SYNTHESIS, AND ANTIMICROBIAL ACTIVITY OF NEW 1, 5-BENZOTHIAZEPINES USING LANTHANUM NITRATE AS A CATALYST

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ABSTRACT
We applied simple and convenient procedure for the synthesis of optically active 1,5-benzothiazepine derivatives by reaction of 2-aminothiophenol with newly synthesized Chalcones under mild conditions in the presence of catalytic amount of Lanthanum Nitrate in short reaction time with excellent yield (75-85%). The compounds (4a-l) were tested for purity by TLC and characterized by M.P, IR and ¹H NMR and Mass spectral studies. The synthesized compounds have been screened for antibacterial activity against Staphylococcus aureus gram +ve, Escherichia coli gram –ve Bacillus subtilis gram +ve, Salmonella typhi gram –ve, and antifungal activity against Aspergillus oryzone, Aspergillus niger, using disc diffusion method. The compounds show the moderate to good activity against bacteria and fungi.

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INTRODUCTION

Literature survey revealed that the broad spectrum of biological activity of compounds bearing the 1, 5-benzothiazepine moiety has stimulated interest in developing new synthetic protocols for their synthesis. There remains the necessity to develop a more effective and convenient synthetic procedure for the synthesis of 1, 5-benzothiazepine derivatives. It has been well established that, all chalcones react with 2-aminothiophenol to give 1, 5-benzothiazepines. For more than a century heterocyclic compounds have constituted one of the largest areas of research in organic synthesis[1]. Over the last two decades, synthesis of nitrogen and sulphur containing heterocyclic compounds especially 1, 5-benzothiazepines retained the interest of researchers due to the unique structural properties and broad spectrum of biological activities of these compounds[2]. Benzothiazepines and their derivatives play a vital role in the treatment of cardiovascular disorders[3], as Ca2+ channel blockers[4], inhibitors of HIV-I integrase[5], antibiotics[6], muscle relaxants[7], and cytotoxic agents[8]. They are also known to have antimicrobial[9-11] and antihypertensive activities[12] besides being used in the treatment of diabetes[13], recently anticancer activity[14,15], hemodynamic effects[16], antiulcer activity[17,18], and spasmylytic activities[19-23] have also been reported. Keeping in view this broad spectrum of biological activity associated with these compounds, for their synthesis several procedures are introduce in the literature[24,25], these include condensation of 2-aminothiophenol with carbonyl compounds, and different relationships have been observed between substrate and products formed[26-36]. Although these reaction have been investigated by different research groups, however to get newer insight in the formation of benzothiazepines, modification of molecules and introduction of simple and convenient procedure for their synthesis are important and needed.

The purpose of this study is to develop a simple convenient procedure 2, 3-Dihydro-1, 5-Benzothiazepines by condensation of 2-aminothiophenol with novel chalcones under mild conditions catalyzed by Lanthanum Nitrate.

This method has following distinct advantages which makes it a useful method.

1. Mild reaction condition.
2. Changing the size of lead compound its bioactivity is enhanced.
3. Readily available catalyst.
4. Excellent yields of products.
5. Simple experimental work-up procedure.

Owing to the pharmaceutical properties of different 1,5-benzodiazepines, these compounds are synthesized from different starting compounds like α, β-unsaturated ketones (Chalcones); aldehydes and ketones; only aldehydes and only ketones by employing different environmentally benign catalyst.

MATERIAL AND METHODS

The purity and completion of reaction was monitored by TLC. Melting points of the compounds were determined in open capillary tubes and are uncorrected. IR Spectra were recorded on Shimadzu FT-IR, the sample was mixed with KBr and pellet technique was adopted to record the spectra in cm⁻¹, ¹H NMR spectra was determined on a Bruker Avance II 400 Spectrometer against TMS as internal standard DMSO-d6 as solvent. Mass spectra were recorded on waters Micromass Q-T of Micro spectrometry.

General Procedure for the Synthesis of 2, 4-(substituted-aryl)-2, 3-dihydro-1, 5-benzothiazepines

An equimolar mixture of 2-aminothiophenol and Chalcones, Lanthanum Nitrate (10 mol%) in 10ml MeCN was stirred on hotplate magnetic stirrer at room temperature for 60min, the corresponding 1,5-benzothiazepines were obtained in 75-85 % yield [Scheme-1], Completion of the reaction was monitored by TLC. [eluent: ethyl acetate: pet. ether (3:7)], the reaction mixture was poured on crushed ice. The solid crude product was washed with water and purified by recrystallisation using suitable solvent, which were further purified by column chromatography [ethyl acetate : Pet. Ether (3:7)]. Substituted data of synthesized benzothiazepine in Table-1. All the synthesized compounds didn’t give positive red coloration with concentrated H₂SO₄, which confirm the absence of carbonyl group.
RESULT AND DISCUSSION

The aim of the present work was to synthesize derivatives of benzoxazepines with potential biological activity. A novel benzoxazepines were synthesized by reaction of 2-aminothiophenol and Chalcones in the presence of Lanthanum Nitrate as acatalist. Work up procedure is simple and yield of the product is excellent. All the newly (4a-l) synthesized compounds were characterized by their chemical, physical and spectral analysis data (Table-2), and are further subjected to antimicrobial studies (Table-3) which exhibit moderate to good activity.
Spectral analysis of the selected compound:

9a- (R)-4-(2-(1H-indol-3-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-2,6-diiodophenol.

**Compound 9a:**
M.P = 108-110 °C, Yield = 80%
FTIR (KBr, cm⁻¹): 3052(CH), 2929(C-H), 1609(C=N), 1441(C-C Aromatic str).
¹HNMR: 2.47 (dd, 1H, J=12Hz), 3.52 (dd, 1H, J=12Hz), 4.65 (s, 1H, NH), 5.40 (t, 1H, J=12Hz), 6.91-7.96 (m, 8H, Ar-H), 8.22 (2H, H₅), 8.89 (s, 1H, H₄), 12.03 (s, 1H, OH).
M.S. (m/z): (M)= 494(M-1).

9g-(R)-2-(2-(5-bromothiophen-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-4-chloro-6-iodophenol.

**Compound 9g:**
M.P = 166° C, Yield = 75%
FTIR (KBr, cm⁻¹): 3062(C-H), 1582(C=N), 1469(C-C Aromatic str), 683(C-Br).
¹HNMR: 2.79 (dd, 1H, J=12), 3.78 (dd, 1H, J=12), 5.64 (t, 1H, J=12), 6.40-7.41 (m, 8H, Ar-H), 6.92 (d, 1H, H₄), 7.09 (d, 1H, H₅), 7.95 (s, 1H, H₄), 8.03 (s, 1H, H₁₀), 15 (s, 1H, OH).
M.S. (m/z): (M)= 576(M⁻).

**Antimicrobial activity.**
Antimicrobial screening was done using disc diffusion method at a concentration of 100µg/ml. The test was performed according to the disk diffusion method adopted with some modification for the prepared compound using Penciline and streptomycin as references. The prepared compounds were tested against one strain of Gram +ve bacteria, Gram –ve bacteria, fungi. The compounds were evaluated for antibacterial activity against Staphylococcus aureus gr +ve, Escherichia coli gr –ve Bacillus subtilis gr +ve, Salmonela typhi gr –ve, and antifungal activity against Aspergillus oryze, Aspergillus niger. DMSO was used as solvent control. The results of antimicrobial data are summarized in Table 3. The compounds show the moderate to good activity against bacteria and fungi.
Table 3: Antimicrobial activity of synthesized compounds (4a-l).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Gram positive bacteria</th>
<th>Gram negative bacteria</th>
<th>Fungus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Staph aureus</td>
<td>Bacillus subtilis</td>
<td>S. typhi</td>
</tr>
<tr>
<td>4a</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4b</td>
<td>+</td>
<td>++</td>
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<tr>
<td>4i</td>
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<td>++</td>
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<td>4l</td>
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<td>-</td>
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<tr>
<td>Penciline 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Streptomycin 2</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Greseofulvin</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

++ = Clear Zone of Inhibition, + = Minimum Zone of Inhibition, - = No Effect
X = Not applicable, Standard 1 Penciline +, Standard 2 Streptomycin ++ (bacteria).Greseofulvin (fungus)

CONCLUSION
Successfully, we have synthesized 2, 3 dihydro 1, 5 benzothiazepine derivatives by using a novel La(NO_3)_3.6H_2O catalyst which has the advantage of mild and efficient chemistry techniques, reaction time is short the work out is easy, reaction conditions are mild and inexpensive catalyst with high yields of products, The newly synthesized compounds may prove as lead molecules and good candidates for the future investigations. We have selected original papers included in the references which will be helpful for the reader to find the useful information regarding 1, 5-benzothiazepine derivatives.

List of abbreviations
IR Infrared
Ms Mass spectroscopy
NMR Nuclear-Magnetic Resonance
KBr Potassium Bromide
DMSO Dimethylsulfoxide
TLC Thin-Layer chromatography
M.P Melting point
H_2SO_4 Sulfuric acid
MeCN Acetonitrile
Min Minute
TMS Tetramethylsilane
µg/ml Microgram per milliliter
ppm Part(s) per million
s Singlet (spectral)
d Doublet (spectral)
t Triplet (spectral)

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REFERENCES