


### Chapter 4

**Ring Transformations of 1-Methyl-3-benzothiazolium/thiazolium cations with beta haloketones**

Heterocyclic scaffolds play an important role in the design of new structural entities that exhibit enhanced activity profiles. Seven membered heterocycles considered once, chemical eccentrics, no longer remain rarefied species as numerous efficient routes have been developed for their syntheses. Amongst various seven membered heterocycles containing different heteroatoms (N, S, O etc. in different combinations) with varied degree of saturation, fused with other aromatics/ heteroaromatics- thiazepines and benzothiazepines remain privileged entities that contain sulphur and nitrogen on account of which these compounds possess a broad range of pharmacological activities [Urbanski *et al.*, 2003; Cherkupally *et al.*, ...]
The distinctive feature of benzothiazepines has been its core nucleus to be active against different families of targets [Tailor et al., 2014]. Immense chemotherapeutic and biological activities (antiarrhythmic, antispasmodic, angiogenic and CNS activities etc.) of these ring systems have been reported [Ellis et al., 2006; Drewe et al., 2007; Zask et al., 2005; Ding et al., 2008]. First molecule, Diltiazem having 1,4-benzothiazepine core nucleus has been clinically used for cardiovascular action followed by another benzothiazepine derivative- Clentiazem employed for the same pharmaceutical use. Dibenzo [b,f][1,4]thiazepine, Quetiapine- derivatives of benzothiazepine has been used as antipsychotic drugs for the treatment of schizophrenia and bipolar disorder [Mahale et al., 2011, Mahale et al., 2008]. Several derivatives of 1,4-thiazepine fragments have also been present in a wide range of natural and synthetic biologically active agents. The manifold applications of thiazepines and benzothiazepine encouraged us to extend the reactions of 1-methylbenzthiazolium cations to beta-haloketones that could provide the synthetically useful and desired seven membered benzo-/thiazepines.

In benzothiazepines, the thiazepine ring is fused to benzene ring. Depending on the position of the nitrogen and sulfur atoms in a seven membered ring, benzothiazepines/thiazepines have been categorized as 1,3-/ 1,4/- 1,5-benzothiazepines/ thiazipines. The benzothiazepine nucleus justifies its importance in the discovery of potent drugs. Various synthetic procedures comprising of cyclocondensations, additions, nucleophilic substitutions, ring transformations have been reported for the syntheses of these seven membered heterocycles. A brief account for the synthesis of thiazepine and benzothiazepine derivatives follows and subsequently the results of the present investigations have been discussed.
Synthesis of Benzothiazepines

α, β- unsaturated ketones (1) (prepared by condensation of aldehyde derivatives) through Clasein- Schmidt condensation with o-aminothiophenol in dry acidic methanol produce 2,3-dihydro-1,5-benzothiazepines (2) that exhibit in vitro cholinesterase inhibitory activity (Scheme-1) [Ansari et al., 2012].

Similarly, 2,3-dihydro-1,5-benzothiazepines (4) were synthesised from Wang resin [p-benzyloxy benzyl alcohol resin (HMP resin)] associated with chalcones (3) (prepared from 3-hydroxy acetophenone with different aldehydes) and o-aminothiophenol (Scheme-2) [Ansari et al., 2012].

On refluxing chalcones/ polyflourochalcones (5) condense with o-aminothiophenol to yield benzo [1,5] thiazepine derivatives (6) along with a byproduct 3-(2-aminophenylthio)-3-(substituted)-1-phenylpropan-1-ol (7) (Scheme-3) [Shmuilovich et al., 2011].
R = -H, o-OH; R¹ = -H, p-CH₃, p-NO₂, p-Cl, p-F, m-OCH₃, p-OCH₃.

Scheme-1
R= -Cl, -OH, NO₂, -CH₃, -N(CH₃)₂.

**Scheme-2**

**Scheme-3**

4-Methyl sulphonamidoacetophenone (8) (prepared from 4-amino acetophenone and p-toluene sulphonylchloride) on reaction with 2-chloro-substituted quinoline-3-carbaldehyde (9) in alcoholic KOH furnishes chalcones (10). The latter on condensation with o-aminothiophenol and bi-catalyst affords 1,5-benzothiazepine derivatives (11) which possesses antibacterial activity (Scheme-4) [Jagrut et al., 2011].

1,3-Diaryl-2-propenone (12) reacts with o-aminothiophenol and fluoroboric acid adsorbed on silica-gel (HBF₄–SiO₂) through selective thia-Michael addition yield the corresponding adducts 3-(2-amino-phenylsulfanyl)-1,3-disubstituted phenylpropan-1-one (13). The latter when refluxed in MeOH/HBF₄–SiO₂ afford 2,3-dihydro-1,5-benzothiazepines (14) (Scheme-5) [Sharma et al., 2008].
A microwave assisted condensation of chalcones (15) with o-aminothiophenol produce 1,5-benzothiazepines (16) using Er(OTf)$_3$ as a catalyst (Scheme-6) [Nardi et al., 2011].

While, o-aminothiophenol when refluxed with the chalcone derivatives (17) in the presence of Ga(OTf)$_3$ (10mol%) (Lewis acid catalyst) afford 1,5-benzothiazepines (18). The thiol group (-SH) attacks the C=C bond, which subsequently form the cyclised product (Scheme-7) [Pan et al., 2008].

Under thermal solvent free conditions, 1,3-dialyl-2-propenones (19) undergo cyclocondensation with o-aminothiophenol in the presence of cyanuric chloride (2, 4, 6-trichlorotriazine) catalyst to yield 1,5-benzothiazepines (20). Cyanuric acid catalyse the reaction as it generates HCl (in situ). Thus, activating the carbonyl group and subsequently form a carbocation which furnishes the desired product (Scheme-8) [Sun et al., 2011].
Scheme-4

With an inorganic support (alumina/ silica gel) 2, 3-dihydro-2(1, 3-benzodipoxol-5-yl) 4-phenyl derivative-1, 5-benzothiazepines (22) have been synthesized from chalcones (21) and o-aminothiophenol. The mechanism of the reaction reveal that nucleophilic nature of sulfur atom, attacks the β-carbon of chalcones to produce an intermediate which easily undergoes dehydration in a non-aqueous medium to yield 1,5-benzothiazepine derivatives. The latter show antibacterial activities (Scheme-9) [Saini et al., 2008].
R=R_1= -H; R= -H, R_1= -Cl; R= -Cl, R_1= -H; R= -H, R_1= -NO_2; R= -H, R_1= -OCH_3; R= -OCH_3, R_1= -H.

**Scheme-5**

R=R_1= -H, p-OCH_3; R_2= -H, o-OH.

**Scheme-6**
(17) 

\[
\text{NH}_2 \text{SH} + \text{R} \text{R}_1 \text{O} \text{R} \rightarrow \text{Ga(OTf)}_3 \rightarrow \text{NH}_2 \text{SH} \text{NH}_2 \\
10 \text{ mol \%}, \text{CH}_3\text{CN}
\]

\( R = R_1 = -H; \ R = -H, \ R_1 = o-\text{OH}; \ R = p-\text{OCH}_3, \ R_1 = o-\text{OH}; \ R = R_1 = o-\text{OH}; \ R = p-\text{OH}, \ R_1 = -H. \)

Scheme-7

(19) 

\[
\text{NH}_2 \text{SH} + \text{R} \text{R}_1 \text{O} \text{R} \rightarrow \text{Cyanuric chloride} \rightarrow \text{Stirring}
\]

\( R = R_1 = -H; \ R = -H, \ R_1 = p-\text{OCH}_3, \ R_1 = -H; \ R = p-\text{OH}, \ R_1 = o-\text{OH}; \ R = -H, \ R_1 = -\text{Cl}; \ R = -H, \ R_1 = -\text{NO}_2; \ R = -\text{Cl}, \ R_1 = -\text{OCH}_3; \ R = p-\text{Cl}, \ R_1 = o-\text{Cl}, \ R = o-\text{OH}; \ R_1 = p-\text{OH}. \)

Scheme-8
R = -H, -CH₃, -Br, -Cl, -NO₂

Scheme-9

On refluxing the chalcones (23) (synthesized from 3-acetyl coumarin derivative and aromatic aldehydes) in ethanol and acetic acid condense with o-aminothiophenol to give 2-aryl-4-(2H-2-oxo-[1]-benzopyran-3-yl]-2,3-dihydro-1,5-benzothiazepines (24) whereas in the presence of piperidine 2-aryl-4-[2H-2-oxo-[1]benzopyran-2-one-3-yl]-2,5-dihydro-1,5-benzothiazepines (25) have been procured (Scheme-10) [Rao et al., 2006].

In a green chemical protocol, chalcones (26) (prepared from the aldehyde derivatives and the ketones on a suitable solid support Mont. KSF under microwave) on reaction with o-aminothiophenol derivatives produce the benzothiazepines (27) (Scheme-11) [Dandia et al., 2004].

Further, one pot reaction of chalcones (28) with 1-amino-2-mercapto-5-phenyl-1,3,4-triazole (29) in the presence of sodium acetate undergo heterocyclization to yield 1,5-thiadiazepines (30). The mechanism reveals that there has been the formation of an intermediate by the 1,2- and 1,4- addition of the carbonyl group which further undergoes cyclization to yield 1,5-thiadiazepines derivatives (Scheme-12) [Nagaraja et al., 2006].

Samarium diiodide (SmI₂) intermediate (31) (synthesized from bis(o-nitrophenyl)disulfide and SmI₂) undergo ring-closure reaction with α,β-unsaturated ketones to furnish 2,3-dihydro-1,5-benzothiazepines (32) (Scheme-13) [Zhong et al., 2001].

α-Bromo-4-methyl sulfonylacetophenone (33) on condensation with sodium-p-tolylsulphinate (34) yield α-(4-methyl sulfonyl phenyl)-4-methyl sulfonylacetophenone (35) which further undergo Claisen Schmidt condensation with aryl aldehydes to produce an
intermediate 1-[(4- methyl sulfonyl)phenyl]-2-[(4-methyl phenyl)sulfonyl]-prop-2-en-1-ones (36). The latter on refluxing with o-aminothiophenol in the presence of trifluoroacetic acid afford 2-(substituted phenyl)-3-[(methyl phenyl) sulfonyl] [(methyl sulfonyl)phenyl]-2, 3-dihydro-1,5-benzothiazepines (37). While, (36) on reaction with o-aminothiophenol on silica gel at 80°C produce tri-substituted 1,5-benzothiazepines in better yield (Scheme-14) [Karale et al., 2011].

Scheme-10
2-Chloro-3-quinilinecarbaldehyde (38) on reaction with phenol in alkaline medium yield 2-phenoxy-3-quinilinecarbaldehyde (39). The latter via Claisen-Schmidt condensation with 1-arylethanones afford (2E)-3-(2-phenoxy-quinolin-3-yl)-1-(4-substituted-phenyl)-2-propen-1-one (40) which further, under reflux with o-aminothiophenol CH₃COOH (catalyst) in ethanol furnishes 2,3-dihydro-2-(2-phenoxy-quinolin-3-yl)-4-(4-substituted-phenyl)-1,5-benzothiazepine (41) (Scheme-15) [Dong et al., 2011].

On refluxing, 1-phenyl-2-(1H-1,2,4-triazol-1-yl) ethanone (42) (synthesised from 2-bromo-1-phenyl ethanone and 2H-1,2,3-triazole) with benzaldehyde and piperidine (catalyst) yield (Z)-1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl)prop-2-en-1-one (43). The latter on refluxing with o-aminothiophenol in the presence of CF₃COOH affords (Z)-2,3-dihydro-2,4-diphenyl-3-(1H-1,2,4-triazol-1-yl-) benzo[b][1,4] thiazepine (44) (Scheme-16) [Chen et al., 2011].
The reaction of 2-phenyl-1,2,3-triazol-4-yl-α, β-unsaturated ketones (45) (prepared from the substituted aromatic aldehydes and 2-phenyl-4-acetyl-1,2,3-triazole) with o-amino-thiophenol in the presence of CF₃COOH produce sterioselective 2-aryl-4-(2-phenyl-1,2,3-triazole-4-yl)-2,3-dihydro[1,5] benzothiazepine (46) (Scheme-17) [Yang et al., 2008].

\[ \text{R}= -\text{H}, -\text{NO}_2, -\text{Cl}, -\text{OH}, -\text{OCH}_3, -\text{CH}_3 \]

**Scheme-12**

Similarly, 2-phenyl-1,2,3-triazole-4-yl-α,β-unsaturated ketones (47) (prepared from condensation of 4-acetyl-2-phenyl-1,2,3-triazole with substituted aldehydes) when refluxed with o-aminobenzenethiol in presence of CF₃COOH produce 2-aryl-4-(2-phenyl-1,2,3-triazole-4-yl)-2,3-dihydro-[1,5] benzothiazepine (48) in better yield (Scheme-18) [Shen et al., 2010].
R\_\text{NO2} \xrightarrow{\text{SmI2, THF, r. t.}} R\_\text{N(SMI\_2)2} \xrightarrow{\text{MeOH}} R\_\text{NH2}

R = \text{H, -Cl; } R^1 = \text{-C}_6\text{H}_5, p\text{-Cl-C}_6\text{H}_4, p\text{-CH}_3\text{-C}_6\text{H}_4; \quad R^2 = \text{-C}_6\text{H}_5, -\text{CH}_3, C_6H_5CH=CH

Scheme-13

H\_3C\text{SO}_\text{2}Br \quad + \quad \text{NaSO}_\text{2}C\text{H}_3 \xrightarrow{\text{DCM/ Water, TBAB}} \text{HCO}_\text{2}S\text{O}_\text{4} \text{CHO} \xrightarrow{\text{Ethylene dichloride, piperidine}} \text{R}_1\text{R}_2\text{CHO}

R = \text{H; } R^1 = \text{H, OCH}_2\text{CH}_3, -\text{Cl;} \quad R^2 = \text{-H, -CH}_3.

Scheme-14
Substituted o-aminothiophenol (49), when irradiated in microwave with the α,β-unsaturated ketones (50) and Lanthanum-containing Y zeolite (LaY) catalyst, afford 8-substituted-2-carboxy-2,3-dihydro-1,5-benzothiazepines (51) under solvent free condition. It was proposed that the active site of the zeolite plays a major role in the formation of the desired product and even less amount of this catalyst in microwave conditions produce excellent yield (Scheme-19) [Arya et al., 2008].

β-Benzoyl acrylic acid (52), 5-substituted-o-aminothiophenol derivatives and 2-chloroacetyl chloride on irradiation with microwave (MW) over solid support basic alumina
yields intermediate (53). The latter, on irradiated for another 15-20 minutes furnishes bio-active, azeto[2,1-d][1,5]benzothiazepines (54) (Scheme-20) [Dandia et al., 2008].

![Chemical diagram](image)

**Scheme-16**

One pot efficient facile, solvent-free microwave assisted cyclocondensation of o-aminothiophenol and 1,3-substituted-prop-2-en-1-ones (55) (prepared via Claisen-Schmidt condensation of acetophenone or substituted acetophenone in basic medium) afford 1,5-benzothiazepine derivatives (56) in the presence of zinc acetate (Scheme-21) [Nikalje et al., 2011].
R= -H, -CH₃, -Cl, -NO₂, -OCH₃

Scheme-17
$R = \text{-H, -CH}_3, \text{-OCH}_3, \text{-Cl, -NO}_2$

Scheme-18

\[
\begin{align*}
\text{R=SH} & \quad \text{F-} \quad \text{CH} \quad \text{COOH} \\
\text{(49)} & \quad \text{(50)} & \quad \text{(51)} \\
\end{align*}
\]

$R= 8\text{-OCH}_3, 8\text{-CH}_3, 6\text{-Cl, 6-Br, 6-F.}$

Scheme-19

$N$-[4-(2-Oxo-2$H$-Chromen-3-yl)-1,3-thiazol-2-yl]acetamide (57) (prepared from 3-(2-amino-1,3-thiazol-4-yl)-2$H$-chromen-2-one and acetyl chloride) on reaction with aromatic aldehydes yield $N$-(4-(2-oxo-2$H$-chromen-3-yl)thiazol-2-yl) cinnamamide derivatives (58). The latter on reaction with o-aminothiophenol and glacial CH$_3$COOH under MW yield 2,3-dihydro-2-aryl-4-[4-(2-oxo-2$H$-chromen-3-yl)-1,3-thiazol-2-ylamino]1,5-benzothiazepines (59) (Scheme-22) [Raval et al., 2008].

A low temperature (0-5$^\circ$C) cyclocondensation of 1-(4-(4,6-bis(phenylamino)-1,3,5-triazin-2-ylamino)phenyl)-3-(4-methoxyphenyl)propen-1-one derivatives (60) with o-aminothiophenol and glacial CH$_3$COOH affords 1,5- benzothiazepine derivative having triazine ring (61) (Scheme-23) [Solankie et al., 2008].
R = -OCH₃, -CH₃, -Cl, -Br, CF₃, -F

Scheme-20

R=R¹= -H, -Cl; R²= p-NO₂-C₆H₄, -C₆H₅, o-NO₂-C₆H₄, p-CH₃O-C₆H₄, -C₄H₃O, -C₄H₃S.

Scheme-21
R = m-CH₃, p-OH, o-Cl, p-Cl, o, p-(Cl)₂, o-OCH₃, p-OCH₃, m, p, o-(OCH₃)₂, p-N(CH₃)₂

**Scheme-22**

R = p-Cl, p-NO₂, m, p-OCH₃, p-OCH₃

**Scheme-23**
Substituted o-aminothiophenol derivatives, when irradiated with 3- (substituted benzoyl)-2-propionic acid (62) in the presence of Mont. KSF under microwave yield antifungal 2-carboxy-2,3-dihydro-1,5-benzothiazepines (63) (Scheme-24) [Dandia et al., 2007].

\[
\begin{align*}
\text{R} &= \text{-H, -CH}_3, \text{-F, -Cl, -Br, -OCH}_3, \text{-OC}_2\text{H}_5, \text{-CF}_3; \\
\text{R}^1 &= \text{-H, -CF}_3, \text{-CH}_3; \\
\text{R}^2 &= \text{-H, -Br, -Cl, -CF}_3, \text{-CH}_3; \\
\text{R}^3 &= \text{-H, -CH}_3; \\
\text{R}^4 &= \text{-H, -Cl, -CF}_3, \text{-Cl}; \\
\text{R}^5 &= \text{-F, -H, -OH}
\end{align*}
\]

Scheme-24

2-Enoic acids (64) (prepared from substituted benzene and maleic anhydride in the presence of anhydrous AlCl\(_3\)) undergo addition with o-aminothiophenol lead to the formation of an intermediate (65). The latter through intramolecular cyclization followed by dehydration give benzothiazepines (66) (Scheme-25) [Zhang et al., 2009].

3-(2-Chlorophenyl)-1-(4-chlorophenyl)-2-propen-one (67), on reaction with 5-substituted-2-aminobenzenethiol derivatives in the presence of dry HCl gas yields a Michael adduct (68) which undergo cyclization to give 2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5 benzothiazepines (69) which proved to be promising anti microbial agents (Scheme-26) [Pant et al., 2008].
Tetracyclic 1,5-benzothiazepines (71) were procured from the reaction of \( \alpha \)-aminothiophenol and exocyclic \( \alpha,\beta,\gamma,\delta \)-unsaturated ketones (70) (Scheme-27) [Levai et al., 2008].

\[
\begin{align*}
&\text{R} + \text{AlCl}_3 \rightarrow \text{R} \rightarrow \text{C}_2\text{H}_5\text{OH} \rightarrow \text{NaOH/H}_2\text{O} \\
&\text{R} = \text{-H, -F, -Cl, -Br, -OCH}_3, \text{-CH}_3
\end{align*}
\]
R = p-Cl-C₆H₄, o-C₆H₅S; R¹ = -F, -Cl, -Br, -CH₃, -OCH₃, -OC₂H₅.

Scheme-26

(70) \[ \text{Acetic acid, toluene} \rightarrow (71) \]

X = O, S; R = -H, -OMe, -NO₂, R = -C₄H₃O, p-CH₃-C₆H₄.

Scheme-27

Gem acetyl/ gem benzoyl nitro styrene (72) on condensation with o-aminothiophenol afford benzothiazepine derivatives (73 & 74). The mechanism revealed that gem acetyl nitro styrene undergoes heterocyclization, whereas in case of benzoyl nitro styrene, the S-adduct gets isolated which has been attributed to difference in the carbonyl group activity when attached to acetyl or benzoyl functionalities (Scheme-28) [Berestovitskaya et al., 2011].
4-Aryl-3-nitrobut-3-en-2-ones (75) undergo nucleophilic addition with o-aminothiophenol followed by subsequent heterocyclization of S-adduct (without a catalyst) and dehydration to yield diastereoisomerically pure 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines (76) (Scheme-29) [Baichurin et al., 2010].
R = -C₆H₅, p-CH₃-C₆H₄, p-MeO-C₆H₄, p-(CH₃)₂N-C₆H₄

Scheme-29

6-Arylidene- 2, 3-dimethyl/ 3-methyl- 6, 7, 8, 9-tetrahydro-benzo[a]cyclohepten-5-one (77) (prepared from 2,3-dimethylbenzocyclohepten-5-one and substituted aldehyde) on reaction with 2-aminothiophenol in dry ethyl alcohol and dry HCl affords 1,5- benzothiazepine derivatives (78) along with dimer as a byproduct (79). The 1,5- benzothiazepine derivatives so procured possess anti-inflammatory, anti-bacterial and anti-fungal activity (Scheme-30) [Apparao et al., 2010].

One pot microwave assisted diastereoselective cyclocondensation of o-amino-3-ethoxy/phenoxythiophenol derivatives with methyl cis(3-(4-methoxyphenyl) glycidate (80) under nitrogen atmosphere furnishes cis-2-(4-methoxyphenyl)-3- hydroxy-6-ethoxy/ phenoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (81) (Scheme-31) [Singh et al., 2002].
R= R\textsuperscript{1} = -\text{CH}_3, \text{R}^2 = \text{p}-\text{Br}-\text{C}_6\text{H}_4; R=\text{R}^1 = -\text{CH}_3, \text{R}^2 = -\text{C}_6\text{H}_5; R=\text{R}^1 = -\text{CH}_3, \text{R}^2 = -\text{H}, \text{R}^2 = -\text{C}_6\text{H}_5; R=\text{R}^1 = -\text{CH}_3, \text{R}^2 = \text{p}-\text{H}_3\text{C}-\text{C}_6\text{H}_4; R=\text{CH}_3, \text{R}^1 = -\text{H}, \text{R}^2 = \text{p}-\text{H}_3\text{C}-\text{C}_6\text{H}_4.

\textbf{Scheme-30}

\( R=\text{-OC}_2\text{H}_5, \text{-OC}_6\text{H}_5 \)

\textbf{Scheme-31}

\( \alpha\)-Aminothiophenol, when irradiated with oxirane-2-carboxylate (82) in microwave afford \textit{trans-} and \textit{cis-}3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4-ones (83 & 84). It has been observed that microwave irradiation time and the input power, highly effect the yield of the diastereomers (cis/ trans ratio) (Scheme-32) [Besson \textit{et al.}, 2006].
Claisen-Schmidt condensation between 2-acetyl-1-methylpyrrole (85) and aromatic/heteroaromatic aldehydes in the presence of KOH yield an intermediate 1-(1-methyl-1H-pyrrol-2-yl)-3-(substituted)-2-propen-1-ones (86). The latter subsequently condensed with 2-aminothiophenol in the presence of acetic acid in microwave to produce 1,5-benzothiazepine derivatives (87) (Scheme-33) [Yenupuri et al., 2014].

\[
\begin{align*}
\text{Scheme-32} \\
\text{R} = \text{-H, -CH}_3, \text{-Br}
\end{align*}
\]
2(3H)-Benzothiazolones (88) undergo N-alkylation with chloroacetone to produce 6-substituted-3-(2-oxopropyl)-2(3H)-benzothiazolone (89) in the presence of dry K$_2$CO$_3$ and benzyltriethylammonium chloride (TEBA-Cl). 89 through ring transformation with primary amines yield 1-(2-mercaptophenyl)-2H-imidazol-2-ones (90). The latter again on alkylation with chloroacetic acid give 1-(2-carboxymethylthiophenyl)-2H-imidazol-2-ones (91). Intramolecular acylation of latter in polyphosphoric acid (PPA) affords 2-alkyl-3-methyl-1,2,4,5-tetrahydrobenzo[b]imidazo[1,5-d]-[1,5]thiazepine-1,4-dione (92) (Scheme-34) [Petrova et al., 2003].

$p$-Chlorobenzoyl chloride (93), on stirring with phenyl acetylene, PdCl$_2$(PPh$_3$)$_2$ and Cul in the presence of triethylamine affords an alkynone which on addition with o-aminothiophenol in acetic acid under microwave irradiation yields 4-(4-Chlorophenyl)-2-phenylbenzo[b][1,5]thiazepine (94) (Scheme-35) [Willy et al., 2010].

Oxidative cyclocondensation of the phenolic $\beta$-diketones (95) with o-aminothiophenol afford oxygen-bridged 1,5-benzothiazepines (96) (Scheme-36) [Ahmad et al., 2000].

Piperidine catalyzed Knoevenagel condensation of aromatic aldehydes with 2,4-pentanedione in dry benzene afford 3-arylidenepentane-2,4-dione derivatives (97). The latter through Michael addition with o-aminothiophenol yield the corresponding 3-(1-aryl-1-o-aminophenylthio methyl)-2,4-pentandiones (98), which further by intramolecular cyclisation and subsequent dehydration in a presence of CH$_3$COOH/MeOH furnish 2,5-dihydro-4-methyl-2-aryl-3-acetyl-1,5-benzothiazepine (99) (Scheme-37) [Wang et al., 2009].
R= -H, -Br; R\(^1\)= -CH\(_3\), -C\(_2\)H\(_5\), -C\(_3\)H\(_7\), i-C\(_4\)H\(_9\), -CH\(_3\)-C\(_6\)H\(_4\), C\(_6\)H\(_{11}\)

**Scheme-34**

**Scheme-35**
Scheme-36

\[
\text{R} = \text{-H, -Cl, -F, -OCH}_3
\]

Scheme-37

The reaction of 1,3-dihydro-3-(2-phenyl-2-oxoethylidene)indol-2-one (100) with \( \sigma \)-aminothiophenol derivative under microwave and thermal irradiation in the presence of ethylene glycol and piperidine produce \emph{spiro}[benzo[b][1, 4] thiazepine-2,3-indolin]-2-ones (101) (Scheme-38) [Beson \emph{et al.}, 2006].
Propane-1-(1,3-benzodioxol-5-yl)-3-phenyl-1,3-dione (102) on reaction with o-aminothiophenol afford 2,4-disubstituted 1,5-benzothiazepines (103) (Scheme-39) [Nigam et al., 2003].

\[
\begin{align*}
R= & \text{-H, -Br} \\
(100) + (101) \\
(102) + (103)
\end{align*}
\]

R= -H, -CH\(_3\), -Cl, -Br, -OCH\(_3\), -OH, -NH\(_2\), -NO\(_2\), -OC\(_2\)H\(_5\)

Scheme-38

Isatin (104) when irradiated in microwave with 3-methyl-1-phenyl-2-pyrazolin-5-one (105) followed by cyclocondensation with o-aminothiophenol and Mont. K10 yield spiro[indolepyrazolo[4, 3-c][1, 5]benzothiazepines (106). The Mont. K10 (catalyst) gives better yield in lesser time as compared to other catalysts viz. acidic, basic, or neutral alumina, silica,
Mont KSF, whereas the desired product has been produced in less yield along with byproduct when refluxed in ethanol (Scheme-40) [Dandia et al., 2005].

\[
\text{Scheme-40}
\]

Substituted 2-chloro-3-formyl-1,8-naphthyridines (107) undergo Mannich condensation with substituted o-aminothiophenol derivatives in the presence of crystalline Bi(NO\(_3\))\(_3\)·5H\(_2\)O (catalyst) to produce 1,5-benzothiazepine [7, 6-b]-1,8-naphthyridines (108). The reaction has been performed with different solid support including silica-gel, acidic alumina, basic alumina, neutral alumina, and molecular sieves (5 Å). But, Bi(NO\(_3\))\(_3\)·5H\(_2\)O catalyst yield the desired product under microwave irradiation regioselectively and neatly as compared to conventional method (refluxing) (Scheme-41) (Naik et al., 2007).

Further, o-aminothiophenol when refluxed and stirred with the 1-trialkylsilyl-1-perfluoroalkyl-alkan-1-ols/1-alkyl-1-(trialkylsiloxy)perfluoroalk-1-anes/hemifluorinatedenones (109) yield benzothiazepine derivatives (110) (Scheme-42) [Chanteau et al., 2004].
R = -H, -CH₃, -OCH₃, -Cl; R¹ = -H, -OCH₃; R² = -H, -Cl; R³ = -H

Scheme-41
R\textsubscript{1} = \text{-C_{6}H_{5}}, p-\text{Cl-C_{6}H_{4}}, p-\text{F-C_{6}H_{4}}, p-\text{CH_{3}O-C_{6}H_{4}}; R\textsubscript{2} = \text{R}^{1} = \text{-CH_{3}}; R\textsubscript{F} = \text{-C_{4}F_{9}}, \text{-C_{2}F_{5}}.

**Scheme-42**

3-(((E)-3-(dimethylamino)acryloyl)-4-hydroxy-1-methylquinolin-2(1H)-one (111) when refluxed with alicyclic secondary amines (112) yield an intermediate (113). The latter cyclocondenses with o-aminothiophenol in the presence of benzyl triethyl ammonium chloride (BTEAC) to afford 1,5-benzothiazepine derivatives (114) (Scheme-43) [Annapurna et al., 2014]

Asymmetric sulfa-Michael addition of $\alpha$, $\beta$-unsaturated pyrazolamide (115) with 2-aminothiophenol and subsequent cyclization in the presence of chiral Lewis acid Yb(OTf\textsubscript{3})/ L-RaPr\textsubscript{2} yields enantioselective 1,5-benzothiazepine derivative (116) (Scheme-44) [Liu et al., 2016]
bis-Chalcones (117) undergoes cyclocondensation with o-aminothiophenol in piperidine to yield bis-[1,5]-benzothiazepine derivatives (118). The latter exhibit good antimicrobial activity (Scheme-46) [Dengea et al., 2016]

Scheme-46
N-acyl-N-(2-(phenylthio)ethylmethaniminium (119) cyclized in the presence of PTSA to yield 2,3,4,5-tetrahydrobenzo[1,4]thiazepines (120) (Scheme-47) [ Deng et al., 2017]

Scheme-47
1-Phenyl-4-(pyrazol-1-yl)butane-1,3-dione derivatives (121), when refluxed 2-aminoethanethiol (122) in pyridine for 4 hrs afford 1,4-thiazepine derivatives (123) (Scheme-48) [Kumari et al., 2017]

R= -C₆H₅, p-Cl-C₆H₄, p-F-C₆H₄, p-CH₃O-C₆H₄
Scheme-48

From the above review of literature, it has been noticed that the benzothiazepines have mainly been obtained from the cyclocondensation reactions and some ring transformations. Also, it has been observed that employability of the eco-friendly procedures is quite less. Therefore, with an objective to compare the synthetic methodologies i.e conventional with green protocols, the lesser explored ring transformations to procure benzothiazepines/thiazepines have been carried out.

Material and method

4. Materials

4.1. Chemicals

The chemicals used in the research work were procured from various firms viz. Himedia, Sigma Aldrich, Rankem, Spectrochem, Alfa aesar etc. The solvents used for the synthesis of various compounds in the research work were of analytical grade and were used without further purification. Thin layer chromatography (TLC) was performed with glass plates coated with silica gel ‘G’ and were exposed to iodine vapors to check the progress of the reaction.

4.2. Instruments

- Melting points of the compounds were determined through melting point apparatus.
- Microwave synthesizer (Anton Paar, Monowave 300) was used for performing Microwave assisted reactions.
- Ultrasonication was done through ultrasonic cleaner model GB-2500 B (Microsil, India). It operates at a power of 500 W±15% and a frequency of 40 KHz. Operating voltage of
the ultrasonic cleaner was 220-240 V. The temperature range of ultrasonic cleaner was 0-60 °C.

- $^1$H and $^{13}$C NMR spectra were taken in CDCl$_3$ on a BRUKER ADVANCE II 400 NMR spectrometer using tetramethylsilane (TMS) as an internal reference (standard). The values have been given in ppm (δ). The coupling constant values have been given in Hertz (Hz). While citing $^1$H NMR data, following abbreviations have been used: s- singlet, d-doublet, t-triplet, q-quartet and m-multiplet. $^{13}$C NMR spectra were recorded on the same instrument with complete noise decoupling.

- Mass spectra were recorded on Waters Q-T Micromass (LC-MS) and Shimadzu GCMS-QP 2010 gas chromatogram mass spectrometer. The relative intensities of the peaks have been given in the parenthesis.

- Infrared spectra (IR) were recorded on IR Agilent Cary-660 with KBR pellets and the results have been reported in cm$^{-1}$. Only principle absorption peaks of interest have been reported.

- UV spectra were run on a UV-1800 (Shimadzu).

- Fluorescence spectra were recorded on a RF-5301 PC Spectro-fluorophotometer (Shimadzu).

4.3. General procedure for the synthesis of N-methylbenzothiazolium iodide/ N-methylthiazolium iodide:

An equimolar mixture of 1,3-benzothiazole/ 1,3-thiazole (1 equivalent) and methyl iodide (1.1 equivalent) was subjected to ultrasonication under solvent free conditions for 4-5 hrs to obtain
light yellow colored solid. Thus, the solid thus obtained was washed with diethyl ether to remove unreacted material (yield: 95%).


General Procedure

To a solution of N-methylbenzothiazolium iodide / N-methylthiazolium iodide (1 equivalent) in methanol and 3-chloro-1-(substituted phenyl)-propan-1-one (1 equivalent), 4% methanolic NaOH solution (3 mL, 3.5 equivalent) was added dropwise (5 min) during ultrasonication. The completion of the reaction was monitored by TLC using chloroform and hexane (90: 10). After the completion, the reaction mixture was poured into crushed ice to obtain the product. The product was further washed and recrystallized from chloroform and pet ether (3:1).

4.4.1. ((Z)2,5-dihydro-5-methylbenzo[b][1,4]thiazepin-3-yl)(phenyl)methanone (124a; R= -H, X= -H): cream white solid; yield: 82%; m.p: 95°C; M⁺m/z 281; IR (KBr): 1672 cm⁻¹ (C=O); ¹H NMR (CDCl₃, 400 MHz): δ = 3.27 (3H, s, N-CH₃); 3.31 (2H, s, S-CH₂); 7.15-7.17(1H, q, J= 9.0 Hz, J= 6.4 Hz); 7.22-7.26 (1H, m); 7.34-7.38 (1H, m); 7.40-7.42 (1H, q, J= 9.36 Hz, J= 6.48 Hz); 7.45-7.49 (2H, t, J= 7.84Hz); 7.56-7.60 (1H, q, J= 16.00Hz, J= 7.40 Hz); 7.92-7.94 (2H, t, J= 7.16 Hz); 8.1 (1H, s); ¹³C NMR (CDCl₃, 100MHz): δ = 197.5 (C=O); 163.2, 140.0, 136.2, 133.5, 129.1, 128.7, 128.6, 128.0, 127.9, 126.5; 37.7, 32.8, 26.5.

4.4.2. (4-Bromophenyl)((z)-2,5-dihydro-5-methylbenzo[b][1,4]thiazepin-3-yl)methanone (124b) (R= H; X= -Br): white solid; yield: 80%; m.p: 100°C; (M+2H)⁺m/z 362, 364 (1:1); IR (KBr): 1683 cm⁻¹ (C=O); 618 cm⁻¹ (C-Br); ¹H NMR (CDCl₃, 400 MHz): δ = 3.21 (3H, s, N-CH₃); 3.30 (2H, s, S-CH₂); 7.15-7.18 (1H, q, J= 9.04 Hz, J= 6.44 Hz); 7.23-7.27 (1H, m); 7.34-7.41 (2H, m); 7.59-7.62 (2H, m);
7.78-7.84 (2H, m); 8.01 (1H, s); $^{13}$C NMR (CDCl$_3$, 100MHz): δ 196.5 (C=O); 163.1, 140.0, 136.1, 134.9, 132.1, 131.9, 129.6, 129.5, 129.1, 128.8, 128.6, 127.9, 126.6; 37.6, 32.8, 26.4.

4.4.3. **(Z)2,5-dihydro-5-methyl-8-nitrobenzo[b][1,4]thiazepin-3-yl)(phenyl)methanone (124c)**

(R= -NO$_2$; X= -H): yellow solid; yield: 86%; m.p: 85°C; IR (KBr): 1593 cm$^{-1}$ (C=O); $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.09 (3H, s, N-CH$_3$); 3.26 (2H, s, S-CH$_2$); 6.52-6.54 (1H, d, J = 8.76 Hz); 6.76 (1H, s); 7.91-7.96 (7H, m); $^{13}$C NMR (CDCl$_3$, 100MHz): δ 180.7(C=O); 149.8, 139.8, 124.5, 123.5, 117.6, 103.9, 101.3, 49.5; m/z 349 (M+Na)$^+$. 

4.4.4. **(4-Bromophenyl) (2,5-dihydro-5-methyl-8-nitrobenzo[b][1,4] thiazepin-3-yl)methanone (124d)**

(R= -NO$_2$; X= -Br): yellow solid; yield 85%; m.p: 85°C; (M+ CH$_3$CN)$^+$ m/z 445,447(1:1); IR (KBr): 1592 cm$^{-1}$ (C=O); $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.12 (3H, s, N-CH$_3$); 3.14 (2H, s, S-CH$_2$); 6.43-6.45 (2H, d, J = 9.40 Hz); 6.72 (2H, s); 8.02-8.05 (4H, m); $^{13}$C NMR (CDCl$_3$, 100MHz): δ 190.5(C=O); 144.6, 139.3, 137.9, 137.0, 129.3, 113.8, 113.7, 113.6, 36.5.

4.4.5. **((2Z,5Z)-4,7-dihydro-4-methyl-1,4-thiazepin-yl)(phenyl)methanone (124e)**

(R= H; X= H): white oil; yield: 78%; (M+ CH$_3$CN)$^+$ m/z 272; IR (KBr): 1670 cm$^{-1}$ (C=O); $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.12 (3H, s, N-CH$_3$); 3.29-3.33 (2H, d, J = 6.92 Hz, S-CH$_2$); 5.59- 5.61 (1H, d, J= 8.12 Hz); 6.19- 6.21 (1H, d, J = 8.12 Hz); 7.27- 7.50 (2H, m); 7.57-7.61 (1H, m); 7.94- 7.97 (2H, m); 8.24-8.25 (1H, d, J= 3.92 Hz); $^{13}$C NMR (CDCl$_3$, 100MHz): δ 197.8(C=O); 163.0, 161.5, 136.3, 133.3, 133.2, 128.7, 128.6, 128.4, 128.1, 128.0, 39.4, 38.7, 29.7, 29.3, 25.4, 25.0, 18.2.

4.4.6. **(4-Bromophenyl) ((2Z,5Z)-4,7-dihydro-4-methyl-1,4-thiazepin-yl) methanone (124f)**

(R= -H; X= -Br): white solid; yield: 81%; m.p: 50°C; (M+ CH$_3$CN)$^+$ m/z 350,352 (1:1); IR (KBr): 1678 cm$^{-1}$ (C=O); $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.12 (3H, s, N-CH$_3$); 3.28-3.29 (2H, d, J = 6.92 Hz, S-CH$_2$); 8.26
(1H, s); 5.57-5.59 (1H, d, J= 8.12 Hz); 6.20-6.22 (1H, d, J= 8.12 Hz); 7.61-7.63 (2H, d, J= 8.48 Hz); 7.81-7.83 (2H, d, J= 8.48 Hz); 13C NMR (CDCl₃, 100MHz): δ 196.8 (C=O); 162.7, 135.1, 135.0, 132.0, 129.5, 128.7, 126.8, 123.3, 113.1, 111.9; 39.8; 35.2; 31.22, 29.4; 29.2.

4.4.7. **((2Z,5Z)-4,7-dihydro-2,3,4-trimethyl-1,4-thiazepin-yl)(phenyl)methanone (124g) (R= -CH₃; R¹= -CH₃; X= -H):** light yellow oil; yield: 75%; (M+ CH₃CN)⁺ m/z 300; IR (KBr): 1592 cm⁻¹ (C=O); ¹H NMR(CDCl₃, 400 MHz): δ= 1.92 (3H, s, C-CH₃); 2.10 (3H, s, C-CH₃); 2.90 (3H, s, N-CH₃); 3.17- 3.19 (2H, d, S-CH₂, J= 7.48 Hz); 7.46-7.49 (2H, m); 7.57- 7.60 (1H, t, J= 7.36 Hz); 7.89- 7.98 (3H, m). ¹³C NMR (CDCl₃, 100MHz): δ= 197.8 (C=O); 162.7, 162.1, 136.4, 136.3, 133.5, 133.4, 128.7, 128.6, 128.0, 126.7, 123.2, 113.4, 112.1, 39.0, 31.2, 29.7, 29.6, 29.5, 29.4, 14.1.

4.4.8. **(4-Bromophenyl)((2Z,5Z)-4,7-dihydro-2,3,4-methyl-1,4-thiazepin-yl) methanone (124h) (R= -CH₃; R¹= -CH₃; X= -Br):** white solid; yield: 83%; m.p:55°C; (M+ CH₃CN)⁺ m/z 380,382(1:1) IR (KBr): 1591 cm⁻¹ (C=O); ¹H NMR(CDCl₃, 400 MHz): δ 1.92 (3H, s, CH₃); 2.10 (3H, s, C-CH₃); 2.90 (3H, s, N-CH₃); 3.13- 3.15 (2H, d, S-CH₂, J= 8.00 Hz); 7.89 (1H, s); 7.78- 7.80 (2H, d, J= 8.52 Hz); 7.60- 7.63 (2H, q, J= 12.48 Hz, J= 4.56 Hz). ¹³C NMR (CDCl₃, 100MHz): δ 196.7 (C=O); 162.9, 161.4, 135.0, 133.3, 132.1, 132.0, 129.6, 129.5, 128.7, 128.3, 39.4, 38.6, 34.1, 29.3, 25.2, 24.8, 18.2, 18.1.

4.5. Biological activities

4.5.1. **Methodology for antioxidant activity (DPPH radical scavenging activity)**

The methodology for DPPH radical scavenging activity was same as adopted in chapter 2.

4.5.2. **Antimicrobial activity (Agar diffusion method)**

The methodology for antimicrobial activity undertaken was same as in chapter 2.

4.5.3. **Antihypertensive activity**
The compound of interest were tested at three concentrations 10, 50 and 100 µg. The samples were dissolved in respective solvents and mixed with assay buffer (10mM HEPES buffer containing NaCl (0.3M) and ZnSO₄(10µM)) containing kidney cortex plasma membranes (20µL) (ACE enzyme source) and Hippuryl-His-Leu as substrate (1mM) [Jimsheena, 2009; Hooper, 1987].

The compounds were incubated with the enzyme for 10 minutes at 37°C. Then 10 µL of substrate (1 mM) was added which makes a final reaction volume of 50µl and incubated for 45min at 37°C. The reaction was terminated by the addition of 1M HCl (0.1 mL). The yellow color was developed by the addition of 100µL of pyridine and 50µl of benzene sulphonyl chloride. The yellow color that formed was measured at 410 nm in an ELISA Plate Reader (iMARK, BIORAD).

Compounds with an inhibitory potential, block the substrate availability to the enzyme and thereby cause enzyme inhibition and hence the yellow color was not formed. The inhibition has been represented in the form of percentage over control. Captopril, a known ACE inhibitor has been tested in this assay as a standard compound.

4.6. Results and discussion

With an objective to introduce facile and eco-friendly methodologies, resist the use of hazardous solvents and decrease the reaction time, green protocols have been employed in the present investigations. It was envisaged that benzothiazolium salts with β-haloketones viz. 3-chloro-1-(phenyl) propan-1-one and its derivatives would provide corresponding seven membered heterocycles in basic medium. Further, these reactions have only been carried out in ultrasonication bath.
N-methylbenzothiazolium iodide on reaction with 3-chloro-1-(phenyl) propan-1-one in 4% NaOH provides a cream white solid in 82% yield with M⁺ m/z 281. Its ¹H NMR exhibits signals at δ 3.27 (3H, s, N-CH₃), 3.31 (2H, s, S-CH₂), 7.15-7.17 (1H, q, J = 9.09 Hz, J = 6.40 Hz), 7.22-7.26 (1H, m), 7.34-7.38 (1H, m), 7.40-7.42 (1H, q, J = 9.36 Hz, J = 6.48 Hz), 7.45-7.49 (2H, t, J = 7.84Hz), 7.56-7.60 (1H, q, J = 16.00Hz, J = 7.40 Hz), 7.92-7.94 (2H, t, J = 7.16 Hz) and 8.1 (1H, s). Further, in the ¹³C NMR the product shows signals at δ 197.5 (C=O), 163.2, 140.0, 136.2, 133.5, 129.1, 128.7, 128.6, 128.0, 127.9, 126.5; 37.7, 32.8 and 26.5. Its IR spectrum shows absorption band at 1672 cm⁻¹ due to C=O group in the molecule. From the above data the structure (Z)2,5-dihydro-5-methylbenzo[b][1,4]thiazepin-3-yl)(phenyl)methanone (124a; R= -H, X= -H) has been assigned to the compound.

The other derivatives (124b-124h) have been prepared by the base induced reaction of 3-chloro-1-(substituted phenyl)propan-1-one with N-methylbenzothiazolium iodide. The structures of synthesized compounds have also been confirmed through spectral data - ¹H NMR, ¹³C NMR, Mass spectra, IR and UV spectra. In the ¹H NMR, a singlet in the region of δ 2.9-3.2 has been due to presence of N-CH₃, doublet/singlet around δ 3.1-3.3 corresponds to the S-CH₂ linkage. An additional singlet at δ 2.10 and δ 2.90 has been attributed to two –CH₃ group in compound (124g) and (124h), respectively. The peak in ¹³C NMR spectrum in the range 180-200 ppm in all the compounds confirms the presence of C=O group.

The absorption spectra of all the compounds have been recorded in chloroform with 1x 10⁻⁴ mol L⁻¹ (Figure 1). The spectra shows maximum absorption in the region 200-300 nm due to the presence of C=O group in the compounds that has been attributed to  n-π*, π-π* transitions. Further, a red shift has been observed due to the presence of auxochrome [methyl
group and halogen group in compounds (124b), (124d), (124e) and (124g)]. Also, a prominent shift has been observed in the derivatives (124c) and (124d) which has been attributed to presence of $-\text{NO}_2$ group that exerts electron withdrawing effect on the compounds. Furthermore, an absorption band at 380-410 nm in (124c) and (124d) due to $\pi-\pi^*$ transition in $-\text{NO}_2$ group has also been observed.

The IR spectra of compounds (124a-124g) show a strong and sharp band in the region 1590-1690 cm$^{-1}$ due to presence of C=O group in all the compounds. The weak and sharp absorption band at 800-760 cm$^{-1}$ in synthesized compounds pertain to C-S-C linkage of seven membered ring. The vibration band of the $-\text{NO}_2$ group in compounds (124c) and (124d) has been in the range of 1500-1510 cm$^{-1}$ (asymmetric stretching) and 1318-1325 cm$^{-1}$ (symmetric stretching). Further, a strong stretching band at 690-515 cm$^{-1}$ has been attributed the presence of C-Br bond in (124b), (124d), (124e), and (124g) compounds. Furthermore, the compounds exhibit the C-H (aliphatic and aromatic), C=C stretching vibrations at their usual positions. Lastly, the $M^+$ value obtained from mass spectrometry confirmed the formation the compounds.

The ring expansion via ultrasonication has been carried out by the reaction of benzothiazolium and thiazolium salts with 3-chloro-1-(substituted phenyl)-propan-1-one in methanol in the presence of a base at room temperature (Scheme-49 & Scheme-50). Initially, intermediate pseudobase has been proposed to be formed in situ by a nucleophilic attack of hydroxide ion at C-2 position in benzothiazolium/ thiazolium salts which leads to C-S bond cleavage. Further, reaction with $\beta$-haloketone, generation of $\beta$-thiocarbanion and dehydrative cyclisation provides the desired product (Scheme-51). It has been observed that ring
expansions get effected by the basicity and nucleophilicity of the base. Numerous commonly available bases (strong and weak base) with different concentrations have been employed to optimize the reaction condition. A 4% methanolic solution of sodium hydroxide, proved to be best for the transformantions in hand. The present ring transformatin have been temperature dependent that is with the increase in temperature, the reaction does not proceed to give the final product. Instead, the reaction results in numerous byproducts/ intermediates. Hence, employing optimised condition, a variety of thiazolium and benzothiazolium salts have been treated with 3-chloro-1-(substituted phenyl)-propan-1-one to get the corresponding thiazepine and benzothiazepine derivatives in good to excellent yield. Moreover, electron withdrawing and releasing group effect the ring expansion pathway. Electron withdrawing group –NO₂ in compounds (124c) and (124d), facilitates hydrogen abstraction which enhances the yield of the product and also reduces the reaction time whereas the electron releasing group, -CH₃ in compounds (124g) and (124h) increases the electron density on S-CH₂-CH₂, and hinders abstraction of proton. The substituents have been observed to affect the time and yield of synthesized thiazepines.

\[
\begin{align*}
\text{SN}^+\text{CH}_3\text{I}^- & \quad \text{ClCH}_2\text{CH}_2\text{COAr-X} \\
\text{R} & \quad \text{H; NO}_2 \\
\text{X} & \quad \text{H, Br}
\end{align*}
\]
Scheme-49

\[ R = H; \text{CH}_3 \]
\[ X = H, \text{Br} \]

Scheme-50

Scheme-51
4.6.1. Fluorescence spectroscopy

The fluorescence absorption and emission spectra of the compounds (124a-d, 124f, 124h) have been recorded at a concentrations of $1 \times 10^{-6}$ and $3 \times 10^{-7}$ mol L$^{-1}$ in chloroform [Table-1]. Figure 2 and Figure 3 show emission spectra of compounds (124a-d, 124f, 124h). The single fluorescence emission peaks at 365, 480, 482, 333, 366, and 436 nm in the compounds (124a-d, 124f, 124h), show that these motifs exhibit fluorescent character.
**Figure 2.** Emission spectra of compound (124a), (124d) and (124f).

**Figure 3.** Emission spectra of compound (124b), (124c) and (124h).

**Table- 1.** Maximum excited and emission wavelengths of compounds (124a-d, 124f, 124h).

<table>
<thead>
<tr>
<th>Compound</th>
<th>CHCl₃</th>
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<tbody>
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<td></td>
<td>λex</td>
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4.7. Computational studies

The molecular geometry optimization and $^1$H and $^{13}$C NMR spectra calculations have been taken up with Gaussian 09W software package [Frisch et al., 2009] with the use of DFT

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<tbody>
<tr>
<td>(124a)</td>
<td>259</td>
<td>365</td>
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<tr>
<td>(124b)</td>
<td>394</td>
<td>480</td>
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<td>(124c)</td>
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<td>333</td>
</tr>
<tr>
<td>(124f)</td>
<td>271</td>
<td>366</td>
</tr>
<tr>
<td>(124g)</td>
<td>360</td>
<td>436</td>
</tr>
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</table>
methods along with B3LYP (Becke three parameter Lee-Yang-Parr) exchange correlation functional, which further combines the hybrid exchange functional of Becke [Becke, 1988] with the gradient-correlation functional of Lee, Yang and Parr [Lee et al., 1988]. The calculations for the gas phase of the compound (124a) has been carried out with 6-31G(d) basis set.

To predict the geometry of the molecules, the DFT calculations has been carried out. By geometry optimization at B3LYP/6-31G(d) level, the optimized bond lengths and bond angles for the structure 124a have been presented in Table-2. Through the DFT method, the calculated bond lengths of C=C, C-S and C-N bonds in 124a have been 1.3020 Å, 1.797 Å and 1.4506 Å, respectively whereas the calculated bond angles for N7-C8-C9, C5-S11-C4 and O17-C6-C9 bond angles in benzothiazepine ring (124a) are 158.38˚, 122.44˚ and 120.71˚, respectively. The optimized configuration of structure with atom numbering scheme has been shown in (Figure 4).

The total energy of highest occupied molecular orbitals and energy of lowest unoccupied molecular orbitals for structures (124a) have been obtained by theoretical calculations. Further, the highest occupied molecular orbitals (HOMOs) have been observed to be mainly localized on the seven membered thiazepine ring (124a), which suggests that the seven membered ring is the most active part of the molecule. The stationary points for the molecule (124a) have been verified by the frequency calculations. In the absence of negative frequency, the assigned geometry to the molecules has been considered to be energy minimum. The calculated total energy of compound (124a) is -1,589.96 kcal/mol. The estimated dipole moment of the molecule is 4.765 D.
**Figure 4.** Optimized structure of (124a).

**Table- 2.** Calculated parameters of compound (124a).

<table>
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<tr>
<th>Parameters</th>
<th>Calculated</th>
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<td><strong>Bond lengths(Å)</strong></td>
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<tr>
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<tr>
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<td>S(11)-C(5)</td>
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<tr>
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<tr>
<td>C(12)-C(14)</td>
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</tbody>
</table>
4.8. Antioxidant activity

The unique structure of thiazepine and benzothiazepine motif makes them potentially bioactive compounds. The antioxidant activity of the synthesised compounds has been evaluated by the DPPH radical scavenging assay using ascorbic acid as a standard antioxidant. The experiments have been carried out by employing five different concentrations and the results summarized in Table-3 which clearly depicts that when the concentration increases, the antioxidant activity also increases. Compound (124b) shows the maximum DPPH free radical scavenging. However, the antioxidant activity of all the compounds has been quite less than that of the standard (ascorbic acid) (Figure 5).

**Table-3.** Antioxidant activity of compounds (124a-d, 124f, 124h).

<table>
<thead>
<tr>
<th>Test samples</th>
<th>% Radical Scavenging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1mg/l 2mg/l 3mg/l 4mg/l 5mg/l</td>
</tr>
<tr>
<td>(124a)</td>
<td>29.12% 31.22% 33.53% 35.34% 41.66%</td>
</tr>
<tr>
<td>(124b)</td>
<td>43.36% 46.34% 50.85% 55.06% 60.33%</td>
</tr>
<tr>
<td>(124c)</td>
<td>N A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$N(7)$-$C(8)$-$C(9)$</th>
<th>158.38</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C(9)$-$C(16)$-$C(17)$</td>
<td>120.76</td>
</tr>
<tr>
<td>$C(12)$-$N(7)$-$C(20)$</td>
<td>106.72</td>
</tr>
<tr>
<td>$C(16)$-$C(18)$-$C(20)$</td>
<td>117.41</td>
</tr>
</tbody>
</table>
(124d)  3.43%  4.31%  4.50%  6.18%  10.51%
(124f)  1.32%  2.99%  4.12%  8.66%  11.36%
(124h)  3.65%  7.45%  10.12%  15.13%  20.14%
Ascorbic  58.42%

[a] ([NA- Not active])

Figure 5. Graphical representation of antioxidant activity of compounds (124a-d, 124f, 124h).

4.9. Antimicrobial activity

The synthesised compounds exhibit good antimicrobial activity, benzothiazepine derivatives being better than thiazepines. The compounds viz. (124b), (124d), (124f) and (124h) have been observed to be more active against the microbial strains that may be due to presence of electron withdrawing group (-Br). The results of antimicrobial activity test have been summarized in Table-4 (Figure 6).
Table-4. Antimicrobial activity of compounds (124a-h).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Staph. Aureus</th>
<th>E. Coli</th>
<th>C. Albicans</th>
<th>A. Niger</th>
</tr>
</thead>
<tbody>
<tr>
<td>124(a)</td>
<td>18.87</td>
<td>11.84</td>
<td>9.29</td>
<td>10.14</td>
</tr>
<tr>
<td>124(b)</td>
<td>20.85</td>
<td>13.46</td>
<td>13.31</td>
<td>11.06</td>
</tr>
<tr>
<td>124(c)</td>
<td>16.67</td>
<td>12.34</td>
<td>10.70</td>
<td>10.50</td>
</tr>
<tr>
<td>124(d)</td>
<td>20.98</td>
<td>14.67</td>
<td>12.91</td>
<td>11.80</td>
</tr>
<tr>
<td>124(e)</td>
<td>11.67</td>
<td>9.78</td>
<td>11.81</td>
<td>10.21</td>
</tr>
<tr>
<td>124(f)</td>
<td>12.77</td>
<td>10.30</td>
<td>13.70</td>
<td>11.35</td>
</tr>
<tr>
<td>124(g)</td>
<td>10.66</td>
<td>9.44</td>
<td>11.02</td>
<td>9.67</td>
</tr>
<tr>
<td>124(h)</td>
<td>14.75</td>
<td>9.66</td>
<td>14.31</td>
<td>10.04</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>35</td>
<td>35</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Amphotericin</td>
<td>24</td>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing antimicrobial activity](image-url)
4.10. Antihypertensive activity

The data indicates that the compounds exhibit significant antihypertensive activity which could be attributed to the presence of thiazepine ring. Further, increase in concentration correspondingly increases the antihypertensive activity (Table-5 and Figure 7).

Table-5. Antihypertensive activity of compounds (124a-h).

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Compounds</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(124a)</td>
<td>(124b)</td>
</tr>
<tr>
<td>10</td>
<td>39.11</td>
<td>37.12</td>
</tr>
<tr>
<td>50</td>
<td>68.12</td>
<td>65.15</td>
</tr>
<tr>
<td>100</td>
<td>75.16</td>
<td>72.73</td>
</tr>
</tbody>
</table>

**Figure 6.** Graphical representation of antimicrobial activity of compound (124a-h).

**Figure 7.** Graphical representation of compounds (124a-h).
From the results it has been concluded that N-methylbenzothiazolium/ thiazolium cation undergo convenient reaction with β-haloketones in the basic medium to furnish ring expanded benzothiazipine/thiazepines; an extension of the ring expansions analogous to the synthesis of 1,4-benzothiazines. The synthesised compounds exhibit considerable antihypertensive activity besides other biological activities.

References


