4.1. Biological importance of indoles

Indole nucleus is found in many medicinal compounds and hence is considered to be a very important heterocyclic moiety [1]. The protein farnesyltransferase (PFTase) inhibitors kurasoin B, isolated from the fermentation broth of the soil fungus *Paecilomyces sp.* FO-36841 (Figure 4.1), is found to exhibit anticancer activity [2]. Among the serotonin like compounds studied, the discovery of the anti migraine drug sumatriptan stimulated the development of other 5-HT\textsubscript{1D} receptor agonists [3], and several serotonin like compounds such as sumatriptan [4], avitriptan [5], almotriptan [6] and rizatriptan [7] are well known antimigraine and anti-inflammatory drugs [8]. Echinosulfone A [1e, 9] a sulfone from the marine sponge, *Echinodictyum* is having a bisindole core and is found to exhibit antibacterial and antiparasitic properties. Indole and its derivatives possess a wide spectrum of biological activities including anti-inflammatory [10], anti-microbial [11], anti-bacterial [12], anticonvulsant [13], cardiovascular [14] and HIV-integrase inhibitor [15] behaviour.

![Figure 4.1. Structures of indole drugs](image)

4.2. Fischer Indole synthesis

The Fischer indole synthesis, first described by Emil Fischer in 1883, has prevailed as the flagship indolization method for more than a century [16]. The Fischer reaction often provides a simple and efficient method for the transformation of enolizable $N$-arylhdrozones into indoles. In many cases, the indolization reaction is carried out by simply heating the ketone or aldehyde and the arylhydrazone with appropriate acid catalyst without isolation of the hydrazone intermediate. Advantages of the Fischer
reaction include the acceptance of a wide range of compatible functional groups around the aromatic ring and lack of requirement for a functional group to form the new C-C and C-N bonds. Few examples of the Fischer indole reactions for the construction of indole derivatives are described below.

Nenajdenko et al. [17] described the synthesis of indolylalkylamides 3 from the indolization of arylhydrazines 1 with N-acylketones 2 in acetic acid with gaseous hydrogen chloride under reflux condition.

\[
\begin{align*}
\text{R}^1 & = \text{C}_6\text{H}_5, 4-\text{MeC}_6\text{H}_4, 2,4-(\text{MeO})_2\text{C}_6\text{H}_3; \text{R}^1 & = \text{H}, 5-\text{F}, 5-\text{Cl}, 5-\text{Br}, 5-\text{OMe}
\end{align*}
\]

Smith et al. [18] reported the synthesis of chloroindole 6 by adding the solution of hydrazone 5 to a two-phase mixture of 6 M phosphoric acid and butyl acetate at 105 °C. The hydrazone 5 was synthesized from the reaction of hydrazine 4 with 5-chlorovaleraldehyde in NEt₃.

Liu et al. [19] reported the synthesis of 2-(2-bromophenyl)-indole 9 via the Fischer indole reaction of phenylhydrazine hydrochloride 7 with 2-bromoacetophenone 8 in polyphosphoric acid under thermal condition.

Jiang et al. [20] described a p-toluenesulphonic acid promoted one-pot synthesis of multi-substituted 2-trifluoromethyl indole derivatives 13. For instance, 2-
trifluoromethyl-3-phenylindoles could be obtained from the reaction of 1,1,1-trifluoro-3-phenylacetone 10 with arylhydrazines 11 via Fischer indole synthesis.

\[
\begin{align*}
10 & \quad + \quad 11 \\
\text{F}_{3}C-\text{CH}=\text{CH} & \quad + \quad \text{Ph}-\text{NHNNH}_{2} \\
\text{F}_{3}C-\text{CH}=\text{CH} & \quad + \quad \text{Ph}-\text{NHNNH}_{2} \\
\text{F}_{3}C-\text{CH}=\text{CH} & \quad + \quad \text{Ph}-\text{NHNNH}_{2} \\
\text{F}_{3}C-\text{CH}=\text{CH} & \quad + \quad \text{Ph}-\text{NHNNH}_{2}
\end{align*}
\]

\[
R = \text{Ph}, \text{CO}_{2}\text{Me}; \quad R^{1} = \text{H}, \text{Cl}, \text{F}, \text{OMe}, \text{NO}_{2}
\]

Bratulescu et al. [21] reported the synthesis of indole derivatives 16 from the reaction of arylhydrazines 14 with pyruvic acid 15 under microwave irradiation using zinc chloride and phosphorous pentachloride via the Fischer indole synthesis-decarboxylation.

\[
\begin{align*}
14 & \quad + \quad 15 \\
\text{PhNHNNH}_{2} & \quad + \quad \text{CO}_{2}\text{H} \\
\text{PhNHNNH}_{2} & \quad + \quad \text{CO}_{2}\text{H} \\
\text{PhNHNNH}_{2} & \quad + \quad \text{CO}_{2}\text{H} \\
\text{PhNHNNH}_{2} & \quad + \quad \text{CO}_{2}\text{H}
\end{align*}
\]

\[
R^{1} = \text{H}, \text{OMe}; R^{2} = \text{H}, \text{NO}_{2}, \text{Br}; R^{3} = \text{H}, \text{OMe}; R^{4} = \text{H}, \text{Me}, \text{NO}_{2}, \text{Cl}
\]

Lim et al. [22] described the synthesis of indole derivatives 19 from the Fischer indole reaction of N-Boc-arylhydrazines 17 and ketones 18 in the presence of p-toluenesulphonic acid in ethanol at reflux condition.

\[
\begin{align*}
17 & \quad + \quad 18 \\
\text{NBOc} & \quad + \quad \text{CH}_{3}\text{C}O_{2}\text{H} \\
\text{NBOc} & \quad + \quad \text{CH}_{3}\text{C}O_{2}\text{H} \\
\text{NBOc} & \quad + \quad \text{CH}_{3}\text{C}O_{2}\text{H} \\
\text{NBOc} & \quad + \quad \text{CH}_{3}\text{C}O_{2}\text{H}
\end{align*}
\]

\[
R^{1} = \text{H}, \text{OMe}, \text{Ph}, \text{alkyl}, \text{COPh}, \text{CO}_{2}\text{Et}; R^{2} = \text{Me}, \text{Aryl}; R^{3} = \text{Et}, \text{Bu}, \text{CH}_{2}\text{CO}_{2}\text{H}
\]

Acton et al. [23] reported the synthesis of 2-methylindole derivatives 22 from the Fischer indolization of arylhydrazine hydrochlorides 20 with ketone 21 in the presence of phosphoric acid in toluene under reflux condition.

\[
\begin{align*}
20 & \quad + \quad 21 \\
\text{PhNHNNH}_{2}\text{HCl} & \quad + \quad \text{CO}_{2}\text{S}\text{HCOOH} \\
\text{PhNHNNH}_{2}\text{HCl} & \quad + \quad \text{CO}_{2}\text{S}\text{HCOOH} \\
\text{PhNHNNH}_{2}\text{HCl} & \quad + \quad \text{CO}_{2}\text{S}\text{HCOOH} \\
\text{PhNHNNH}_{2}\text{HCl} & \quad + \quad \text{CO}_{2}\text{S}\text{HCOOH}
\end{align*}
\]

\[
R = \text{OMe}, \text{OCF}_{3}, \text{i-Pr}, \text{F}, \text{Pr}, \text{OPh}
\]
Lipinska et al. [24] reported triethylene glycol with catalytic quantity of zinc chloride (ZnCl₂/TEG) as a new and efficient reaction medium for Fischer synthesis, leading to indoles 25. Transformation of the 3-acetyl-1-methylthiocycloalka[c]pyridine phenylhydrazones 24 into 2-(2-pyridyl)indoles 25 is carried out under controlled microwave irradiation in dry zinc chloride solution in TEG.

Jeanty et al. [25] described Fischer indole cyclization for the synthesis of 4-azaindoles 28 and 6-azaindoles 29, bearing an electron-donating group on the starting pyridylhydrazines 26 with acyclic and cyclic ketones 27 in presence of aqueous sulphuric acid at 100 °C.

Karthikeyan et al. [26] reported the synthesis of 2-aryl-3,4-dihydro-2H-thieno[3,2-b]indoles 32 via the Fischer indolization of 5-aryldihydro-3(2H)-thiophenones 31 with phenylhydrazine hydrochlorides 30 in ethanol under microwave irradiation condition.

Ar = C₆H₅, 4-ClC₆H₄, 4-MeC₆H₄, 2,4-Cl₂C₆H₄, 3-NO₂C₆H₄, 2-BrC₆H₄, 2-ClC₆H₄, 3-FC₆H₄; X = H, Cl, F
4.3. Applications of Fischer indole synthesis

Watson et al. [27] reported the large-scale preparation of MDL-103371 \( 38 \), an \( N \)-methyl-\( D \)-aspartate (NMDA)-type glycine receptor antagonist for the potential treatment of stroke, by a three-step synthesis based on Fischer indolization chemistry. The reaction of 3,5-dichlorophenylhydrazine hydrochloride \( 33 \) with ethyl pyruvate \( 34 \) in ethanol afforded the hydrazone \( 35 \) as an \( E/Z \) mixture. Fischer cyclization using polyphosphoric acid in toluene at 95-100 °C provided the indole ethylcarboxylate \( 36 \) as a crystalline solid. Finally, Vilsmeier-Haack formylation gave kilogram quantities of indole aldehyde \( 37 \), which is subsequently converted in six steps to the \( E \)-ene-acid \( 38 \) in 49% overall yield.

\[
\begin{align*}
\text{Cl} & \quad \text{NH}_2 \\
\text{Cl} & \quad \text{NH}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{COOEt} \\
\text{Cl} & \quad \text{COOEt} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{NH} & \quad \text{COOEt} \\
\text{Cl} & \quad \text{NH} & \quad \text{COOEt} \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{H} & \quad \text{COOEt} \\
\text{N} & \quad \text{H} & \quad \text{COOEt} \\
\end{align*}
\]

Duval et al. [28] reported the synthesis of naltrindole \( 41 \) and their analogs, which are used for \( \delta \)-opioid receptor binding assays \textit{in vitro} [29] using the Fischer synthesis under mild acidic and purely aqueous conditions.

Andersen et al. [30] reported the stereoselective synthesis of a drug, AMG 076, which has been identified as a potent MCHr1 (Melanin-concentrating hormone receptor 1) antagonist for the treatment of obesity, using Fischer indolization as a key step. The
Fischer-indole reaction between octahydroisoquinolinone 43 and 4-trifluoromethyl phenylhydrazine 42 was performed in dioxane at 70 °C with sulfuric acid, leading to indole 44. Two reductive amination strategies employing either aldehyde 45 or lactol 46 led to the synthesis of AMG 076 (47).

An elegant asymmetric synthesis of the strychnos alkaloid Tubifolidine 51 relied on the chiral indole derivative 49 as a key intermediate to set the remaining asymmetric centers. Indole 48 was assembled using a highly regioselective Fischer indolization between ketone 48, available via asymmetric Michael reaction, and phenylhydrazine hydrochloride in acetic acid at 80 °C. Decarboxylation gave indole 49 in very high yield and enantiomeric purity. Indole 49 was successfully converted to Tubifolidine 50 via a multistep synthesis with complete diastereocntrol [31].
4.4. Biological importance of bisindoles

Bisindole alkaloids have received considerable attention for several years because of their broad range of biological properties [32]. For example, bisindole alkaloid hyrtiosin B 52 has been shown to possess weak cytotoxic activity against human epidermoid carcinoma KB cells in vitro [33]. Marine sponge topsentins 53 and its dihydro analogs have received considerable attention because of their properties such as antitumor, antiviral, and anti-inflammatory activities [34]. Nortopsentins A-C, having 2,4-bis(3'-indolyl)-imidazole 54 moieties, exhibit in vitro cytotoxicity against P388 cells [35]. Hamacanthin B, having a characteristic 3,5-bis(3'-indolyl)pyrazinone 55 skeleton, exhibits cytotoxic activities against a wide range of human tumor cell lines with GI50 values at micromolar concentration [36]. Moreover, a very interesting group of these bisindole derivatives incorporating a five or six-membered heterocyclic ring between the two indole rings, such as 2,4-bis(3'-indolyl)pyrimidine 56 [37] and 2,5-bis(3'-indolyl)thiophene 57 [38], demonstrate strong inhibitory effects against a variety of tumor cell lines, including leukemia, ovarian, colon, renal and breast cancer (Figure 4.2).

![Figure 4.2. Structures of some bisindole alkaloids](image)

4.5. Synthesis of bisindoles via the Fischer indole synthesis

Alford et al. [39] reported the synthesis of both symmetrical and unsymmetrical 2,3'-bisindoles 60 in good to excellent yields via the Fischer indole synthesis of 3-acetyl-
1-(phenylsulfonyl)indole 59 with phenylhydrazine hydrochloride 58 by a two step process.

Talaz et al. [40] described the Fisher indolization reaction of cyclooctane-diones 61 with phenylhydrazine using different catalysts viz., acetic acid-sulphuric acid, acetic acid-zinc chloride, acetic acid-TFA and ethanol-zinc chloride leading to the construction of the three structural isomers of bisindole 62-64 and monoindole 65.
4.6. Synthesis of di(2-aryl-1H-3-indolyl)sulfides 70 and 1-aryl-2-[(2-aryl-1H-3-indolyl)sulfanyl]-1-ethanones 71 - The present work

In the present investigation, we report here a very simple and highly selective method for the synthesis of di(2-aryl-1H-3-indolyl) sulfides 70 and 1-aryl-2-[(2-aryl-1H-3-indolyl)sulfanyl]-1-ethanones 71 by the reaction of 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanones with phenylhydrazine hydrochloride in ethanol and THF respectively (Scheme 4.1).

A mixture of 2-[(2-oxo-2-phenylethyl)sulfanyl]-1-phenyl-1-ethanone 66a (1 mmol) and phenylhydrazine hydrochloride 67 (2.5 mmol) when refluxed in ethanol (7 ml) gave di(2-phenyl-1H-3-indolyl) sulphide (70a) in 85% yield (Table 4.1). It is interesting to note that whatever be the mole ratio between 2-[(2-oxo-2-phenylethyl)sulfanyl]-1-phenyl-1-ethanone 66a and phenylhydrazine hydrochloride 67 (1:1; 1:1.5; 1:2, 1:2.5), only the diheteroaryl sulphide and no monoindole was obtained. The best yield was noticed with 1:2.5 ratio (Table 4.1, scheme 4.2). Under this optimized conditions for the generation of 70, various substituted diketones 66 were selected to react with phenylhydrazine hydrochloride 67 to give different di(2-aryl-1H-3-indolyl) sulfides 70 in high yields (76-85%) within three hours (Table 4.2). The reaction proceeded efficiently, tolerating both electron donating and withdrawing substituents on the aromatic ring. When the reaction was performed in methanol, 2-propanol and ethylene glycol, the yield of 70a decreased considerably (Table 4.1). When solvents like toluene, chloroform, dichloromethane and DMF were used, either
a viscous mass with no recognisable products was obtained or the starting materials were recovered unchanged. A notable observation is that the reaction has led to a mixture of \(70a\) and \(71a\), when investigated in acetonitrile (Table 4.1). Interestingly, when this reaction between \(66a\) and \(67\) was performed in THF in different mole ratios (1:1, 1:1.5, 1:2 and 1:2.5), only the monoindole, 1-phenyl-2-[(2-phenyl-1H-3-indolyl)sulfanyl]-1-ethanone \(71a\) was obtained in good yield (Table 4.1).

**Table 4.1. Reaction of \(66a\) with \(67\) under different conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Mole ratio, (1a : 2)</th>
<th>Time (h)</th>
<th>Yield of (70a) (%) (^a)</th>
<th>Yield of (71a) (%) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>1:2.5</td>
<td>3</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>1:2.0</td>
<td>3</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>1:1.5</td>
<td>3.5</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>1:2.5</td>
<td>3</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2-Propanol</td>
<td>1:2.5</td>
<td>3</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ethylene glycol</td>
<td>1:2.5</td>
<td>3</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>1:2.5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>1:2.5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>CH(_3)CN</td>
<td>1:2.5</td>
<td>5</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>CH(_2)Cl(_2)</td>
<td>1:2.5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>1:2.5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>1:1.0</td>
<td>3</td>
<td>0</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
<td>THF</td>
<td>1:1.5</td>
<td>3</td>
<td>0</td>
<td>82</td>
</tr>
<tr>
<td>14</td>
<td>THF</td>
<td>1:2.0</td>
<td>3</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>15</td>
<td>THF</td>
<td>1:2.5</td>
<td>3.5</td>
<td>0</td>
<td>82</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield after purification by column chromatography

**Scheme 4.2 Synthesis of mono- and bisindoles**

The cleanest conversion and highest yield of \(71a\) was achieved when 1.5 equiv. of the phenylhydrazine hydrochloride for 1.0 equivalent of 2-[(2-oxo-2-
phenylethyl)sulfanyl]-1-phenyl-1-ethanone 66a was used. This protocol for 71a was used to generate a range of monoindoles 71a-f in 78-85% isolated yield (Table 4.2).

### Table 4.2. Reaction of 66 with 67 in ethanol / THF under optimized conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>in EtOH</th>
<th>in THF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield of 70 (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>a</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>b</td>
<td>p-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>c</td>
<td>p-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>d</td>
<td>p-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1.5</td>
<td>79</td>
</tr>
<tr>
<td>e</td>
<td>p-PhC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>2</td>
<td>81</td>
</tr>
<tr>
<td>f</td>
<td>2-Naphthyl</td>
<td>1.5</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup>isolated after recrystallisation

The product selectivity of the reaction has been further explored by the experiments depicted in Scheme 4.3. When diphenacyl sulfide 66a was allowed to react with phenylhydrazine in ethanol at reflux condition for 30 minutes, it afforded bis(2-phenyl-2-(2-phenylhydrazono)ethyl)sulfane 69a. Bishydrazone 69a subsequently reacted with concentrated hydrochloric acid in ethanol yielding (82%) the bisindole 70a. However, when 69a was treated with hydrochloric acid in THF medium, only the monoindole 71a was obtained in 85% yield. It can be noticed that (i) the cyclization has occurred at one end and (ii) the phenylhydrazo group has got hydrolyzed to ketone at the other end (Scheme 4.3). In a separate experiment, 71 was allowed to react with phenylhydrazine in ethanol, which yielded 73. The second indolization of monoindole 71 can be effected in a facile manner with phenylhydrazine hydrochloride in ethanol medium (Table 4.3).

### Table 4.3. Reaction of 71 with PhNHNH<sub>2</sub>/ PhNHNH<sub>2</sub>HCl in ethanol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield of 70 with PhNHNH&lt;sub&gt;2&lt;/sub&gt;HCl (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield of 73 with PhNHNH&lt;sub&gt;2&lt;/sub&gt; (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>p-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>b</td>
<td>p-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>c</td>
<td>p-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>83</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after purification by recrystallisation from ethylacetate

It is again interesting that the reaction of 66 with phenylhydrazine in THF yielded only the mono hydrazone 72, (Table 4.4) which on further treatment with another mole of phenylhydrazine in ethanol, provided the bishydrazone 69. But in THF
medium, even after prolonged heating for 8 hours, the mono hydrazone 72 did not react with another mole of phenylhydrazine (Scheme 4.3).

\[ \text{PhNHNH}_2 \text{ EtOH/THF} \]

Scheme 4.3

Table 4.4 Reaction of 66 with phenylhydrazine in ethanol/THF

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield of 69 in EtOH (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield of 72 in THF (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>86</td>
<td>89</td>
</tr>
<tr>
<td>b</td>
<td>p-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>c</td>
<td>p-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>d</td>
<td>p-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>e</td>
<td>p-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>86</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after purification by recrystallisation from ethanol

It is noted that simple 1,5-diketone 74, on reaction with phenylhydrazine in ethanol resulted in mono and bisindole derivatives depending on the proportion of reagents [41]. In the present investigation, the reaction of 74 with phenylhydrazine was attempted in THF medium. But the reaction has not given any desirable products (Scheme 4.4). Obviously the selectivity is more pronounced only in diaroyl sulphides, not in other 1,5-diketones.
The striking difference between the protic and aprotic solvents in dictating the course of the above reaction makes us believe that the reason for the observed selectivity is related to hydrogen bonding, assisted by sulfur. Probably in THF, the molecules prefer to have intermolecular hydrogen bonding between the carbonyl of one unit and the NH of the other, thus explaining the preferential formation of 71 or 72. Hence in THF, the reactivity of carbonyl is reduced/prevented. In ethanol, this intermolecular hydrogen bonding may not be there, as ethanol can solvate the molecules. Thus in ethanol, the second carbonyl is as reactive as the first one as evident from the formation of 69, 70 and 73.

The structure of the symmetrical bisindoles 70 is in accord with the NMR spectroscopic data as illustrated for di[2-(4-methylphenyl)-1H-3-indolyl] sulphide 70b. The 1H NMR spectrum of 70b has two triplets at 7.08 and 7.18 ppm (J = 7.5 Hz) which are assignable to H-5 and H-6 of indole ring respectively. These protons show C,H-COSY correlation with C-5 at 120.2 and C-6 at 122.4 ppm. Both H-5 and H-6 protons further show HMBCs with C-3a at 131.2, C-7 at 111.3 ppm and C-7a at 136.1, C-4 at 119.3 ppm respectively. The H-4 hydrogen gives a doublet at 7.55 ppm with J = 7.5 Hz, which shows C,H-COSY correlation with the signal at 119.3 ppm assignable to C-4 and HMBCs with C-3 at 102.4, C-3a at 131.2, C-7a at 136.2, C-6 at 122.4 ppm (Figure.4.3). The doublet at 7.37 ppm with J = 7.5 Hz is due to H-7 hydrogen and is having HMBC correlation with C-3a at 131.2 and C-5 at 120.2 ppm. The H-7 further gives C,H-COSY correlation with the signal at 111.3 ppm due to C-7. The NH proton appeared as a singlet at 10.68 ppm. (Figure 4.4 to 4.13).

![Figure 4.3. Selected HMBCs and 1H and 13C chemical shifts in compound 70b](image-url)
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Figure 4.4. $^1$H NMR Spectrum 70b (recorded in Acetone-d$_6$)

Figure 4.5. $^1$H NMR Spectrum 70b (expanded)
Figure 4.6. $^{13}$C NMR Spectrum of 70b (recorded in Acetone-$d_6$)

Figure 4.7. DEPT-135 Spectrum of 70b
Figure 4.8. H,H-COSY Spectrum of 70b

Figure 4.9. H,H-COSY Spectrum of 70b (expanded)
Figure 4.10. HMBC Spectrum of 70b

Figure 4.11. HMBC Spectrum of 70b (expanded)
Figure 4.11. HMBC Spectrum of 70b (expanded)

Figure 4.12. C,H-COSY Spectrum of 70b
The $^1$H NMR spectrum of 1-(4-bromophenyl)-2-[2-(4-bromophenyl)-1H-3-indolyl]sulfanyl-1-ethanone (Figure 4.14) 71d, the H-5 and H-6 protons of the indole ring appears as triplet of doublets at 7.15 and 7.22 ppm ($J = 7.8, 1.2$ Hz) respectively, these protons exhibit C,H-COSY correlation with C-5 at 120.8 ppm and C-6 at 123.8 ppm respectively and they further show HMBCs with C-3a at 131.3 ppm, C-7 at 112.1 ppm and C-4 at 119.4 ppm, C-7a at 136.8 ppm. The H-4 proton appears as a doublet at 7.67 ppm ($J = 7.8$ Hz) which shows C,H-COSY correlation with the signal at 119.4 ppm assignable to C-4 and HMBCs with C-6 at 123.3, C-7a at 136.8 ppm. The multiplet at 7.45-7.47 ppm is due to H-7 hydrogen. The NH proton appears as a singlet at 10.99 ppm. The formation of monoindole is confirmed by the CH$_2$ proton singlet at 4.00 ppm, which shows (i) C,H-COSY correlation with carbon signal at 41.4 ppm, due to C-2", (ii) HMBCs with C-3 at 100.8, C-1" at 193.4 ppm and C-1" at 134.9 ppm. The mass spectrum for the compound 71b is obtained as m/e 372.1 [M+1] (calcd. 372.1 [M+1]) (Figure 4.15 to 4.25)
Figure 4.14. Selected HMBCs and $^1$H and $^{13}$C chemical shifts in compound 71d

Figure 4.15. $^1$H NMR Spectrum 71d (recorded in Acetone-$d_6$)
Figure 4.16. $^1$H NMR Spectrum 71d (expanded)

Figure 4.17. $^{13}$C NMR Spectrum of 71d (recorded in Acetone-$d_6$)
Figure 4.18. DEPT-135 Spectrum of 71d

Figure 4.19. H,H-COSY Spectrum of 71d
Figure 4.20. H,H-COSY Spectrum of 71d (expanded)

Figure 4.21. HMBC Spectrum of 71d
Figure 4.22. HMBC Spectrum of 71d (expanded)

Figure 4.23. C,H-COSY Spectrum of 71d
In the NMR spectrum of 72d, two methylene groups appear at 3.79 and 3.86 ppm and NH appears at 9.50 ppm. Thirteen proton of benzene ring appears from 6.89 to 7.87 ppm. In the $^{13}$C NMR spectrum the methylene carbons can be identified at 25.9 and 36.6 ppm which can also be confirmed from DEPT spectrum. The carbonyl carbon is appearing at 194.3 ppm. The mass spectrum for the compound 72a is obtained as m/e 359.1 [M-1] (calcd. 359.1 [M-1]) (Figure 4.26 to 4.31).
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Figure 4.26. $^1$H NMR Spectrum 72d (recorded in CDCl$_3$)

Figure 4.27. $^1$H NMR Spectrum 72d (expanded)
Figure 4.28. $^{13}$C NMR Spectrum of 72d (recorded in CDCl$_3$)

Figure 4.29. $^{13}$C NMR Spectrum of 72d (expanded)
In the NMR spectrum of 73b methylene group appears at 3.75 ppm and NH appears at 8.18 ppm. Seventeen protons of benzene ring appear from 6.45 to 7.94 ppm. In the $^{13}$C NMR the methylene carbon appears at 28.9 ppm which can also be confirmed.
from DEPT spectrum. The mass spectra for the compound 73c is obtained as m/e 589.9 [M+1] (calcd. 589.9 [M+1]) (Figure 4.32 to 4.37).

Figure 4.32. $^1$H NMR Spectrum 73b (recorded in CDCl$_3$)

Figure 4.33. $^1$H NMR Spectrum 73b (expanded)
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Figure 4.34. $^{13}$C NMR Spectrum of 73b (recorded in CDCl$_3$)

Figure 4.35. $^{13}$C NMR Spectrum of 73b (expanded)
The mass spectrum for the compound 69d is obtained as m/e 604.8 [M-1] (calcd. 605.0 [M-1]) (Figure 4.38).
In THF medium, a plausible mechanism for the formation of the monoindoles 71 involving a [3,3]-sigmatropic rearrangement of the enehydrazine tautomer 77 to 79 with concomitant cyclization and aromatization with the loss of ammonia was depicted in Scheme 4.5. In ethanol medium, the bisindoles 70 was formed exclusively via the double indolization of 69. To support this mechanism, the starting compound 66 was treated with phenylhydrazine in both ethanol and THF at reflux condition for 30 min. The reaction yielded bis(-2-aryl-2-(2-phenylhydrazono)ethyl)sulfanes 69. 69 subsequently reacted with concentrated hydrochloric acid to give the corresponding mono- 71 and bisindoles 70 in THF and ethanol medium respectively. To our delight it was observed that bis(2-aryl-2-(2-phenylhydrazono)ethyl)sulfane 69 on reflux with hydrochloric acid in THF medium resulted only monoindole 71, not retaining the hydrazone 73 of second keto group. In another experiment the monoindole 71 was subjected to second indolization or phenyl hydrazone formation in THF medium but in vain (Scheme 4.5).
In conclusion, it is shown that solvents THF / EtOH play a vital role in deciding the course of the reaction between diphenacyl sulfide and phenylhydrazine / phenylhydrazine hydrochloride. In ethanol medium bisphenylhydrazone and in THF monophenylhydrazone were selectively formed from diphenacyl sulfide. The exclusive formation of either one or two indole rings with THF and ethanol respectively illustrates the dramatic selectivity by the solvents in Fisher indole synthesis. The selectivity was further observed in the reaction between monoindole and phenylhydrazine / phenylhydrazine hydrochloride. All the synthesized compounds were well characterized using NMR and mass analysis.

**Scheme 4.5.** Proposed mechanism for formation of mono-indole 71 in THF

**4.7. Conclusion**

In conclusion, it is shown that solvents THF / EtOH play a vital role in deciding the course of the reaction between diphenacyl sulfide and phenylhydrazine / phenylhydrazine hydrochloride. In ethanol medium bisphenylhydrazone and in THF monophenylhydrazone were selectively formed from diphenacyl sulfide. The exclusive formation of either one or two indole rings with THF and ethanol respectively illustrates the dramatic selectivity by the solvents in Fisher indole synthesis. The selectivity was further observed in the reaction between monoindole and phenylhydrazine / phenylhydrazine hydrochloride. All the synthesized compounds were well characterized using NMR and mass analysis.
4.8. Experimental section

4.8.1 General Methods

All melting points reported in this work were measured in open capillaries. The $^1$H and $^{13}$C NMR spectra have been measured at 300 and 75 MHz respectively using Bruker 300 MHz (Avance) instrument in CDCl$_3$ using tetramethylsilane (TMS) as internal standard. Chemical shifts are reported as $\delta$ values (ppm). All one- and two-dimensional NMR spectra were obtained using standard Bruker software throughout. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet).

4.8.2 General procedure for di(2-aryl-1H-3-indolyl)sulphide (70): A mixture of 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanone 66 (1 mmol) and phenylhydrazine hydrochloride 67 (2.5 mmol) in ethanol (7 ml) was refluxed for 3 h. After completion of the reaction, monitored by TLC, the mixture was poured into ice cold water and the solid separated was purified by recrystallisation from ethylacetate.

4.8.2.1. Di(2-phenyl-1H-3-indolyl)sulphide (70a). Isolated as colorless solid; m.p. 132-133 $^\circ$C; IR (KBr): 3380 (NH), 3054 (C-H) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 6.99 (t, 4H, $J = 7.5$ Hz, Ar-H), 7.09-7.27 (m, 12H, Ar-H), 7.57 (d, 2H, $J = 7.8$ Hz, Ar-H), 8.10 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 104.0, 110.8, 120.0, 120.9, 123.1, 127.8, 127.9, 128.0, 130.7, 130.9, 135.4, 142.3. Anal. Calcd. for C$_{28}$H$_{20}$N$_2$S: C, 80.74; H, 4.84; N, 6.73%. Found: C, 80.69; H, 4.80; N, 6.77%.

4.8.2.2. Di[2-(4-methylphenyl)-1H-3-indolyl]sulphide (70b). Isolated as colorless solid; m.p. 126-127 $^\circ$C; IR (KBr): 3374 (NH), 3052 (C-H) cm$^{-1}$; $^1$H NMR (300 MHz, Acetone-d$_6$) $\delta$H: 2.20 (s, 6H, CH$_3$), 6.81 (d, 4H, $J = 8.1$ Hz, Ar-H), 7.08 (t, 2H, $J = 7.5$ Hz, Ar-H), 7.18 (t, 2H, $J = 7.5$ Hz, Ar-H), 7.31 (d, 4H, $J = 8.1$ Hz, Ar-H), 7.37 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.55 (d, 2H, $J = 7.5$ Hz, Ar-H), 10.68 (s, 2H, NH); $^{13}$C NMR (75 MHz, Acetone-d$_6$) $\delta$C: 20.4, 102.4, 111.3, 119.3, 120.2, 122.4, 127.9, 128.3, 128.4, 131.2, 136.2, 137.6, 143.0. Anal. Calcd. for C$_{30}$H$_{24}$N$_2$S: C, 81.05; H, 5.44; N, 6.30%. Found: C, 81.00; H, 5.41; N, 6.35%.

4.8.2.3. Di[2-(4-chlorophenyl)-1H-3-indolyl]sulphide (70c). Isolated as colorless solid; m.p. 132-133 $^\circ$C; IR (KBr): 3378 (NH), 3060 (C-H) cm$^{-1}$; $^1$H NMR (300 MHz,
CDCl₃) δ_H: 6.92 (d, 4H, J = 8.4 Hz, Ar-H), 7.11 (d, 4H, J = 8.4 Hz, Ar-H), 7.15-7.22 (m, 2H, Ar-H), 7.26-7.27 (m, 4H, Ar-H), 7.62 (d, 2H, J = 8.1 Hz, Ar-H), 8.15 (s, 2H, NH); ¹³C NMR (75 MHz, CDCl₃) δ_C: 104.4, 110.9, 120.0, 121.2, 123.6, 128.1, 128.6, 129.0, 130.7, 134.0, 135.4, 140.9. Anal. Calcd. for C₂₂H₁₈Cl₂N₂S: C, 69.28; H, 3.74; N, 5.77%. Found: C, 69.25; H, 3.69; N, 5.81%.

4.8.2.4. Di[2-(4-bromophenyl)-1H-3-indolyl]sulphide (70d). Isolated as colorless solid; m.p. 179-180 °C; IR (KBr): 3378 (NH), 3058 (C-H) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ_H: 7.06-7.26 (m, 14H, Ar-H), 7.62 (d, 2H, J = 7.8 Hz, Ar-H), 8.03 (s, 2H, NH); ¹³C NMR (75 MHz, CDCl₃) δ_C: 104.6, 111.0, 120.0, 121.3, 122.3, 123.7, 128.9, 129.5, 130.7, 131.0, 135.5, 140.8. Anal. Calcd. for C₂₂H₁₈Br₂N₂S: C, 58.56; H, 3.16; N, 4.88%. Found: C, 58.52; H, 3.13; N, 4.91%.

4.8.2.5. Di[2-(biphenyl)-1H-3-indolyl]sulphide (70e). Isolated as colorless solid; m.p. 166-167 °C; IR (KBr): 3384 (NH), 3058 (C-H) cm⁻¹; ¹H NMR (300 MHz, Acetone-d₆) δ_H: 7.08-7.19 (m, 4H, Ar-H), 7.28 (d, 4H, J = 7.5 Hz, Ar-H), 7.35 (d, 4H, J = 7.2 Hz, Ar-H), 7.44 (t, 4H, J = 7.2 Hz, Ar-H), 7.50-7.62 (m, 6H, Ar-H), 7.69-7.71 (m, 2H, Ar-H), 8.08 (d, 2H, J = 7.2 Hz, Ar-H), 10.79 (s, 2H, NH); ¹³C NMR (75 MHz, Acetone-d₆) δ_C: 102.9, 111.4, 119.3, 120.3, 122.7, 126.0, 126.5, 126.6, 127.3, 128.3, 128.6, 128.8, 130.0, 131.2, 136.3, 140.1. Anal. Calcd. for C₄₀H₂₈N₂S: C, 84.47; H, 4.96; N, 4.93%. Found: C, 84.42; H, 4.92; N, 4.98%.

4.8.2.6. Di[2-(2-naphthyl)-1H-3-indolyl]sulphide (70f). Isolated as colorless solid; m.p. 182-183 °C; IR (KBr): 3378 (NH), 3058 (C-H) cm⁻¹; ¹H NMR (300 MHz, Acetone-d₆) δ_H: 7.13-7.25 (m, 6H, Ar-H), 7.30-7.41 (m, 6H, Ar-H), 7.49 (d, 2H, J = 8.7 Hz, Ar-H), 7.60 (dd, 2H, J = 8.4, 1.5 Hz, Ar-H), 7.68-7.42 (m, 4H, Ar-H), 7.90 (s, 2H, Ar-H), 10.86 (s, 2H, NH); ¹³C NMR (75 MHz, Acetone-d₆) δ_C: 103.2, 111.5, 119.4, 120.5, 122.8, 125.7, 125.8, 126.1, 127.1, 127.2, 127.3, 128.2, 128.5, 131.3, 132.8, 132.9, 136.4, 142.7. Anal. Calcd. for C₃₆H₂₄N₂S: C, 83.69; H, 4.68; N, 5.42%. Found: C, 83.64; H, 4.65; N, 5.46%.

4.8.3. General procedure for 1-aryl-2-[2-aryl-1H-3-indolyl]sulfonyl]-1-ethanones (71): A mixture of 2-[2-oxo-2-arylethyl]sulfanyl]-1-aryl-1-ethanone 66 (1 mmol) and phenylhydrazine hydrochloride 67 (1.5 mmol) in THF (10 ml) was refluxed for 3 h. After completion of the reaction, monitored by TLC, the mixture was filtered to
remove phenylhydrazine hydrochloride and the filtrate was poured into ice cold water and the solid separated was purified by recrystallisation from ethyl acetate. Spectroscopic data for 71 are given below:

4.8.3.1. 1-Phenyl-2-[(2-phenyl-1H-3-indolyl)sulfanyl]-1-ethanone (71a). Isolated as colorless solid; m.p. 160-161 °C; IR (KBr): 3345 (NH), 3054 (C-H), 1654 (C=O) cm⁻¹; ¹H NMR (300 MHz, Acetone-d₆) δ_H: 4.09 (s, 2H, CH₂), 7.12 (td, 1H, J = 8.1, 1.2 Hz, Ar-H), 7.31-7.40 (m, 5H, Ar-H), 7.46 (d, 1H, J = 7.8 Hz, Ar-H), 7.51-7.56 (m, 1H, Ar-H), 7.65 (d, 1H, J = 7.8 Hz, Ar-H), 7.78 (dd, 2H, J = 8.1, 1.8 Hz, Ar-H), 7.86 (dd, 2H, J = 8.1, 1.8 Hz, Ar-H); ¹³C NMR (75 MHz, Acetone-d₆) δ_C: 41.5, 100.0, 111.5, 118.9, 120.1, 122.5, 128.0, 128.1, 128.2, 128.3, 128.4, 131.0, 131.7, 132.7, 135.6, 136.1, 141.5, 194.1. m/e 342.0 [M-1] calcd. 342.1 [M-1]. Anal. Calcd. for C₂₂H₁₇NOS: C, 76.94; H, 4.99; N, 4.08%. Found: C, 76.91; H, 4.95; N, 4.13%.

4.8.3.2. 1-(4-Methylphenyl)-2-[2-(4-methylphenyl)-1H-3-indolyl]sulfanyl-1-ethanone (71b). Isolated as colorless solid; m.p. 153-154 °C; IR (KBr): 3344 (NH), 3052 (C-H), 1654 (C=O) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ_H: 2.32 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 3.91 (s, 2H, CH₂), 7.03 (d, 2H, J = 8.1 Hz, Ar-H), 7.07 (d, 2H, J = 8.1 Hz, Ar-H), 7.12-7.16 (m, 2H, Ar-H), 7.18-7.23 (m, 1H, Ar-H), 7.52 (d, 2H, J = 8.1 Hz, Ar-H), 7.57 (d, 2H, J = 8.1 Hz, Ar-H), 7.64-7.67 (m, 1H, Ar-H), 8.65 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ_C: 21.2, 21.6, 41.9, 100.5, 111.2, 119.2, 120.6, 122.8, 128.1, 128.5, 128.7, 128.9, 129.0, 131.0, 133.0, 135.5, 138.1, 141.7, 143.6, 194.7. m/e 372.1 [M+1] calcd. 372.1 [M+1]. Anal. Calcd. for C₂₄H₂₁NOS: C, 77.59; H, 5.70; N, 3.77%. Found: C, 77.55; H, 5.65; N, 3.81%.

4.8.3.3. 1-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)-1H-3-indolyl]sulfanyl-1-ethanone (71c). Isolated as colorless solid; m.p. 153-154 °C; IR (KBr): 3346 (NH), 3050 (C-H), 1656 (C=O) cm⁻¹; ¹H NMR (300 MHz, Acetone-d₆) δ_H: 4.02 (s, 2H, CH₂), 7.15 (t, 1H, J = 7.5 Hz, Ar-H), 7.22 (t, 1H, J = 7.5 Hz, Ar-H), 7.32-7.36 (m, 5H, Ar-H), 7.56 (d, 1H, J = 7.5 Hz, Ar-H), 7.67 (d, 2H, J = 8.4 Hz, Ar-H), 7.78 (d, 2H, J = 8.4 Hz), 10.93 (s, 1H, NH); ¹³C NMR (75 MHz, Acetone-d₆) δ_C: 40.9, 100.1, 111.6, 118.9, 120.4, 122.8, 128.1, 128.2, 128.3, 129.9, 130.1, 130.3, 130.8, 133.5, 133.9,
138.3, 140.7, 192.7. Anal. Calcd. for C_{22}H_{15}Cl_{2}NOS: C, 64.08; H, 3.67; N, 3.40%. Found: C, 64.04; H, 3.62; N, 3.43%.

4.8.3.4. 1-(4-Bromophenyl)-2-[2-(4-bromophenyl)-1H-3-indolyl]sulfanyl-1-ethanone (71d). Isolated as colorless solid; m.p. 164-165 °C; IR (KBr): 3345 (NH), 3051 (C-H), 1656 (C=O) cm⁻¹; ¹H NMR (300 MHz, Acetone-đ₆) δ_H: 4.00 (s, 2H, CH₂), 7.15 (td, 1H, J = 7.8, 1.2 Hz, Ar-H), 7.22 (td, 1H, J = 7.8, 1.2 Hz, Ar-H), 7.45-7.47 (m, 3H, Ar-H), 7.51(d, 2H, J = 8.7 Hz, Ar-H), 7.59 (d, 2H, J = 8.7 Hz, Ar-H), 7.67 (d, 1H, J = 7.8 Hz, Ar-H), 7.71 (d, 2H, J = 8.7 Hz, Ar-H), 10.99 (s, 1H, NH); ¹³C NMR (75 MHz, Acetone-đ₆) δ_C: 41.4, 100.8, 112.1, 119.4, 120.9, 122.2, 123.3, 127.5, 130.7 (2C), 131.1, 131.4, 131.6, 131.7, 135.0, 136.7, 141.2, 193.4. Anal. Calcd. for C_{22}H_{15}Br_{2}NOS: C, 52.72; H, 3.02; N, 2.79%. Found: C, 52.69; H, 3.00; N, 2.84%.

4.8.3.5. 1-(Biphenyl)-2-[2-(biphenyl)-1H-3-indolyl]sulfanyl-1-ethanone (71e). Isolated as colorless solid; m.p. 204-205 °C; IR (KBr): 3344 (NH), 3051 (C-H), 1660 (C=O) cm⁻¹; ¹H NMR (300 MHz, Acetone-đ₆) δ_H: 4.07 (s, 2H, CH₂), 6.88 (td, 2H, J = 8.1, 0.9 Hz, Ar-H), 7.06 (td, 2H, J = 8.1, 0.9 Hz, Ar-H), 7.30-7.63 (m, 10H, Ar-H), 7.70-7.78 (m, 6H, Ar-H), 8.09 (d, 2H, J = 8.7 Hz, Ar-H), 10.79 (s, 1H, NH); ¹³C NMR (75 MHz, Acetone-đ₆) δ_C: 41.3, 104.2, 111.3, 111.6, 119.0, 119.3, 119.8, 120.4, 122.3, 122.7, 126.1, 126.6, 126.7, 127.0, 127.4, 128.0, 128.4, 128.8 (2C), 129.0, 131.1, 131.4, 134.6, 136.3, 140.3, 193.5. Anal. Calcd. for C_{34}H_{25}NOS: C, 82.39; H, 5.08; N, 2.83%. Found: C, 82.36; H, 5.04; N, 2.87%.

4.8.3.6. 1-(2-Naphthyl)-2-[2-(2-naphthyl)-1H-3-indolyl]sulfanyl-1-ethanone (71f). Isolated as colorless solid; m.p. 172-173 °C; IR (KBr): 3348 (NH), 3052 (C-H), 1659 (C=O) cm⁻¹; ¹H NMR (300 MHz, Acetone-đ₆) δ_H: 4.05 (s, 2H, CH₂), 7.11-7.26 (m, 3H, Ar-H), 7.33-7.42 (m, 3H, Ar-H), 7.47-7.53 (m, 4H, Ar-H), 7.59-7.64 (m, 4H, Ar-H), 7.67-7.83 (m, 3H, Ar-H), 7.88 (s, 1H, Ar-H), 10.69 (s, 1H, NH); ¹³C NMR (75 MHz, Acetone-đ₆) δ_C: 41.5, 103.0, 111.2, 111.6, 119.3, 119.7, 120.1, 120.4, 122.4, 122.9, 125.2, 125.9, 126.3, 126.4, 127.2, 127.3, 128.2, 128.6, 128.7 (2C), 129.4, 129.5, 130.4, 131.8 (2C), 132.7, 135.3, 136.7, 140.6, 192.7. Anal. Calcd. for C_{36}H_{21}NOS: C, 81.23; H, 4.77; N, 3.16%. Found: C, 81.18; H, 4.72; N, 3.21%.

4.8.4. General procedure for 1-aryl-2-(2-aryl-2-[2-phenylhydrazono]ethylsulfanyl)-1-ethanone 1-phenylhydrazone 69: A mixture of
2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanone 66 (1 mmol) and phenylhydrazine 68 (2.5 mmol) in ethanol (7 ml) was refluxed for 2-3 h. After completion of the reaction, monitored by TLC, the mixture was poured into ice cold water and the solid separated was purified by recrystallisation from ethanol. The spectral data for bisphenyl hydrazones are given below.

4.8.4.1 1-Phenyl-2-(2-phenyl-2-[2-phenylhydrazono]ethylsulfanyl)-1-ethanone 1-phenyl hydrazone (69a). Isolated as colorless solid; m.p. 111-112 °C; IR (KBr): 3283 (NH), 3054 (C-H), 1634 (C=N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 3.86 (s, 4H, CH$_2$), 6.89 (t, 2H, $J = 7.2$ Hz, Ar-H), 7.07 (d, 4H, $J = 7.5$ Hz, Ar-H), 7.19-7.36 (m, 10H, Ar-H), 7.77 (d, 4H, $J = 7.2$ Hz, Ar-H), 8.15 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 25.8, 113.5, 120.9, 125.2, 128.2, 128.6, 129.2, 137.5, 137.8, 144.5. Anal. Calcd. for C$_{28}$H$_{26}$N$_4$S: C, 74.63; H, 5.82; N, 12.43%. Found: C, 74.60; H, 5.78; N, 12.47%.

4.8.4.2. 1-(4-Methylphenyl)-2-(2-(4-methylphenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone 1-phenylhydrazone (69b). Isolated as colorless solid; m.p. 121-122 °C; IR (KBr): 3285 (NH), 3057 (C-H), 1633 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 2.33 (s, 6H, CH$_3$), 3.84 (s, 4H, CH$_2$), 6.87 (t, 2H, $J = 7.2$ Hz, Ar-H), 7.06 (d, 4H, $J = 8.1$ Hz, Ar-H), 7.18-7.27 (m, 8H, Ar-H), 7.65 (d, 4H, $J = 8.1$ Hz, Ar-H), 8.16 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 21.1, 25.9, 113.6, 120.6, 125.3, 128.3, 129.1, 129.2, 137.9, 138.0, 144.8. m/e 477.0 [M-1] calcd. 477.1 [M-1]. Anal. Calcd. for C$_{30}$H$_{30}$N$_4$S: C, 75.28; H, 6.32; N, 11.71%. Found: C, 75.25; H, 6.28; N, 11.75%.

4.8.4.3. 1-(4-Chlorophenyl)-2-(2-(4-chlorophenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone 1-phenylhydrazone (69c). Isolated as colorless solid; m.p. 135-136 °C; IR (KBr): 3280 (NH), 3055 (C-H), 1632 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 3.69 (s, 4H, CH$_2$), 6.93 (t, 2H, $J = 7.2$ Hz, Ar-H), 7.03 (d, 4H, $J = 8.4$ Hz, Ar-H), 7.20-7.32 (m, 8H, Ar-H), 7.64 (d, 4H, $J = 8.4$ Hz, Ar-H), 8.14 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 25.5, 113.6, 121.2, 126.4, 128.5, 128.7, 129.3, 136.1, 136.2, 144.3. Anal. Calcd. for C$_{28}$H$_{26}$Cl$_2$N$_4$S: C, 64.74; H, 4.66; N, 10.79%. Found: C, 64.70; H, 4.63; N, 10.83%.
4.8.4.4. 1-(4-Bromophenyl)-2-(2-(4-bromophenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone 1-phenylhydrazone (69d). Isolated as colorless solid; m.p. 125-126 °C; IR (KBr): 3282 (NH), 3057 (C-H), 1634 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 3.79 (s, 4H, CH$_2$), 6.92 (t, 2H, $J = 7.2$ Hz, Ar-H), 7.03 (d, 4H, $J = 8.4$ Hz, Ar-H), 7.19-7.27 (m, 6H, Ar-H), 7.43 (d, 4H, $J = 8.4$ Hz, Ar-H), 7.59 (d, 2H, $J = 8.4$ Hz, Ar-H), 8.13 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 25.5, 113.6, 121.3, 126.7, 128.5, 129.3, 131.7, 136.1, 136.6, 144.2. m/e 604.8 [M-1] calcd. 605.0 [M-1]. Anal. Calcd. for C$_{28}$H$_{24}$Br$_2$N$_4$S: C, 55.28; H, 3.98; N, 9.21%. Found: C, 55.24; H, 3.95; N, 9.25%.

4.8.4.5. 1-(4-Methoxyphenyl)-2-(2-(4-methoxyphenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone 1-phenylhydrazone (69e). Isolated as colorless solid; m.p. 119-120 °C; IR (KBr): 3282 (NH), 3055 (C-H), 1634 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 3.77 (s, 4H, CH$_2$), 3.80 (6H, OCH$_3$), 6.84 (t, 2H, $J = 6.9$ Hz, Ar-H), 7.05 (d, 4H, $J = 8.4$ Hz, Ar-H), 7.18-7.31 (m, 8H, Ar-H), 8.05 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 25.7, 55.2, 113.5, 113.9, 120.5, 126.6, 129.1, 129.2, 137.9, 144.8, 159.6. m/e 511.2 [M+1] calcd. 511.2 [M+1]. Anal. Calcd. for C$_{30}$H$_{30}$N$_4$O$_2$S: C, 70.56; H, 5.92; N, 10.97%. Found: C, 70.52; H, 5.89; N, 11.01%.

4.8.5. General procedure for 1-aryl-2-(2-aryl-2-[2-phenylhydrazono]ethylsulfanyl)-1-ethanone 72: A mixture of 2-[(2-oxo-2-arylethyl)sulfanyl]-1-aryl-1-ethanone 66 (1 mmol) and phenylhydrazine 68 (1.5 mmol) in THF (5 ml) was refluxed for 2-3 h. After completion of the reaction, monitored by TLC, the mixture was allowed to cool and then poured into ice cold water and the solid separated was purified by recrystallisation from ethanol.

4.8.5.1. 1-Phenyl-2-(2-phenyl-2-[2-phenylhydrazono]ethylsulfanyl)-1-ethanone (72a). Isolated as colorless solid; m.p. 143-144 °C; IR (KBr): 3245 (NH), 3055 (C-H), 1674 (C=O), 1610 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 3.79 (s, 2H, CH$_2$), 3.83 (s, 2H, CH$_2$), 6.82-6.89 (m, 1H, Ar-H), 7.21 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.28-7.34 (m, 6H, Ar-H), 7.41 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.74 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.79 (d, 2H, $J = 8.4$ Hz, Ar-H), 9.59 (s, 1H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 25.8, 36.8, 113.5, 120.8, 125.2, 127.7, 128.2, 128.5, 128.6, 128.8, 129.1, 133.9, 137.5,
4.8.5.2. 1-(4-Methylphenyl)-2-(2-(4-methylphenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone (72b). Isolated as colorless solid; m.p. 116-117 °C; IR (KBr): 3247 (NH), 3056 (C-H), 1674 (C=O), 1612 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 2.35 (s, 3H, CH$_3$), 2.41 (s, 3H, CH$_3$), 3.81 (s, 2H, CH$_2$), 3.86 (s, 2H, CH$_2$), 6.87 (t, 1H, J = 6.9 Hz, Ar-H), 7.20 (d, 2H, J = 8.1 Hz, Ar-H), 7.26-7.37 (m, 6H, Ar-H), 7.70 (d, 2H, J = 8.1 Hz, Ar-H), 7.89 (d, 2H, J = 8.1 Hz, Ar-H), 9.53 (s, 1H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 21.1, 21.7, 26.2, 36.7, 113.3, 120.0, 125.2, 128.8, 129.0, 129.1, 129.5, 132.6, 135.0, 137.7, 138.0, 145.0, 145.5, 194.9. Anal. Calcd. for C$_{22}$H$_{20}$N$_2$OS: C, 73.30; H, 5.59; N, 7.77%. Found: C, 70.26; H, 5.54; N, 7.80%.

4.8.5.3. 1-(4-Chlorophenyl)-2-(2-(4-chlorophenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone (72c). Isolated as colorless solid; m.p. 151-152 °C; IR (KBr): 3245 (NH), 3055 (C-H), 1672 (C=O), 1614 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 3.80 (s, 2H, CH$_2$), 3.87 (s, 2H, CH$_2$), 6.88-6.93 (m, 1H, Ar-H), 7.31-7.34 (m, 6H, Ar-H), 7.48 (d, 2H, J = 8.7 Hz, Ar-H), 7.72 (d, 2H, J = 8.7 Hz, Ar-H), 7.94 (d, 2H, J = 8.7 Hz, Ar-H), 9.52 (s, 1H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 21.1, 21.7, 26.2, 36.7, 113.3, 120.5, 126.5, 128.6, 129.0, 129.2, 129.3, 130.1, 133.3, 133.6, 136.2, 136.3, 145.1, 194.1. Anal. Calcd. for C$_{22}$H$_{18}$Cl$_2$N$_2$OS: C, 61.54; H, 4.23; N, 6.52%. Found: C, 61.50; H, 4.20; N, 6.56%.

4.8.5.4. 1-(4-Bromophenyl)-2-(2-(4-bromophenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone (72d). Isolated as colorless solid; m.p. 161-162 °C; IR (KBr): 3249 (NH), 3055 (C-H), 1675 (C=O), 1610 (C=N) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 3.79 (s, 2H, CH$_2$), 3.86 (s, 2H, CH$_2$), 6.92 (tt, 1H, J = 8.1, 2.4 Hz, Ar-H), 7.27-7.35 (m, 4H, Ar-H), 7.47 (d, 2H, J = 8.7 Hz, Ar-H), 7.64 (d, 2H, J = 8.7 Hz, Ar-H), 7.65 (d, 2H, J = 8.7 Hz, Ar-H), 7.85 (d, 2H, J = 8.7 Hz, Ar-H), 9.50 (s, 1H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 25.9, 36.6, 113.4, 120.6, 121.9, 126.8, 129.2, 129.5, 130.2, 131.5, 132.3, 133.7, 136.3, 136.6, 145.0, 194.3. Anal. Calcd. for C$_{22}$H$_{18}$Br$_2$N$_2$OS: C, 50.98; H, 3.50; N, 5.41%. Found: C, 50.95; H, 3.46; N, 5.46%.

4.8.5.5. 1-(4-Methoxyphenyl)-2-(2-(4-methoxyphenyl)-2-[2-phenylhydrazono]ethyl sulfanyl)-1-ethanone (72e). Isolated as colorless solid; m.p.
146-147 °C; IR (KBr): 3245 (NH), 3053 (C-H), 1675 (C=O), 1615 (C=N) cm \(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 3.74 (s, 2H, CH\(_2\)), 3.77 (s, 2H, CH\(_2\)), 3.79 (s, 6H, OCH\(_3\)), 6.82-6.85 (m, 1H, Ar-H), 7.04 (d, 2H, \(J = 8.7\) Hz, Ar-H), 7.24-7.30 (m, 4H, Ar-H), 7.67 (d, 2H, \(J = 9.0\) Hz, Ar-H), 7.72 (d, 2H, \(J = 8.7\) Hz, Ar-H), 7.92 (d, 2H, \(J = 9.0\) Hz, Ar-H), 9.53 (s, 1H, NH); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 26.0, 36.4, 55.2, 55.3, 113.4, 113.9, 114.9, 120.4, 126.6, 129.1, 129.2, 131.0, 132.4, 137.9, 144.8, 159.7, 164.1, 193.7. Anal. Calcd. for C\(_{24}\)H\(_{24}\)N\(_2\)O\(_3\)S: C, 68.55; H, 5.75; N, 6.66%. Found: C, 68.51; H, 5.72; N, 6.70%.

4.8.6. General procedure for 1-(aryl)-2-[2-(aryl)-1\(H\)-3-indolyl]sulfanyl-1-ethanone 1-phenylhydrazone 73: A mixture of 1-aryl-2-[(2-aryl-1\(H\)-3-indolyl)sulfanyl]-1-ethanone 71 (1 mmol) and phenylhydrazine 68 (1.5 mmol) in ethanol (10 ml) was refluxed for 2-3 h. After completion of the reaction, monitored by TLC, the mixture was poured into ice cold water and the solid separated was recrystallised from ethyl acetate to get pure product.

4.8.6.1. 1-(4-Methylphenyl)-2-[2-(4-methylphenyl)-1\(H\)-3-indolyl]sulfanyl-1-ethanone 1-phenylhydrazone (73a). Isolated as colorless solid; m.p. 145-146 °C; IR (KBr): 3375 (NH), 3272 (NH), 3045 (C-H), 1598 (C=N) cm \(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 2.31 (s, 3H, CH\(_3\)), 2.32 (s, 3H, CH\(_3\)), 3.84 (s, 2H, CH\(_2\)), 6.58 (d, 2H, \(J = 8.4\) Hz, Ar-H), 6.79 (t, 1H, \(J = 7.5\) Hz, Ar-H), 7.02 (d, 2H, \(J = 7.8\) Hz, Ar-H), 7.08-7.16 (m, 4H, Ar-H), 7.28-7.35 (m, 3H, Ar-H), 7.43 (d, 2H, \(J = 8.1\) Hz, Ar-H), 7.50 (d, 2H, \(J = 7.5\) Hz, Ar-H), 7.54 (s, 1H, NH), 7.93 (m, 1H, Ar-H), 8.25 (brs, 1H, NH); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 21.2, 21.3, 30.2, 100.5, 111.5, 113.1, 119.0, 119.9, 121.3, 123.2, 125.3, 128.2, 128.4, 128.7, 128.8, 129.3, 130.9, 134.9, 135.4, 137.4, 138.6, 140.6, 142.5, 145.1. Anal. Calcd. for C\(_{30}\)H\(_{27}\)N\(_3\)S: C, 78.06; H, 5.90; N, 9.10%. Found: C, 78.02; H, 5.85; N, 9.14%.

4.8.6.2. 1-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)-1\(H\)-3-indolyl]sulfanyl-1-ethanone 1-phenylhydrazone (73b). Isolated as colorless solid; m.p. 203-204 °C; IR (KBr): 3378 (NH), 3272 (NH), 3048 (C-H), 1598 (C=N) cm \(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 3.75 (s, 2H, CH\(_2\)), 6.46 (d, 2H, \(J = 8.4\) Hz, Ar-H), 6.82 (t, 1H, \(J = 7.2\) Hz, Ar-H), 7.05-7.21 (m, 7H, Ar-H), 7.28-7.34 (m, 5H, Ar-H, NH), 7.41 (d, 2H, \(J = 8.4\) Hz, Ar-H), 7.93 (m, 1H, Ar-H), 8.18 (brs, 1H, NH); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\):
28.9, 100.5, 111.8, 113.0, 120.4, 121.2, 121.6, 123.8, 126.3, 128.0, 128.6, 128.9, 129.2, 129.8, 130.8, 133.4, 134.6, 135.5, 135.7, 138.7, 141.6, 144.5. m/e 502.0 [M+1] calcd. 502.0 [M+1]. Anal. Calcd. for C\textsubscript{28}H\textsubscript{21}Cl\textsubscript{2}N\textsubscript{3}S: C, 66.93; H, 4.21; N, 8.36%. Found: C, 66.90; H, 4.17; N, 8.41%.

4.8.6.3. 1-(4-Bromophenyl)-2-[2-(4-bromophenyl)-1\textit{H}-3-indolyl]sulfanyl-1-etanone 1-phenylhydrazone (73c). Isolated as colorless solid; m.p. 179-180 °C; IR (KBr): 3376 (NH), 3271 (NH), 3048 (C-H), 1597 (C=N) cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\)\textsubscript{H}: 3.77 (s, 2H, CH\textsubscript{2}), 6.47 (d, 2H, \(J = 7.5\) Hz, Ar-H), 6.83 (t, 1H, \(J = 7.5\) Hz, Ar-H), 7.16 (t, 1H, \(J = 7.5\) Hz, Ar-H), 7.21-7.44 (m, 13H, Ar-H), 7.96 (m, 1H, Ar-H), 8.24 (brs, 1H, NH); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\)\textsubscript{C}: 28.8, 100.6, 111.8, 113.0, 119.0, 120.4, 121.6 (2C), 122.9, 123.8, 126.6, 129.0, 129.7, 130.0, 130.8, 130.9, 131.5, 135.5, 136.1, 138.6, 141.6, 144.5. m/e 589.9 [M+1] calcd. 589.9 [M+1]. Anal. Calcd. for C\textsubscript{28}H\textsubscript{21}Br\textsubscript{2}N\textsubscript{3}S: C, 56.87; H, 3.58; N, 7.11%. Found: C, 56.82; H, 3.54; N, 7.15%.


