CHAPTER 4
CHAPTER-4

Synthesis of new indeno[2,1-c]thiophene and indeno[1,2-b]thiophene derivatives

In this chapter we report the synthesis of novel indeno[2,1-c]thiophene by cyclocondensation of 2,3-dihydro-5,6-dimethoxyinden-1-one, carbon disulphide and phenacyl bromide. One pot and two step routes were studied for synthesis of indeno[2,1-c]thiophene. The newly synthesized ethyl 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carboxylate having C2 ester functionality was successfully utilized for the synthesis of novel 2-substituted indeno[1,2-b]thiophene derivatives. Indeno[1,2-b]indole, isoquolin-2-one, quinolin-2-one, 5,6-dihydroxyinden-1-one were synthesized from 2,3-dihydro-5,6-dimethoxyinden-1-one by using alternative route to literature methods.

4.1 Introduction
Thiophenes are important heterocyclic compounds, are widely used as building blocks in many agrochemicals [1]. Thiophene derivatives possesses antimicrobial [2], analgesic and anti-inflammatory [3], antihypertensive [4], diabetes mellitus [5], Gonadotropin releasing hormone antagonist [6], cholesterol inhibition [7], antiallergic [8], antitumor [9] activities. Polysubstituted thiophenes are important heterocycles found in numerous biologically active and natural compounds [10-14]. The interest in this kind of heterocycles has spread from dye chemistry [15] to modern drug design [16], biodiagnostics [17], electronic and optoelectronic devices [18], conductivity-based sensors [19] and self-assembled superstructures [20].
The wide applications of this type of heterocyclic chemistry gave importance to the present study, where the synthesis and reactivity of various C2 substituted thiophenes are systematized and analyzed. Emphasis is given to recent studies, in which the most general approach to the synthesis of thiophenes with reactive substituent at C2 position. N substituted thiophene-2-carbohydrazides derivatives are the lead molecules of pharmaceutical industries owing to their interesting biological activities displayed over a broad range of therapeutic classes. For example, thiophene-2-carbohydrazide derivatives were reported for c-Src enzyme inhibition and c-Src inhibition [21], anticonvulsants activity [22], as anti-inflammatory, analgesic agents [23]. On the other hand, indenone derivatives are reported as the pharmaceutically novel compounds having broad range of activities [24-27].

Indeno[1,2-b]indole derivatives were identified as potent human protein kinase CK2 inhibitors [28], an enhancer of TCDD-induced gene expression potassium channel opening activity [29] and also showed antioxidant activity [30], antitumor activity [31], antiproliferative activity towards cancer cell [32]. In literature, many articles described synthesis of indeno[1,2-b]indole derivatives by using 2,2-dihydroxy-2H-indene-1,3-dione [28], mono substituted inden-1-one [30], 2-phenylquinoline-3,4-dicarboxylic anhydride [33], nitrobenzylphthalides [34] as starting materials. Particularly, 2,3-dimethoxy-5,10-dihydroindeno[1,2-b]-indole was synthesized by photostimulated reaction of enolate anions 2,3-dihydro-5,6-dimethoxyinden-1-one with o-iodoaniline in DMSO by the S_{RN1} mechanism in only 43% yield [35]. Which describe requirement of new route for synthesis of 2,3-dimethoxy-5,10-dihydroindeno[1,2-b]-indole with improved yield.
Literature survey revealed that, Lewis acid i.e. ZrCl$_4$ catalyzed Beckmann rearrangement of 2,3-dihydro-5,6-dimethoxyinden-1-one oxime in methanesulfonyl chloride (MsCl) increases the efficiency of rearrangement to gave 3,4-dihydro-6,7-dimethoxyquinolin-2(1H)-one as compared to 3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-one. Synthesized quinolin-2-one and isoquinolin-2-one were separated by using column chromatography [36]. In this chapter, we report different route for synthesis of quinolin-2-one and isoquinolin-2-one and partial separation by simple recrystallisation method.

**Literature updates for synthesis of thiophene, indole, isoquinolin-2-one and quinolin-2-one from carbonyl compounds containing two α-hydrogens**

During the last decade, chemistry of heterocyclic compounds with thiophene and indole moiety has received considerable importance due to their wide range of applications. The work represented in current chapter is concerned with the synthesis, characterization of new indenothiophene derivatives and synthesis of known heterocyclic compounds with different route from 2,3-dihydro-5,6-dimethoxyinden-1-one.

1) Wang Ing et al. and co-workers [37] obtained 2-aminoindeno[2,1-b]thiophene 3

![Scheme 1](image)

$X = \text{CN, COOEt}$

Scheme 1
derivatives using Gewald’s reaction by cyclization reaction of ethyl(1-indanylidene)-
cyanoacetate/2(inden-3-ylidene)malononitrile 2 with elemental sulfur (Scheme 1).

2) Pravinkumar Sable et al. and co-workers [38] reported convenient one-pot three-
component method for the preparation of tetra-substituted thiophene derivatives.
Reaction of acetyl acetone 4, phenyl isothiocyanate 5 and 2-chloromethyl derivatives 7 in
the presence of potassium carbonate afforded the target compounds 8, 9 (Scheme 2).

\[ \text{R}_1 = \text{OCH}_3, \text{OCH}_2\text{CH}_3, \text{CH}_3, \text{Cl} \]

\[ \text{R}_2 = \text{COCOOEt}, \text{\text{CH}_2\text{COOEt}} \]

Scheme 2

3) In this new version Hollas et al. and co-workers [39] used more stable dimeric forms
of α-sulfanylcarbonyl substituted 1,4-dithiane-2,5-diols 10, which undergo condensation
and subsequent cyclization with α-activated acetonitrile 11 requiring an amine in
stochiometric amount yielded 12 (Scheme 3).

\[ \text{R}^1 = \text{H & Alkyl, R}^2 = \text{H, X= CN, CONH}_2 \]

Scheme 3

4) Scammells et al. and co-workers [40] have presented the synthetic pathway to 5-
bromo substituted 2-aminothiophenes 15. In this pathway, substituted 2-bromo-1-
phenylethanones 13 were reacted with 3-oxo-3-phenylpropanenitrile 14 and sulfur in the presence of diethylamine as a base in ethanol to afford compound 15 (Scheme 4).

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{13} & \quad + \quad \text{O} - \text{CN} \\
\text{14} & \quad \xrightarrow{\text{S}_8, \text{Et}_3\text{NH}, \text{EtOH}, \text{45°C, 5h}} \quad \text{COPh} \\
\text{R} & \quad \text{=} \quad \text{H, CF}_3, \text{NO}_2, \text{CN}
\end{align*}
\]

Scheme 4

5) Daniel Sutherlin et al. and co-workers [41] has reported heterogeneous organic reactions using reagents immobilized on porous solid support advantageous over conventional solution phase reaction. The acylation of commercially available AgroGel® Wang resin 16 with cyanoacetic acid under standard DIC/DMAP coupling conditions gave the resin-bound cyanoacetic ester 17. Gewald reaction was performed on 17 with α-methylene carbonyl compounds, sulfur and morpholine in ethanol. Final 2-aminothiophene carboxylic acids were isolated as N-acetyl protected derivatives 19 upon the cleavage of the resin with trifluoroacetic acid (Scheme 5).

\[
\begin{align*}
\text{HO} & \quad \text{NC} - \text{OH} \\
\text{16} & \quad \xrightarrow{\text{DIC, DMAP, CH}_2\text{Cl}_2} \quad \text{NC} - \text{O} - \text{CO} - \text{OH} \\
\text{17} & \quad \xrightarrow{\text{R}_1 = \text{H or Alkyl, Morphpoline, S}_8, \text{EtOH, } \triangle} \quad \text{R}_2 - \text{O} - \text{O} - \text{NH}_2 \\
\text{18} & \quad \xrightarrow{1. \text{AcCl, CH}_2\text{Cl}_2, \text{EtN}(\text{I-Pr})_2} \quad \text{R}_1 - \text{O} - \text{OH} \\
\text{19} & \quad \xrightarrow{2. \text{TFA, H}_2\text{O, CH}_2\text{Cl}_2} \quad \text{R}_2 - \text{O} - \text{NH}
\end{align*}
\]

Scheme 5

6) Shah et al. and co-workers [42] has reported the synthesis of novel 5-amino-3-methyl-1H-thieno[3,2-c]pyrazole-6-carbonitrile 23 by Gewald thiophene reaction. The 3-methyl-1H-pyrazol-5(4H)-one 20 on condensation with malononitrile afforded open chain compound 22, which on further cyclization reaction with elemental sulphur and catalytic amount of morpholine yielded o-aminocarbonitrile 23 (Scheme 6).
7) Kirsh et al. and co-workers has reported synthesis of 2-alkylthiophenes 26 [43] by the addition of a carbanion of cyclohexane-1,3-dione 24 to carbon disulfide with a subsequent S-dialkylation. Similar methodology was used by Abbas Shafiee et al. and co-workers [44] in order to synthesize thiophene 28. Potassium dithiolate salt 25 was monoalkylated with ethyl bromo acetate and cyclised under basic conditions to gave 27, which was further alkylated to gave 28 (Scheme 7).

8) Hu Yi et al. and co-workers [47] has reported Gewald synthesis of 2-amino thiophenes 56 catalyzed by ethylenediammonium diacetate (EDDA) (Scheme 8).
9) Sridhar et al. and co-workers [45] has presented as an easy access to polysubstituted thiophenes by using microwave enhanced Gewald reaction in combination with solid-support. A variety of ketones 32 were reacted with ethyl cyanoacetate 33a or malononitrile 33b and sulfur in the presence of KF-alumina (as a base) producing thiophene derivatives 34 in good yields (Scheme 9).

![Scheme 8](image)

10) David Brown et al. and coworkers [46] has reported synthesis of antioxidants incorporating indeno[1,2-b]indole 37 and indeno[2,1-b]indole 38 chromophores. Condensation of lithiated aniline 35 with 2-halo-2,3-dihydro-5-methoxy-4,6-

dimethylinden-1-one 36 gave indole derivative 37 (when halogen was bromine) or 38 (when halogen was Chlorine) (Scheme 10).
11) John Butera et al. and co-workers [47] prepared substituted 5,10-dihydro-indeno[1,2-b]indole-1-carboxylic acid derivatives 42 by using fisher indole synthesis. Indenone 39 was condensed with 2-hydrazinylbenzoic acid 40 in ethanol to gave intermediate 41, which was cyclised under acidic conditions to gave indole derivatives 42 (Scheme 11).

\[
\begin{array}{cccc}
R_1 & \text{O} & \text{CO}_2\text{H} \\
\text{EtOH, H}^+ & \text{NHNH}_2 & \text{N}-\text{NH} & \text{CO}_2\text{H} \\
\text{AcOH reflux} & \text{R}_1 & \text{H} & \text{OCH}_3 \\
\end{array}
\]

Scheme 11

12) Dae Chi and Byoung Lee [48] has reported the Lewis acid catalyzed i.e. AlCl₃ beckmann rearrangement of 1-indanone oxime 43 providing hydrocarbostyril 45 as major product in 91% yield via tosylate 44 under low temperature conditions (Scheme 12).

\[
\begin{array}{cccc}
\text{N-} & \text{O} & \text{TsCl, 4N NaOH, acetone, -10 °C to rt} \\
\text{N'-OH} & \text{N'-OTs} & \text{AlCl₃, CH}_2\text{Cl}_2, -40 °C to rt} \\
\text{43} & \text{44} & \text{45} & \text{46} \\
\end{array}
\]

Scheme 12

13) Yasuhiro Torisawa et al. and co-workers [49] has revealed that use of TiCl₄ as Lewis acid catalyst leads to selective and controlled production of the isomeric hydroisocarbostyril derivative 49 from Beckmann rearrangement of 48 (Scheme 13).
4.2 Present Work

These literature reports inspired us to synthesize new indeno[2,1-c]thiophene, indeno[1,2-b]thiophene and known heterocyclic compounds like indeno[1,2-b]indole, 3,4-dihydro-isoquinolinone, 3,4-dihydro-quinolinone by new route from 2,3-dihydro-5,6-dimethoxyinden-1-one.

4.2.1 Synthesis of (1-mercapto-5,6-dimethoxy-8H-indeno[2,1-c]thiophen-3-yl)(phenyl)methanone (54)

The synthesis of (1-mercapto-5,6-dimethoxy-8H-indeno[2,1-c]thiophen-3-yl)(phenyl)methanone 54 can be achieved by simple acidification of 53. Salt 53 could be obtained by cyclisation of 52. Compound 50 on reaction with CS₂ can yield 51 which on mono
alkylation with phenacyl bromide can give compound 52. Salt 53 can also be obtained by one pot reaction of compound 50 with CS₂ and phenacyl bromide.

**4.2.2 Synthesis of ethyl 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carboxylate (56)**

Synthesis of ethyl 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carboxylate 56 can be achieved from 3-chloro-5,6-dimethoxy-1H-indene-2-carbaldehyde 55 by cyclocondensation with thioglycolate. Synthesis of 3-chloro-5,6-dimethoxy-1H-indene-2-carbaldehyde 55 can be achieved by Vilsmeier Haack formylation on 2,3-dihydro-5,6-dimethoxyinden-1-one 50.

![Chemical structures](image)

**4.2.3 Synthesis of N'-acetyl-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (58)**

The compound 58 could be obtain by acylation of 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide 57. Synthesis of 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide 57 could be obtained from ester 56 by substitution reaction with hydrazine hydrate.

![Chemical structures](image)
4.2.4 Synthesis of \((E)-N'\text{-arylidene}-6,7\text{-dimethoxy-4H-}\text{inden}[1,2-b]\text{thiophene-2-carbohydrazide 60(a-d)}\)

The synthesis of 60a-d can be achieved by condensation of aldehydes 59a-d and 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide 57.

![Chemical structure diagram](image)

4.2.5 Synthesis of 5,10-dihydro-2,3-dimethoxyinden[1,2-b]indole (62)

The synthesis of 5,10-dihydro-2,3-dimethoxyinden[1,2-b]indole 62 can be achieved by cyclization of \((E)-1\text{-}\text{(1,2-dihydro-5,6-dimethoxyinden-3-ylidene)-2-phenylhydrazine 61}\) under acidic condition. The Schiff base 61 can be obtained by condensation reaction of 2,3-dihydro-5,6-dimethoxyinden-1-one 50 and phenyl hydrazine.

![Chemical structure diagram](image)

4.2.6 Synthesis of 3,4-dihydro-6,7-dimethoxyisoquinolin-1(2H)-one (64) and 3,4-dihydro-6,7-dimethoxyquinolin-2(1H)-one (65)

The synthesis of 3,4-dihydro-6,7-dimethoxyisoquinolin-1(2H)-one 64 and 3,4-dihydro-6,7-dimethoxyquinolin-2(1H)-one 65 can be achieved by Beckman rearrangement of oxime 63. Oxime 63 can be obtained by condensation of 2,3-dihydro-5,6-dimethoxyinden-1-one 50 and hydroxyl amine hydrochloride.
4.2.7 Synthesis of 2,3-dihydro-5,6-dihydroxyinden-1-one (66)

The compound 2,3-dihydro-5,6-dihydroxyinden-1-one 66 could be prepared by demethylation of 2,3-dihydro-5,6-dimethoxyinden-1-one 50 under acidic condition.

4.3 Results and Discussion

The structural diversity and biological importance of thiophene have made them attractive target for the synthesis as discussed in literature survey. The synthesis of thiophene derivatives 54, 56-58, 60(a-d) were done from starting compound 2,3-dihydro-5,6-dimethoxyinden-1-one 50. Indenone 50 was also used for synthesis of indeno[1,2-
In the course of our study, we are interested in establishing a convenient, practical and most general methodology for the synthesis compound 54. Hence, condensation of indanone 50 with phenacyl bromide and carbon disulphide was studied using two
different routes aiming to obtain high yield of product (*Experiment No. 1, Page No. 233*).

In first instance, we focused on multi step reactions (**Route 1**) for synthesis of compound **54**. Previously, salt similar to **52** was isolated during the synthesis of thienopyrazole derivatives [50], similarly in this route salt **52** was isolated. For this 2,3-dihydro-5,6-dimethoxyinden-1-one **50** was reacted with carbon disulfide in presence of sodium ethoxide in dry ethanol afforded sodium dithiolate salt **51**, which on monoalkylation by using one equivalent phenacyl bromide gave the stable monoalkylthio derivative **52**. Salt **52** was isolated by simple filtration under vacuum. Isolated salt was not **53** which was confirmed by dissolving it in water and neutralizing with dil. HCl. The solid obtained showed presence of three compounds on TLC. Mixture of three compounds was non separable by column chromatography or by recrystallization and \( R_f \) value of any of these compounds did not matches with \( R_f \) value of compound **54**. Compound **52** was cyclized by refluxing in sodium ethoxide in ethanol to furnish salt **53**, which on acidification afforded (1-mercapto-5,6-dimethoxy-8\(H\)-inden[2,1-c]thiophen-3-yl)(phenyl)methanone **54** with only 52% yield.

In two step process (**Route 2**), we obtain salt **53** without isolating any intermediate. Indanone **50** was refluxed with carbon disulfide in presence of sodium ethoxide in ethanol. Reaction mixture cooled at 0-5 °C and one equivalent of phenacyl bromide was added to it and stirred at 0-5 °C for 0.5 h, at room temperature for 1 h and then refluxed for 2 h. The solution was evaporated under reduced pressure and the formed solid product **53** dissolved in water. Compound **54** was precipitated by neutralization with dil. HCl in excellent yield (79%) as compare to the route 1. The
structure of 54 was established by spectral and analytical data. The compound 5 showed -SH and C=O stretching frequencies at 3560 and 1690 cm\(^{-1}\) respectively. The \(^1\)H NMR spectrum of 54 in DMSO-\(d_6\) showed singlets at \(\delta\) 3.88 and 3.79, 3.90 for two protons of CH\(_2\) group and six protons of two methoxy group respectively. Singlet at \(\delta\) 10.18 for -SH proton and all aromatic protons appear in the respective region (Spectrum No. 1, Page No. 215).

\[\text{Spectrum No. 1: } ^1\text{H NMR Spectrum of (1-mercapto-5,6-dimethoxy-8H-indeno[2,1-c]thiophen-3-yl)(phenyl) methanone}, \ 54\ \text{in DMSO-}d_6\]
The $^{13}$C NMR spectrum (DMSO-$d_6$) of this solid exhibited the peaks at $\delta$ 34.6, 55.6, 55.7 and 184.2 for aliphatic and ketone carbons respectively. (Spectrum No. 2, Page No. 216).

Mass spectrum $m/z = 368$ (mol.wt. = 368.47) and the elemental analyses both are in agreement with the proposed structure of (1-mercapto-5,6-dimethoxy-8H-indeno[2,1-c]thiophen-3-yl)(phenyl)methanone 54.
4.3.2 Synthesis of ethyl 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carboxylate (56)

After successful synthesis of indeno[2,1-c]thiophene 54, we have extended our work to construct the indeno[1,2-b]thiophene having C2-ester carbonyl on thiophene ring. For this purpose, Vilsmeier Haack reaction was carried out on compound 50 at 0-5 °C to gave 3-chloro-5,6-dimethoxy-1H-indene-2-carbaldehyde 55 in 75% yield (Experiment No. 2, Page No. 235). Work up of reaction was done below 10 °C and product was stored below 25 °C in amber color bottle as product of reaction decomposes above 30 °C and by exposcer to sunlight for more than 1 h. Further, cyclo condensation on compound 55 with ethyl 2-mercaptoacetate furnished ethyl 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carboxylate 56 in 82% yield (Experiment No. 3, Page No. 236). The IR of compound 55 showed carbonyl frequency at 1720 cm⁻¹. The 1H NMR spectrum of 55 in DMSO-d₆ showed singlets at δ 3.79, 3.80 for two OCH₃ groups and at δ 3.91 for indene CH₂ group respectively. Singlets at δ 7.23, 8.11 and 12.56 for aromatic protons and aldehyde proton, respectively (Spectrum No. 3, Page No. 218).
The mass spectrum of 55 showed M⁺ and M+2 at 238 and 240 m/z respectively due to presence of one chlorine.

The reaction of 55 with ethyl 2-mercaptoacetate yielded indeno[1,2-b]thiophene 56 was confirmed by disappearance of aldehyde carbonyl and appearance of ester carbonyl at 1708 cm⁻¹ in its IR. The ¹H NMR spectrum of 56 in CDCl₃ showed the triplet at δ 1.46, for three protons of methyl group and quartet at δ 4.43 for two protons of methylene group with J = 6.5 Hz. Three singlets appear at δ 4.01, 3.81 and 3.96 observed for two OCH₃ group and one indene CH₂ group respectively. Each aromatic proton appeared as singlet at δ 7.24, 8.15 and 8.38. (Spectrum No. 4, Page No. 219).
Further, elemental analyses of 55 and 56 were in agreement with the molecular formula C_{12}H_{11}ClO_{3} and C_{16}H_{16}O_{4}S respectively. On the basis of this spectral and analytical data structure 55 and 56 were assigned to compound i.e. 3-chloro-5,6-dimethoxy-1\(H\)-indene-2-carbaldehyde and ethyl 6,7-dimethoxy-4\(H\)-indeno[1,2-\(b\)]thiophene-2-carboxylate.
4.3.3 Synthesis of 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (57)

Scheme 16

Compound 56 having ester functionality was transformed to hydrazide derivative 57 by reaction with hydrazine hydrate. Thus, compound 56 upon heating with hydrazine hydrate in ethanol under reflux temperature for 4 h afforded 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide 57 as a colorless solid in 85% yield (Experiment No. 4, Page No. 237). The obtained solid was characterized by its IR, \(^1\)H NMR, Mass Spectroscopy and elemental analysis. The compound 57 showed stretching frequencies at 3290, 3267, 3190 cm\(^{-1}\) and 1661 cm\(^{-1}\) for NH\(_2\)/NH and C=O, respectively. The \(^1\)H NMR in DMSO-\(d_6\) showed singlets at \(\delta\) 3.78 and 3.89 for protons of two OCH\(_3\) groups and singlet at \(\delta\) 3.84 was assigned to two protons (CH\(_2\)) attached to cyclopentane ring. Two broad singlets at \(\delta\) 5.63 and \(\delta\) 10.42 were assigned for two protons of NH\(_2\) and one proton of NH respectively (Spectrum No. 5, Page No. 221). The mass spectral analysis showed the molecular ion peak at \(m/z = 290\) and the elemental analyses were in agreement with the molecular formula C\(_{14}\)H\(_{14}\)N\(_2\)O\(_3\)S.
4.3.4 Synthesis of \( N'\)-acetyl-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (58)

Acylation of carbohydrazide 57 was carried out by stirring it in acetic anhydride at 50-60 °C for 10 h to afford N-acetyl derivative 58 in 89% yield (Experiment No. 5, Page No. 238). The IR spectrum of this solid exhibit absorption bands due to two amide carbonyls.
at 1690 and 1682 cm$^{-1}$. The $^1$H NMR spectrum of 58 (DMSO-$d_6$) showed singlets at $\delta$ 2.15 and 3.85 for CH$_3$ and CH$_2$ group respectively. Two singlets at $\delta$ 3.82, 3.88 for protons of two OCH$_3$ groups. Singlets at $\delta$ 11.60 and 12.01 each for one proton of NH group. The aromatic protons appear as singlets at $\delta$ 7.25, 8.19 and 8.38 (Spectrum No. 6, Page No. 222). In $^{13}$C NMR carbonyl showed at $\delta$ 161.1, 163 and all other SP$^2$, SP$^3$ carbons appeared at their respective chemical shift (Spectrum No. 7, Page No. 223). The mass spectrum showed molecular ion peak M$^+$ at 332 m/z. Further, the elemental analysis obtained was in agreement with the molecular formula C$_{16}$H$_{16}$N$_2$O$_4$S.
4.3.5 Synthesis of (E)-N'-(arylidene)-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide 60(a-d)

Spectrum No. 7: $^{13}$C NMR Spectrum of N'-acetyl-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide, 58 in DMSO-$d_6$
The compound 57 having carbohydrazide functionality upon reaction with one equivalent of 3,4,5-trimethoxybenzaldehyde 59a in presence of catalytic amount of acetic acid in ethanol under reflux for 12-15 h afforded compound 60a in 86% yields (Experiment No. 6, Page No. 239) which was characterized by spectroscopic methods. The IR spectrum of 60a showed absorption bands at 1680 and 3272 cm\(^{-1}\) for amide carbonyl and NH group respectively. The \(^1\)H NMR spectrum (DMSO-\(d_6\)) of this solid showed five singlets at \(\delta\) 3.77, 3.82, 3.84, 3.85, 3.94 for five OCH\(_3\) groups and singlet at 3.89 for protons of CH\(_2\) group of indene ring. Singlets appear at \(\delta\) 8.42 for proton of N=CH group and at \(\delta\) 11.55 for protons of NH group, respectively. All other aromatic protons appeared at their respective chemical shift positions and splitting pattern in between \(\delta\) 6.91-8.32 (Spectrum No. 8, Page No. 224).

![Spectrum No. 8: \(^1\)H NMR Spectrum of(E)-N'-((2,3,4-trimethoxybenzylidene)-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide, 60a in DMSO-\(d_6\)](image)
The mass spectrum showed molecular ion peak for 60a at 468. The elemental analysis obtained was in agreement with the molecular formula C24H24N2O6S. On the basis of this analysis structure 60a was assigned to this compound i.e. \((E)-N'-(2,3,4-trimethoxybenzylidene)-6,7-dimethoxy-4\text{-}H\text{-}inden[1,2-\text{b}]thiophene-2-carbohydrazide.

Similarly, compounds 60(b-d) were synthesized and the structures were established on the basis of spectral and analytical data.

4.3.6 Synthesis of 5,10-dihydro-2,3-dimethoxyinden[1,2-b]indole (62)

Fisher indole synthesis was used for synthesis of 5,10-dihydro-2,3-dimethoxyinden[1,2-b]indole 62. The reaction of indanone 41 and phenyl hydrazine in acetic acid as solvent at room temperature gave 1-(1,2-dihydro-5,6-dimethoxyinden-3-ylidene)-2-phenylhydrazine 61 in 92% yield (Experiment No. 7, Page No. 242). Compound 61 was cyclized by refluxing in acetic acid in presence of catalytic amount of TFA to gave indeno[1,2-b]indole 62 in 89% yield (Experiment No. 8, Page No. 243). Structure of compound 61 was established by using IR, \(^1\text{H} \text{NMR}, \text{mass spectrometry and elemental analysis. For example, } ^1\text{H} \text{NMR (CDCl}_3\text{)} \text{ spectrum showed two triplets at } \delta 2.70 \text{ and } 3.04 \text{ with } J = 6.2 \text{ Hz for four protons of CH}_2-\text{CH}_2 \text{ group. Singlets appeared at } \delta 3.87 \text{ and } 3.94 \text{ for two OCH}_3 \text{ groups and a broad singlet at } \delta 6.91 \text{ for one proton assignable to NH group. All the aromatic protons appear in their respective region (Spectrum No. 9, Page}
No. 226). The mass spectral analysis showed the molecular ion peak $M^+$ at 282 and the elemental analysis was in agreement with the molecular formula $C_{17}H_{18}N_2O_2$. The $^1$H NMR of Indole 62 in DMSO-$d_6$ confirms cyclization reaction on compound 61 by showing presence of only one $CH_2$ as singlet at $\delta$ 3.58 and singlet at $\delta$ 11.40 for indole NH proton. Six aromatic protons appear in between $\delta$ 7.0-7.50 with expected splitting pattern (Spectrum No. 10, Page No. 227). The mass spectrum of 62 showed $M^+$ at 265 less than 17 from compound 61 due to loss of NH$_3$ during cyclisation. Further, elemental analyses of 61 and 62 were in agreement with the molecular formula $C_{17}H_{16}N_2O_2$ and $C_{17}H_{15}NO_2$ respectively.

![Spectrum No. 9: $^1$H NMR Spectrum of (E)-1-(1,2-dihydro-5,6- dimethoxy inden -3-ylidene)-2-phenylhydrazine, 61 in CDCl$_3$](image)

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On the basis of this spectral and analytical data structure 61 and 62 were assigned to compound i.e. (E)-1-(1,2-dihydro-5,6-dimethoxyinden-3-ylidene)-2-phenylhydrazine and 5,10-dihydro-2,3-dimethoxyindeno[1,2-b]indole.
4.3.7 Synthesis of 3,4-dihydro-6,7-dimethoxyisoquinolin-1(2H)-one (64) and 3,4-dihydro-6,7-dimethoxyquinolin-2(1H)-one (65)

Although, synthesis of isoquinolin-1(2H)-one 65 and quinolin-2(1H)-one 64 was reported previously, [36, 51] we use new route for synthesis of compounds 64 and 65. 2,3-Dihydro-5,6-dimethoxyinden-1-one 50 was treated with hydroxylamine hydrochloride in pyridine to furnish oxime 63 (Experiment No. 9, Page No. 244). The structure of 63 was established by spectral and analytical data. The compound 63 in its IR showed hydroxyl functionality at 3178 cm$^{-1}$. The $^1$H NMR spectrum of 63 in CDCl$_3$ showed two triplets at $\delta$ 2.70 and 3.21 with $J = 6.5$ Hz for four protons of two adjacent methylene groups and singlet at $\delta$ 3.98 for six protons of two OCH$_3$ groups. Two singlets at 6.8, 7.2 for two aromatic protons and broad singlet at 8.87 for one proton of OH group (Spectrum No. 11, Page No. 230). Mass spectrum $m/z = 207$ (M$^+$) and the elemental analyses is in agreement with the proposed structure of 2,3-dihydro-5,6-dimethoxyinden-1-one oxime 63. The oxime 63 was converted to mixture of amide 64 and 65 by Beckmann rearrangement (Experiment No. 10, Page No. 245). Accordingly, oxime 63 was treated with thionyl chloride in dry diethyl ether and after workup obtained solid shows presence
of two compounds on TLC. The solid was recrystallized using various solvents. It was observed that in ethyl acetate one of the compound get partially recrystallized while the filtrate shows mixture of two compounds on TLC. IR, $^1$H NMR, MS and elemental analysis data suggest isolated compound was 3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-one 65. For example, the IR of compound 65 showed carbonyl frequency at 1680 cm$^{-1}$ and broad peak for NH at 3260 cm$^{-1}$. The $^1$H NMR spectrum of 65 in DMSO-$d_6$ showed the two triplets at $\delta$ 2.93 and 3.56 with $J = 6.3$ Hz, for four protons of two adjacent methylene groups. Two methoxy group protons appear as one singlet at $\delta$ 3.93 and broad singlet at $\delta$ 6.5 for NH proton. The two singlets appeared at $\delta$ 6.68 and 7.57 each correspond to one aromatic proton (Spectrum No. 12, Page No. 230). Further, physical constant 135-137 °C (lit. m.p. 130-137 °C [51]) confirms the structure of compound 65. The solvent from filtrate was removed under reduced pressure and solid obtained was purified by column chromatography eluting with chloroform: methanol (9:1) gave 65 and 64 in 5% and 35% yield respectively. Observed physical constant 173-175 °C (lit. m.p. 174-175 °C [36, 51]) of compound 64 confirms it as 3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-one.
Spectrum No. 11: $^1$H NMR Spectrum of 2,3-dihydro-5,6-dimethoxy
-inden-1-one oxime, 63 in CDCl$_3$

Spectrum No. 12: $^1$H NMR Spectrum of 3,4-dihydro-6,7-
dimethoxyquinolin-1(2H)-one 65, in CDCl$_3$
4.3.8 Synthesis of 2,3-dihydro-5,6-dihydroxyinden-1-one (66)

In literature, compound 66 has been synthesized by the reaction of indanone 50 with HBr under reflux condition in only 59% yield [52]. The same compound has also been synthesized by treating indanone 1 with BBBr in DCM as solvent with 98% yield [53,54]. Although, yield was higher for later method, it suffered from disadvantage of requirement of low temperature i.e. -78 °C. In continuation of our work we used different route for the synthesis of 2,3-dihydro-5,6-dihydroxyinden-1-one 66. Previously, double demethylation of 3-acetyl-4-hydroxy-6,7-dimethoxy-1- methylquinolin-2(1H)-one was reported by Stadlbauer et al. [55] by stirring in Conc. H₂SO₄ at 140 °C. Same strategy implied herein for double demethylation of 2,3-dihydro-5,6-dimethoxyinden-1-one 50 by stirring in conc. H₂SO₄ at 140 °C furnish compound 57 in 82% yield (Experiment No. 11, Page No. 246). The ¹H NMR spectrum of 66 in CDCl₃ showed two doublets at δ 2.51 and 2.93 each corresponding to two protons of CH₂ with J = 6.2. Two singlets appeared at δ 6.91 and 7.04 each corresponds to one aromatic proton. Also, two singlets appeared at δ 9.12 and 9.40 each corresponds to one OH proton. (Spectrum No. 13, Page No. 232). The mass spectrum of 66 showed M⁺ at 164 m/z. Further, elemental analyses of 66 were in agreement with the molecular formula C₉H₆O₃.
4.4 Conclusion

A new class of indeno[2,1-c]thiophene and indeno[1,2-b]thiophene were obtained in good yield from 2,3-dihydro-5,6-dimethoxyinden-1-one with simple workup and clean product. Indeno[1,2-b]thiophene-2-carbohydrazide give facile and clean reaction with aromatic aldehydes, and acetic anhydride to yield novel thiophene derivatives in good yield. Selectively 3,4-dihydro-6,7-dimethoxyquinolin-2(1H)-one was partially isolated by simple recrystallization from mixture of 3,4-dihydro-6,7-dimethoxyquinolin-2(1H)-one and 3,4-dihydro-6,7-dimethoxyiso-quinolin-2(1H)-one. Simple and convenient method for the synthesis of 2,3-dihydro-5,6-dihydroxyinden-1-one was used. These compounds are new addition to the library’s of heterocyclic compounds having future pharmaceutical and technical applications.
4.5 Experimental Part

Experiment No. 1

4.5.1 Synthesis of (1-mercapto-5,6-dimethoxy-8H-indeno[2,1-c]thiophen-3-yl)(phenyl)methanone (54)

**Route 1:** To a solution of sodium metal (0.46 g, 0.02 mol) in dry ethanol (20 mL) 2,3-dihydro-5,6-dimethoxyinden-1-one 50 (1.92 g, 0.01 mol) was added portion wise at room temperature. Reaction mixture was refluxed for 20 min and cooled to room temperature. Carbon disulphide (0.72 mL, 0.012 mol) was added drop wise to reaction mixture. The reaction mixture stirred at room temperature for 0.5 h, and then refluxed for 0.5 h to give
intermediate sodium dithiolate salt 51. The solution was cooled and phenacyl bromide (1.99 g, 0.01 mol) was portion wise added at 0-5 °C for 0.5 h and stirred at room temperature for 1 h. The solution was evaporated under reduced pressure and the formed solid product was collected by filtration gave salt 52. (Isolated salt was 52 and not 53 confirmed by dissolving it in dil. HCl, which gives mixture of unseparable three compounds. Rf value of these compounds did not matches with Rf value of compound 54). In next step, a solution of compound 52 (4.24 g, 0.01 mol) and sodium metal (0.46 g, 0.02 mol) dissolved in absolute ethanol (20 mL) was refluxed for 2 h. The excess solvent removed under reduced pressure and the formed solid product 53 was dissolved in water and neutralized with dilute hydrochloric acid. The solid formed was collected by filtration and purified by column chromatography eluting with chloroform: methanol (9:1) afforded compound 54 as pale yellow solid in 52% yield.

**Route 2:** A solution of sodium metal (0.46 g, 0.02 mol) dissolved into dry ethanol (20 mL), 2,3-dihydro-5,6-dimethoxyinden-1-one 50 (1.92 g, 0.01 mol) and Carbon disulphide (0.72 mL, 0.012 mol) was refluxed for 1 h. The solution was cooled and phenacyl bromide (1.99 g, 0.01 mol) was portion wise added at 0-5 °C for 0.5 h, stirred at room temperature for 1 h and then refluxed for 2 h. The solution was evaporated under reduced pressure and the formed solid product 53 was dissolved in water and neutralized with dilute hydrochloric acid. The solid formed was collected by filtration and purified by column chromatography eluting with chloroform: methanol (9:1) to afford compound 54 as pale yellow solid.

Pale yellow solid; m.p.: 277-279 °C;

Yield Route I: 1.91 g, (52%), Route II: 2.90 g, (79%).
IR (KBr): 1220 (C=O), 1690 (C=O), 3560 (SH) cm$^{-1}$.

$^1$H NMR (DMSO-d$_6$): $\delta$ = 3.79 (s, 3H, OCH$_3$), 3.88 (s, 2H, CH$_2$), 3.90 (s, 3H, OCH$_3$), 7.44-7.46 (m, 3H, ArH), 7.89 (s, 1H, ArH), 8.01-8.05 (m, 2H, ArH), 8.19 (s, 1H, ArH), 10.18 (s, 1H, SH).

$^{13}$C NMR (DMSO-d$_6$): $\delta$ = 34.6, 55.6, 55.7, 111.2, 117.4, 127.6, 129.2 (2C), 129.8, 130.2 (2C), 133.2, 134.8, 138.1, 139.7, 140.7, 142.2, 146.7, 147.8, 184.2.

MS: m/z (%) = 102 (10), 173 (31), 348 (82), 368 (M$^+$, 40).

Analysis Calculated for C$_{20}$H$_{16}$O$_3$S$_2$: C, 65.19; H, 4.38%

Found: C, 65.35; H, 4.21%

**Experiment No. 2**

### 4.5.2 Synthesis of 3-chloro-5,6-dimethoxy-1H-indene-2-carbaldehyde (46)

Phosphorus oxychloride (2.79 mL, 0.03 mole) was added dropwise to DMF (3.85 ml, 0.05 mole) maintained at 0-5 °C under stirring over period of 0.5 h. Then, 2,3-dihydro-5,6-dimethoxyinden-1-one 50 (1.92 g, 0.01 mol) was portion wise added for 0.5 h and reaction mixture was stirred for 1 h at 0-5 °C (TLC monitoring, chloroform-methanol, 9:1 v/v). The reaction mass quenched in ice water and stirred for 1 h below 10 °C and solid obtained was filtered (temperature of water below 10 °C) washed with cold ethanol (below 10 °C) several time to gave crude compound 55. Compound 55 dissolved in ethyl acetate (20 ml, 10 °C) and hexane (8 ml, 10 °C) was added to it. The solid obtained filtered to afford analytically pure compound 55. Compound 55 stored below 25 °C in
amber color bottle as compound decomposes above 30 °C or after exposed to sunlight for more than 1 h.

Yellow amorphous solid; m.p.: decomposes above 30 °C;

Yield 1.78 g, (75%).

IR (KBr): 1230, 1641, 1720 (C=O), 2835 cm⁻¹.

¹H NMR (DMSO- d₆): δ 3.79 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.91 (s, 2H, CH₂), 7.23 (s, 1H, ArH), 8.11 (s, 1H, ArH), 12.56 (s, 1H, CHO).

MS: m/z (%) = 209 (15), 238 (M⁺, 100), 240 (M+2, 33).

Analysis Calculated for C₁₂H₁₁C₅O₃: C, 60.39; H, 4.65%

Found: C, 60.48; H, 4.49%

**Experiment No. 3**

**4.5.3 Synthesis of ethyl 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carboxylate (56)**

![Reaction Scheme](image)

To a mixture of 3-chloro-5,6-dimethoxy-1H-indene-2-carbaldehyde 55 (2.78 g, 0.01 mol) and potassium carbonate (2.76 g, 0.02 mol) in DMF (15 ml) maintained at 0-5 °C ethyl mercapto acetate (1.2 ml, 0.01 mol) was added dropwise for 1 h and stirred mixture was stirred for 3 h at 0-5 °C and for 4 h at room temperature (TLC check, chloroform: methanol, 9:1 v/v). The reaction mixture was poured into cold water and neutralized with dilute hydrochloric acid. The solid obtained was isolated by filtration under vacuum, dried and recrystallized to gave compound 56.
Recrystallized from ethanol; Colorless amorphous solid; m.p.: 180-182 °C; Yield 2.49 g, (82%).

IR (KBr): 1225, 1615, 1708 (C=O) cm⁻¹.  

¹H NMR (CDCl₃): δ = 1.46 (t, J = 6.5 Hz, 3H, CH₃), 3.81 (s, 3H, OCH₃), 3.96 (s, 2H, CH₂), 4.01 (s, 3H, OCH₃), 4.43 (q, J = 6.5 Hz, 2H, CH₂), 7.24 (s, 1H, ArH), 8.15 (s, 1H, ArH), 8.38 (s, 1H, ArH, thiophene).

MS: m/z (%) = 231 (10), 259 (40), 304 (M⁺, 100).

Analysis Calculated for C₁₆H₁₆O₄S: C, 63.14; H, 5.30%  
Found: C, 63.37; H, 5.48%

**Experiment No. 4**

**4.5.4 Synthesis of 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (57)**

Solution of ethyl 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carboxylate 56 (3.04 g, 0.01 mol) and hydrazine hydrate (99%) (1 ml, 0.02 mol) in ethanol (25 ml) was heated under reflux for 4 hours (TLC check, ethylacetate: hexane, 7:3, v/v). The reaction mixture was then allowed to cool, the solid product was collected by filtration, dried and recrystallized to gave compound 57.

Recrystallized from ethanol:DMF (8:2); Colorless fluppy solid, m.p.: 212-214 °C; Yield 2.46 g, (85%).
IR (KBr): 1223 (C-O), 1661 (C=O), 3290, 3267, 3190 (NH/NH2) cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 3.78\) (s, 3H, OCH\(_3\)), 3.84 (s, 2H, CH\(_2\)), 3.89 (s, 3H, OCH\(_3\)), 5.63 (bs, 2H, NH\(_2\)), 7.22 (s, 1H, ArH), 8.11 (s, 1H, ArH), 8.37 (s, 1H, ArH, thiophene), 10.42 (bs, 1H, NH).

MS: m/z (%) = 231 (25), 269 (70), 290 (M\(^+\), 100).

Analysis Calculated for C\(_{14}\)H\(_{14}\)N\(_2\)O\(_3\)S: C, 57.92; H, 4.86; N, 9.65%

Found: C, 57.85; H, 4.90; N, 9.61%

**Experiment No. 5**

4.5.5 Synthesis of \(N'\)-acetyl-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (58)

\[
\begin{align*}
\text{57} & \quad \overset{\text{Ac}_2\text{O}}{\text{50-60 °C,} \quad 10 \text{ h}} \quad \text{58} \\
\text{H}_2\text{CO} & \quad \text{O} \quad \text{NHNH}_2 \\
\text{H}_2\text{CO} & \quad \text{S} \\
\text{H}_2\text{CO} & \quad \text{O} \\
\text{H}_2\text{CO} & \quad \text{NHNH}_2 \quad \text{COCH}_3 \\
\end{align*}
\]

A mixture of compound 57 (2.90 g, 0.01 mol) and acetic anhydride (10 mL) was stirred at 50-60 °C for 10 hours (TLC check, ethyleacetate: hexane, 7:3 v/v). Reaction mixture was cooled, solid separated was filtered, washed with cold ethanol and recrystallized to gave compound 58.

Recrystallized from ethanol:DMF (8:2); yellow amorphous solid; m.p.: 284-286 °C;

Yield 2.95 g, (89%).

IR (KBr): 1265 (C-O), 1690 (C=O), 1682 (C=O), 3238, 3250 (NH) cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 2.15\) (s, 3H, CH\(_3\)), 3.82 (s, 3H, OCH\(_3\)), 3.85 (s, 2H, CH\(_2\)), 3.88 (s, 3H, OCH\(_3\)), 7.25 (s, 1H, ArH), 8.19 (s, 1H, ArH), 8.38 (s, 1H, ArH, thiophene), 8.37 (s, 1H, ArH, thiophene), 10.42 (bs, 1H, NH).
11.60 (s, 1H, NH), 12.01 (s, 1H, NH).

$^{13}$C NMR (DMSO-$d_6$): $\delta$ 24.1, 34.4, 55.6, 55.7, 112.1, 114.4, 131.8, 130.5, 137.3, 138.2, 136.9, 141.8, 146.3, 147.6, 161.1, 163.

MS: m/z (%) = 228 (19), 286 (57), 317 (79), 332 (M$^+$, 100).

Analysis Calculated for C$_{16}$H$_{16}$N$_2$O$_4$S: C, 57.82; H, 4.85; N, 8.43%

Found: C, 58.05; H, 4.71; N, 8.40%

**Experiment No. 6**

4.5.6 Synthesis of (E)-N'-(arylidene)-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide 60(a-d)

Equimolar quantities of 6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide 57 (2.90 g, 0.01 mol) and selected aromatic aldehyde 59a-d (0.01 mol) in presence of few drop of glacial acetic acid in ethanol (10 ml) was refluxed for 12-15 hours (TLC check chloroform: methanol, 9:1 v/v). The reaction mixture on cooling was poured in cold water (50 ml). The precipitated solid was filtered, dried and recrystallized from appropriate solvent to gave compounds 60a-d.
4.5.6.1 (E)-N'-{(2,3,4-Trimethoxybenzylidene)-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (60a)

Recrystallized from ethanol:DMF (8:2); Colorless amorphous solid; m.p.: 235-237 °C; Yield 4.02 g, (86%).

IR (KBr): 1130, 1220 (C=O), 1680 (C=O), 2954, 3272 (NH) cm⁻¹.

¹H NMR (DMSO-d₆): δ = 3.77 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.89 (s, 2H, CH₂), 3.94 (s, 3H, OCH₃), 6.91 (d, J = 8.1 Hz, 1H, ArH), 7.20 (s, 1H, ArH), 7.82 (d, J = 8.1 Hz, 1H, ArH), 8.09 (s, 1H, ArH), 8.32 (s, 1H, ArH, thiophene), 8.42 (s, 1H, N=CH), 11.55 (s, 1H, NH).

MS: m/z (%) = 209 (42), 231 (12), 259 (88), 468 (M⁺, 100).

Analysis Calculated for C₂₄H₂₄N₂O₆S: C, 61.52; H, 5.16; N, 5.98%

Found: C, 61.68; H, 5.10; N, 6.17%

4.5.6.1 (E)-N’{(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (60b)

Recrystallized from ethanol:DMF (8:2); Colorless amorphous solid; m.p.: 249-251 °C; Yield 3.67 g, (84%).

IR (KBr): 1224 (C=O), 1612, 1685 (C=O), 2929, 3286 (NH) cm⁻¹;

¹H NMR (DMSO-d₆): δ = 3.77 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 7.02 (d, J = 8.1 Hz, 1H, ArH), 7.22 (s, 1H, ArH), 7.37 (d, J = 8.1 Hz, 1H, ArH), 7.66 (s, 1H, ArH), 8.10 (s, 1H, ArH), 8.34 (s, 1H, ArH, thiophene), 8.51 (s, 1H, N=CH), 11.63 (bs, 1H, NH).

MS: m/z (%) = 179 (39), 438 (M⁺, 100).

Analysis Calculated for C₂₃H₂₂N₂O₅S: C, 63.00; H, 5.06; N, 6.39%

Found: C, 63.13; H, 5.11; N, 6.29%
4.5.6.2 (E)-N’-(4-Methylbenzylidene)-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (60c)

Recrystallized from ethanol: DMF (8:2); Colorless amorphous solid; m.p.: 220-222 °C;
Yield 3.13 g, (80%).
IR (KBr): 1208 (C=O), 1597, 1687 (C=O), 2922, 3278 (NH) cm⁻¹.
¹H NMR (DMSO-d₆): δ = 2.15 (s, 3H, CH₃), 3.76 (s, 3H, OCH₃), 3.88 (s, 2H, CH₂), 3.92
(s, 3H, OCH₃), 7.23 (s, 1H, ArH), 7.27 (d, J = 8.2 Hz, 2H, ArH), 7.77 (d, J = 8.2 Hz, 2H,
ArH), 8.11 (s, 1H, ArH), 8.38 (s, 1H, ArH, thiophene), 8.59 (s, 1H, N=CH), 11.65 (s, 1H,
NH).
MS: m/z (%) = 91 (8), 133 (62), 259 (28), 392 (M⁺, 100).
Analysis Calculated for C₂₂H₂₀N₂O₃S: C, 67.33; H, 5.14; N, 7.14%
Found: C, 67.30; H, 5.17; N, 7.09%

4.5.6.4 (E)-N’-(3-Nitrobenzylidene)-6,7-dimethoxy-4H-indeno[1,2-b]thiophene-2-carbohydrazide (60d)

Recrystallized from ethanol: DMF (8:2); Colorless amorphous solid; m.p.: 278-280 °C;
Yield 3.21 g, (76%).
IR (KBr): 1278 (C=O), 1310, 1530 (NO₂), 1695 (C=O), 2958, 3310 (NH) cm⁻¹.
¹H NMR (DMSO-d₆): δ = 3.77 (s, 3H, OCH₃), 3.92 (s, 2H, OCH₂), 3.94 (s, 3H, OCH₃),
7.26 (s, 1H, ArH), 7.76 (m, 1H, ArH), 8.13 (s, 1H, ArH), 8.25 (d, J = 7.5 Hz, 1H, ArH),
8.42 (d, J = 7.2 Hz, 1H, ArH), 8.40 (s, 1H, ArH, thiophene), 8.62 (s, 1H, ArH), 8.73 (s,
1H, N=CH), 12.31 (bs, 1H, NH).
MS: m/z (%) = 122 (24), 164 (39), 231 (9), 423 (M⁺, 100).
Analysis Calculated for C₂₁H₁₉N₃O₅S: C, 59.57; H, 4.05; N, 9.92%
Found: C, 59.40; H, 4.21; N, 9.81%
Experiment No. 7

4.5.7 Synthesis of (E)-1-(1,2-dihydro-5,6-dimethoxyinden-3-ylidene)-2-phenylhydrazine (61):

A solution of 2,3-dihydro-5,6-dimethoxyinden-1-one 50 (1.92 g, 0.01 mol) and phenyl hydrazine (2.22 mL, 0.01 mol) in acetic acid (10 mL) was stirred at room temperature for 8 h (TLC check, chloroform: methanol, 9:1 v/v). The solid obtained was filtered, washed with cold methanol and recrystallized to gave compound 61.

Recrystallized from ethanol; Yellow amorphous solid, m.p.: 168-170 °C;

Yield 2.59 g, (92%).

IR (KBr): 1220 (C-O), 1610, 1622 (C=N), 3230 (NH) cm⁻¹.

¹H NMR (CDCl₃): δ = 2.70 (t, J = 6.2 Hz, 2H, CH₂), 3.04 (t, J = 6.2 Hz, 2H, CH₂), 3.87 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 6.74 (s, 1H, ArH), 6.82 (t, J = 8.2 Hz, 1H, ArH), 6.91 (bs, 1H, NH), 7.12-7.15 (d, J = 7.8 Hz, 2H, ArH), 7.23-7.29 (m, 3H, ArH).

MS: m/z (%) = 106 (30), 178 (10), 282 (M⁺, 100).

Analysis Calculated for C₁₇H₁₈N₂O₂: C, 72.32; H, 6.43; N, 9.92%

Found: C, 72.51; H, 6.21; N, 10.09%
**Experiment No. 8**

4.5.8 Synthesis of 5,10-dihydro-2,3-dimethoxyindeno[1,2-b]indole (62):

\[
\begin{array}{c}
\text{H}_3\text{CO} & \text{N'NH} & \text{H}_3\text{CO} \\
\text{61} & \text{TFA, AcOH} & \text{reflux, 3h} \rightarrow \\
\text{H}_3\text{CO} & \text{62} & \text{89%}
\end{array}
\]

(E)-1-(1,2-dihydro-5,6-dimethoxyinden-3-ylidene)-2-phenylhydrazine 61 (2.82 g, 0.01 mol) and catalytic amount of trifluoro acetic acid in acetic acid was refluxed for 3 h (TLC check, chloroform: methanol, 9:1 v/v). The solution was cooled, solid obtained was filtered off and recrystallized to gave compound 62.

Recrystallized from ethanol:DMF (80:20); Colourless solid, m.p.: 230-232 °C (Lit. m.p.: 232-233 [35]);

Yield 2.35 g, (89%).

IR (KBr): 1226 (C-O), 1620, 2933, 3380 (NH) cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 3.58\) (s, 2H, CH\(_2\)), 3.80 (s, 3H, OCH\(_3\)), 3.84 (s, 3H, OCH\(_3\)), 7.0-7.03 (m, 2H, ArH), 7.22-7.24 (m, 2H, ArH), 7.41 (d, \(J = 7.5\) Hz, 1H, ArH), 7.49 (d, \(J = 7.49\) Hz, 1H, ArH), 11.40 (s, 1H, NH).

MS: m/z (%) = 174 (22), 189 (55), 265 (M\(^+\), 100).

Analysis Calculated for C\(_{17}\)H\(_{15}\)NO\(_2\): C, 76.96; H, 5.70; N, 5.28%

Found: C, 76.75; H, 5.86; N, 5.20%
4.5.9 Synthesis of 2,3-dihydro-5,6-dimethoxyinden-1-one oxime (63)

A mixture of 2,3-dihydro-5,6-dimethoxyinden-1-one 50 (1.92 g, 0.01 mol) and hydroxyl amine hydrochloride (0.69 g, 0.01 mol) in pyridine (10 mL) was stirred at 75 °C for 5 h (TLC check, chloroform: methanol, 9:1 v/v). The solution was cooled, poured into cold water and neutralized with dilute hydrochloric acid. The solid obtained was isolated by filtration under vacuum and recrystallized to gave compound 63.

Recrystallized from ethanol; pale yellow solid, m.p.: 180-182 °C;
Yield 1.87 g, (90%).

IR (KBr): 1215 (C-0), 1613 (C=C arom.), 1622 (C=N), 3178 (OH) cm⁻¹.

¹H NMR (CDCl₃): δ = 2.70 (t, J = 6.5 Hz, 2H, CH₂), 3.21 (t, J = 6.5 Hz, 2H, CH₂), 3.98 (s, 6H, 2×OCH₃), 6.8 (s, 1H, ArH), 7.2 (s, 1H, ArH), 8.87 (bs, OH).

MS: m/z (%) = 160 (5), 176 (11), 191 (82), 207 (M⁺, 100).

Analysis Calculated for C₁₁H₁₃NO₃: C, 63.76; H, 6.32; N, 6.76%
Found: C, 63.69; H, 6.48; N, 6.64%
**Experiment No. 10**

**4.5.10 Synthesis of 3,4-dihydro-6,7-dimethoxyisoquinolin-1(2H)-one (64) and 3,4-dihydro-6,7-dimethoxyquinolin-2(1H)-one (65)**

A solution of oxime 63 (2.07 g, 0.01 mol) and thionyl chloride (1.5 mL, 0.02 mol) in dry ether (15 mL) was stirred at room temperature for 5 h (TLC check, chloroform: methanol, 9:1 v/v). The excess of solvent was removed under reduced pressure. The oily residue obtained was added into cold water and stirred overnight. The solid obtained was filtered, washed with cold methanol and recrystallized from ethyl acetate afforded compound 65 as white solid in 40% yield. After recrystallization solvent from filtrate was removed under reduced pressure and solid obtained was purified by column chromatography eluting with chloroform: methanol (9:1) gave 65 and 64 in 5% and 35% yield respectively.

**3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-one (64)**

Colorless solid, m.p.: 173-175 °C (lit. m.p.: 174-175 °C [36, 51])

Yield 0.72 g, (35%).

IR (KBr): 1230 (C-O), 1625 (C=C arom.), 1664 (C=O, amide), 3240 (NH) cm$^{-1}$.

$^1$H NMR (CDCl$_3$) : $\delta = 2.52$ (t, $J = 6.5$ Hz, 2H, CH$_2$), 3.48 (t, $J = 6.5$ Hz, 2H, CH$_2$), 3.91 (s, 3H, OCH$_3$), 3.93 (s, 3H, OCH$_3$), 6.65 (bs, 1H, NH), 6.70 (s, 1H, ArH), 7.65 (s, 1H, ArH).

MS: m/z (%) = 179 (53), 207 (M$^+$, 100).
Analysis Calculated for C_{11}H_{13}NO_3: C, 63.76; H, 6.32; N, 6.76%

Found: C, 63.72; H, 6.40; N, 6.65%

3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-one (65)

Colorless solid, m.p.: 135-137 °C (lit. m.p.: 130-136 °C [36]).

yield 0.93 g, (45%).

IR (KBr): 1220 (C-O), 1620 (C=C arom.), 1680 (C=O, amide), 3260 (NH) cm^{−1}.

^{1}H NMR (CDCl_{3}): δ = 2.93 (t, J = 6.3 Hz, 2H, CH_{2}), 3.56 (t, J = 6.3 Hz, 2H, CH_{2}), 3.93 (s, 6H, 2 × OCH_{3}), 6.5 (bs, 1H, NH), 6.68 (s, 1H, ArH), 7.57 (s, 1H, ArH).

MS: m/z (%) = 74 (10), 102 (31), 144 (19), 206 (41), 207 (M^+ 100).

Analysis Calculated for C_{11}H_{13}NO_3: C, 63.76; H, 6.32; N, 6.76%

Found: C, 63.89; H, 6.51; N, 6.62%

Experiment No. 11

4.5.11 Synthesis of 2,3-dihydro-5,6-dihydroxyinden-1-one (66)

![Reaction scheme](image)

Compound 50 (1.92 g, 0.01 mol) was stirred in conc. H_{2}SO_{4} (15 mL) at 140 °C for 40 min (TLC check, chloroform: methanol, 9:1 v/v). The reaction mass was then added to crushed ice (150 mL) and neutralized with saturated NaHCO_{3} (20 mL). The solid separated was filtered, washed with cold ethanol and dried to afford analytically pure compound 66.

Colourless solid, m.p.: 109-111 °C (lit. m.p.: 107-109 °C [52, 53, 54]).
Yield 1.34 g, (82%).

IR (KBr): 1625, 1695 (C=O, ketone), 3340 (OH) cm⁻¹.

¹H NMR (DMSO-d₆): δ = 2.51 (t, J = 6.2 Hz, 2H, CH₂), 2.93 (t, J = 6.2 Hz, 2H, CH₂), 6.91 (s, 1H, ArH), 7.04 (s, 1H, ArH), 9.12 (s, 1H, OH), 9.40 (s, 1H, OH).

MS: m/z (%) = 97 (15), 112 (12), 161 (39), 164 (M⁺, 100).

Analysis Calculated for C₉H₈O₃: C, 65.85; H, 4.91%

Found: C, 65.63; H, 5.11%

4.6 References


[29] Graupner, P. R.; Mahon, M. F.; Ninan, A.; Sainsbury, M.; Shertzer, H. G.


Léonce, S.; Pierré, A.; Boussard, M. F.; Rousseau, A.; Wierzbicki, M.; Bailly, C.

[32] Peng, W.; Świtalska, M.; Wang, L.; Mei, Z.; Edazawa, Y.; Pang, C.; El-


[38] Sable, P. N.; Ganguly, S.; Chaudhari, P. D. *Chin. Chem. Lett.* 2014 DOI: 10.1016/j.cclet.2014.03.044


<table>
<thead>
<tr>
<th>Reference</th>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
<th>Volume</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>[52]</td>
<td>Choi, T.; Ma, E.</td>
<td>Molecules</td>
<td>2007</td>
<td>12</td>
<td>74</td>
</tr>
</tbody>
</table>
LIST OF PUBLICATIONS:


4) Syntheses of New Unsymmetrical 2,5-Disubstituted-1,3,4-oxadiazoles and 1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazoles Bearing Thieno[2,3-c]pyrazolo Moiety, S. P. Patil, S. B. Kanawade, D. C. Bhavsar, P. S. Nikam, S. A. Gangurde and R. B. Toche *J. Heterocycl. Chem.*, 51, 368-373, 2014.
