Chapter-V

Synthesis of benzodiazepino, benzothiazepino and benzoxazepino incorporated analogues of 1,5-benzodiazepines linked on its 2-position through an oxyphenoxy bridge
CHAPTER-V
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**ABSTRACT**

This chapter describes the synthesis of 2- (1,5-benzodiazepino,1,5-benzothiazepino and 1,5-benzoxazepino incorporated analogues of 1,5-benzodiazepine 5.044-5.049 linked to it through an oxyphenyl bridge from the corresponding dimethylamino methylene ketone and chalcone derivatives (5.043, 5.039) following the strategies depicted in schemes 5.9 and 5.10 respectively. The structures of all compounds have been established by elemental analysis, IR, $^1$HNMR and MS spectral data.
5.1 INTRODUCTION

It was mentioned earlier in chapter-1 that heterocyclic systems containing 1,5-benzodiazepines have attracted the attention of chemists owing to this nuclei having been identified in the literature as most promising pharmacophores in drug design and synthesis\(^1\). Literature is replete with the chemistry of azepines and their derivatives to form an important pharmacophores in exhibiting broad spectrum of biological properties\(^2\) including the anti-HIV activity.

It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exert a profound influence on the biological profile of the molecules. Based on these observations, it was anticipated that incorporation of the bioactive azepine moiety\(^2\) into the molecular framework of 1,5-benzodiazepines could produce interesting series of compounds with enhanced biological activities.

This chapter describes the study based on this assumption and presents the synthesis of azepine incorporated analogues of 1,5-benzodiazepine nucleus from the corresponding active synthons such as the chalcones and dimethylamino methylene ketones.

The heterocyclic systems with seven atoms, once considered as chemical oddities, are today just as easily obtained as five and six membered analogues, and these compounds no longer remain the esoteric species, they were once considered to be. Hence, the pace of research and development in this area is witnessing acceleration due to the substantial advancement in the synthetic art that has been made in this field in the last few decades. As a result of that, there seems to be virtually no limit in the number of interesting ring systems that can be created in the laboratory today by the combination of ingenuity and perseverance. The vast commercial success of these medicinal agents and their benefit to society in the modern treatment of mental illness and other wide variety of disease have caused the chemistry of these systems to evolve into a major area of research in the field of heterocyclic chemistry\(^5\).
5.2 BIOLOGICAL ASPECTS

5.2.1 Biological aspects of 1, 5-benzodiazepine

Already discussed in chapter 1 in section 1.2.1

5.2.2 Biological aspects of benzothiazepine derivatives

Heterocyclic compounds containing nitrogen and sulphur in a seven
membered ring such as benzothiazepines and benzodiazepines have received
considerable attention in recent years. Benzothiazepines have been claimed for
various therapeutic activities, but the investigation of their chemistry commenced
rather slowly. It is only recently that attention is being directed to the synthetic
methods, chemical, and biological properties. Benzothiazepines possess wide
variety of activities like anti-convulsant\(^6\), CNS depressant\(^7\), \(\text{Ca}^{++}\) channel blockers,
anti-cancer\(^8\), anti-fungal\(^9\), anti-HIV\(^{10}\), and anti-psychotic properties etc. However
there are fewer reports on their CNS action, especially anti-convulsant and CNS
depressant. One of the approaches to analog-based drug discovery is the concept of
‘bioisosteric replacement’ which continues to play an important role in bioorganic
and medicinal chemistry to design novel pharmacological tools as well as new
therapeutic agents with potent pharmacological profiles and improved
pharmacokinetic properties. Benzothiazepines are bioisosters of benzodiazepines
and contain a sulphur atom in place of one nitrogen atom.

The 1,5-benzothiazepine scaffolds are extremely versatile and features in a
great number of important drugs. Diltiazem\(^{11}\) (5.01) is used in the treatment of
hypertension, angina pectoris, arrhythmias and other related cardiac disorders. It
also increases the supply of blood and oxygen to heart. Thiazem\(^{12}\) (5.02) act as
psychotopic agent, clentiazem\(^{13}\) (5.03) have anti-atherogenic effect, and
clothiapine\(^{14}\) (5.04) is very active on 5-HT2 receptors and also possess anti-
muscarinic potential. (Fig.-5.1)
5.2.3 Biological aspects of benzoxazepine derivatives

1,5-Benzoxazepines makeup a broad class that attracted attention of researchers in the past few years owing to their wide range of biological activities especially anti-convulsant and CNS depressant activities. Benzoxazepines have been proven to possess an effective medicinally potent agents *e.g.* orexin receptor antagonists are used for the treatment of obesity and sleep disorders. They are found to be potent as active angiotensin converting enzyme inhibitors and thus are effective for the treatment of hypertension in man. They have a neuroleptic biochemical profile with mainly anti-dopaminergic activity at D$_2$-type receptors and are effective for the treatment of schizophrenia. Loxapine (5.05) is an anti-psychotic agent. It has a neuroleptic biochemical profile with mainly anti-dopaminergic activity at D$_2$-type receptors. It may be effective for the treatment of schizophrenia but it may cause extra-pyramidal adverse effects compared with typical drugs. Amoxapine (5.06) is used clinically as an anti-depressant. It binds to D$_2$-receptors and inhibits the norepinephrine neurotransporter to block neuronal norepinephrine reuptake, to show antidepressant activity. (Fig.-5.2)
5.3 SYNTHETIC ASPECTS

The broad spectrum of medicinal properties associated with these molecules has triggered the development of a variety of methods for the synthesis of these materials and has led to an impressive armoury of synthetic strategies to be devised in the literature for this class of compounds. In this context it seems necessary to present in the discussion to follow a brief outline of the available literature methods, for their synthesis.

5.3.1 Synthetic aspects 1, 5-benzodiazepines

Already discussed in chapter 1 in section 1.2.2

Synthetic aspects of 1, 5-benzothiazepines

A few important methods which have appeared in the literature for the synthesis of 1,5-benzothiazepines are described below:

1. $N$-Substituted cinnamamides (5.10) [derived of $N$-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-yl]acetamide (5.08)] were obtained using various aldehydes. $N$-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-yl] acetamide (5.08) was itself prepared from 3-(2-amino-1,3-thiazol-4-yl)-2H-chromen-2-one (5.07) by acetylation with acetyl chloride in chloroform. Further, 5.10 on treatment with 2-aminobenzenethiol in the presence of glacial acetic acid as catalyst and methanol as reaction mediator afforded 2,3-dihydro-2-aryl-4-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-ylamino]-1,5-benzothiazepine (5.12) (Scheme-5.1).
Scheme Reagents and reaction conditions: (i) \(\text{CH}_3\text{COCl}/\text{CHCl}_3\), 0°C, 8hr (ii) Conventional: \(\text{CH}_3\text{OH}/\%\text{NaOH}\), reflux, 6-8hr. Microwave: \(\text{CH}_3\text{OH}/2\%\text{NaOH}\), MWI, 2.0-3.5 min. (iii) Conventional: \(\text{CH}_3\text{OH}/\text{glacial CH}_3\text{COOH}\), reflux, 60-70hr. Microwave: \(\text{CH}_3\text{OH}/\text{glacial CH}_3\text{COOH}\), MWI, 2.0-3.5min.

2. 1,3-Substituted-prop-2-en-1-one (5.015) were synthesized by microwave-assisted Claisen-Schmidt condensation of acetylated \(\alpha\)-naphthol with aldehydes in presence of alkali and ethanol. The 5.015 was converted to 5.017 with the reaction of various aldehydes in basic medium. Synthesis of 2, 3-dihydro-2-substituted-4- (naphthalene-2'-ol)-yl-1,5-benzothiazepines (5.018) was carried out by cyclocondensation of 1,3-substituted-prop-2-en-1-one (5.017) with 2-aminothiophenol in the presence of eco-friendly catalyst zinc acetate in the solvent free condition under microwave irradiation (Scheme-5.2)\(^22\).

![Scheme-5.2](image)

3. (±)cis-2-(4-Methoxyphenyl)-3-hydroxy-2,3-dihydro-1, 5-benzothiazepin-4(5H)-ones (5.021) have been synthesized by the condensation of 2-amino-benzenethiol (5.019) with methyl (±) trans-3-(4-methoxyphenyl)glycidate (5.020) in xylene at 160°C for 16-20 hrs under a nitrogen atmosphere (Scheme-5.3)\(^23\).
4. The starting compound (E)-1-(5-chloro-2-hydroxyphenyl)-3-(4-fluorophenyl) prop-2-en-1-one \((5.024)\) was prepared by the Claisen-Schmidt condensation of various substituted acetophenones \(5.022\) with aromatic aldehydes in presence of ethanol/KOH. The cyclisation of chalcones \(5.024\) by 2-aminothiophenol using ethanol and acetic acid on reflux gave substituted 1,5-benzodiazepines \((5.026)\) (Scheme-5.4)\(^{24}\).

**Synthetic aspects of 1, 5-benzoxazepine**

On account of the variety of therapeutic applications, significant amount of work has been done on the synthesis of 1,5-benzoxazepine derivatives. In view of interest in this area of research, several synthetic strategies have been explored for the synthesis of 1,5-benzoxazepine derivatives. Some of them are described here as follows:

1. 1, 5-Benzoxazepines \((5.029)\) have been synthesized from 2-chloro-6-methylquinoline-3-carbaldehyde \((5.027)\), 2-aminophenol \((5.028)\) and KI (Scheme-5.5)\(^{25}\).
2. Reaction of $\alpha$-oxoketene-S,S-acetals (5.030) with $\alpha$-aminophenol (5.031) gives the corresponding 1,5-benzoazepines (5.032) (Scheme-5.6).  

3. The 2,3,4,5-tetrahydro-1,5-benzoazepine (5.035) has been synthesized by the reaction of 2-aminophenol (5.033) with 1,3-dibromopropane (5.034) in anhydrous dimethylformamide in the presence of sodium hydride (Scheme-5.7).  

4. 7,9-Dihydro-6,6,9,9-tetramethyl-11-(2-methylpropenyl)-6H-pyrido[2,1-d][1,5]-benzoazepine (5.038) have been synthesized by the reaction of 2-aminophenol (5.036) and a large excess of acetone (5.037), as a solvent and reagent, in the presence of p-toluenesulphonic acid catalyst. (Scheme-5.8)
5.4 PRESENT WORK

It was mentioned earlier in this chapter, that a large number of compounds containing 1,5-benzoazepine nucleus have been patented, as chemotherapeutic agents\(^3\). Benzo-1,5-substituted azepines constitute an important class of psychopharmacopeia, in particular as tranquilizers and also as potent virucides and non-nucleoside inhibitors of HIV-1 reverse transcriptase\(^4\)\(^-\)\(^5\). Beside this, benzo-1,5-substituted azepines show antifungal, antibacterial, antifeedant, anti-inflammatory, analgesic, antihypnotic, anticonvulsant, antidepressive and sedative activities\(^28\)\(^-\)\(^30\). In view of this, it was expected that incorporation of azepine nucleus to 1,5-benzodiazepine framework could produce interesting compounds with enhanced biological properties.

Chalcone and dimethylamino methylene ketones have received considerable attention due to their synthetic importance for the construction of a variety of fused heterocyclic systems. In view of the interesting biological properties exhibited by azepines\(^31\)\(^-\)\(^34\) and 2-chloro-4-methyl-1,5-benzodiazepines it was considered of interest in the present work to design molecules in which these moieties were present in a single molecular framework, to provide an additive effect on the overall biological efficacy in the resulting molecules.

5.5 RESULTS AND DISCUSSION

In view of the impressive pharmacodynamic applications\(^28\)\(^-\)\(^30\) of substituted azepines and 1,5-benzodiazepines much attention has concentrated towards developing new synthetic routes to heteroring fused azepine and 1,5-
benzodiazepines. The synthesis of this series of heterocycles was undertaken in the present work with this assumption that incorporation of one or more than one heterocyclic moiety into bioactive 1,5-benzodiazepine framework could result in molecules with enhanced bioactivity. Chalcones and dimethylaminomethylene ketones are very reactive intermediates in synthesis: chalcones and are prone to undergo Micheal addition reaction with various nucleophiles such as o-phenylenediamine, o-aminothiophenol, o-aminophenol etc. (Chalcones and dimethylamino methylene ketones were synthesized by the sequence of reactions, already shown in chapter-II under the heading of synthesis of starting materials). These were found to react smoothly with o-phenylenediamine, o-aminothiophenol, o-aminophenol in ethanol and acetic acid to afford the corresponding 1,5-benzodiazepino (5.044 and 5.047) (Scheme-5.9 and 5.10), 1,5-benzothiazepine (5.045 and 5.048) and 1,5 benzoxazepino (5.046 and 5.094) incorporated analogues of 1,5-benzodiazepines linked on its 2- position through anoxyphenyl bridge (Scheme-5.9 and 5.10) respectively.
Structures of compounds whose synthesis is described in this chapter
Table 5.01: Physical and analytical data of the compounds:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound No.</th>
<th>Molecular Formula</th>
<th>M.W.</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
<th>Elemental analysis</th>
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<td>(Cal./exp.) C</td>
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<td>(Cal/exp.) H</td>
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<td>(Cal/exp.) N</td>
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<td></td>
<td>(Cal./exp.) S</td>
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<td>1.</td>
<td>5.044</td>
<td>C_{31}H_{24}N_{4}O</td>
<td>468.55</td>
<td>180-182</td>
<td>72</td>
<td>79.46/79.85</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.16/5.18</td>
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<td></td>
<td></td>
<td></td>
<td>11.96/12.01</td>
</tr>
<tr>
<td>2.</td>
<td>5.045</td>
<td>C_{31}H_{23}N_{3}O_{2}</td>
<td>469.53</td>
<td>196-198</td>
<td>67</td>
<td>79.30/79.65</td>
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<td>4.94/5.92</td>
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<td></td>
<td></td>
<td>8.95/8.91</td>
</tr>
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<td>3.</td>
<td>5.046</td>
<td>C_{31}H_{23}N_{3}O_{2}</td>
<td>485.60</td>
<td>160-163</td>
<td>70</td>
<td>76.67/76.31</td>
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<td>4.77/4.79</td>
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<td></td>
<td>8.65/8.61</td>
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<td></td>
<td>6.60/7.75</td>
</tr>
<tr>
<td>4.</td>
<td>5.047</td>
<td>C_{36}H_{22}N_{2}O</td>
<td>392.45</td>
<td>171-175</td>
<td>74</td>
<td>76.79/77.17</td>
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<td></td>
<td></td>
<td>5.35/5.32</td>
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<td></td>
<td></td>
<td>13.90/14.20</td>
</tr>
<tr>
<td>5.</td>
<td>5.048</td>
<td>C_{36}H_{21}N_{2}O</td>
<td>393.44</td>
<td>179-181</td>
<td>71</td>
<td>76.32/76.70</td>
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<td>5.46/5.48</td>
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<td></td>
<td></td>
<td>13.85/14.20</td>
</tr>
<tr>
<td>6.</td>
<td>5.049</td>
<td>C_{36}H_{21}N_{2}O</td>
<td>409.50</td>
<td>177-179</td>
<td>78</td>
<td>79.10/78.71</td>
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<td>5.01/5.03</td>
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<td>7.61/7.79</td>
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<td></td>
<td></td>
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<td>7.70/7.83</td>
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Table 5.02: Spectral data of compounds 5.044 and 5.049:

<table>
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<th>S. No.</th>
<th>Compound No.</th>
<th>IR(KBr) cm(^{-1})</th>
<th>(^1)HNMR(CDCl(_3)) δ ppm and MS (rel. abundance) %</th>
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<tbody>
<tr>
<td>1.</td>
<td>5.044</td>
<td>3300 [N-H str.]</td>
<td>7.34-7.41 [m, 4H, ArH]</td>
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<tr>
<td></td>
<td></td>
<td>3310 [C-H str. ArH]</td>
<td>7.02 [d, 2H, aromatic protons of phenoxy group]</td>
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<tr>
<td></td>
<td></td>
<td>1500 [C=N str.]</td>
<td>7.65 [d, 2H, aromatic protons of phenoxy group]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1190 [C-O str.]</td>
<td>4.60 [s, 1H, CH]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1550 [C=C str. ArH]</td>
<td>2.67 [s, 2H, CH(_2)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.52 [s, 3H, CH(_3)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.0 [s, 1H, NH]</td>
</tr>
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<td></td>
<td>6.89-7.23 [m, 5H, ArH]</td>
</tr>
<tr>
<td>2.</td>
<td>5.045</td>
<td>3000 [C-H str. ArH]</td>
<td>7.12-7.53 [m, 4H, ArH]</td>
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<tr>
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<td></td>
<td>2208 [CN str.]</td>
<td>7.35-7.58 [m, 4H, ArH]</td>
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<td></td>
<td></td>
<td>1555 [C=C str. ArH]</td>
<td>7.05 [d, 2H, aromatic protons of phenoxy group]</td>
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<td></td>
<td></td>
<td>1595 [C=N str.]</td>
<td>7.83 [d, 2H, aromatic protons of phenoxy group]</td>
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<td></td>
<td></td>
<td>1150 [C-O str.]</td>
<td>3.48 [s, 1H, CH]</td>
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<td>2.55 [s, 2H, CH(_2)]</td>
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<td>1.95 [s, 3H, CH(_3)]</td>
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<td>6.68-7.34 [m, 4H, ArH]</td>
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<tr>
<td>3.</td>
<td>5.046</td>
<td>794 [C-S str.]</td>
<td>7.11-7.20 [m, 5H, ArH]</td>
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<td>3015 [C-H str. ArH]</td>
<td>7.57 [d, 2H, aromatic protons of phenoxy group]</td>
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<td>1600 [C=N str.]</td>
<td>7.21 [d, 2H, aromatic protons of phenoxy group]</td>
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<td>1560 [C=C str. ArH]</td>
<td>2.88 [s, 2H, CH(_2)]</td>
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<td>1105 [C-O str.]</td>
<td>1.56 [s, 3H, CH(_3)]</td>
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<td>7.02-7.56 [m, 4H, ArH]</td>
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<td>7.15-7.54 [m, 4H, ArH]</td>
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<td></td>
<td></td>
<td></td>
<td>485.6 (42%), 486.2 (22%), 487.1 (12%), 423.4 (4%), 372.2 (100%)</td>
</tr>
<tr>
<td>S. No.</td>
<td>Compound No.</td>
<td>IR(KBr) cm⁻¹</td>
<td>¹H NMR(CDCl₃) δ ppm and MS (rel. abundance)%</td>
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<td>4.</td>
<td>5.047</td>
<td>3310 [N-H str.] 3030 [C-H str. ArH] 1150 [C-O str.] 1557 [C=C str. ArH] 1596 [C=N str.]</td>
<td>7.19-7.22 [m, 4H, ArH] 7.70 [d, 2H, aromatic protons of phenoxy group] 7.21 [d, 2H, aromatic protons of phenoxy group] 5.78 [d, 1H, CH] 4.89 [d, 1H, CH] 4.10 [s, 1H, NH] 2.59 [s, 2H, CH₂] 1.41 [s, 3H, CH₃] 7.26-7.68 [m, 4H, ArH] 392.4 (31%), 393.9 (22%), 394.4 (15%), 357.2 (5%), 251.2 (100%)</td>
</tr>
<tr>
<td>5.</td>
<td>5.048</td>
<td>3040 [C-H str. ArH] 1120 [C-O str.] 1600 [C=C str. ArH] 1720 [C=N str.]</td>
<td>7.36-7.40 [m, 4H, ArH] 7.69 [d, 2H, aromatic protons of phenoxy group] 7.03 [d, 2H, aromatic protons of phenoxy group] 5.18 [d, 1H, CH] 4.57 [d, 1H, CH] 2.46 [s, 2H, CH₂] 1.67 [s, 3H, CH₃] 6.95-7.16 [m, 4H, ArH]</td>
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<tr>
<td>6.</td>
<td>5.049</td>
<td>810 [C-S str.] 3015 [C-H str. ArH] 1090 [C-O str.] 1590 [C=C str. ArH] 1550 [C=N str.]</td>
<td>7.33-7.46 [m, 4H, ArH] 7.66 [d, 2H, aromatic protons of phenoxy group] 7.05 [d, 2H, aromatic protons of phenoxy group] 7.85 [d, 1H, CH] 6.10 [d, 1H, CH] 2.73 [s, 2H, CH₂] 1.54 [s, 3H, CH₃] 7.17-7.39 [m, 4H, ArH]</td>
</tr>
</tbody>
</table>
5.6 INTERPRETATION OF SPECTRAL DATA FOR THE ELUCIDATION OF STRUCTURE OF COMPOUNDS 5.044-5.049

Structure of all the compounds 5.044-5.049 were established on the basis of microanalysis, IR, $^1$H NMR, and MS spectral data, physical data of all the compounds were found to be consistent to the structures assigned to these molecules.

The physical data, microanalyses, infrared and $^1$HNMR spectral data of all the compounds are presented in the table 5.01 and 5.02 and spectral graphs of a few selected compounds are shown in the spectral charts 5.1 to 5.6.

IR spectra of compound 5.039 on KBr exhibited a medium intensity bands at 3088 cm$^{-1}$ (C-H str. of $\alpha,\beta$-unsaturation ketone), 1640 cm$^{-1}$ (C=C of $\alpha,\beta$-unsaturation ketone). Along with this IR spectrum also exhibited band at 2929 cm$^{-1}$ (C-H str. ArH), 1532 cm$^{-1}$ (C=N str.), 1610 cm$^{-1}$ (C=C str. ArH), 1290 cm$^{-1}$ (C-N str.) and 1090 cm$^{-1}$ (C-O str.).

Appearance of strong absorption band at 3300 cm$^{-1}$ [N-H str.] and 1500 cm$^{-1}$ (C=N str. of 1,5 benzodiazepine ring ) in IR spectrum of compound 5.044, indicated clearly the incorporation of 1,5 benzodiazepine ring in compound 5.044. This was further supported by the disappearance of band for (C=C of $\alpha,\beta$-unsaturation ketone) at 1640 cm$^{-1}$ 5.044. This provided a good evidence for the formation of 5.044 from its precursor 5.039.

In a likewise manner the formation of compounds 5.045, 5.046 from compound 5.039 were ascertained on the basis of IR spectrum.

Appearance of additional peaks 3310 [N-H str.], 1596 [C=N str.of 1,5 diazepine ring] in IR spectrum of compounds 5.047 indicated clearly the incorporation of 1,5-benzodiazepine ring in compound 5.047. This was further supported by the disappearance of band for (C=C of $\alpha,\beta$-unsaturation ketone) at 1640 cm$^{-1}$. In this clearly way, its formation was ascertained on the basis of IR spectrum.

In a likewise manner the formation of compounds 5.048, 5.049 from compound 5.043 were ascertained on the basis of IR spectrum.
\(^1\)HNMR spectra

\(^1\)HNMR spectrum of compound **5.039** at 400 MHz in CDCl\(_3\) displayed characteristic signals for the presence of twenty six protons in the molecule. Appearance of a multiplet for four protons at \(\delta\) 7.34-7.41 were attributed to benzene protons. A sharp singlet at \(\delta\) 4.6 for CH of 1,5- benzodiazepine ring , broad singlet at \(\delta\) 4.01 for one proton of NH confirmed the formation of the compound **5.044** its formation was further supported by the appearance of a multiplet in region of \(\delta\) 6.89-7.23 for five protons of phenyl ring attached to 1,5– benzodiazepine ring in **5.044**.

In a likewise manner the formation of compounds **5.045, 5.046** from compound **5.039** were ascertained on the basis of \(^1\)HNMR spectrum.

\(^1\)HNMR spectrum of compound **5.047** at 400MHz in CDCl\(_3\) displayed characteristic signals for the presence of twenty two protons in the molecule. Its formation was indicated by the appearance of two doublets at \(\delta\) 5.78 and \(\delta\) 4.89 for two protons of 1,5-benzodiazepines ring, and a broad singlet at \(\delta\) 4.10 for one proton of NH .The formation of the compound **5.047** was further supported by the appearance of a multiplet for four aromatic protons in the region of \(\delta\) 7.26-7.68 which was attributable to four arene protons of 1,5-benzodiazepine ring and in the region of \(\delta\) 7.19-7.22 for four other aromatic protons of the incorporated 1,5-benzodiazepine ring.

In a likewise manner the formation of compounds **5.048, 5.049** from compound **5.043** were confirmed on the basis of \(^1\)HNMR spectrum.
5.7 MECHANISM OF FORMATION OF COMPOUNDS 5.044-5.049

5.7.1 Mechanism of formation of compound 5.044 from 5.039

The mechanistic pathway for the formation of 5.045-5.046 from 5.039

Scheme-5.11
5.7.2 Mechanism of formation of compound 5.045-5.046 from 5.039

The mechanistic pathway for the formation of 5.045-5.046 from 5.039

Scheme-5.12
5.7.3 Mechanism of formation of compound 5.047 from 5.043

The mechanistic pathway for the formation of \textit{5.047} from \textit{5.043}

Scheme-5.13

5.7.4 Mechanism of formation of compound 5.048-5.049 from 5.043

The mechanistic pathway for the formation of \textit{5.048-5.049} from \textit{5.043}

Scheme-5.14
5.8 EXPERIMENTAL SECTION

1. Melting points were determined in open glass capillaries and are uncorrected.
2. The purity of the compounds was checked by TLC on silica gel (G) plates.
3. IR spectra were recorded on KBr (SHIMADZU) FTIR-8400S.
4. $^1$HNMR spectra were recorded on model AVANCE II 400 (BRUKER) using CDCl$_3$ as solvent and TMS as an internal reference. Chemical shift are expressed in $\delta$ ppm.
5. Before analysis all samples were dried for one hour under reduced pressure.
6. Physical and spectral data for all the compounds are given in table 5.01 and 5.02.

Synthetic Procedure

Experimental procedure for the preparation of 5.044-5.049 is described below in a stepwise manner

*Preparation of 2-[4'(2'"-(4"'-phenyl-1"',5"'-benzodiazepino)-phenoxy-4-methyl-1,5-benzodiazepine (5.044)*

A mixture of o-phenylenediamine (1.08 g., 0.01mol), (2-(methyl-4-(4-(4-phenylbuta-1,3-dien-2-yl) phenoxy)-3H-1,5-benzo [1,5] diazepine (5.039) (4.56g.,0.012 mol) in ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 5.044a 2-Iodoxybenzoic acid (0.56g., 0.0020 mol) was added all at once to a solution of 5.044a (1.49g., .0029mol) in deionized water (6.5 mL,0.0045 M) in a 100 mL flask. The reaction mixture was warmed to 70-75°C over 20 min. and magnetically stirred at this temperature for 3 h. The nature of the mixture varied consistently during the reaction. The initial thick slurry coating on the walls of the flask eventually became a finely dispersed, easy to be stirred suspension of solid that sedimented easily upon stopping the stirring. The suspension was then cooled to 5°C and left at this temperature for 1.5 h. with slow stirring. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with water and acetone to give 5.044 (0.39., yield 74%); m.p:-180-182°C.
**Synthesis of benzodiazepino, benzothiazepino and benzoxazepino ……**

**Preparation of 2-[4'-(2''-(2''-phenyl-1'',5''-benzoxazepino)-phenoxy]-4-methyl-1,5-benzodiazepine (5.045)**

A mixture of o-aminophenol (1.09 g., 0.01mol), (2-(methyl-4-(4-(4-phenylbuta-1,3-dien-2-yl) phenoxy)-3H-1,5-benzo [1,5] diazepine (5.039) (4.56g.,0.012 mol) in ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 5.044 2-Iodoxybenzoic acid (0.56g., 0.0020 mol) was added all at once to a solution of 5.044 (1.49g., .0029mol) in deionized water (6.5 mL,0.0045 M) in a 100mL flask. The procedure described in the preparation of 5.044 was applied to this to give 5.045 (0.46., yield 69%); m.p:-196-198ºC.

**Preparation of 2-[4'-(2''-(2''-phenyl-1'',5''-benzothiazepino)-phenoxy]-4-methyl-1,5-benzodiazepine (5.046)**

A mixture of o-aminothiophenol (1.09 g., 0.01mol), (2-(methyl-4-(4-(4-phenylbuta-1,3-dien-2-yl) phenoxy)-3H-1,5-benzo [1,5] diazepine (5.039) (4.56g.,0.012 mol) in ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 5.046 2-Iodoxybenzoic acid (0.56g., 0.0020 mol) was added all at once to a solution of 5.046 (1.49g., .0029mol) in deionized water (6.5 mL,0.0045 M) in a 100mL flask. The procedure described in the preparation of 5.044 was applied to this to give 5.046. (0.55., yield 76%); m.p:-160-163ºC.

**Preparation of 2-[4'-(2'-(1'',5''-benzodiazepino)-phenoxy]-4-methyl-1,5-benzodiazepine (5.047)**

A mixture of o-phenylenediamine (1.08 g., 0.01mol), 3-(dimethylamino)-1-(4-(4-methyl-3H-1, 5-benzodiazein-2-yloxy)phenyl) prop-2-en-l-one (5.043) (4.16g., 0.012 mol) in ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 5.047 (0.42g., yield 68%); m.p:171-175ºC.
Synthesis of benzodiazepino, benzothiazepino and benzoazepino …

Preparation of 2-[4'-(2''-(1'',5''-benzoxazepino))-phenoxy]-4-methyl-1,5-benzodiazepine (5.048)

A mixture of o-aminophenol (1.09g., 0.01mol), 3(dimethylamino)-1-(4-(4-methyl-3H-1,5-benzodiazepine-2-yl)oxy)phenyl)prop-2-en-1-one (5.043) (4.16g., 0.012 mol) in ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 5.048 (0.45 g., yield 70%); m.p:179-181ºC.

Preparation of 2-[4'-(2''-(1'',5''-benzothiazepino))-phenoxy]-4-methyl-1,5-benzodiazepine (5.049)

A mixture of o-aminothiophenol (1.25 g., 0.01mol), 3-(dimethylamino)-1-(4-(4-methyl-3H-1,5-benzodiazepin-2-yl)oxy) phenyl)prop-2-en-1-one (5.043) (4.16g., 0.012 mol) and ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 5.049 (0.50 g., yield 74%); m.p:177-179ºC.
Spectrum No. 5.1: IR Spectrum of 2-[4''-(2''-(2''-phenyl-1'',5''-benzothiazepino)]-phenoxy-4-methyl-1,5-benzodiazepine (5.046)

Spectrum No. 5.2: IR Spectrum of 2-[4''-(2''-(1'',5''-benzodiazepino)]-phenoxy-4-methyl-1,5-benzodiazepine (5.047)
Spectrum No. 5.3: $^1$HNMR Spectrum of 2-[4'-(2''-(2''-phenyl-1'','5''-benzothiazepino)]-phenoxy-4-methyl-1,5-benzodiazepine (5.046)

Spectrum No. 5.4: $^1$HNMR Spectrum of 2-[4'-(2''-(1''','5''-benzodiazepino)]-phenoxy-4-methyl-1,5-benzodiazepine (5.047)
Spectrum No. 5.5: Mass Spectrum of 2-[4'-(2''-(1'',5''-benzodiazepino)-phenoxy)-4-methyl-1,5-benzodiazepine (5.047)

Spectrum No. 5.6: Mass Spectrum of 2-[4'-(2''-(2''-phenyl-1'',5''-benzothiazepino))-phenoxy]-4-methyl-1,5-benzodiazepine (5.046)
5.9 REFERENCES


22. Raval J. P., Desai J. T., Desai C. K., and Desai K. R., A comparative study of microwave assisted and conventional synthesis of 2,3-dihydro-2-ary1-4-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-ylamino]-1,5-benzothiazepines and its antimicrobial activity. ARKIVOC 2008, (xii), 233-244.


