Synthesis of [1,2,4]-triazolo-[3',4':2,3][1,3,4]thiadiazepino[7,6-b]coumarins

The work incorporated in this section is on the synthesis of various [1,2,4]triazolo-[3',4':2,3][1,3,4]thiadiazepino[7,6-b]coumarins. The [1,2,4]triazolo-[3',4':2,3][1,3,4]-thiadiazepino-[7,6-b]coumarins have been synthesized by reacting 4-chloro-3-formylcoumarins with various 4-amino-5-substituted-3-mercaptop-1,2,4-triazoles in ethanol in the presence of catalytical amount of K$_2$CO$_3$ and glacial acetic acid. The structures of all the synthesized compounds have been supported by analytical and spectral data.

4.4 Introduction

A large number of heterocyclic fused coumarin derivatives in which the coumarin is fused with other heterocyclic ring via lactone ring are known for their varied biological activities. Among the heterocyclic fused coumarins, pyrido coumarins, pyrazolo coumarins, furo coumarins, pyrano coumarins etc are extensively studied in literature, while sulfur or sulfur and nitrogen containing heterocyclic fused coumarins are less studied by the researchers.

Triazole is a five membered heterocyclic compound bearing three N atoms and exists in two isomeric forms, 1,2,4 and 1,2,3 triazoles. Among these two isomeric forms, 1,2,4-triazole derivatives are more important from biological view point and are widely studied by chemists.

![Chart 1](image-url)
The chemistry of triazoles are well documented in the literature. The triazoles have been of much interest due to their useful application in medicine, agriculture and in industry. Furthermore, some of the triazoles are known to be used as analytical reagents, dyes and photographic chemicals. Certain triazole derivatives are used in the preparation of some useful polymers.

Certain 1,2,4-triazole derivatives are reported to possess various biological activities such as antimicrobial, antidepressant, antiinflammatory, antitumour, antiviral and antifungal activities. Some important triazole based drugs are shown in Chart.2.

The fusion of 1,2,4-triazole with thiadiazepine results in the formation of triazolo thiadiazepines derivatives. Many such triazolo thiadiazepine derivatives are reported in literature and possess varied biological activities like in vitro antibacterial, antifungal activity and antitubercular activity.

During our literature survey on the further fusion of triazolo thiadiazepines with other heterocycles, we noticed that researcher have reported various furano fused triazolo thiadiazepines, benzopyrano fused triazolo thiadiazepines, quinolino fused triazolo thiadiazepines and hydrazono triazolo thiadiazepines. All these heterocyclic fused compounds are also reported to have excellent biological activities. The survey also revealed that so far no chemists
have made efforts to synthesize triazolo thiadiazepino fused coumarins and therefore in the present work it was thought worthwhile to synthesize triazolo thiadiazepino fused coumarins via simple condensation reaction.

4.5 Present work

As discussed in introduction, in the present work various [1,2,4]-triazolo-[3′,4′:2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3a-l) have been synthesized.

4.5.1 Synthesis of [1,2,4] triazolo-[3′,4′:2,3][1,3,4]-thiadiazepino [7,6-b]coumarins (3a-l):

The synthesis of [1,2,4]triazolo-[3′,4′:2,3][1,3,4]-thiadiazepino[7,6-b]coumarins (3a-l) has been carried out by reacting various 4-chloro-3-formyl coumarins (1a-c) with 4-amino-5-substituted-3-mercapto-1,2,4-triazoles (2a-d) in ethanol in the presence of catalytical amount of K$_2$CO$_3$ and glacial acetic acid at room temperature Scheme 1.

The required starting material 4-chloro-3-formyl coumarins (1a-c) were prepared by the Vilsmeier-Haack reaction of an appropriate 4-hydroxycoumarin using POCl$_3$ and DMF as reagents. The starting material 4-amino-5-substituted-3-mercapto-1,2,4-triazoles (2a-d) were prepared by reacting appropriate acid hydrazide with CS$_2$ and hydrazine under alkaline condition.
The heterocyclization reaction of 4-chloro-3-formyl coumarins (1a-c) and 4-amino-5-substituted-3-mercato-1,2,4-triazoles (2a-d) proceeded smoothly and gave the expected products (3a-l) in 75-90% yield. The structures of all the synthesized compounds (3a-l) were confirmed by analytical and spectral data. The plausible mechanism for the formation of compounds 3a-l is outlined below. (Scheme 2)
Thus, the reaction of 4-chloro-3-formyl coumarin (1a) and 4-amino-5-methyl-3-mercapto-1,2,4-triazole (2a) in the presence catalytical amount of K$_2$CO$_3$ and glacial acetic acid gave a compound (3a) as pale yellow product in 75% yield.

The IR spectrum of 3a (Fig 1) showed a strong band at 1714 cm$^{-1}$, which is due to carbonyl stretching of $\delta$-lactone ring present in coumarin moiety. The band observed at 756 cm$^{-1}$ is due to C-S-C stretching vibrations. The bands observed at 1586 cm$^{-1}$ and 1476 cm$^{-1}$ are due to aromatic C=C and C=N stretching vibrations respectively. The bands observed at 2952 cm$^{-1}$ and 3043 cm$^{-1}$ are due to aliphatic C-H and aromatic C-H stretching vibrations respectively.

The $^1$H-NMR spectrum of compound 3a (CDCl$_3$) (Fig 2) showed singlet at 2.47 integrating for three protons, is due to CH$_3$ group. The multiplet observed between 7.20-8.39 $\delta$ integrating for five protons is for aromatic as well as -CH=N group protons.

The $^{13}$C-APT spectrum of compound 3a (Fig 3) showed signals at 20.88, 112.80, 113.76, 115.83, 117.54, 125.24, 128.77, 130.48, 134.98, 136.63, 138.50, 155.90 and 160.43 $\delta$ corresponding to thirteen different types of carbon atoms present in the compound. The most downfield signal appearing at 160.43 $\delta$ can be assigned to the carbonyl carbon of the $\delta$-lactone ring of coumarin. The inverted signals appeared at 125.24, 128.77, 130.48, 134.98 and 138.50 are due to five tertiary carbon atoms.

The mass spectrum of compound 3a (Fig 4) showed M$^+$ peak at 284(100%) (m/z %) along with some other fragments peaks at 257 (23%), 160(17%), 77(12%),57(11%), 44(100%), etc. The appearance of molecular ion peak at 284 mass unit supports the structure of compound 3a.

The IR and NMR data for other compounds 3b-1 are given below.

**Compound 3b**

| IR
|\footnotesize{\text{(cm$^{-1}$)}} | $\nu_{max}$ 1714 (C=O stretching of $\delta$-lactone of coumarin), 1600 and 1542 (aromatic C=C and C=N stretchings),754 (C-S-C stretching vibration), 2856 (aliphatic C-H stretching), |
3057 (aromatic C-H stretching).

$\text{H-NMR}$ ($\delta$, ppm)  
(Fig 5)

2.44 (6H, singlet, 2×CH$_3$), 7.33-8.42 (4H, multiplet, aromatic + -CH=N- protons)

$^{13}$C-APT ($\delta$, ppm)  
(CDCl$_3$+TFA) (Fig 6)

20.85(CH$_3$), 23.14(CH$_3$), 115.14(C), 117.85(CH), 119.40(C), 123.15(C), 124.55(CH), 128.05(C), 129.45(CH), 131.51(CH), 135.95(C), 138.43(C), 152.80(C), 162.61(CO of coumarin).

**Compound 3c**

IR ($\text{cm}^{-1}$)  

$\nu_{\text{max}}$ 1719 (C=O stretching of $\delta$-lactone of coumarin), 1584 and 1473 (aromatic C=C and C=N stretchings), 752 (C=SC stretching vibration), 2854 (aliphatic C-H stretching), 3041 (aromatic C-H stretching).

$\text{H-NMR}$ ($\delta$, ppm)  
(Fig 7)

2.35 (3H, singlet, CH$_3$), 7.33-8.38 (4H, multiplet, aromatic + -CH=N- protons)

$^{13}$C-APT ($\delta$, ppm)  
(CDCl$_3$+TFA) (Fig 8)

20.95(CH$_3$), 115.34(C), 117.35(CH), 119.50(C), 123.25(C), 125.55(CH), 128.69(C), 129.99(CH), 131.25(C), 134.95(C), 138.43(CH), 157.80(C), 161.81(CO of coumarin).

**Compound 3d**

IR ($\text{cm}^{-1}$)  

$\nu_{\text{max}}$ 1715 (C=O stretching of $\delta$-lactone of coumarin), 1585 and 1476 (aromatic C=C and C=N stretchings), 756 (C=SC stretching vibration) 703 and 760 (C-H bending vibrations of mono substituted benzene ring),3045 (aromatic C-H stretching).

$\text{H-NMR}$ ($\delta$, ppm)  
(Fig 9)

7.21-8.95 (10H, multiplet, aromatic + -CH=N- protons)

$^{13}$C-APT ($\delta$, ppm)  
(CDCl$_3$+TFA) (Fig 10)

114.55(C), 115.60(C), 115.65(C), 117.12(CH), 124.05(CH), 125.36(CH), 125.99(CH), 128.95(CH), 129.55(C), 130.01(CH), 133.70(CH), 141.94(C), 143.56(C), 150.88(C), 156.66(C), 161.56(CO of coumarin).

**Compound 3e**

IR ($\text{cm}^{-1}$)  

$\nu_{\text{max}}$ 1719 (C=O stretching of $\delta$-lactone of coumarin), 1581
and 1475 (aromatic C=C and C=N stretchings), 751 (C-S-C stretching vibration), 703 and 760 (C-H bending vibrations of mono substituted benzene ring), 2854 (aliphatic C-H stretching), 3041 (aromatic C-H stretching).

\[ ^1\text{H-NMR} \]  
\( (\delta, \text{ ppm}) \)  
(Fig 11)  
2.34 (3H, singlet, CH\textsubscript{3}), 7.30-8.52 (9H, multiplet, aromatic + -CH=N- protons),

\[ ^{13}\text{C-APT} \]  
(\( \delta, \text{ ppm} \))  
(CDCl\textsubscript{3}+ TFA)  
(Fig 12)  
20.68(CH\textsubscript{3}), 112.80(C), 113.70(C), 115.63(C), 117.52(CH), 118.46(C), 125.04(CH), 128.70(CH), 130.43(CH), 135.03(C), 136.33(CH), 138.90(C), 143.43(CH), 145.73(CH), 153.48(C), 155.04(C), 163.98(CO of coumarin).

**Compound 3f**

**IR**  
\( \nu_{\text{max}} \)  
1719 (C=O stretching of \( \delta-lactone \) of coumarin), 1582 and 1476 (aromatic C=C and C=N stretchings), 754 (C-S-C stretching vibration), 3043 (aromatic C-H stretching).

\[ ^1\text{H-NMR} \]  
(\( \delta, \text{ ppm} \))  
(Fig 13)  
7.30-8.52 (9H, multiplet, aromatic+ -CH=N- protons)

\[ ^{13}\text{C-APT} \]  
(\( \delta, \text{ ppm} \))  
(CDCl\textsubscript{3}+ TFA)  
(Fig 14)  
111.57(C), 113.80(C), 114.70(C), 115.63(C), 117.52(CH), 118.90(C), 125.04(CH), 128.70(CH), 130.43(CH), 135.03(CH), 136.33(CH), 138.98(CH), 143.43(CH), 153.04(C), 156.98(C), 162.48(CO of coumarin)

**Compound 3g**

**IR**  
\( \nu_{\text{max}} \)  
1719 (C=O stretching of \( \delta-lactone \) of coumarin), 1581 and 1475 (aromatic C=C and C=N stretchings), 751 (C-S-C stretching vibration), 3041 (aromatic C-H stretching).

\[ ^1\text{H-NMR} \]  
(\( \delta, \text{ ppm} \))  
(Fig 15)  
7.22-8.88 (9H, multiplet, aromatic + -CH=N- protons)

\[ ^{13}\text{C-APT} \]  
(\( \delta, \text{ ppm} \))  
(CDCl\textsubscript{3}+ TFA)  
(Fig 16)  
110.21(C), 113.02(C), 115.65(C), 117.76(CH), 118.29(C), 120.23(C), 125.86(CH), 125.97(C), 128.96(CH), 131.81(CH), 135.28(CH), 138.39(CH), 142.98(CH), 152.98(C), 163.81(CO of coumarin).
Compound 3h

IR (cm\(^{-1}\)) \(v_{\text{max}}\) 1712 (C=O stretching of \(\delta\)-lactone of coumarin), 1585 and 1475 (aromatic C=C and C=N stretchings), 756 (C-S-C stretching vibration) 2854 (aliphatic C-H stretching), 3045 (aromatic C-H stretching).

\(^1\)H-NMR (\(\delta\), ppm) (Fig 17) 2.24 (3H, singlet, CH\(_3\)), 7.23-8.89 (8H, multiplet, aromatic + -CH=N- protons)

\(^{13}\)C-APT (\(\delta\), ppm) (CDCl\(_3\)+ TFA) (Fig 18) 20.43(CH\(_3\)), 111.31(C), 112.73(C), 113.80(C), 115.57(C), 117.58(CH), 118.37(C), 125.16(C), 126.13(CH), 131.72(CH), 136.03(C), 139.89(CH), 142.37(CH), 145.13(CH), 152.43(C), 163.79(CO of coumarin).

Compound 3i

IR (cm\(^{-1}\)) \(v_{\text{max}}\) 1715 (C=O stretching of \(\delta\)-lactone of coumarin), 1580 and 1472 (aromatic C=C and C=N stretchings), 754 (C-S-C stretching vibration) ,3045 (aromatic C-H stretching).

\(^1\)H-NMR (\(\delta\), ppm) (Fig 19) 7.21-8.58 (8H, multiplet, aromatic + -CH=N- protons)

\(^{13}\)C-APT (\(\delta\), ppm) (CDCl\(_3\)+ TFA) (Fig 20) 111.22(C), 112.82(C), 115.65(C), 117.77(CH), 118.29(C), 120.23(C), 125.66(CH), 125.77(C), 129.16(CH), 131.81(CH), 136.18(C), 140.36(CH), 143.82(CH), 153.28(C), 163.41(CO of coumarin)

Compound 3j

IR (cm\(^{-1}\)) \(v_{\text{max}}\) 1712 (C=O stretching of \(\delta\)-lactone of coumarin), 1582 and 1475 (aromatic C=C and C=N stretchings), 754 (C-S-C stretching vibration) 3046 (aromatic C-H stretching).

\(^1\)H-NMR (\(\delta\), ppm) (Fig 21) 7.06-8.34 (8H, multiplet, aromatic+ -CH=N- protons)

\(^{13}\)C-APT (\(\delta\), ppm) (CDCl\(_3\)+ TFA) (Fig 22) 101.43(CH), 109.89(CH), 112.72(C), 113.80(C), 115.54(C), 117.50(CH), 118.37(C), 125.06(CH), 126.03(C), 129.11(CH), 131.73(CH), 136.52(C), 139.08(CH), 153.49(C), 163.99(CO of coumarin).
**Compound 3k**

IR (cm\(^{-1}\)) \(\nu_{\text{max}}\) 1715 (C=O stretching of \(\delta\)-lactone of coumarin), 1580 and 1472 (aromatic C=C and C=N stretchings), 754 (C-S-C stretching vibration), 2854 (aliphatic C-H stretching) 3045 (aromatic C-H stretching)

\(^1\)H-NMR (\(\delta\), ppm) (Fig 23) 2.34 (3H, singlet, CH\(_3\)), 7.06-8.33 (7H, multiplet, aromatic + -CH=N- protons)

\(^{13}\)C-APT (\(\delta\), ppm) (CDCl\(_3\)+ TFA) (Fig 24) 23.32(CH\(_3\)), 107.32(CH), 109.92(C), 112.74(C), 115.28(C), 115.57(C), 118.39(C), 119.23(CH), 128.89(CH), 129.10(CH), 131.72(CH), 132.05(C), 137.58(CH), 138.42(CH), 142.38(C), 153.48(C), 163.31(CO of coumarin).

**Compound 3l**

IR (cm\(^{-1}\)) \(\nu_{\text{max}}\) 1718 (C=O stretching of \(\delta\)-lactone of coumarin), 1585 and 1475 (aromatic C=C and C=N stretchings), 756 (C-S-C stretching vibration), 3041 (aromatic C-H stretching).

\(^1\)H-NMR (\(\delta\), ppm) (Fig 25) 7.08-8.36 (7H, multiplet, aromatic + -CH=N- protons)

\(^{13}\)C-APT (\(\delta\), ppm) (CDCl\(_3\)+ TFA) (Fig 26) 101.32(CH), 109.92(C), 112.74(C), 115.28(C), 115.57(C), 118.39(C), 119.23(CH), 128.89(CH), 129.10(CH), 131.72(CH), 132.05(C), 137.58(CH), 138.42(CH), 142.38(C), 153.48(C), 163.31(CO of coumarin).
Fig 1  IR spectrum of compound 3a

Fig 2  $^1$H-NMR spectrum of compound 3a
Fig 3  $^{13}$C-APT spectrum of compound 3a

Fig 4  Mass spectrum of compound 3a
Fig 5 $^1$H-NMR spectrum of compound 3b

Fig 6 $^{13}$C-APT spectrum of compound 3b
Fig 7 $^1$H-NMR spectrum of compound 3c

Fig 8 $^{13}$C-APT spectrum of compound 3c
Fig 9 $^1$H-NMR spectrum of compound 3d

Fig 10 $^{13}$C-APT spectrum of compound 3d
**Fig 11** $^1$H-NMR spectrum of compound 3e

**Fig 12** $^{13}$C-APT spectrum of compound 3e
Fig 13 \( ^1\)H-NMR spectrum of compound 3f

Fig 14 \( ^{13}\)C-APT spectrum of compound 3f
Fig 15 $^1$H-NMR spectrum of compound 3g

Fig 16 $^{13}$C-APT spectrum of compound 3g
Fig 17 \( ^1\text{H-NMR} \) spectrum of compound 3h

Fig 18 \( ^{13}\text{C-APT} \) spectrum of compound 3h
**Fig 19** $^1$H-NMR spectrum of compound 3i

**Fig 20** $^{13}$C-APT spectrum of compound 3i
Chapter 4sec 2  

1,2,4-triazolo thiadiazepino fused coumarins

Department of Chemistry, Sardar Patel University  

Fig 21 1H-NMR spectrum of compound 3j

Fig 22 13C-APT spectrum of compound 3j
**Fig 23** $^1$H-NMR spectrum of compound 3k

**Fig 24** $^{13}$C-APT spectrum of compound 3k
Fig 25 $^1$H-NMR spectrum of compound 31

Fig 26 $^{13}$C-APT spectrum of compound 31
4.6 Experimental

4.6.1 Preparation of 4-hydroxy coumarin and 6-methyl-4-hydroxy coumarin.

The following general procedure was used.

In a 500 mL round bottom flask attached with a reflux condenser and gas absorption trap, a mixture of appropriate phenol (0.2 mol), malonic acid (0.2 mol), anhydrous zinc chloride (0.6 mol) and phosphorous oxychloride (0.4 mol) was heated with stirring at 60-65°C for 35 hours. The yellow colored mixture was cooled and decomposed with water and left overnight. The resulting crude 4-hydroxy coumarin was filtered out, washed with water and dried. This crude product was purified by dissolving it in 10% sodium bicarbonate solution, filtering and reprecipitating by adding dilute HCl solution. The product was separated out as a yellowish-white solid. This was filtered out, washed with water, dried and recrystallized from ethanol.

4-Hydroxy coumarin: R = R1 = H; Yield: 60%, mp 204°C (lit.58 mp 206°C)

6-Methyl-4-hydroxy coumarin: R = CH3, R1 = H; Yield: 43%, mp 239°C (lit.58 mp 240°C)

4.6.2 Preparation of 6-chloro-4-hydroxy coumarin.

In a 250 mL round bottom flask fitted with reflux condenser, a mixture of p-chloro phenol (0.2 mol), malonic acid (0.1 mol) and phosphorous oxychloride (0.2 mol) was placed. The reaction mixture was heated for 30 minutes on boiling water bath. It was cooled and poured into ice-cold water. The white solid obtained was filtered and
washed with cold water. It was then washed with saturated sodium bicarbonate solution to remove unreacted malonic acid. Finally it was washed with water and dried. Thus diester was obtained which was recrystallized from ether-hexane.

Yield: 68% mp 115°C

The above diester (20 g) and anhydrous aluminum chloride (20.6 g) were taken in a round bottom flask. The flask was stoppered and shaken vigorously for 2-3 minutes. A reflux condenser provided with gas absorption tube was attached and the flask was heated in an oil bath at 180-185°C for 30 minutes. The reaction mixture was allowed to cool to room temperature and then flask was immersed in an ice bath. The reaction mixture was decomposed by dilute HCl (1:7) over a period of about 2 hours. The content was then heated on steam bath for 30 minutes with vigorous stirring in order to effect the complete decomposition. The solid product obtained was filtered out and washed with water and dried. The product was then dissolved in 5% aqueous sodium hydroxide solution and the solution was filtered. The product was then reprecipitated by adding dilute HCl, until solution was acidic. The precipitates were filtered out, washed with water and dried. It was recrystallized from ethyl acetate-hexane.

**6-Chloro-4-hydroxy coumarin**: Yield: 66% mp 263°C (lit\textsuperscript{59} mp 264°C)

### 4.6.3 Preparation of 4-chloro-3-formyl coumarins(1a-c).

![Chemical structure diagram](image)

In a 250 mL three necked round bottom flask fitted with addition funnel and guard tube, an appropriate 4-hydroxy coumarin (0.06 mole) was taken in anhydrous dimethyl formamide (DMF) (0.6 mole) and the reaction mixture was cooled to 0°C with stirring. In this
well stirred reaction mixture, phosphorous oxychloride (POCl$_3$) (0.18 mole) was added dropwise during one hour. After addition was completed, the reaction mixture was further stirred at 0°C for one hour. The reaction mixture was then heated at 65-70°C for two hours. It was then poured into crushed ice (200 g) and left overnight in refrigerator, during which a solid product was separated out which was filtered off, washed with 5% sodium carbonate (3 x 30 mL) and water. It was then dried and recrystallized from acetone-water.

**Compound 1a**: $R = R_1 = H$, Yield: 58%, mp 155°C (lit.$^{60}$ mp 156°C)

**Compound 1b**: $R = H$, $R_1 = CH_3$, Yield: 58%, mp 155°C (lit.$^{60}$ mp 156°C)

**Compound 1c**: $R = Cl$, $R_1 = H$, Yield: 50%, mp 240°C (lit.$^{60}$ mp 242°C)

### 4.6.4 Preparation of 4-amino-5-substituted-3-mercapto-1,2,4,-triazoles(2a-d)

![Diagram of the reaction](image)

**Step-1 Synthesis of aryl acidhydrazides:**

In a 250ml of round bottom flask fitted with a reflux condenser an appropriate methylbenzoate (0.12mole) and hydrazine hydrate (0.12mole) were taken in ethanol(40ml). The reaction mixture was refluxed on water bath for 3hours. Upon cooling acidhydrazides were separated out which were filtered out and wash with cold ethanol and dried.
**Step-2 Preparation of potassium dithiocarbazinates:**

An appropriate above prepared acid hydrazide (0.01mole) was dissolved in absolute ethanol (15ml) in a 250ml of round bottom flask fitted with a reflux condenser. To this, potassium hydroxide (0.03mole) was added with stirring. Then after solution was cooled to 0°C in an ice bath and carbon disulfide (0.05mole) was added in small portion with constant stirring. The reaction mixture was stirred for 10hrs at room temperature. Dry ether (10ml) was added to the reaction mixture and the yellow product separated out was filtered out. It was dried and was subjected to used without further purification.

**Step-3 Preparation of 4-amino-5-substituted-1, 2, 4-triazoles:**

A mixture of above prepared potassium salt (0.02mole) in water (25ml) and hydrazine hydrate (0.04mole) was taken in a 250ml of round bottom flask fitted with a reflux condenser. The reaction mixture was refluxed on water bath until the evaluation of hydrogen sulfide ceased. (which was checked by lead acetate paper). Then after the reaction mixture was allowed to come to room temperature and 30ml of cold water was added. It was then acidify with dilute HCl (50%). The product was separated out as white solid which was filtered out, washed with water and dried. It was then recrystallized from ethanol.

The following 4-amino-5-substituted-1, 2, 4-triazoles were prepared:

- **Compound2a**: R₂ = CH₃, Yield: 58%, mp 202°C (lit. mp 204°C)
- **Compound2b**: R₂ = phenyl, Yield: 62%, mp 200°C (lit. mp 198°C)
- **Compound2c**: R₂ = 4-pyridyl, Yield: 50%, mp 235°C (lit. mp 238°C)
- **Compound2d**: R₂ = 2-thiophenyl, Yield: 55%, mp 246°C (lit. mp 248°C)
4.6.5 Synthesis of [1,2,4]triazolo[3’,4’:2,3][1,3,4]thiadiazepino [7,6-b]coumarins:(3a-l)

The following general procedure was used.

In a 100 ml of round bottom flask an appropriate 4-amino-5-substituted-3-mercapto-1,2,4-triazole (2a-d) (0.025 mol) was taken in ethanol (5 ml). To this catalytical amount of K$_2$CO$_3$ (0.03 mol) was added with stirring for 30 minutes at room temperature. To this solution an appropriate 4-chloro-3-formyl coumarin (1a-d) (0.025 mol) in ethanol (15 mL) was added followed by addition of 2-3 drops of acetic acid. The reaction mixture was further stirred at room temperature for two hours. The solid obtained was filtered out and washed with hexane-chloroform and dried.

**Compound 3a:**  R = R$_1$ = H, R$_2$ = CH$_3$

Yield = 85%  
mp 198-201°C  
Molecular Formula: C$_{13}$H$_8$N$_4$O$_2$S

Analysis  
% C  % H  % N

Found  54.97  2.80  19.68
Calculated  54.92  2.84  19.71

**Compound 3b:**  R = H,  R$_1$ = R$_2$ = CH$_3$

Yield = 75%  
mp 193-196°C  
Molecular Formula: C$_{14}$H$_{10}$N$_4$O$_2$S

Analysis  
% C  % H  % N

Found  56.32  3.31  18.72
<table>
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<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Molecular Formula</th>
<th>Analysis</th>
<th>Found</th>
<th>Calculated</th>
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<th>Calculated</th>
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<td>3c</td>
<td>H</td>
<td>Cl</td>
<td>79%</td>
<td>200-202</td>
<td>C₁₃H₇N₄O₂SCl</td>
<td>% C 56.37</td>
<td>48.91</td>
<td>48.99</td>
<td>% H 3.38</td>
<td>2.15</td>
<td>2.21</td>
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<tr>
<td>3d</td>
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<td>Ph</td>
<td>79%</td>
<td>212-214</td>
<td>C₁₈H₁₀N₄O₂S</td>
<td>% C 62.38</td>
<td>62.42</td>
<td>62.32</td>
<td>% H 2.86</td>
<td>2.91</td>
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<tr>
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<td>75%</td>
<td>230-232</td>
<td>C₁₉H₁₂N₄O₂S</td>
<td>% C 63.28</td>
<td>63.32</td>
<td>63.32</td>
<td>% H 3.32</td>
<td>3.36</td>
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<tr>
<td>3f</td>
<td>H</td>
<td>Cl</td>
<td>79%</td>
<td>215-217</td>
<td>C₁₈H₉N₄O₂SCl</td>
<td>% C 56.71</td>
<td>56.77</td>
<td>56.77</td>
<td>% H 2.35</td>
<td>2.38</td>
<td>2.38</td>
</tr>
<tr>
<td>3g</td>
<td>R₁</td>
<td>4-pyridyl</td>
<td>82%</td>
<td>252-254</td>
<td>C₁₇H₉N₅O₂S</td>
<td>% C 58.75</td>
<td>58.78</td>
<td>58.78</td>
<td>% H 2.60</td>
<td>2.61</td>
<td>2.61</td>
</tr>
<tr>
<td>3h</td>
<td>H</td>
<td>CH₃</td>
<td>86%</td>
<td>268-270</td>
<td>C₁₈H₁₁N₅O₂S</td>
<td>% C 59.75</td>
<td>59.75</td>
<td>59.75</td>
<td>% H 8.10</td>
<td>8.10</td>
<td>8.10</td>
</tr>
</tbody>
</table>
### Compound 3i:

- **Chemical Formula**: \( \text{C}_{17}\text{H}_{8}\text{N}_{5}\text{O}_{2}\text{SCl} \)
- **Yield**: 79%
- **M.p.**: 236-237°C
- **Found Analysis**:
  - % C: 53.45
  - % H: 2.08
  - % N: 18.30
- **Calculated Analysis**:
  - % C: 53.48
  - % H: 2.11
  - % N: 18.34

### Compound 3j:

- **Chemical Formula**: \( \text{C}_{16}\text{H}_{8}\text{N}_{4}\text{O}_{2}\text{S}_{2} \)
- **Yield**: 79%
- **M.p.**: 211-214°C
- **Found Analysis**:
  - % C: 54.50
  - % H: 2.25
  - % N: 15.86
- **Calculated Analysis**:
  - % C: 54.53
  - % H: 2.29
  - % N: 15.90

### Compound 3k:

- **Chemical Formula**: \( \text{C}_{17}\text{H}_{10}\text{N}_{4}\text{O}_{2}\text{S}_{2} \)
- **Yield**: 82%
- **M.p.**: 225-227°C
- **Found Analysis**:
  - % C: 55.70
  - % H: 2.74
  - % N: 15.27
- **Calculated Analysis**:
  - % C: 55.72
  - % H: 2.75
  - % N: 15.29

### Compound 3l:

- **Chemical Formula**: \( \text{C}_{16}\text{H}_{7}\text{N}_{4}\text{O}_{2}\text{S}_{2}\text{Cl} \)
- **Yield**: 90%
- **M.p.**: 226-229°C
- **Found Analysis**:
  - % C: 49.65
  - % H: 1.84
  - % N: 14.36
- **Calculated Analysis**:
  - % C: 49.68
  - % H: 1.82
  - % N: 14.40
References

1. M Krzeszewski, O Vakuliuk and D T Gryko

2. a) L L Andreani, E Lapi
   b) L Bonsignore, G Loy, D Secci, A Calignano

   b) L Labrecque, S Lamy, A Chapus, S Mihoubi, Y Durocher,
      B Cass, M W Bojanowski, D Gingras, R Beliveau,
      arcinogenesis, 26, 821 (2005)

4. G Cozza, A Gianoncelli, P Bonvini, E Zorzi, R Pasquale, A Rosolen,
   L A Pinna, F Meggio, G Zagotto, S Moro

5. K Koch, J Podlech, E Pfeiffer, M Metzler

6. C Tamm
   Arzneim.-Forsch., 22, 1776 (1972)

7. R W Pero, D Harvan and M C Blois

8. K Suzuki

9. K Suzuki

10. U Weiss, K YoshiHIRA, R J HIGHT, R J White, T T Wei,

11. S Madan and C-H Cheng

12. A D Patten, N H Nguyen, S J Danishefsky
13. U Hacksell, G D Daves


*Molecules*, **19**, 5088-5108 (2014)

17. W R H Hurtley

*J. Chem. Soc.*, 1870 (1929)

18. H Valizadeh, A Fakhari


20. H Togo, T Muraki, Y Hoshina, K Yamaguchi, M Yokoyama


21. M S Tremblay and D Sames


23. T M Harris and J V Hay


24. P Langer, N N R Saleh, I Freifeld


25. Emam A, Eweis M, Elbadry M

*Drug discoveries and therapeutics*, **4**(6), 399-404 (2010)

26. Cordell, Geoffrey A


27. Cardoso-Lopes, Elaine Monterio, Maier, James Andreas, Silva, Marcelo Rogerio, Regasini, Luis Octivio, Simote, Simone
Yasue, Lopes, Norbertopeporine, Pirani Jose rubers, Bolzani, Vanderlan Dasilva, Young, Maria Claudia Marse
*Molecules, 15(12),* 9205-9213 (2010)

28.  Emam A, Eweis M, Elbadry M
*Drug discoveries and therapeutics, 4(6),* 399-404 (2010)

29.  K Eichinger, P Nussbaumer, S Balkan, G Schulz
*Synthesis,* 1061 (1987)

30.  Sashibala Singh

31.  C F Koelsch
*J. Am. Chem. Soc., 72,* 2993 (1950)

32.  T V P Rao and V R Rao

*Int. J. of Chemical and Pharmaceutical Sci, 2(3),* 9-14 (2011)

34.  a)  S Sarveswaran, S C Gautam, J Ghosh
*Int. J. Oncol., 41,* 2191 (2012)

b)  K Ukawa, T Ishiguro, Y Wada, A Nohara
*Heterocycles, 24,* 1931 (1986)

*Phytomed., 21,* 240 (2014)

d)  K V Sashidhara, M Kumar, R K Modukuri, R Sonkar, G Bhatia, A K Khanna, S Rai, R Shukla

e)  M Campos-Toimil, F Orallo, L Santanab, E Uriarteb

f)  C C Chiang, M J Cheng, C F Peng, H Y Huang, I S Chen
dx.doi.org/10.1016/j.tetlet.2015.01.028
b) T S Symeonidis, K E Litinas
c) A T Khan, D K Das, K Islam, P Das

36. a) V V Mulwad, J M Shirodkar
b) I Strakova, M Petrova, S Belyakov, A Strakova
c) M Cacic, M Trkovnik, E Has-Schon

37. a) F Risitano, G Grassi, F Foti and C Bilardo
b) G Raffa, M Rusch, G Balme, N Monteiro
Org. lett., **11(22)**, 5254 (2009)
c) L Chen, Yi Li, Ming-Hua Xu
d) C-J Lee, Y-J Jang, Zong-Ze Wu, and W Lin
Org. lett., **14(7)**, 1906 (2012)

38. a) K E Litinas, T S Symeonidis
Tetrahedron, **66**, 1289 (2010)
b) S Ahadi, M Zolghadr, H R Khavasi, A Bazgir
c) P Selles, U Mueller

39. a) J.L.Reibsome and D A Stautller
Jor.Org.Chem,**16**(1951),1643
b) H A R Prasad, T Ramalingum,A B Rao,P V Diwan,P B Sattu,

40. H A R Prasad, T Ramalingum,A B Rao,P V Diwan,P B Sattu,
Chapter 4sec 2  
1,2,4-triazolo thia diaepino fused coumarins


41. S Bala. R P Gupta,  
Ind J. of Chem, 16B, 1978, 481

42. J Mohan,  
Ind J. of Chem, 22B, 1983, 270

43. T Nakaic, S Meedu, T Kurakshi,  
Jpn Pat, 73, 1953, 89932

44. R J Colter, M Matzner, Ring terming polymerisation, part-B-  
‘Heterocyclic ring’ Academic, NEW YORK,, 1972

45. a) S Sharad, M Ganesh, G Sunil, G Charansingh,  
Biorg Med Chem Lett., 20, 2010, 7200

b) M Koparir, C Orek, A E Parlak, A Soylemez, P Koparir, M Karatee, S D Dastan  

c) Y Ruan, L H Jin, J He, S yang, P S Bhadury, M He, Z C Wang, B A Song,  
Afr Jou Pharm Pharmacol, 5, 602, 2011

46. Kane J M, Dudley M W, Sorenen S M, Mliller F P  

47. J R Maxwell, D A Wasdaul, A C WAOLFSON  
J. of Med Chem, 27, 1565, 1984

48. Demirbas N, Demirbas U A,  
Biorg Med Chem, 10, 3717, 2002,

49. El-Essaway A, El-Sayed W A, El-Kafrawy S A, Moorshed A S,  
Abdel Rahman A H,  
Z Naturforsch, 63(C), 667-674, 2008

Elsevier, 666-671, Chap 47, 2005,

51. A Subageetha, R Vijayraj, T. Rajkumar and R S Anand ,  

52. E Banfi, G Scialino and C M Bragadin,  
J. Antimicrobial Chemother, 52, 796, 2003