(\delta\) 22.4, 22.4, 22.8, 33.4, 102.5, 111.4, 114.3, 114.5, 129.6, 130.5, 131.9, 136.1, 144.4, 148.0, 159.4, 160.6; MS (70 eV) \(m/z = 339\) (M\(^+\), 100%), 341 (M+2, 33%). Analysis Calculated for C\(_{18}\)H\(_{14}\)ClN\(_3\)S (339.06): Calcd: C, 63.62; H, 4.15; N, 12.36 %

\[\text{Found: C, 63.50; H, 4.24; N, 12.18 %}\]

5'-\(\text{4-Chlorophenyl}\)-4'-imino-1',4'-dihydrospiro[cyclopentane-1,2'-thieno[2,3-\(\text{d}\)\]1,3]oxazine]-6'-carbonitrile, 27a

This compound was obtained as an off white amorphous solid; Yield 0.233 g (68%); m.p.: 244-246 °C; IR (KBr) : 3168, 2935, 2205, 1669, 1620 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.04-2.50 (m, 4H, 2 CH\(_2\)), 2.64-2.87 (m, 4H, 2 CH\(_2\)), 4.93 (bs, 1H, NH), 6.50 (bs, 1H,
NH), 7.48 (d, \( J = 8.4 \text{ Hz}, 2\text{H, Ar-H} \)), 7.60 (d, \( J = 8.4 \text{ Hz}, 2\text{H, Ar-H} \)); MS (70 eV) \( m/z = 343 (M^+, 100\%), 345 (M+2, 33\%) \).

Analysis Calculated for \( \text{C}_{17}\text{H}_{15}\text{ClN}_{2}\text{O}_{3} \) (343.05): Calcd: C, 59.38; H, 4.10; N, 12.22 %

Found: C, 59.24; H, 4.22; N, 12.35 %

5'-\text{(4-Chlorophenyl)-4'-imino-1',4'-dihydrospiro[cyclohexane-1,2'-thieno[2,3-d]-[1,3]oxazine]-6'-carbonitrile, 27b}

This compound was obtained as an off white amorphous solid; Yield 0.250 g (70%); m.p.: 252-253 °C; IR (KBr): 3180, 2934, 2209, 1663, 1626 cm\(^{-1}\); \( ^1\text{H NMR (CDCl}_3) \): \( \delta \) 1.80-1.85 (m, 4H, 2CH\(_2\)), 2.34 (m, 2H, CH\(_2\)), 2.92 (t, \( J = 5.4 \text{ Hz}, 2\text{H, CH}_2\)), 4.04 (t, \( J = 5.4 \text{ Hz}, 2\text{H, Ar-H} \)), 5.16 (bs, 1H, NH), 6.13 (bs, 1H, NH), 7.47 (d, \( J = 8.2 \text{ Hz}, 2\text{H, Ar-H} \)), 7.56 (d, \( J = 8.2 \text{ Hz}, 2\text{H, Ar-H} \)); MS (70 eV) \( m/z = 357 (M^+, 100\%), 359 (M+2, 33\%) \).

Analysis Calculated for \( \text{C}_{18}\text{H}_{16}\text{ClN}_{3}\text{O}_{3} \) (357.07): Calcd: C, 60.41; H, 4.51; N, 11.74 %

Found: C, 60.59; H, 4.71; N, 11.60 %

Experiment No. 3

5-(4-Chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 28

![Scheme 17](image)

**Procedure**

Compound 23 (0.259 g, 0.001 mol) in formic acid (5 mL) was refluxed for 12 h (TLC check, chloroform: methanol, 8:1). On cooling to room temperature, the obtained residue was filtered, washed thoroughly with water, dried and purified by column...
chromatography (silica gel 5-20 μm) in chloroform: methanol (8:1) as an eluent to afford pale yellow crystals;

Yield 0.244 g (80%); m.p.: 265-266 °C; IR (KBr): 3400, 3302, 3263, 1668, 1641 cm\(^{-1}\);  
\(^1\)H NMR (DMSO-\(d_6\)): δ 6.40-6.56 (bs, 2H, amide NH), 7.27 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.44 (d, \(J = 8.4\) Hz, 2H, Ar-H), 8.42 (s, 1H, CH), 11.41 (bs, 1H, NH); MS (70 eV) m/z = 305 (M\(^+\), 100%), 307 (M+2, 33%).

Analysis Calculated for C\(_{13}\)H\(_8\)ClN\(_3\)O\(_2\)S (305.00): Calcd: C, 51.07; H, 2.64; N, 13.74 %  
Found: C, 51.19; H, 2.79; N, 13.59 %

Experiment No. 4

\textbf{N-(4-(4-Chlorophenyl)-3,5-dicyanothiophen-2-yl)acetamide, 29}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme18.png}
\end{center}

\textbf{Procedure}

To a mixture of 23 (0.259 g, 0.001 mol) and acetic anhydride (5 mL), a drop of conc. H\(_2\)SO\(_4\) was added and then stirred at room temperature for 1 h (TLC check, chloroform: methanol, 8:2). Resulting reaction mixture was poured over crushed ice and stirred overnight. The separated solid was filtered, washed with cold water, dried under vacuum and crystallized with ethanol: DMF (2:1) afforded pale yellow amorphous solid;

Yield 0.287 g (90%); m.p.: 298-300 °C; IR (KBr): 3267, 2212, 2216, 1703, 1625 cm\(^{-1}\);  
\(^1\)H NMR (DMSO-\(d_6\)): δ 2.31 (s, 3H, CH\(_3\)), 7.64 (d, \(J = 8.7\) Hz, 2H, Ar-H), 7.73 (d, \(J = 8.7\) Hz, 2H, Ar-H), 12.63 (s, 1H, NH); \(^{13}\)C NMR (DMSO-\(d_6\)): δ 22.3, 92.7, 96.4, 112.9,
113.7, 129.0, 129.4, 130.3, 135.0, 147.8, 153.1, 170.2; MS (70 eV) m/z = 301 (M⁺, 100%), 303 (M+2, 33%).

Analysis Calculated for C₄H₅ClN₃OS (301.10): Calcd: C, 55.72%; H, 2.67%; N, 13.93%

Found: C, 55.66%; H, 2.52%; N, 13.75%

Experiment No. 5

5-Amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide, 30

![Chemical Structure](image)

**Procedure**

Compound 23 (2.59 g, 0.01 mol) was stirred in conc. H₂SO₄ (10 mL) at room temperature for 6 h (TLC check, chloroform: methanol, 8:2). The reaction mass was then added to crushed ice (250 mL) and neutralized with saturated NaHCO₃ (30 mL). The crude solid separated was filtered, washed with water dried and recrystallized from ethanol: DMF (8:2) afforded pale yellow crystals;

Yield 2.65 g (90%); m.p.: 200-202 °C; IR (KBr): 3327, 3306, 3252, 3169, 3475, 3345, 1668, 1672 cm⁻¹; ¹H NMR (DMSO-d₆): δ 4.82 (bs, 2H, amide NH₂), 6.84 (bs, 2H, amide NH₂), 7.38 (d, J = 8.3 Hz, 2H, Ar-H), 7.56 (d, J = 8.3 Hz, 2H, Ar-H), 7.69 (bs, 2H, NH₂); ¹³C NMR (DMSO-d₆): δ 109.3, 114.7, 129.2, 131.1, 133.6, 134.3, 139.0, 162.9, 163.0, 166.8; MS (70 eV) m/z = 295 (M⁺, 100%), 297 (M+2, 33%).

Analysis Calculated for C₁₂H₁₀ClN₃O₂S (295.02): Calcd: C, 48.73%; H, 3.41%; N, 14.21%

Found: C, 48.82%; H, 3.62%; N, 14.12%
Experiment No. 6

Syntheses of (E)-N'-((4-(4-chlorophenyl)-3,5-dicyanothiophen-2-yl)-N,N-dimethylformamidine, 31 and 3-amino-5-(4-chlorophenyl)-4-imino-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonitrile, 32

**Scheme 20**

**Procedure for intermediate, 31**

Compound 23 (0.259 g, 0.001 mol) in dry p-xylene (5 mL) and (0.133 mL, 0.001 mol) DMF-DMA was refluxed for 3 h (TLC check, chloroform: methanol 8:2). After evaporating the solvent *in vacuo*, the obtained residue was stirred in hexane for 1 h and filtered, dried and recrystallized from ethanol: DMF (2:1) gave yellow amorphous solid; Yield 0.283 g (90%); m.p.: 210-211 °C; IR (KBr): 3312, 2950, 2208, 2210, 1625 cm⁻¹; ¹H NMR (CDCl₃): δ 3.21-3.23 (bs, 6H, 2 CH₃), 7.50 (d, J = 8.4 Hz, 2H, Ar-H), 7.61 (d, J = 8.4 Hz, 2H, Ar-H), 7.84 (s, 1H, CH); MS (70 eV) m/z =315 (M+1, 100%), 317 (M+2, 33%).

Analysis Calculated for C₁₅H₁₁ClN₄S (314.04): Calcd: C, 57.23; H, 3.52; N, 17.80 %

**Procedure for 32**

A mixture of 7 (0.314 g, 0.001 mol), hydrazine hydrate (0.05 mL, 0.001 mol) in absolute ethanol (10 mL) was refluxed for 6 h (TLC check, chloroform: methanol 8:2). The solvent was evaporated *in vacuo*, to give solid residue which was filtered, washed
with cold ethanol and dried to afford analytically pure pale yellow amorphous solid; yield 0.24 g (80%); m.p.: 302-304 °C; IR (KBr): 3381, 3306, 3205, 2200, 1637 cm⁻¹; 
¹H NMR (DMSO-d₆): δ 5.59 (s, 2H, NH₂), 6.40 (s, 1H, NH), 7.45 (d, J = 8.3 Hz, 2H, Ar-H), 7.51 (d, J = 8.3 Hz, 2H, Ar-H), 8.42 (s, 1H, CH); MS (70 eV) m/z = 301 (M⁺, 100%), 303 (M+2, 33%).

Analysis Calculated for C₁₃H₄ClN₂S (301.02): Calcd: C, 51.74; H, 2.67; N, 23.21.

Found: C, 51.56; H, 2.51; N, 23.11.

Experiment No. 7
Syntheses of 5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2-(aryl)-4-oxothieno[2,3-d]-pyrimidine-6-carboxamide, (33a-c)

![Diagram](33a-c)

<table>
<thead>
<tr>
<th>33</th>
<th>Ar-</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-ClC₆H₄</td>
<td>52</td>
</tr>
<tr>
<td>b</td>
<td>2,4-diMeOC₆H₃</td>
<td>55</td>
</tr>
<tr>
<td>c</td>
<td>4-NO₂C₆H₄</td>
<td>55</td>
</tr>
</tbody>
</table>

General procedure
A mixture of compound 30 (0.295 g, 0.001 mol) and aromatic aldehydes (0.001 mol) in ethanol (10 mL) with catalytic amount of piperidine were refluxed in oil bath with stirring for 10-12 h (TLC check, chloroform: methanol, 8:2). The reaction mixture was
cooled, stirred in crushed ice (25 mL). The residue obtained was filtered and purified by column chromatography (silica gel 5-20\mu m) in chloroform: methanol (8:2) as an eluent.

2,5-Di-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 33a

This compound was obtained as colourless amorphous solid; Yield 0.242 g (52%); m.p.: 310-312 °C; IR (KBr): 3475, 3327, 3308, 1689, 1641 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 5.82 (s, 1H, CH), 6.31-6.48 (bs, 2H, amide NH\(_2\)), 7.42 (d, \(J = 8.1\) Hz, 2H, Ar-H), 7.49 (d, \(J = 8.1\) Hz, 2H, Ar-H), 7.62 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.49 (d, \(J = 8.4\) Hz, 2H, Ar-H), 8.4 (bs, 1H, NH), 8.16 (d, \(J = 8.4\) Hz, 2H, Ar-H), 8.32 (d, \(J = 8.4\) Hz, 2H, Ar-H), 12.76 (bs, 1H, NH); MS (70 eV) \(m/z = 417 (M^+, 100\%)\), 419 (M+2, 65%), 421 (M+4, 11%).

Analysis Calculated for C\(_{19}\)H\(_{13}\)Cl\(_2\)N\(_3\)O\(_2\)S (417.01): Calcd: C, 54.56; H, 3.13; N, 10.05 %
Found: C, 54.64; H, 3.24; N, 9.89 %

5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2-(2,4-dimethoxyphenyl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 33b

This compound was obtained as pale green amorphous solid; Yield 0.243 g (55%); m.p.: 330-332 °C; IR (KBR): 3472, 3330, 3310, 1687, 1641, 1242 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 3.84 (s, 3H, OCH\(_3\)), 3.86 (s, 3H, OCH\(_3\)), 5.86 (s, 1H, CH), 6.52-7.11 (bs, 2H, amide NH\(_2\)), 6.65-6.80 (m, 2H, Ar-H), 7.72 (d, 1H, Ar-H), 8.21 (d, \(J = 8.3\) Hz, 2H, Ar-H), 8.32 (d, \(J = 8.3\) Hz, 2H, Ar-H), 8.50 (bs, 1H, NH), 9.78 (bs, 1H, NH); MS (70 eV) \(m/z = 441 (M^+, 100\%), 443 (M+2, 33\%)\).

Analysis Calculated for C\(_{21}\)H\(_{18}\)ClN\(_3\)O\(_4\)S (441.06): Calcd: C, 56.82; H, 4.09; N, 9.47 %
Found: C, 56.95; H, 4.21; N, 9.35 %
5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2-(4-nitrophenyl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 33c

This compound was obtained as yellow amorphous solid; Yield 0.236 g (55%); m.p.: 329-330 °C; IR (KBr): 3476, 3339, 3315, 1687, 1640, 1531, 1323 cm⁻¹; ¹H NMR (DMSO-d₆): 6 6.60-7.20 (bs, 2H, amide NH₂), 6.65 (s, 1H, CH), 7.25 (d, J = 8.4 Hz, 2H, Ar-H), 7.32 (d, J = 8.4 Hz, 2H, Ar-H), 7.82 (d, J = 8.9 Hz, 2H, Ar-H), 8.16 (d, J = 8.9 Hz, 2H, Ar-H), 8.52 (bs, 1H, NH), 11.08 (bs, 1H, NH); MS (70 eV) m/z = (M⁺, 100%), 431 (M+2, 33%).

Analysis Calculated for C₁₉H₁₃ClN₄O₄S (429.04): Calcd: C, 53.21; H, 3.06; N, 13.06 %
Found: C, 53.37; H, 3.24; N, 12.90 %

Experiment No. 8

Syntheses of 5'-(4-Chlorophenyl)-3',4'-dihydro-4'-oxo-1'H-spiro[cycloalkane-1,2'-thieno[2,3-d'] pyrimidine]-6'-carboxamide, 34a-b

![Scheme 22](image)

General procedure

Stoichiometric amounts of 30 (0.295 g, 0.001 mol) and cyclohexanone/ cyclopentanone (0.001 mol) in a round-bottomed flask (10 mL) sealed with a teflon cap was vigorously stirred for 2-3 h (TLC check, chloroform: methanol, 8:2). After standing overnight at room temperature, the solid separated was then stirred in diethyl ether (5 mL) for 1 h. It
was then filtered, dried and without any further purification directly analyzed by spectroscopic methods.

5′-(4-Chlorophenyl)-3′,4′-dihydro-4′-oxo-1′H-spiro[cyclopentane-1,2′-thieno[2,3-d]pyrimidine]-6′-carboxamide, 34a

This compound was obtained as white amorphous solid; Yield 0.353 g (98%);
m.p.: 264-265 °C; IR (KBr): 3490, 3469, 3380, 3290, 3312, 2935, 1660, 1630 cm⁻¹; ¹H NMR (DMSO-d₆): δ 1.90-1.92 (m, 4H, 2 CH₂), 2.18-2.24 (m, 4H, 2 CH₂), 6.47 (bs, 2H, amide NH₂), 7.32 (d, J = 8.3 Hz, 2H, Ar-H), 7.50 (d, J = 8.3 Hz, 2H, Ar-H), 7.52 (bs, 1H, NH), 8.26 (bs, 1H, NH); MS (70 eV) m/z = 361 (M⁺, 100%), 363 (M+2, 33%).
Analysis Calculated for C₁₇H₁₆ClN₃O₂S (361.07): Calcd.: C, 56.43; H, 4.46; N, 11.61 %
Found: C, 56.34; H, 4.59; N, 11.51 %

5′-(4-Chlorophenyl)-3′,4′-dihydro-4′-oxo-1′H-spiro[cyclohexane-1,2′-thieno[2,3-d]pyrimidine]-6′-carboxamide, 34b

This compound was obtained as white amorphous solid; Yield 0.371 g (99%);
m.p.: 240-242 °C; IR (KBr): 3498, 3473, 3381, 3288, 3213, 2937, 1654, 1629 cm⁻¹; ¹H NMR (DMSO-d₆): δ 1.19-1.48 (m, 4H, 2 CH₂), 1.76-1.87 (m, 4H, 2 CH₂), 2.25 (m, 2H, CH₂), 5.37 (bs, 1H, NH), 7.18-7.38 (bs, 2H, amide NH₂), 7.27 (d, J = 8.3 Hz, 2H, Ar-H), 7.44 (d, J = 8.3 Hz, 2H, Ar-H), 8.30 (s, 1H, NH); ¹³C NMR (DMSO-d₆): δ 20.9, 24.4, 26.3, 36.3, 41.2, 70.3, 110.1, 117.7, 127.8, 131.0, 132.3, 134.1, 139.6, 159.1, 160.3, 163.0; MS (70 eV) m/z = 375 (M⁺, 100%), 377 (M+2, 33%).
Analysis Calculated for C₁₈H₁₆ClN₃O₂S (375.08): Calcd.: C, 57.52; H, 4.83; N, 11.18 %
Found: C, 57.46; H, 4.68; N, 11.30 %
Experiment No. 9

Syntheses of 5-(4-Chlorophenyl)-3,4-dihydro-2-(aryl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 35a-c

\[
\text{Cl} \quad \begin{array}{c} \text{NH}_2 \\ \text{H}_2\text{N} \\ \text{O} \end{array} \quad \text{ArCHO, I}_2 \quad \begin{array}{c} \text{Cl} \\ \text{H}_2\text{N} \\ \text{O} \end{array} \quad \text{Ar}
\]

Scheme-23

<table>
<thead>
<tr>
<th>35</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-ClC_6H_4</td>
<td>65</td>
</tr>
<tr>
<td>b</td>
<td>2,4-diMeOC_6H_3</td>
<td>68</td>
</tr>
<tr>
<td>c</td>
<td>4-NO_2C_6H_4</td>
<td>66</td>
</tr>
</tbody>
</table>

General procedure

To a mixture of compound 30 (0.295 g, 0.001 mol) and aromatic aldehyde (0.001 mol) in dry acetonitrile (5 mL), iodine (0.14 g, 0.0011 mol) was added. The mixture was refluxed for 8-10 h (TLC check, chloroform: methanol (8:2) as an eluent. After reaction was completed, the mixture was cooled to room temperature. An aqueous solution of sodium thiosulphate (5%, 5 mL) was added and the resulted solid was filtered off, dried and washed with water. The crude product was purified by column chromatography (silica gel 5-20μm) in chloroform: methanol (8:2) as an eluent.

2,5-Di(4-chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 35a

This compound was obtained as colourless amorphous solid; Yield 0.269 g (65%);
m.p.: 340-342 °C; IR (KBr): 3470, 3330, 3308, 1686, 1639 cm⁻¹; ¹H NMR (DMSO-d₆): δ 6.40-6.50 (bs, 2H, amide NH₂), 7.43 (d, J = 8.1 Hz, 2H, Ar-H), 7.52 (d, J = 8.1 Hz, 2H, Ar-H), 7.53 (d, J = 8.3 Hz, 2H, Ar-H), 8.02 (d, J = 8.3 Hz, 2H, Ar-H), 11.98 (bs, 1H, NH); MS (70 eV) m/z = 415 (M⁺, 100%), 417 (M+2, 65%), 419 (M+4, 11%).

Analysis Calculated for C₁₉H₁₁Cl₂N₃O₂S (417.01): Calcd.: C, 54.82; H, 2.66; N, 10.09 %

Found: C, 54.64; H, 2.79; N, 9.99 %

5-(4-Chlorophenyl)-3,4-dihydro-2-(2,4-dimethoxyphenyl)-4-oxothieno[2,3-d]pyrimidin-6-carboxamide, 35b

This compound was obtained as off white amorphous solid; Yield 0.299 g (68%);
m.p.: 336-337 °C; IR (KBr): 3470, 3332, 3313, 1688, 1638, 1240 cm⁻¹; ¹H NMR (DMSO-d₆): δ 3.84 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.53-7.62 (bs, 2H, amide NH₂), 6.67-6.70 (m, 2H, Ar-H), 7.39 (d, J = 8.5 Hz, 2H, Ar-H), 7.46 (d, J = 8.5 Hz, 2H, Ar-H), 7.79 (d, 1H, NH); MS (70 eV) m/z = 441 (M⁺, 100%), 443 (M+2, 33%).

Analysis Calculated for C₂₁H₁₆C₁₂N₃O₄S (441.06): Calcd.: C, 57.08; H, 3.65; N, 9.51 %

Found: C, 57.18; H, 3.59; N, 9.62 %

5-(4-Chlorophenyl)-3,4-dihydro-2-(4-nitrophenyl)-4-oxothieno[2,3-d]pyrimidin-6-carboxamide, 35c

This compound was obtained as yellow amorphous solid; Yield 0.282 g (66%);
m.p.: 345-346 °C; IR (KBr): 3474, 3341, 3318, 1684, 1638, 1530, 1320 cm⁻¹; ¹H NMR (DMSO-d₆): δ 6.67-7.70 (bs, 2H, amide NH₂), 7.41 (d, J = 8.5 Hz, 2H, Ar-H), 7.48 (d, J = 8.5 Hz, 2H, Ar-H), 8.36 (d, J = 9.0 Hz, 2H, Ar-H), 8.38 (d, J = 9.0 Hz, 2H, Ar-H), 12.99 (bs, 1H, NH); MS (70 eV) m/z = 428 (M⁺, 100%), 430 (M+2, 33%).

Analysis Calculated for C₁₉H₁₇ClN₃O₃S (428.09): Calcd.: C, 56.17; H, 3.09; N, 8.81 %

Found: C, 56.20; H, 2.99; N, 8.78%
Analysis Calculated for $C_{10}H_{11}ClN_4O_4S(428.03)$: Calcd.: C, 53.46; H, 2.60; N, 13.13. %

Found: C, 53.58; H, 2.49; N, 13.09 %

Experiment No. 10

Syntheses of 5-(4-Chlorophenyl)-3,4-dihydro-2-alkyl-4-oxothieno[2,3-$d$]pyrimidine-6-carboxamide, 36a-d

![Scheme-24](image)

<table>
<thead>
<tr>
<th>36</th>
<th>-R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-CH$_3$</td>
<td>65</td>
</tr>
<tr>
<td>b</td>
<td>-C$_6$H$_5$</td>
<td>62</td>
</tr>
<tr>
<td>c</td>
<td>-CH$_2$Cl</td>
<td>70</td>
</tr>
<tr>
<td>d</td>
<td>-CH$_2$CH$_2$CH$_2$Cl</td>
<td>65</td>
</tr>
</tbody>
</table>

General procedure

A mixture of 3 (0.295 g, 0.001 mol) and various acid chlorides (0.001 mol) were stirred at 115 °C in glacial acetic acid (4 mL) for 10-12 h (TLC check, chloroform: methanol, 8:2). Excess acetic acid was distilled off under vacuum and residue obtained was poured over crushed ice (15 mL), filtered and dried. The solid was then purified by column chromatography (silica gel 5-20μm) in chloroform: methanol (8:2) as an eluent.

5-(4-Chlorophenyl)-3,4-dihydro-2-methyl-4-oxothieno[2,3-$d$]pyrimidine-6-carboxamide, 36a

This compound was obtained as an off white amorphous solid; Yield 0.207 g (65%);
m.p.: 277-280 °C; IR (KBr): 3490, 3470, 1668, 1629 cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.14 (s, 3H, CH₃), 6.32-6.54 (bs, 2H, amide NH₂), 7.34 (d, J = 8.4 Hz, 2H, Ar-H), 7.49 (d, J = 8.4 Hz, 2H, Ar-H), 11.29 (bs, 1H, NH); MS (70 eV) m/z = 319 (M⁺, 100%), 321 (M+2, 33%).

Analysis Calculated for C₁₄H₁₀ClN₃O₂S (319.02): Calcd: C, 52.59; H, 3.15; N, 13.14 %
Found: C, 52.48; H, 3.21; N, 13.21 %

5-(4-Chlorophenyl)-3,4-dihydro-2-phenyl-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 36b

This compound was obtained as white amorphous solid; Yield 0.236 g (62%);
m.p.: 268-270 °C; IR (KBr): 3488, 3468, 2931, 1665, 1624 cm⁻¹; ¹H NMR (DMSO-d₆): δ 6.31-6.56 (bs, 2H, amide NH₂), 7.10-7.40 (m, 5H, Ar-H), 7.45 (d, J = 8.4 Hz, 2H, Ar-H), 7.52 (d, J = 8.4 Hz, 2H, Ar-H), 11.25 (bs, 1H, NH); MS (70 eV) m/z = 381 (M⁺, 100%), 383 (M+2, 33%).

Analysis Calculated for C₁₉H₁₂ClN₃O₂S (381.03): Calcd: C, 59.76; H, 3.17; N, 11.00 %
Found: C, 59.68; H, 3.28; N, 11.16 %

5-(4-Chlorophenyl)-3,4-dihydro-2-(chloromethyl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide, 36c

This compound was obtained as white amorphous solid; 0.246 g (70%);
m.p.: 267-269 °C; IR (KBr): 3489, 3468, 1665, 1630 cm⁻¹; ¹H NMR (DMSO-d₆): δ 4.56 (s, 2H, CH₂), 6.35-6.58 (bs, 2H, amide NH₂), 7.36 (d, J = 8.3 Hz, 2H, Ar-H), 7.52 (d, J = 8.3 Hz, 2H, Ar-H), 12.04 (bs, 1H, NH); ¹³C NMR (DMSO-d₆): δ 166.0, 164.9, 163.4, 143.2, 136.8, 133.7, 133.1, 131.6, 128.9, 125.6, 120.2, 42.4; MS (70 eV) m/z = 353 (M⁺, 100%), 355 (M+2, 65%), 357 (M+4, 11%).

Analysis Calculated for C₁₄H₉Cl₂N₃O₂S (352.98): Calcd: C, 47.47; H, 2.56; N, 11.86 %
Found: C, 47.31; H, 2.42; N, 11.76 %

5-(4-Chlorophenyl)-3,4-dihydro-2-(3-chloropropyl)-4-oxothieno-[2,3-d]pyrimidine-6-carboxamide, 36d

This compound was obtained as colourless amorphous solid; 0.247 g (65%);
m.p.: 274-275 °C; IR (KBr): 3456, 3356, 3311, 3169, 1672, 1649 cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.15-2.17 (m, 4H, 2CH₂), 3.31 (m, 2H, CH₂), 6.51-7.39 (bs, 2H, amide NH₂), 7.36 (d, J = 8.3 Hz, 2H, Ar-H), 7.52 (d, J = 8.3 Hz, 2H, Ar-H), 11.30 (bs, 1H, NH); MS (70 eV) m/z = 381 (M⁺, 100%), 383 (M+2, 65%), 385 (M+4, 11%).

Analysis Calculated for C₁₆H₁₃Cl₂N₃O₂S (381.01): Calcd: C, 50.27; H, 3.43; N, 10.99 %

Found: C, 50.19; H, 3.19; N, 10.85 %
1.6 References


