CHAPTER-6

Part A: Synthesis of 4-(naphtho[2,1-b]furan-2-yl)-2-(substituted)phenyl-2,5-dihydro-1H-1,5-benzodiazepines

Part B: Synthesis of 3-Phenyl-6-(naphtho[2,1-b]furan-2-yl)-8-(substituted)phenyl-5,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines
Part A: Synthesis of 4-naphtho[2,1-b]furan-2-yl-2-(substituted) phenyl-2,5-dihydro-1H-1,5-benzodiazepines
Introduction

The chemistry of the compounds containing the condensed diazepine has been fascinating field of investigation in heterocyclic chemistry during the last few years. The interest in these seven membered heterocycles as sprung up in connection with the studies on certain rearrangements and valuable therapeutic properties associated with it. Amongst the several benzodiaepines 3\textit{H}-1,4-benzodiazepines I and 3\textit{H}-1,5-benzodiazepines II have shown sufficient pharmacological and clinical activity to warrant introduction as new drugs.

\begin{figure}[ht]
\centering
\includegraphics[width=0.5\textwidth]{dia.png}
\caption{Structures of benzodiazepines I and II}
\end{figure}

1,4-Diazepines form the most extensively investigated group in this series. However 1,5-benzodiazepines received considerable attention because most of the compounds containing this moiety have been reported to be most extremely consumed psychotic drugs world wide due to their anxiolytic and anticonvulsant activity\textsuperscript{1}. These are also useful as precursors for the synthesis of some fused heterocycles containing 1,5-benzodiazepine and triazolo-, oxadiazolo-, oxazinones etc\textsuperscript{2-4}. The derivatives of 1,5-benzodiazepines are reported to posses cytotoxic activity against human cancer cell lines, namely SW707 (colon cancer), MCF-7 (breast cancer), A549 (lung cancer), and HCV29T (bladder cancer) and also serve as antiproliferative agents\textsuperscript{5}.

Benzodiazepines are found to be present in biological fluids like serum and urine. Son \textit{et al.}, extracted various derivatives of benzodiazepine using solid phase extraction and analyzed by liquid chromatographic technique\textsuperscript{6}.
Clozapine III, a derivative of benzodiazepine have been shown to possess neuroleptic activity and block preferentially D4 receptors. 1,5-Benzodiazepine acts as Caspase-1-inhibitors. Agarwal et al., synthesized 5-phenyl-3-ureido-1,5-benzodiazepine IV which was shown to act as Cholecystokinin-A receptors antagonists.

Rodriguez et al., synthesized the derivatives of 1,5-benzodiazepine by reacting 1,2-diamino benzene with chalcones derived from substituted acetophenones and 2-nitrobenzaldehyde. Some of the synthesized compounds are found to be light sensitive.

It is known that many benzodiazepines affect the CNS and some 2,4-diaryl-7,8-dimethyl-2,3-dihydro1H-1,5-benzodiazepines have been tested against breast cancer and have shown moderate activity, in addition many of such compounds have been known to exhibit various biological activites.
Hetero fused 1,5-benzodiazepine have been synthesized and evaluated towards HIV reverse transcriptase inhibition\textsuperscript{14}. Roman \textit{et al.}, synthesised 1,5-benzodiazepine and naphthodiazepines by reacting between \textit{o}-phenylene diamine and Mannich bases\textsuperscript{11}.

\[
\begin{align*}
\text{Ar} \text{N} & (\text{CH}_3)_2 \text{HCl} \\
\text{anhy.CH}_3\text{COONa} & \rightarrow \text{HN} (\text{CH}_3)_2 \text{HCl} \\
- \text{H}_2\text{O} & \rightarrow \\
\end{align*}
\]

Benzodiazepines form one of the pharmacological and clinically important drugs, which can modulate gamma aminobutyric acid (GABA) receptor\textsuperscript{15-16}.

The above observation lead many synthetic chemists to take up the research work for the synthesis of 1,5-benzodiazepine and thus various methods are now available to accomplish the synthesis of 1,5-benzodiazepine. Pozarentzi \textit{et al.}, synthesized 1,5-benzodiazepine derivatives under microwave irradiation without using solvent\textsuperscript{17}.

\[
\begin{align*}
\text{R}_1 \text{NH}_2 & + \text{R}_2 \text{NH}_2 \\
\text{microwave} & \rightarrow \\
\text{CH}_3\text{COOH} & \rightarrow \\
\end{align*}
\]

Scandium(III)triflate has received considerable attention as a mild Lewis acid catalyst for a large number of organic transformations. It is because of the catalyst is stable in water and is reusable. De and Gibbs used this catalyst for the synthesis of 1,5-benzodiazepine derivatives\textsuperscript{18}.
Similarly Chari and Syamasundhar used PVP supported ferric chloride for this synthesis, the catalyst is recyclable and heterogeneous and synthesis can be carried out under solvent free conditions and microwave irradiation\textsuperscript{19}.

Indium(III)bromide has also been used as catalyst for the synthesis for 1,5-benzodiazepine\textsuperscript{20}. Balakrishna and Kaboudin synthesized 1,5-benzodiazepine by reacting o-phenylenediamine with ketones in presence of magnesia and phosphorous oxy chloride under solvent free conditions\textsuperscript{21}.

Zhong \textit{et al.}, carried out the synthesis of 2,3-dihydro-1\textit{H}-1,5-benzodiazepines by simultaneous reduction of nitro and azide groups induced by TiCl\textsubscript{4}/Sm system\textsuperscript{22}. Ionic liquids such as 1,3-n-dibutylimidazolium bromide has also been used to synthesise 1,5-benzodiazepine derivatives at room temperature and under ambient condition\textsuperscript{23}.

In view of the above finding and also due to the fact that there is no work done so far on the synthesis of heterocyclic systems consisting of naphtho[2,1-b]furan and 1,5-benzodiazepine ring systems the present work of synthesizing of 4-naphtho[2,1-b]furan-2-yl-2-(substituted)phenyl-2,5-dihydro-1\textit{H}-1,5-benzodiazepines was under taken.
Present work

Amongst the various methods available for the construction of 1,5-benzodiazepine ring, the method used by Rodriguez was adopted which makes use of o-phenylenediamine and chalcones as starting materials.

2-Acetylnaphtho[2,1-b]furan 1 synthesized during the present work served as an excellent starting material for the synthesis of the title compounds. The synthesis was achieved in two steps, first by converting 2-acetylnaphtho[2,1-b]furan into corresponding chalcones by treating with appropriate aldehydes, followed by reaction with o-phenylenediamine. The sequence of the reaction is depicted in scheme-1.

Scheme-1

\[
\begin{align*}
1 & \quad \text{CH}_3 \\
& \quad \text{O} \\
& \quad \text{W} \\
& \quad \text{H} \\
& \quad \text{R} \\
2a-f & \quad \text{NaOH/ Ethanol} \\
& \quad \text{NH}_2 \\
& \quad \text{NH}_2 \\
& \quad \text{R} \\
3a-f & \quad \text{R} \\
3a & 4-\text{OCH}_3 \\
3b & 4-\text{Cl} \\
3c & 4-\text{NO}_2 \\
3d & \text{H} \\
3e & 2-\text{OH} \\
3f & 2-\text{Cl}
\end{align*}
\]
The selection of aromatic aldehydes was based upon presence of electron withdrawing and electron donating groups which could enable to study structure activity relationship during the evaluation of pharmacological activities.

The structures of compounds have been well established by analytical and spectral data. Table-6.1

The IR spectrum of 3a exhibited a broad absorption band at 3387 cm\(^{-1}\) which was attributed to stretching vibration of 2 NH groups. \(^1\)H NMR spectrum of 3a was recorded using DMSO-\(d_6\) solvent. It showed a singlet integrating for three protons at \(\delta\) 3.8 due to OCH\(_3\) group and two doublets integrating for one proton each at \(\delta\) 6.4 and \(\delta\) 6.7 were attributed to C=CH and CCHPh protons respectively. A multiplet at \(\delta\) 7.2-8.6 integrating for seventeen protons was observed this may attributed to fifteen aromatic protons and two NH protons. The structure assigned to 3a has been further substantiated by \(^13\)C NMR which exhibited the peaks at \(\delta\) 112.56, 112.69, 112.77, 113.08, 113.63, 113.74, 113.93, 123.22, 123.52, 123.59, 125.35, 125.65, 127.24, 127.36, 127.60, 127.83, 128.42, 128.50, 128.65, 128.73, 128.92, 129.18, 129.47, 129.54, 129.82, 129.94 and 130.21 assignable to twenty seven carbon atoms present in the aromatic system and a peak at \(\delta\) 54.75 attributed to methoxy carbon atom.

Finally the structure of 3a was confirmed by its mass spectral analysis. It exhibits a molecular ion peak at m/z 418 corresponds to its molecular weight. The other peaks at 404, 298, 179, 139 and 101 are in accordance with the fragmentation pattern shown in scheme-2.

All the compounds have been evaluated for antibacterial, antifungal and anthelmintic activity, which is described in the chapter-7. Some selected compounds have also been investigated for possible anti-inflammatory diuretic, analgesic and antipyretic activity.
$^1$H NMR Spectrum of 3a

**Current Data Parameters**
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- **EXPNO**: 1
- **PROCNO**: 1

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- **PROBDID**: 5 mm QNP 1H
- **PULPROG**: zgpr
- **TD**: 16384
- **SOLVENT**: DMSO
- **NS**: 128
- **DS**: 0
- **SWH**: 8928.606 Hz
- **FIDRES**: 0.544959 Hz
- **AQ**: 0.9175540 sec
- **RG**: 4096
- **SW**: 56.000 usec
- **DE**: 70.000 usec
- **TE**: 300.0 K
- **ML1**: 1 dB
- **ML2**: 0.00002000 sec
- **HI2**: 55 dB
- **PL1**: 1500000.00 usec
- **DI3**: 0.00000400 sec
- **PA**: 11.50 usec
- **SP01**: 400.1390642 MHz
- **NUCLEUS**: 1H

**F2 - Processing parameters**
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- **SF**: 400.1362927 MHz
- **WDW**: EM
- **SSB**: 0
- **LB**: 0.30 Hz
- **GB**: 0
- **PC**: 0.20
$^{13}$C NMR Spectrum of 3a

Current Data Parameters
NAME 1124-kumara-13
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 21.34
INSTRUM amx400
PROBHD 5 mm QNP 1H
FULPROG zgdc
TD 16384
SOLVENT DMSO
NS 2921
DS 0
SWH 27777.777 Hz
FIDRES 1.695421 Hz
AQ 0.2949620 sec
RG 32768
DW 18.000 usec
DE 22.500 usec
TE 300.0 K
D11 0.03000000 sec
CPDPRG waltz16
F11 75.000 usec
S2 17 dB
HL1 17 dB
D1 3.00000000 sec
P1 7.0000 usec
SFO1 100.6255846 MHz
NUCLEUS 13C

F2 - Processing parameters
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SF 100.6143966 MHz
WDW EM
SSB LB 5.00 Hz
GB 0
PC 0.08
Sample Name: BMS 99-S7
Sample ID: HSR/342
Data File Name: D:\DATA\ESI\2006\BMS1\DI\BMS1.137.lcd
Method File Name: D:\METHOD\GEN_ESI_Di.icm
Data Acquired: 2/10/2006 2:14:16 PM

LC CONDITIONS:

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A: WATER : ACN : HCOOH (90:10:0.02)
B: WATER : ACN : HCOOH (10:90:0.02)
FLOW RATE: 0.2 mL/min

MS CHROMATOGRAM

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BG Mode: None
Mass Peaks: 810 Base Peak: 418.15 (7682714) Polarity: Pos Segment 1 - Event 1

MASS Spectrum of 3a

[Chemical structure image]
Scheme-2

Mass fragmentation pattern of 3a
Table 6.1: IR and NMR Spectral data of 4-(naphtho[2,1-b]furan-2-yl)-2-(substituted)-phenyl-2,5-dihydro-1H-1,5-benzodiazepines 3a-f

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>IR (KBr) cm⁻¹ (NH)</th>
<th>(^1)H NMR in ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>4-OCH₃</td>
<td>3387</td>
<td>Δ 3.8 (s, 3H, OCH₃), Δ 6.4 (d, 1H, C=CH), Δ 6.7 (d, 1H, CCHPh), Δ 7.2-8.6 (m, 17H, 15ArH+2NH)</td>
</tr>
<tr>
<td>3b</td>
<td>4-Cl</td>
<td>3375</td>
<td>Δ 6.6 (d, 1H, C=CH), Δ 6.8 (d, 1H, CCHPh), Δ 7.4-8.6 (m, 17H, 15ArH+2NH)</td>
</tr>
<tr>
<td>3c</td>
<td>4-NO₂</td>
<td>3362</td>
<td>Δ 6.5 (d, 1H, C=CH), Δ 6.9 (d, 1H, CCHPh), Δ 7.4-8.5 (m, 17H, 15ArH+2NH)</td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td>3378</td>
<td>Δ 6.4 (d, 1H, C=CH), Δ 6.6 (d, 1H, CCHPh), Δ 7.3-8.3 (m, 18H, 16ArH+2NH)</td>
</tr>
<tr>
<td>3e</td>
<td>2-OH</td>
<td>3369</td>
<td>Δ 4.5 (b, 1H, OH), Δ 6.7 (d, 1H, C=CH), Δ 6.9 (d, 1H, CCHPh), Δ 7.5-8.7 (m, 17H, 15ArH+2NH)</td>
</tr>
<tr>
<td>3f</td>
<td>2-Cl</td>
<td>3381</td>
<td>Δ 6.5 (d, 1H, C=CH), Δ 6.8 (d, 1H, CCHPh), Δ 7.6-8.5 (m, 17H, 15ArH+2NH)</td>
</tr>
</tbody>
</table>
Experimental

Synthesis of 1-(naphtho[2,1-b]furan-2-yl)-3-(substituted)phenylprop-2-en-1-one. 2a-f

2-Acetyl naphtho[2,1-b]furan 1 (2.10 g, 0.01 mol) was dissolved in ethanol (50 mL) containing sodium hydroxide (0.4 g, 0.01 mol), to this 4-methoxybenzaldehyde (1.06 g, 0.01 mol) was added and kept for reflux on water bath for 2 hrs. The reaction mixture was poured in to ice cold water, the separated solid was filtered, dried and recrystallised from ethanol to give 2a.

The compounds 2b-f, were synthesized using, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, benzaldehyde, salicylaldehyde, 2-chlorobenzaldehyde in place of 4-methoxybenzaldehyde by the same method described above.

Synthesis of 4-(naphtho[2,1-b]furan-2-yl)-2-(substituted)phenyl-2,5-dihydro-1H-1,5-benzodiazepine. 3a-f

A mixture of 3-(4-methoxyphenyl)-1-naphtho[2,1-b]furan-2-yl-prop-2-en-1-ones 2a (1.09 g, 0.0033 mol), o-phenylenediamine (0.33 g, 0.0033 mol) containing sodium hydroxide (0.01 mol) in absolute ethanol (50 mL) was refluxed on a water bath for 6 hrs. The contents were cooled and poured on to crushed ice. The solid separated was filtered, washed with water, dried and recrystallised from aqueous DMF to give 3a. The compounds 3b-f, were synthesized from 2b-f by the same method described above.

Physical data of the newly synthesized compounds were reported in Table-6.2
Table-6.2: Physical data of new synthesized compounds.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>M.p. $^\circ$C</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Found (Calcd) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>3a</td>
<td>H</td>
<td>208</td>
<td>70</td>
<td>C$<em>{27}$H$</em>{18}$N$_2$O</td>
<td>83.7 (83.9)</td>
</tr>
<tr>
<td>3b</td>
<td>Cl</td>
<td>225</td>
<td>68</td>
<td>C$<em>{27}$H$</em>{17}$N$_2$OCl</td>
<td>76.8 (77.0)</td>
</tr>
<tr>
<td>3c</td>
<td>NO$_2$</td>
<td>&gt;250</td>
<td>65</td>
<td>C$<em>{27}$H$</em>{17}$N$_3$O$_3$</td>
<td>75.0 (75.1)</td>
</tr>
<tr>
<td>3d</td>
<td>OCH$_3$</td>
<td>238</td>
<td>72</td>
<td>C$<em>{28}$H$</em>{20}$N$_2$O$_2$</td>
<td>80.5 (80.7)</td>
</tr>
<tr>
<td>3e</td>
<td>OH</td>
<td>&gt;250</td>
<td>69</td>
<td>C$<em>{27}$H$</em>{18}$N$_2$O$_2$</td>
<td>80.4 (80.5)</td>
</tr>
<tr>
<td>3f</td>
<td>Cl</td>
<td>231</td>
<td>62</td>
<td>C$<em>{27}$H$</em>{17}$N$_2$OCl</td>
<td>76.9 (77.0)</td>
</tr>
</tbody>
</table>
Reference:


Introduction

N-bridged heterocyclic systems derived from substituted 1,2,4-triazoles, have been explored as potential antimicrobial agents\textsuperscript{1-3}. Some of these compounds i.e., triazolo[3,4-\textit{b}][1,3,4]thiadiazoles have been found to be associated with strong CNS depressant and hypertensive activities\textsuperscript{4-6}. Similarly, fused heterocycles derived from 1,2,4-triazolo and thiadiazoles have received attention of synthetic organic chemists owing to their significant antifungal activity\textsuperscript{7-8}.

\[
\text{N—N}
\]
\[
\text{N—N}
\]
\[
\text{N—N}
\]
\[
\text{NH}_2
\]

I

1,2,4-triazolo[3,4-\textit{b}][1,3,4]thiadiazoles

\[
\text{N—N}
\]
\[
\text{R}
\]
\[
\text{N—N}
\]
\[
\text{S}
\]
\[
\text{R}
\]

II

1,2,4-triazolo[3,4-\textit{b}][1,3,4]thiadiazines

However, triazolo[3,4-\textit{b}][1,3,4]thiadiazepines form a group of bridge head heterocycles, which have been less investigated. There are only few reports concerning this heterocyclic system.

Khan and Giri\textsuperscript{9} synthesized 3-aryl-8-nitro-1,2,4-triazolo[3,4-\textit{b}][1,3,4]benzo thiadiazepines and evaluated them for antifungal activity by broth dilution technique.
against *Aspergillus niger* and *Helminthosporium oryzae* and reported that the two compounds i.e., IIIa and IIIh were most active.

![Chemical structure](image)

Similarly, Kalluraya *et al.*, took up the research work involving incorporation of triazolothiadiazepine moiety in novel heterocyclic compounds and investigated them for antibacterial, antifungal, anti-inflammatory, analgesic and anthelmintic activities.

Recently, microwave assisted one pot synthesis of 8-methyl-3,6,9-triphenyl-5,6-dihydro-9H-pyrazolo[3,4-e][1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines has been reported by Nandeshwarappa *et al*.

Triazolothiadiazepines bearing an asymmetric carbon atom and the radio stability has been investigated and some of these compounds have been shown to possess remarkable antifungal activity, when compared with the standard Mycostatine.
Holla et al., synthesized the compounds in which triazolo[3,4-b][1,3,4]thiadiazine moiety is linked with furan moiety via -CH- bridge and found that these compounds exhibited considerable antibacterial and antiviral activity\(^{14}\).

Survey of literature revealed that, similar type of work, involving triazolo[3,4-b][1,3,4]thiazepines and naphtho[2,1-b]furan, either in condensed form or in coupled form has not been reported. Hence it is thought of interest to synthesise 3-phenyl-6-(naphtho[2,1-b]furan-2-yl)-8-(substituted)phenyl-7,8-dihydro[1,2,4]triazole [3,4-b][1,3,4]thiazepines and evaluated them for possible antimicrobial and pharmacological activities.
Present work

One of the methods for such synthesis, involved reaction of chalcones with 5-phenyl-4-amino-1,2,4-triazole. Hence it was contemplated to make use of chalcones prepared during the course of present investigation (Part-A) for the synthesise of bridge head heterocycles encompassing naphtho[2,1-\(b\)]furan.

The desired synthesise was accomplished in two steps as follows.

1. Synthesis of appropriately substituted triazole. 1
2. Reaction of triazole with chalcones.

1. Synthesis of 5-phenyl-4-amino-3-mercapto-1,2,4-triazole. 1

5-Phenyl-4-amino-3-mercapto-1,2,4-triazole 1 was synthesized by well established procedure by Reid \textit{et al}^{15}. The sequence of the reaction is as follows.

\[
\begin{align*}
\text{Cl} + \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} & \rightarrow \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \\
\text{CS}_2/\text{KOH}/\text{Ethanol} & \rightarrow \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \\
\end{align*}
\]

The formation of 5-phenyl-4-amino-3-mercapto-1,2,4-triazole 1, was confirmed by comparing its melting point, \(R_f\) value and spectral data with authentic sample.
2. Reaction of triazole with chalcones.

Triazole thus obtained was treated with chalcones 2a-f, synthesis of which has been described in Part-A of this chapter, in presence of piperidine and ethanol to obtain the product which were identified as 3-phenyl-6-(naphtho[2,1-b]furan-2-yl)-8-(substituted)phenyl-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines 3a-f, on the basis of analytical and spectral studies.

\[
\begin{align*}
\text{1} & \quad + \quad \text{2a-f} \\
\downarrow \text{piperidine/ ethanol} & \\
\text{3a-f}
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>3a</th>
<th>4-OCH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>4-Cl</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>4-NO₂</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>2-OH</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>2-Cl</td>
<td></td>
</tr>
</tbody>
</table>
The IR spectrum of 3a showed absorption band at 1597 cm\(^{-1}\) due to C=N. The \(^1\)H NMR spectrum (DMSO) exhibits a singlet integrating for three protons at \(\delta\) 3.8 due to OCH\(_3\) protons, and a multiplet integrating for nineteen protons at \(\delta\) 7.0-8.5 were due to aromatic protons, two NH protons, C=CH and CHPh protons. The \(^{13}\)C NMR shows peaks at \(\delta\) 112.21, 112.56, 112.63, 112.94, 113.05, 113.37, 113.50, 113.66, 113.82, 114.44, 123.42, 123.54, 123.66, 124.36, 125.50, 127.12, 127.40, 127.70, 128.18, 128.35, 128.53, 128.69, 128.86, 129.31, 129.45, 129.79, 129.95, 130.09 and 130.43 attributed to twenty nine carbon atoms. Peak at \(\delta\) 54.91 attributed to methoxy carbon atom.

Finally the structure of 3a was confirmed by mass spectral analysis. It exhibits a molecular ion peak at m/z 501. Other peaks appearing at m/z 393, 374, 325, 269, 237 and 179 were in accordance with the fragmentation pattern as shown in scheme-3.

The IR and \(^1\)H NMR spectral data of 3b-f were reported in Table-6.3.
Current Data Parameters
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EXPPNO  2
PROCNO  1

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FULPROG  zgpr
TD  16384
SOLVENT  DMSO
NS  128
DS  0
SWH  8928.606 Hz
FIDRES  0.544959 Hz
AQ  0.9175540 sec
RG  2048
DW  56.000 usec
DE  70.00 usec
TE  300.0 K
ML1  1 dB
ML2  55 dB
P18  1500000.00 usec
D13  0.00000400 sec
P1  11.50 usec
SF01  400.1390642 MHz
NUCLEUS  1H

F2 - Processing parameters
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SF  400.1362913 MHz
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\( ^1H \) NMR Spectrum of 3a
$^{13}$C NMR Spectrum of 3a

Current Data Parameters
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EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
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Time 10.08
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SOLVENT DMSO
NS 5108
DS 0
SWH 27777.777 Hz
FIDRES 1.695421 Hz
AQ 0.2943620 sec
RG 32768
DW 18.000 usec
DE 22.50 usec
TE 300.0 K
D11 0.03000000 sec
CPDPRG waltz16
P31 75.00 usec
S2 17 dB
HL 17 dB
D1 3.00000000 sec
P1 7.00 usec
SF01 100.6254456 MHz
NUCLEUS 13C

F2 - Processing parameters
S1 32768
SF 100.6144099 MHz
VDW EN
SSB 0
LB 5.00 Hz
GB 0
FC 0.08
Sample Name: CABSAN 28 - S7
Sample ID: PKJ/452/4
Data File Name: D:\DATA\ESI\CAB28\DI\CAB28.030.lcd
Method File Name: D:\METHOD\GEN_ESI_DI.lcm
Data Acquired: 3/2/2006 9:50:02 AM

LC CONDITIONS:

MOBILE PHASE: A: B (50: 50)
A: WATER : ACN : HCOOH (90:10:0.02)
B: WATER : ACN : HCOOH (10:90:0.02)

FLOW RATE: 0.2 mL/min

LC CHROMATOGRAM

MSS Spectrum of 3a

MOBILE PHASE:
A: WATER : ACN : HCOOH (90:10:0.02)
B: WATER : ACN : HCOOH (10:90:0.02)

FLOW RATE: 0.2 mL/min

MS CHROMATOGRAM

MS Spectrum Graph

MS Spectrum Graph
Scheme-3

Mass fragmentation pattern of 3a

- $\text{C}_6\text{H}_5, \text{CN}_3\text{S}$
- $\text{C}_6\text{H}_4(\text{OCH}_3)$

$m/z$ 502

$m/z$ 501

$m/z$ 325

$m/z$ 393

$m/z$ 374

$m/z$ 179

$m/z$ 237

$m/z$ 268
Table 6.3: IR and NMR Spectral data of 3-Phenyl-6-(naphtho[2,1-b]furan-2-yl)-8-(substituted)phenyl-5,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines. 3a-f

![Chemical Structure of 3a-f](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>IR (KBr) cm⁻¹ C=N</th>
<th>¹H NMR in ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>4-OCH₃</td>
<td>1597</td>
<td>δ 3.8 (s, 3H, OCH₃), δ 7.0-8.5 (m, 19H, 16ArH +NH +C=CH +CHPh)</td>
</tr>
<tr>
<td>3b</td>
<td>4-Cl</td>
<td>1605</td>
<td>δ 7.2-8.6 (m, 19H, 16ArH+NH+C=CH +CHPh)</td>
</tr>
<tr>
<td>3c</td>
<td>4-NO₂</td>
<td>1586</td>
<td>δ 7.1-8.6 (m, 19H, 16ArH+NH+C=CH +CHPh)</td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td>1610</td>
<td>δ 7.0-8.4 (m, 20H, 17ArH+NH+C=CH +CHPh)</td>
</tr>
<tr>
<td>3e</td>
<td>2-OH</td>
<td>1602</td>
<td>δ 5.3 (b, 1H, OH), δ 7.3-8.8 (m, 19H, 16ArH +NH+ C=CH +CHPh)</td>
</tr>
<tr>
<td>3f</td>
<td>2-Cl</td>
<td>1615</td>
<td>δ 7.1-8.5 (m, 18H, 15ArH+NH+C=CH +CHPh)</td>
</tr>
</tbody>
</table>
Experimental

Synthesis of 5-phenyl-4-amino-3-mercapto-1,2,4-triazole. 1

To a solution of phenyl hydrazide (3.9 g, 0.03 mol) in ethanol (25 mL), carbon disulphide (3.42 g, 3.6 mL, 0.045 mol), KOH (2.52 g, 0.045 mol), were added and kept for stirring for 16 hrs at room temperature. The salt obtained was filtered and washed with diethyl ether. The salt (2.29 g, 0.01 mol) was taken in water (10 mL) and to this hydrazine hydrate (1.12 g, 1.5 mL) was added and refluxed for 4 hrs. The reaction mixture turned to green, which was poured into ice cold water and neutralized with conc. hydrochloric acid. The product was recrystallised from aqueous DMF. Yield 73%. Melting point 191 °C.

Synthesis of 3-phenyl-6-(naphtho[2,1-b]furan-2-yl)-8(substituted)phenyl-5,8-di hydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine. 3a-f

A mixture of 3-phenyl-1-naphtho[2,1-b]furan-2-yl-prop-2-en-1-ones 2a (1.09 g, 0.0033 mol) and 5-phenyl-4-amino-3-mercapto-1,2,4-triazole (0.64 g, 0.0033 mol) and piperidine (0.3 g, 0.004 mol) in absolute ethanol (50 mL) was refluxed on a water bath for 6 hrs. The contents were cooled and poured on to crushed ice and neutralized with dil acetic acid. The solid separated was filtered, washed with water, dried and recrystallised from ethanol to give 3a. The compounds 3b-f, were synthesized from 2b-f by the similar method described above. Physical data of these newly synthesised compounds reported in Table-6.4.
Table-6.4: Physical data of new synthesized compounds.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>M.p.</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Found (Calcd) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>°C</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>3a</td>
<td>H</td>
<td>225</td>
<td>71</td>
<td>C$<em>{29}$H$</em>{18}$N$_{4}$OS</td>
<td>73.8 (74.0)</td>
</tr>
<tr>
<td>3b</td>
<td>Cl</td>
<td>248</td>
<td>70</td>
<td>C$<em>{29}$H$</em>{17}$N$_{4}$O$\text{Cl}$</td>
<td>68.8 (68.9)</td>
</tr>
<tr>
<td>3c</td>
<td>NO$_2$</td>
<td>&gt;250</td>
<td>68</td>
<td>C$<em>{29}$H$</em>{17}$N$_{5}$O$_3$S</td>
<td>67.4 (67.5)</td>
</tr>
<tr>
<td>3d</td>
<td>OCH$_3$</td>
<td>&gt;250</td>
<td>64</td>
<td>C$<em>{30}$H$</em>{20}$N$_{4}$O$_2$S</td>
<td>71.8 (71.9)</td>
</tr>
<tr>
<td>3e</td>
<td>OH</td>
<td>&gt;250</td>
<td>71</td>
<td>C$<em>{29}$H$</em>{18}$N$_{4}$O$_2$S</td>
<td>71.4 (71.5)</td>
</tr>
<tr>
<td>3f</td>
<td>Cl</td>
<td>242</td>
<td>67</td>
<td>C$<em>{29}$H$</em>{17}$N$_{4}$O$\text{Cl}$</td>
<td>68.7 (68.9)</td>
</tr>
</tbody>
</table>
References:


