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# SYNTHESIS, EXPERIMENTAL STUDIES OF THE ANTIMICROBIAL POTENTIAL OF SOME NOVEL 1, 5- BENZO THIAZEPINE DERIVATIVES

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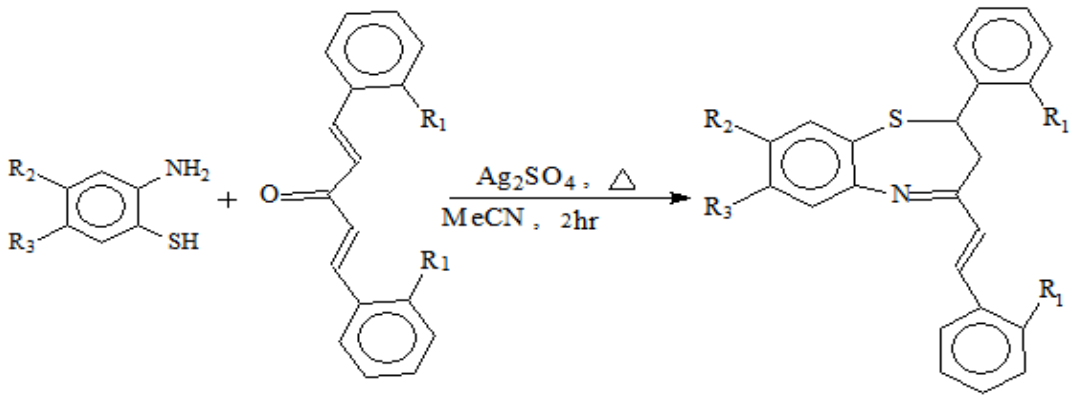
## ABSTRACT

Optically active 1, 5- benzothiazepines belong to the well known benzothiazepine type substances. Some of them possess important bioactivities. In this article, optically active 2, 3-dihydro-1, 5-benzothiazepine derivatives are synthesized by the reaction of new α-β unsaturated carbonyl compounds with 2-aminothiophenol under mild conditions in the presence of silver sulphate in acetonitrile in short reaction time with excellent yield. The structures of newly synthesized compounds were confirmed by spectral evidence and the compounds were evaluated for their anti-bacterial and antifungal activity. All synthesized compounds have shown excellent results.

**INTRODUCTION:** Benzothiazepines are seven member heterocyclic compounds now a day they have received considerable attention and claimed various therapeutic activities and hence, they utilized in drug research [1-14]. Recently, attention is being directed to their synthetic methods, chemical and biological properties. Benzothiazepines posses wide variety of activities like anticonvulsant [15], CNS depressant [16-19], $Ca^{++}$ channel blockers [20], calcium channel modulator [21], calcium channel antagonist [22], anticancer [23], anti fungal [24], antimicrobial [25], anti-HIV [26] and anti-anginal [27]. They are prepared by condensation of 2-aminothiophenol with carbonyl compounds, and different relationships have been observed between substrate and products formed [28-38], these reactions are investigated by different research groups, still research in this area is going on and synthesis of 1, 5-benzothiazepine derivatives containing more than one antibacterial and antifungal pharmacophore site is needed.




**1** **2** **3(a-h)**

**SCHEME 1**

In the present investigation novel optically active 2, 3-dihydro- 1, 5- benzothiazepine derivatives are synthesized by the reaction of new α-β unsaturated carbonyl compounds (Dibenzal Acetone) with 2-aminothiophenol under mild conditions in the presence of silver sulphate in acetonitrile in short reaction time with excellent yield. Dibenzal acetones substrate with 2-aminothiophenol has not yet been used for the synthesis of 1, 5-benzothiazepines. The structures of all newly synthesized compounds were established by M. Pt., IR and $^1$H-NMR spectral data and they were evaluated for antibacterial and antifungal activity (Table 2).

**MATERIALS AND METHODS:** Melting points were taken in open capillaries and are uncorrected. All $H^1$ NMR spectra were recorded in $CDCl_3$/DMSO on Brucker AC 200 and Brucker MSL 300 spectrometers and chemical shift were reported in ppm downfield from tetramethylsilane. Infrared (IR) spectra were recorded on a Perkin Elmer Infra-Red spectro-photometer using KBr discs and Mass spectra were taken on ESI-Esquire 3000 Brukers Daltonics instrument. All SD fine chemicals were used, while the reagents and solvents were of analytical grade purity.

The purity of synthesized compounds have been checked by TLC [Performed on silica gel coated aluminum plates using ethyl acetate and pet ether (3:7 v/v) as eluent visualizing the spots under ultraviolet light and iodine chamber]. The novel starting material dibenzal acetones were synthesized by Clasein Schmidt condensation by reacting, 2 mole of substituted benzaladehyde with 1 mole of acetone in the presence of alkali. The title compounds novel 1, 5-benzothiazepine derivatives were prepared by refluxing upon substituted Dibenzal Acetones with substituted 2- aminothiophenol and silver sulphate in acetonitrile as a solvent (**Scheme 1**). Their structures were confirmed by spectral analysis.

**RESULTS AND DISCUSSIONS:** Silver sulphate is a good reagent, in acetonitrile solvent it efficiently catalyzed the condensation of α-β unsaturated carbonyl compounds (Dibenzal Acetones) with2-aminothiophenol, under mild conditions with excellent yield of the product. In this communication the strategy is, 2- aminothiophenol, α -β unsaturated carbonyl compounds and catalytic amount of silver sulphate in 10ml acetonitrile were refluxed for 2hr, completion of the reaction was monitored by TLC after completion of reaction. The solvent was evaporated under reduced pressure solid separated recrystallized from suitable solvents which was further purified by column chromatography. The compounds 3(a-h) have been characterized by M. Pt., IR and **$^1$**H-NMR and Mass Spectroscopy and were screened for antifungal and antibacterial activities. The results are summarized in **Table 1** and **Table 2**.

**Synthesis:**

**General procedure for the synthesis of 1, 5-benzothiazepines:** A mixture of 2-aminothiophenol **1** (10 mmole), α -β unsaturated carbonyl compounds **2** (10 mmole) and Silver sulphate (catalytic amount) were refluxed in 10ml of acetonitrile for 2hr, completion of the reaction was monitored on TLC. The solvent evaporated under reduced pressure, solid separated recrystallized from suitable solvents which was further purified by column chromatography, to afford novel 1, 5- benzothiazepine derivatives in excellent yield (75-85%) (Scheme 1).

**Spectral data of selected compounds**:

**(3a):** IR (KBr): (C=N) 1591cm$^{-1}$; $^1$HNMR ($CDCl_3$ & DMSO-$d_6$): δ= 3.0(t, 1H, J=12.0 Hz),3.2 (dd, 1H, J=12.0 Hz, 4.0Hz), 4.0 (dd, 1H, J=12.0Hz, 4.0Hz), 5.0 (d, 1H), 5.8 (d, 1H), 7.1-7.5 (m, 14H). GC-MS : m/z, 341.

**(3b):** IR (KBr): (C=N) 1600cm$^{-1}$; $^1$HNMR ($CDCl_3$ & DMSO-$d_6$): δ= 2.1 (s, 3H), 3.3 (t, 1H, J=12.4Hz)), 3.39 (dd, 1H,J=12.4Hz, 4.6Hz), 5.05 (dd, 1H, J=12.4Hz, 4.6Hz), 5.3 (d, 1H), 5.8 (d, 1H),6.7-7.2 (m, 13H)., GC-MS : m/z, 355.

**(3c):** IR (KBr): (C=N) 1599cm$^{-1}$; $^1$HNMR ($CDCl_3$ & DMSO-$d_6$): δ= 2.3 (s, 6H), 3.03 (t, 1H, J=12.4Hz)), 3.4 (dd, 1H, J=12.4Hz,4.7Hz), 5.3 (dd, 1H, J=12.6Hz, 4.8Hz), 5.0 (d, 1H), 5.6 (d, 1H), 6.0-7.2 (m, 12H). GC-MS : m/z, 369.

**(3g):** IR (KBr): (C=N) 1631cm$^{-1}$; $^1$HNMR ($CDCl_3$ & DMSO-$d_6$): δ= 3.0 (t, 1H, J=12.0 Hz), 3.5 (dd, 1H, J=12.0 Hz, 4.0Hz), 4.0 (dd, 1H, J=12.0Hz, 4.0Hz), 5.0 (d, 1H), 5.8 (d, 1H), 7.0 -7.5 (m, 12H).

**(3h):** IR (KBr): (C=N) 1590cm$^{-1}$; $^1$HNMR ($CDCl_3$ & DMSO-$d_6$): δ= 2.3 (s, 3H), 3.6 (t, 1H, J=12.4Hz)), 3.35 (dd, 1H, J=12.4Hz, 4.6Hz), 5.0 (dd, 1H, J=12.4Hz, 4.6Hz), 5.0 (d, 1H), 5.6 (d, 1H), 6.7-7.2 (m, 11H).

**TABLE 1: CHARACTERIZATION DATA OF NEWLY SYNTHESIZED COMPOUNDS 3a-h**

| Entry | R1 | R2 | R3 | Yield {%} | M.P. [$^{o}$C] | Molecular formula |
|---|---|---|---|---|---|---|
| 3a | H | H | H | 75 | 102-104 | $C_{23}H_{19}NS$ |
| 3b | H | Me | H | 78 | 112-113 | $C_{24}H_{21}NS$ |
| 3c | H | Me | Me | 85 | 110-112 | $C_{25}H_{23}NS$ |
| 3d | Cl | H | H | 82 | 118-120 | $C_{23}H_{17}NSCl_2$ |
| 3e | Cl | Me | H | 77 | 108-110 | $C_{24}H_{19}NSCl_2$ |
| 3f | Cl | Me | Me | 80 | 120-121 | $C_{25}H_{21}NSCl_2$ |
| 3g | F | H | H | 85 | 121-123 | $C_{23}H_{17}NSF_2$ |
| 3h | F | Me | H | 82 | 117-119 | $C_{24}H_{19}NSF_2$ |

**Antibacterial Activity:** Antimicrobial screening was done by using cup plate method [39, 40] at a concentration of 100µg/ml. The compounds were evaluated for antibacterial activity against *Bacillus subtilis* gr +ve, *Pseudomonas aeruginosa* gr –ve, *Staphylococcus aureus* gr +ve, *Escherichia coli* gr –ve and antifungal activity against *Aspergillus niger, Aspergillus Flavus, Curvularia* and *Alternaria*. DMSO was used as solvent control. The results of antimicrobial data are summarized in **table 2.** All compounds shows excellent activity against bacteria and fungi.

**TABLE 2: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (100µg/ml)**

| Products | Bacteria (Zone of Inhibition in mm) | | | | Fungi (Zone of Inhibition in mm) | | | |
|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | H |
| 3a | 21 | 20 | 12 | 18 | 32 | --- | --- | 10 |
| 3b | 27 | 18 | 12 | --- | 24 | 18 | 12 | 10 |
| 3c | 11 | --- | --- | 10 | --- | --- | --- | --- |
| 3d | 34 | 29 | 15 | 11 | 25 | --- | 19 | 11 |
| 3e | 15 | 13 | 10 | 13 | 35 | 17 | 15 | 09 |
| 3f | 13 | 11 | --- | 12 | 31 | 12 | 11 | --- |
| 3g | 36 | 28 | 15 | 15 | 30 | --- | 19 | 11 |
| 3h | 30 | 25 | 15 | 18 | 30 | --- | 19 | 10 |

A= *Bacillus subtilis gr +ve,* B= *Pseudomonas aeruginosa gr –ve,* C= *Staphylococcus aureus gr +ve,* D= *Escherichia coli gr –ve,* E= *Aspergillusniger,* F= *AspergillusFlavus,* G= *Curvularia*H= *Alternaria*.

**CONCLUSIONS:** The results of the present investigation can be summarized that we have develop a new, mild and efficient method for the synthesis of 1, 5-benzothiazepines,workout is easy, reaction conditions are mild and yield is excellent 75-85% , structures of the synthesized compounds were confirmed by spectral analysis. It supports the suggested anti-bacterial pharmacophoresites of 1, 5- benzothiazepine derivative. It has been suggested that some functional groups such as halogen group particularly fluorine and side chain present in these compounds displayed roles of biological activity, this, in turn, enhances activity of the compounds and biological absorbance, and so all the synthesized 1, 5-benzothiazepine derivatives containing more than one antibacterial and antifungal pharmacophore site have excellent properties.

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