Chapter 2.

Ring Transformations of N-methyl/(substituted-)phenacylbenzothiazolium cations

Heterocycles constitute one of the main thrust areas of research due to their manifold applications. Numerous heterocyclic rings (3, 4, 5, or higher membered) containing different elements (N, S, O, etc. single or in combinations) occupy a pivotal positions due to their presence almost everywhere in nature. Further, the wide spread existence of heterocycles containing N and S has been an essential reason for an unprecedented growth in their synthetic methodologies. These systems individually or otherwise form a component of numerous biochemical, pharmacological, agrochemical compounds. Since, the investigations undertaken in this section involve the synthesis of 1,4- heterocycles through ring transformation or otherwise, therefore the discussion has been confined to such systems with nitrogen and sulphur atoms.

Thiamine or vitamin B$_1$ (Figure 1), a relatively stable compound comprises of thiazolium ring and pyrimidine ring linked by a methylene bridge [Dwivedi and Arnold, 1973]. The polar nature of thiamine makes it highly soluble in water. Dissolution of thiamine hydrochloride at a concentration of 1% (w/v) in water naturally yields an acidic solution (pH 3.13) in which the thiamine remains stable at room temperature [Sousa et al., 2011]. With the increase in pH beyond 5.5, thiamine becomes gradually unstable [Pachapurkar and Bell, 2005]. The C-2 (H)
proton of thiamine has been observed to be very acidic (pKa = 18.0) and gets abstracted by the protic solvent leading to the formation of the potent nucleophilic thiazolium ylide (Scheme-1) [Haake et al., 1971; Washabaugh and Jencks, 1989]. Thiamine degrades through reversible [Washabaugh et al., 1993] hydroxide-catalysed thiazolium ring opening at pH 7.4 [Duclos and Haake, 1974]. Being highly unstable in alkaline medium, thiamine undergoes C-2 cleavage to produce pseudobase (Scheme-2) which undergoes various transformations, one of which has been the formation of thiazine derivatives. Various such reactions reported in the literature reveal that thiamine undergoes intermolecular ring expansion in alkaline medium to produce thiazines. Due to broad spectrum of biological activities of benzothiazines/thiazines viz. antimicrobial, anticancer, anti-hypertensive, anti-inflammatory etc. and their use as synthetic intermediates prompted various researchers to synthesise these heterocycles [Tandon et al., 2006; Mor et al., 2012].

Further, it has been reported that thiazines and benzothiazines have been synthesized through cyclocondensations, oxidations, reductions, ring transformations from appropriately appended
precursors using conventional and eco-benign methodologies [Tandon et al., 2006; Barton, 2016]. After a comprehensive review on the synthetic protocols of these heterocycles, the results of the present investigations have been discussed.

![Chemical structures](image)

**Scheme-2**

N-amino substituted of benzothiazolium salt (1), on reaction with aldehydes yields two ring expanded products viz. benzothiadiazine derivatives (4) and benzothiazine derivatives (5). After the initial S-C cleavage, the former has been obtained by the intramolecular cyclization of the intermediate (2) that is by the attack of thiolate ion on azomethine carbon, whereas the attack of thiolate ion on olefinic carbon attached with aryl aldehyde in intermediate (3) and a subsequent oxidation provides 5 (Scheme-3) [Filak et al., 2009].
R= R^1= -H; R= -C_4H_7, R^1= -Cl; R= p-H_3C-C_6H_4, R^1= -CH_3, R= p-H_3CO-C_6H_4, R^1= -Br; R= -C_6H_5, R^2=-F.

Scheme-3

One pot organocatalysed, diastereoselective asymmetric ring expansion of coumarin based dihydrobenzothiazoles (6), routed through C-2 ring cleavage followed by nucleophilic attack of thiol on phenacyl bromide derivative in the presence of base (K_2CO_3, KOH, KF, KF/Al_2O_3) yields enolate in situ. The latter through Mannich type reaction produces mixture of cis (7) and trans (8) coumarin based 3,4-dihydro-2H-benzothiazines (Scheme-4) [Khoobi et al., 2012].

Benzothiazolylideneacetates (9) undergo oxidative ring expansion of thiazolium ring in presence of m-CPBA (m-chloroperoxy benzoic acid) to yield 1,4-benzothiazine derivatives (10) (Scheme-5) [Pi et al., 2009].

A decarboxylative coupling reaction of 2-aminobenzothiazoles (11) with alkynyl carboxylic acid and subsequent nucleophilic ring opening in the presence of CuCl catalyst followed by intramolecular hydroamination in the presence of K_3PO_4 furnish 1,4-benzothiazine derivatives (12) (Scheme- 6)[Qiu et al., 2015].
**Scheme-4**

\[ \text{Base, R.T.} \]

\[ \text{Scheme-5} \]

\[ \text{m-CPBA, DCM} \]

\[ R = \text{H, } R^1 = \text{-C}_2\text{H}_5, R^2 = \text{-CH}_3; R = \text{H}, R^1 = R^2 = \text{-CH}_3; R = \text{-H}, R^1 = \text{-CH}_3, R^2 = \text{-C}_2\text{H}_5; R = \text{-F}, R^1 = R^2 = \text{-CH}_3; R = \text{-OCH}_3, R^1 = R^2 = \text{-CH}_3; R = \text{-H}, R^1 = \text{n-C}_5\text{H}_{11}, R^2 = \text{-CH}_3. \]
Cyclocondensation of 2-aminobenzothiazole with α, β-unsaturated acids or esters, or electron deficient alkynes, α-haloketones; condensation and oxidative cyclization of N-unsubstituted and N,N-dialkyldithioanilines with 1,3-dicarbonyls or esters yields various 1,4-benzothiazines [Parai et al., 2009; Saadouni et al., 2014; Meng et al., 2013; Shahwar et al., 2013; Pi et al., 2009]. Similar expansions or formation of bicyclic systems have also been reported for appropriately appended benzo-/thiazolium cations [Barton, 2016].

2-Aminoanthophenol, a versatile intermediate has extensively been used in industry as raw material for the production of medicine, agrochemicals, dyes and variety of heterocyclic derivatives of synthetic importance [Sekhar, 2014]. It has mainly been used as precursor for several biologically active molecules such as benzothiazines, benzothiazepines, thiazepines etc. [El-Shaieb, 2007; Sekhar, 2014] having S and N heteroatom, which find therapeutic applications in many cardiovascular diseases namely Ischemic heart, thrombus, heart failure, arrhythmia etc. Similarly, benzothiazine derivatives and azophenothiazines, a reliable precursor for various pharmaceutically active substances have been prepared from 2-aminothiophenol derivatives [Kajino et al., 1991; Deligne, 1986]. 2-Aminoanthophenol undergoes various reactions like cyclocondensation, oxidation and reduction, nucleophilic reactions etc. mostly through conventional methods to furnish 1,4-benzothiazine derivatives. viz.
Enaminones (13) undergo transamination and C-H bond sulfenylation with o-aminothiophenol derivative in the presence of I$_2$ and ethyl lactate to yield 1,4-benzothiazine derivative (14) (Scheme- 7)[Wan et al., 2018]

\[
\begin{align*}
\text{R= -C}_6\text{H}_5, R^1 = \text{-H};
\text{R= p-H}_3\text{C-C}_6\text{H}_4, R^1 = \text{-H};
\text{R= p-Cl-C}_6\text{H}_4, R^1 = \text{-H};
\text{R= H}_3\text{CO-C}_6\text{H}_4, R^1 = \text{-H};
\text{R= p-NO}_2\text{C}_6\text{H}_4, R^1 = \text{-H};
\text{R= p-Br-C}_6\text{H}_4; R^1 = \text{-H};
\text{R= F}_3\text{C-C}_6\text{H}_4, R^1 = \text{-H}.
\end{align*}
\]

**Scheme- 7**

Condensation of 2-amino-4,6-dimethylbenzenethiol (15) with β-diketones provides intermediate enamine ketone (16). The latter undergoes oxidative cyclization with the scission of S-S bond followed by nucleophilic attack of enaminoketones to give 1,4-benzothiazine derivatives (17) (Scheme-8) [Gupta et al., 2009].
R= -H, R¹ = -CH₃; R= -CH₃, R¹ = -C₆H₅.

**Scheme-8**

While, substituted 2-aminothiophenols (18) on irradiation with β-ketoesters/β-diketones (19) in the presence of alumina in microwave (MW) produce substituted 4H-1, 4-benzothiazine (20) in better yield (Scheme-9) [Gupta, 2011].

Further, o-aminobenzenethiol on treatment with acetyl acetone (21) in DMSO affords 1-(3-methyl-4H-benzo[b][1,4]thiazine-2-yl)ethanone (20) (Scheme-10) [Pawar et al., 2011].

On refluxing o-aminothiophenol with penta-2,4-dione (23) in ethanol produces 1-(3-methyl-4H-1,4-benzothiazin-2yl) ethane (24) along with a byproduct (25) (Scheme-11) [Aloui et al., 2009].
R= -H, R¹= -Cl, R²= -CH₃, R₃= -lC-C₆H₄-NH-; R= -H, R¹= Cl, R²= -C₆H₅, R₃= p-F-C₆H₄; R= -H, R¹= -Br, R²= -C₆H₅, R₃= p-lC- C₆H₄; R= -H, R¹= - OCH₃, R²= -C₆H₅, R₃= p-Br- C₆H₄.

**Scheme-9**

**Scheme-10**

4-(2-Mercaptophenyl)amino-1,1,1-trifluoromethyl-3-butene-2-one (26) (synthesised from flourinated α,β-unsaturated ketones and dinucleophiles like 2-aminothiophenol or 2-amino ethanethiol) cyclizes in DMSO to yield keto-enol isomer of (1Z)-1-(2Hbenzo[b][1,4]thiazin-2-ylidene)-2,2,2-trifluoroethanol (27) in good yield (Scheme-12) [Chu et al., 2001].
Scheme-12

Multicomponent reaction of o-aminothiophenol, aromatic aldehyde and t-BuNC (tert-butyl isocyanide) in the presence of p-toluene sulphonlic acid (PTSA) gives N-tert-butyl-3-phenyl-4H-benzo[b][1,4] thiazin-2-amine (28) (Scheme-13) [Tsirulnikov et al., 2013].

Scheme-13

Deprotonation of substituted 2-aminothiophenols in the presence of nitrate anion gives thiophenolate anion (29). The latter cyclocondenses with substituted 2-bromoalkanoates (30) in the presence of ionic liquid [bmim][NO₃] (a green solvent) to yield an intermediate (31) having ionic liquid attached to carbonyl oxygen. Ionic liquid acts as a polar medium which enhances the dissociation of acidic proton from thiol group and the presence of carbonyl group assists the synthesis of benzothiazinone derivatives (32)(Scheme-14) (Sharifi et al., 2013).
R = R¹ = -H; R = -H, R¹ = -CH₃; R = R¹ = -CH₃; R = -H, R¹ = -C₂H₅; R = -H, R¹ = -COOC₂H₅; R = -CH₃, R¹ = -COOC₂H₅; R = -C₂H₅, R¹ = -COOC₂H₅.

**Scheme-14**

Oxidative-enzyme NAD⁺/FAD obtained from Baker’s yeast abstract H⁺ ion from 2-aminothiophenol (33) followed by nucleophilic attack of mercapto group of other 2-aminothiophenol to form an disulphide intermediate (34). The latter cyclocondenses with 1,3-dicarboxylns to form 1,4-benzothiazines (35) (Scheme-15) [Pratap et al., 2011].
\[ R = -H, R^1 = R^2 = -\text{CH}_3; R = -H, R^1 = -\text{CH}_3, R^2 = -\text{OC}_2\text{H}_5; R = -H, R^1 = -\text{CH}_3, R^2 = -\text{C}_6\text{H}_5; R = R^1 = -\text{CH}_3, R^2 = -\text{OC}_2\text{H}_5; R = \text{Cl}, R^1 = R^2 = -\text{CH}_3; R = -\text{Cl}, R^1 = -\text{CH}_3, R^2 = -\text{C}_6\text{H}_5 \]

**Scheme-15**

Chalcones or 1,3-diphenyl propenone (36) (prepared from benzaldehyde derivative and acetophenone derivative) on reaction with o-aminothiophenol in the presence of Indium trichloride afford 1,4-benzothiazines (37) (Scheme-16) [Al-Jaber *et al.*, 2012].

In the presence of sulfonic acid functionalized nano-\(\gamma\)-\(\text{Al}_2\text{O}_3\), substituted o-aminothiophenol (38) reacts with \(\omega\)-bromoketones (39) to furnish 3-substituted-2H-1,4-benzothiazines (40) in good yield (Scheme-17) [Li *et al.*, 2013].

A Smiles rearrangement on substituted chlorobenzenethiol (41) and optically active (s)-N-furfuryl-2-chloropropanamide (42) in the presence of Cs\(_2\)CO\(_3\) under microwave radiations
yields (R)-4-substituted-2-methyl-2H-benzo[b][1,4]thiazin-3(4H)-ones (43) (Scheme-18) [Meng et al., 2013].

\[
\text{Scheme-16}
\]

\[
\text{Scheme-17}
\]
R= p-Cl, R¹ = -C₆H₅; R= m-Cl, R¹ = -OC₄H₆; R= o-Cl, R¹ = -C₆H₁₁.

**Scheme- 18**

4H-1,4-benzothiazine derivatives (45) have been synthesized when substituted o-aminobenzenethiol was refluxed and stirred with N-(substituted benzothiazol-2-yl)-3-oxo-butyramide (44). The former (45) having CO-NH- linkage along with thiazole and thiazine ring has proved to be effective in biopharmaceutics (Scheme-19) [Rathore et al., 2006].

o-Aminobenzenethiol derivatives (46) on reaction with substituted o-chloro nitrobenzene (47) and formylation produce substituted 2-amino-2-nitrodiphenyl sulphides (48). The latter undergoes Smiles rearrangement and subsequently base catalysed intramolecular cyclization to yield substituted phenothiazines (49) (Scheme-20) [Shukla et al., 2011].

o-Aminothiophenol condenses with maleic anhydride (50) and cyclizes in acidic medium to yield 3,4-dihydro-2-methoxycarboxylmethyl-3-oxo-2H-1,4-benzothiazine (51) (Scheme-21) [Dabholkar et al., 2016].
R = R\(^1\) = R\(^2\) = R\(^3\) = -H; R = R\(^1\) = -CH\(_3\), R\(^2\) = -Cl; R\(^3\) = -H, R\(^1\) = -CH\(_3\), R\(^2\) = -Br, R\(^3\) = -OCH\(_3\).

**Scheme-19**

\[
\begin{align*}
\text{R} = \text{R}^1 = \text{R}^2 = \text{R}^3 = -\text{H}; \text{R} = \text{R}^1 = -\text{CH}_3, \text{R}^2 = -\text{Cl}; \text{R}^3 = -\text{H}, \text{R}^1 = -\text{CH}_3, \text{R}^2 = -\text{Br}, \text{R}^3 = -\text{OCH}_3.
\end{align*}
\]

**Scheme-20**

\[
\begin{align*}
\text{R} = \text{R}^1 = \text{R}^2 = \text{R}^3 = -\text{H}; \text{R}^1 = -\text{H}, \text{R}^2 = -\text{CH}_3, \text{R}^3 = -\text{OCH}_3, \text{R}^1 = -\text{CH}_3, \text{R}^2 = -\text{Cl}, \text{R}^2 = -\text{H}; \text{R} = -\text{H}, \text{R}^1 = -\text{OCH}_3, \text{R}^2 = -\text{Br}, \text{R}^3 = -\text{CH}_3.
\end{align*}
\]
The steroselective (2E,3E)-2H-1,4-benzothiazine-2,3(4H)-dionedioxime (52) has been procured from 2-aminothiophenol and dichloroglyoxime (53) in the presence sodium bicarbonate (Scheme-22) [Zabardasti et al., 2012].

\[
\begin{align*}
\text{NH}_2 & \quad \text{SH} \\
\text{Cl} & \quad \text{Cl} \\
\text{NOH} & \quad \text{NOH}
\end{align*}
\]

\[(52) \quad (53)\]

**Scheme-22**

H\text{\text{-}Aminothiophenol undergoes cyclocondensation with oxalic acid/ diethyl malonate/ \alpha\text{-}haloketonesto yield 2H-1,4-benzothiazine-2, 3(4H)-dione (54), 2H-1,4-benzothiazine-2-carboxylate (55) and 2-phenyl-2H-1,4-benzothiazine (56) respectively (Scheme-23) [Shahwar et al., 2013].

\[
\begin{align*}
\text{NH}_2 & \quad \text{SH} \\
\text{OC}_2\text{H}_5 & \quad \text{OC}_2\text{H}_5
\end{align*}
\]

\[(54) \quad (55) \quad (56)\]

**Scheme-23**
Epoxide (57), through a regioselective ring opening and subsequent condensation with $\omega$-aminothiophenol affords 3-hydroxy-2-aryl-2,4-dihydro-2H-benzo[b][1,4]thiazine-3-carboxylate (58) (Scheme-24) [Saadouni et al., 2014].

\[
\begin{align*}
\text{(57)} & \quad \begin{array}{c}
\text{H} \\
\text{O} \\
\text{COOR} \\
\text{CN}
\end{array} \\
\text{Reflux, -HCN} & \quad \text{CH}_{3}\text{CN} \\
\text{(58)} & \quad \begin{array}{c}
\text{R}^1 \\
\text{OH} \\
\text{H} \\
\text{COOR} \\
\text{N}
\end{array}
\end{align*}
\]

$R = R^1 = -\text{CH}_3$; $R = -\text{CH}_3$, $R^1 = -\text{Cl}$; $R = -\text{C}_2\text{H}_5$, $R^1 = -\text{CH}_3$; $R = -\text{C}_2\text{H}_5$, $R^1 = -\text{Cl}$.

**Scheme-24**

$\omega$-Aminothiophenol oxidizes to give bis(\(\omega\)-amino phenyl)disulfide (59) which via Friendelander’s cyclocondensation with diketones (60) yield an intermediate (61). The latter having lone pair of amino group attacks the carbonyl carbon followed by elimination of water to furnish 1,4-benzothiazine-2-carboxamide derivatives (62) (Scheme-25) [Rajnarendar et al., 2010].
Under microwave radiations, 2-bromo-5,5-dimethylcyclohexane-1,3-dione (63) when treated with 2-substituted aminothiophenol and piperidine yields 7-substituted-2, 2- dimethyl-2, 3-dihydro-1H, 10H-phenothiazine-4-ones (64) (Scheme-26) [Vijay et al., 2006]
\( \text{Scheme-26} \)

\( \alpha \)-Bromobenzenethiol (65) undergoes nucleophilic substitution reaction with Boc-protected amino alcohol derivatives (66) to afford substituted 2-(2-bromophenylthio)-ethanamines (67). The latter via intramolecular N-aryl amination in the presence of copper iodide and cyclization in \( \text{K}_2\text{CO}_3 \) yields 3,4-dihydro-2H-benzo[b][1,4]thiazines (68) (Scheme-27) [Parai et al., 2009].

Besides, the reactions of 2-aminothiophenol with various species viz. diketones, aldehydes acetamides etc. to furnish 1,4-benzothiazine derivatives, a few other precursors have also been reported in the literature to procure the same that follows:

A substituted aromatic amines (69) when treated with carbostyrils (CAB) (70) and 5,5-dimethycyclohexanon-1,2-dione (DIM) (71) in the presence of iodine and sulfur under ultrasonication yield 2,3-(substituted) benzo-1,4-thiazino [5,6-b]-4H-9H-5 /7-substituted -10 oxoquinolines (72) and 7/9-substituted-2,2-dimethyl-2,3-dihydro-1H,10H-phenothiazin-4-one (73) respectively (Scheme-28) [Dabholkar et al., 2008].
In the presence of HCl and atmospheric O₂, 1-alkyl-4-(arylamino) quinolinium-3-thiolate (74) undergoes cyclization to give 5-alkyl-12(H)-quino[3,4-b][1,4]benzothiazine derivatives (75) (Scheme-29) [Zieba et al., 2012].

A convenient sulphuration of benzilmonoarylimine (76) with P₄S₁₀ (phosphorus pentasulfide dimer) followed by the intramolecular [4+2] cyclization yields 2H-benzo [1,4] thiazine derivatives (77) (Scheme-31) [Charrier et al., 2001].
\[ R = R^1 = R^2 = -H, \quad R^3 = -\text{CH}_3; \quad R = R^1 = R^2 = -H, \quad R^3 = -\text{CH}_3; \quad R = R^1 = R^2 = -\text{H}, \quad R^3 = -\text{OCH}_3; \quad R = R^1 = -\text{H}, \quad R^2 = \text{CH}_3, \]
\[ R_2 = \text{OCH}_3; \quad R = R^2 = -\text{H}, \quad R^3 = -\text{Cl}, \quad R^4 = -\text{OCH}_3; \quad R = R^3 = -\text{H}, \quad R^1 = -\text{Br}, \quad R^2 = -\text{CH}_3. \]

Scheme-28

\[ R = -\text{H}, Y = -\text{CH}; \quad R = 9\text{-F}, Y = -\text{CH}; \quad R = 9\text{-CH}_3, Y = -\text{CH}; \quad R = 9\text{-Cl}, Y = -\text{CH}; \quad R = 9\text{-Br}, \quad R = 11\text{-CH}_3, Y = -\text{CH}; \quad R = -\text{H}, \]
\[ Y = -\text{N}; \quad R = R = 9\text{-F}, \quad Y = -\text{N}; \quad R = 9\text{-CH}_3, Y = -\text{N}. \]

Scheme-29
α-Mercaptoalkanoate esters (78) undergo nucleophilic addition with benzoquinone diinines (79) to yield $N^1$-(alkyl)-2-(alkylsulfanyl)-$N^4$-phenyl-1,4-benzenediamines (80) which via intermolecular cyclization in the presence of trifluoroacetic acid afford 2H-1,4-benzothiazin-3(4H)-ones (81) (Scheme-32) [Katritzky et al., 2001].

Alkyl acetoacetates (82) and 2,2-disulfanediyldianiline (electrophile) (83) undergo nucleophilic substitution followed by regioselective intramolecular cyclization in the presence of triethylamine to give 3-methyl-4H-benzo[b][1,4]thiazine-2-carboxylates (84) (Scheme-33) [Sheibani et al., 2006].

Another nucleophilic displacement reaction of 2-chloro-3-phenylsulfanyl-[1,4]naphthoquinone (85) in the presence of $N_3$ (azide) and DMF (solvent) through a nitrene (86) and a final intramolecular cyclization produces 12H-benzo[b]phenothiazine-6,11-diones (87) (Scheme-34) [Tandon et al., 2009].
R = -CH₃, R¹ = -H; R = R¹ = -CH₃; R = H₂C-C₃H₇, R² = -H.

Scheme-32

R = -CH₃, -C₆H₅

Scheme-33
Alkylation of methoxy hydroquinone (88) with diethyl sulfate gives mono ether (89), which on oxidation with cerium ammonium nitrate gives quinone (90). The latter cyclcondenses with hypotaurine (91) to yield mixture of isomer 6-ethyl-7-methoxy-3,4-dihydro-1,1-dioxo-2H-1,4-benzothiazine-5,8-dione (92) and 7-ethyl-6-methoxy-3,4-dihydro-1,1-dioxo-2H-1,4-benzothiazine-5,8-dione (93) (Scheme-35) [Aiello et al., 2010].

2-(4,5-Dimethoxy-2-nitrophenylthio)acetic acid (94) through reduction and subsequent dehydrative cyclization with tin in acidic medium yields 6,7-dimethoxy-2H-1,4-benzothiazin-3(4H)-one (95). The latter on treatment with dimethylformamide/ dimethylacetel (DMF/DMA) affords enaminone (96) which further reacts with different methylene compounds viz. acetylacetone, ethyl acetoacetate, ethyl benzoylacetaetc. to furnish corresponding pyrido[3,2b]-[1,4]benzothiazine (97) (Scheme-36) [Abbas et al., 2010].
1-(Cyanomethyl)sulfonyl-2-nitrobenzene (98) on reaction with benzoyl chloride in the presence of triethylamine yield an intermediate (99). The latter cyclises to produce 1,4-benzothiazine derivative (100) along with byproduct (101) in the presence of iron powder (Scheme-37) [Wilkerson et al., 2017]

2-Aminothiophenol undergoes cyclocondensation with chloroacetate in the presence of potassium carbonate to yield 2H-benzo[b][1,4]thiazin-3(4H)-one (102) (Scheme-38) [Sebbar et al., 2016].
R = -COCH₃, R¹ = -CH₃; R = -COOC₆H₅, R¹ = -C₆H₅; R = COC₆H₅, R¹ = -C₆H₅

Scheme-36
Scheme-37

R= -Cl, -Br

Scheme-38

Literature reveals that ring transformations especially ring expansion through green protocols has been less explored and moreover the other methodologies viz. conventional comprises of cyclocondensation, oxidation reactions that have various disadvantages like harsh reaction conditions, prolonged reaction times, formation of various side products etc. On other hand, greener methods viz. ultasonication and microwave assisted possess a key advantage over conventional procedures and has taken organic synthesis to a reliable and sophisticated level with reductions in temperature, reaction times, enhancement in yields, selectivity and reproducibility. Ultrasonication enables optimization, avoids toxicity, reduces multistep reactions to a single step, and forms less byproducts. In addition to ring expansions by greener
methods, the chemistry of thiamine has been quite interesting. The mechanistic pathway in the reaction of thiamin involves C-2 scission and an intramolecular cyclization takes place to synthesise thiazines. This chemistry motivated us to mimic these reactions in vitro and also study the behaviour of the compounds with less appendages. The substituent effect on variously substituted synthesized benzothiazines has also been studied.

**Material and Method**

2. Materials

2.1. Chemicals

The chemicals used in the research work were procured from various firms viz. Himedia, Sigma Aldrich, Rankem, Spectrochem, Alfa aesar etc. and 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 vapour’s to check the progress of the reaction.

2.2. Instruments

- Melting points of the compounds were determined through melting point apparatus.
- 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$_3$ etc. on a BRUKER ADVANCE II 400 NMR spectrophotometer (Punjab University, Chandigarh) using tetramethylsilane (TMS) as an internal reference standard and the values have been given in ppm (δ). The coupling
constant values are 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 of 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 were reported in cm$^{-1}$. Only principle absorption peaks of interest have been reported.
- UV spectra were run on a UV-1800 (Shimadzu).
- The fluorescence spectroscopy, the spectra were recorded on a RF-5301 PC Spectrofluorophotometer (Shimadzu).
- X-ray diffraction studies was performed on X Calibur EOS OXFORD Diffractometer (from BHU, Banaras).
- DFT studies were carried out on Jaguar software package version 6.5112 and Gaussian 09 W software package by using B3LYP exchange correlation function using 6-31G(d) and basis sets.

2.3. Procedure for the synthesis of N-methylbenzothiazolium iodide/ N-methyl-6-nitrobenzothiazolium iodide (103).

An equimolar mixture of 1,3-benzothiazole/ 6-nitro-1,3-benzothiazole (2.70 g, 0.02mol, 1 equivalent) and methyl iodide (1.245mL, 0.02mol, 1 equivalent) was subjected to
ultrasonication under solvent free conditions. A solid mass appeared after 4-5 hrs. The solid thus obtained was washed with diethyl ether to remove unreacted material (yield: 95%). The m.ps of the synthesized compounds were found to be identical with that reported in literature. [Nadeem et al., 2010; Munawar et al., 2011].

2.4. Synthesis of 1,4-benzothiazine (Series A)

2.4.1. General procedure for the synthesis of 1,4-benzothiazines (104)).

(a) Method A:

A mixture of N-methylbenzothiazolium iodide/N-methyl-6-nitrobenzothiazolium iodide (103) (0.02 mol, 1 equivalent) and appropriate α-haloketone (0.02 mol, 1.1 equivalent), was stirred in DMF. A 5% NaOH solution (18mL, 3.7 equivalent) was added drop wise into the reaction mixture while refluxing and stirring. TLC was used to monitor the progress of the reaction. On completion (4-5 hrs), the reaction mixture was put into ice cold water. The solid, thus separated was filtered, washed with hexane to remove the unreacted reactants and was re-crystallized from chloroform and hexane (yield: 40-58%).

(b) Ultrasonication ( Method B):

A mixture of N-methylbenzothiazolium iodide/N-methyl-6-nitrobenzothiazolium iodide (103) and α-haloketonewereultrasonicated in methanol, while 5% NaOH solution (18 mL, 3.7 equivalent) was added dropwise in first 2-3 minutes. TLC was employed for monitoring the reaction and after the reaction completes (20-25 minutes), it was worked up and the product was isolated as mentioned in Method A.

2.4.1.1. (4-Methyl-4H-benzo[b][1,4]thiazin-2-yl)(phenyl)-methanone (104a; R= -H, X= -H)
Orange colored solid; mp: 170 °C; yield: 50% (Method A), 70% (Method B); M+ m/z 267; ν = 1660 cm⁻¹ (C=O); ¹H NMR (CDCl₃, 400 MHz): δ= 3.06 (s, 3H, N–CH₃), 6.51–6.53 (d, 1H, –C₆H₅ of benzothiazole ring, J = 8.0 Hz), 6.77 (s, 1H, =CH), 6.83–6.88 (m, 2H, –C₆H₅ of benzothiazole ring), 6.92–6.96 (m, 1H, –C₆H₅ of benzothiazole ring), 7.39–7.43 (q, 2H, –C₆H₅ of benzene ring, J =15.7 Hz, J= 6.9 Hz), 7.45–7.49 (m, 1H, –C₆H₅ of benzene ring), 7.52–7.54 (t, 2H, –C₆H₅ of benzene ring, J= 6.8 Hz);

2.4.1.2. (4-Chlorophenyl)(4-methyl-4H-benzo[b][1,4]thiazin-2-yl)methanone (104b; R= -H, X= - Cl)

Orange colored solid; m.p: 190 °C; yield: 53% (Method A), 72%(Method B); m/z 302 (M + H⁺), 304 (3:1); ¹H NMR (CDCl₃, 400 MHz): δ= 3.08 (s, 3H, N–CH₃), 6.53–6.55 (d, 1H, –C₆H₅ of benzothiazole ring, J = 8.0 Hz), 6.74 (s, 1H, =CH), 6.86–6.87 (d, 2H, –C₆H₅ of benzothiazole ring, J= 4.2 Hz), 6.93–6.97 (m, 1H, –C₆H₅ of benzothiazole ring), 7.38–7.40 (d, 2H, –C₆H₅ of benzene ring, J = 8.2 Hz), 7.47–7.50 (d, 2H,–C₆H₅ of benzene ring, J= 8.3 Hz);

2.4.1.3. (4-Bromophenyl)(4-methyl-4H-benzo[b][1,4]thiazin-2-yl)methanone (104c; R= -H, X= - Br).

Orange colored solid; mp: 175 °C; yield: 51% (Method A), 75% (Method B); m/z 346; 348 (1 : 1) (M + H⁺); ¹H NMR (CDCl₃, 400 MHz): δ= 3.07 (s, 3H, N–CH₃), 6.52–6.54 (d, 1H, –C₆H₅ of benzothiazole ring, J= 8.0 Hz), 6.73 (s, 1H, =CH), 6.85–6.86 (m, 2H, –C₆H₅ of benzothiazole ring), 6.92–6.96 (m, 1H, –C₆H₅ of benzothiazole ring), 7.40–7.42 (m, 2H, –C₆H₅ of benzene ring), 7.53–7.56 (m, 2H, –C₆H₅ of benzene ring); ¹³C NMR (100 MHz, CDCl₃): δ= 186.9 (C=O), 149.3, 139.0, 137.0, 131.5, 129.9, 127.5, 127.2, 125.8, 125.3, 122.2, 113.3, 106.7 (C₆H₅), 40.4 (=CH).
2.4.1.4. (4-Methoxyphenyl)(4-methyl-4H-benzo[b][1,4]thiazin-2-yl)methanone (104d; R = -H, X = -OCH₃).

Orange colored solid; mp: 168 °C; yield: 54% (Method A), 72% (Method B); m/z 297 (M⁺), ¹H NMR (CDCl₃, 400 MHz): δ= 3.07 (s, 3H, N–CH₃), 3.85 (s, 3H, –OCH₃), 6.51–6.53 (d, 1H, –C₆H₅ of benzothiazole ring, J = 7.9 Hz), 6.80 (s, 1H, =CH), 6.84–6.90 (m, 2H, –C₆H₅ of benzene ring), 6.92–6.96 (m, 3H, –C₆H₅ of benzothiazole ring), 7.53–7.57 (m, 2H, –C₆H₅ of benzene ring); m/z 297 (M⁺).

2.4.1.5. (4-Methylphenyl)(4-methyl-4H-benzo[b][1,4]thiazin-2-yl)methanone (104e; R = -H, X = -CH₃).

Light orange- yellowish colored solid; mp: 168 °C; yield: 58% (Method A), 78% (Method B); ¹H NMR (CDCl₃, 400 MHz): δ= 2.39 (s, 3H, –CH₃), 3.0 (s, 3H, N–CH₃), 6.51–6.53 (d, 1H, –C₆H₅ of benzothiazolering, J = 8.0 Hz), 6.79 (s, 1H, =CH), 6.84–6.87 (t, 2H, –C₆H₅ of benzothiazole ring, J = 5.0 Hz), 6.91–6.96 (m, 1H, –C₆H₅ of benzothiazole ring), 7.20–7.26 (t, 2H, –C₆H₅ of benzenering, J =15.7 Hz), 7.44–7.46 (d, 2H, =CH₂, J = 7.9 Hz, –C₆H₅ of benzene ring); m/z 281 (M⁺).

2.4.1.6. (4-Methyl-7-nitro-4H-benzo[b][1,4]thiazin-2-yl) (phenyl)- methanone (104f; R = -NO₂, X = -H).

Dark purple colored solid; mp: 290 °C; yield: 56% (Method A), 76% (Method B); m/z 313 (M + H⁺), ¹H NMR (CDCl₃, 400MHz): δ= 3.68 (s, 3H, N–CH₃), 6.84–6.86 (d, 1H, –C₆H₅ of benzothiazole ring, J = 9.0 Hz), 7.01 (s, 1H, =CH), 7.66–7.67 (d, 1H, –C₆H₅ of benzothiazole ring, J = 2.6 Hz), 7.83–7.86 (q, 1H, –C₆H₅ of benzothiazole ring, J = 11.6 Hz, J = 6.3 Hz), 7.56–7.61 (m, 3H, –C₆H₅ of benzene ring), 7.47–7.51 (m, 2H, –C₆H₅ of benzene ring);.
2.4.1.7. (4-Chlorophenyl)(4-methyl-7-nitro-4H-benzo[b][1,4]-thiazin-2-yl)methanone (104g; R= NO$_2$, X= -Cl).

Dark purple colored solid; mp: 293 °C; yield: 49% (Method A), 78% (Method B); m/z 346 (M$^+$); ν= 1781 cm$^{-1}$ (C=O); 1598 cm$^{-1}$, 1366 cm$^{-1}$(NO$_2$); 3068 cm$^{-1}$ (=C–H stretching); 743.23 cm$^{-1}$ (=C–H bending); $^1$H NMR (CDCl$_3$, 400 MHz): δ= 3.14 (s, 3H, N–CH$_3$), 6.84–6.86 (d, 1H, –C$_6$H$_5$ of benzothiazolering, J = 9.0 Hz), 7.05 (s, 1H, =CH), 7.53–7.55 (q, 2H, –C$_6$H$_5$ of benzene ring, J = 8.5 Hz, J = 4.7 Hz), 7.61–7.66 (m, 3H, –C$_6$H$_5$ of benzene ring), 7.83–7.86 (q, 1H, –C$_6$H$_5$ of benzene ring); $^{13}$C NMR (100 MHz, CDCl$_3$): δ= 186.0 (C=O), 149.6, 145.2, 143.9, 130.3, 128.5, 124.09, 123.57, 121.13, 113.89 (C$_6$H$_5$), 40.08 (=CH).

2.4.1.8. (4-Bromophenyl)(4-methyl-7-nitro-4H-benzo[b][1,4]-thiazin-2-yl)methanone (104h; R= -NO$_2$, X= -Br). Dark purple colored solid; mp: 295 °C; yield: 47% (Method A), 82% (Method B); m/z 390(M$^+$); $^1$H NMR (CDCl$_3$, 400 MHz): δ= 3.10 (s, 3H, N–CH$_3$), 6.50–6.52 (d, 1H, –C$_6$H$_5$ of benzothiazolering, J = 8.00 Hz), 6.64 (s, 1H, =CH), 7.43–7.45 (q, 2H, –C$_6$H$_5$ of benzene ring, J = 8.44 Hz, J = 4.84 Hz), 7.57–7.60 (q, 2H, –C$_6$H$_5$ of benzene ring, J = 8.44 Hz, J = 4.80 Hz), 7.65–7.66 (d, 1H, –C$_6$H$_5$ of benzothiazine ring, J = 2.52 Hz), 7.79–7.82 (q, 1H, –C$_6$H$_5$ of benzothiazole ring, J = 11.44 Hz, J = 6.32 Hz).

2.4.1.9. (4-Methyl-7-nitro-4H-benzo[b][1,4]thiazin-2-yl)(p-tolyl)- methanone (104i; R= -NO$_2$, X= -CH$_3$).

Dark purple colored solid; mp: 297 °C; yield: 40% (Method A), 80% (Method B); m/z 327 (M + H$^+$); $^1$H NMR (CDCl$_3$, 400 MHz): δ= 2.51 (s, 3H, –CH$_3$), 3.36 (s, 3H, N–CH$_3$), 6.83–6.85 (d, 1H, –C$_6$H$_5$ of benzothiazole ring, J = 9.12 Hz), 7.01 (s, 1H, =CH), 7.65–7.66 (d, 1H, –C$_6$H$_5$ of benzothiazole ring, J = 2.60 Hz), 7.83–7.86 (q, 1H, –C$_6$H$_5$ of benzothiazole ring, J = 11.60 Hz, J =
6.28 Hz), 7.50–7.52 (d, 2H, –C₆H₅ of benzene ring, J = 8.08 Hz), 7.28–7.30 (d, 2H, –C₆H₅ of benzene ring, J = 7.88 Hz);

**General procedure for the synthesis of N-phenacyl-1,3-benzothiazolium bromide/ N-substituted phenacyl-1,3-benzothiazolium bromide (105):**

1,3-benzothiazole (1 mol) and phenacyl bromide/ substituted phenacyl bromide (1.1 mol) were fused and refluxed (solvent free) at 110°C in an oil bath. The brown crude solid obtained was tritirated with diethyl ether to eliminate unreacted phenacyl bromide. Further, the solid was filtered and dried with the help of rotatory evaporated to remove the traces of solvent.

**2.4.2. Synthesis of 1,4-benzothiazines (106) (Series B)**

**General procedure**

a) **Method (A):**

A mixture of N-phenacylbenzothiazolium bromide/ N-substituted phenacylbenzothiazolium bromide (105) (1 mol, 1 equivalent) and TBAB (tetra butyl ammonium bromide, PTC) (1 mmol) were dissolved in DMF. A 3% NaOH solution (10 mL, 2.7 equivalent) was added drop wise in the reaction mixture. The reaction mixture was refluxed and stirred, the progress of the reaction was checked by TLC. On the completion (2–3 hrs) of reaction, the mixture was poured in ice cold water. The solid, thus separated, filtered and washed with hexane to remove unreacted 107. The product was re-crystallized using chloroform and pet ether.

b) **Ultrasonication (Method B):**

A mixture of N-phenacylbenzothiazolium bromide/ N-substituted phenacylbenzothiazolium bromide (105) and 3% NaOH solution (10 mL, 2.7 equivalent) in methanol was ultrasonicated. By TLC, the progress of the reaction was checked. When the reaction completed (20-25 mts.),
the mixture was poured into cold water (icy). The product further washed with hexane and re-crystallized from chloroform and pet ether mixture (3:1).

2.4.2.1. 2-Phenyl-4H-benzo[b][1,4]thiazine-4-carbaldehyde (106a; Ar= -C₆H₅):

Orange colored solid; m.p: 204 °C; yield: 43% (Method A), 75% (Method B); m/z 254 (M⁺); ν = 1670 cm⁻¹ (C=O, stretch); 2775 cm⁻¹ (C-H, stretch); ¹H NMR (DMSO, 400 MHz): δ= 7.10 (s, 1H, =CH), 7.14-7.16 (d, 1H, -C₆H₅ of benzothiazole ring, J= 8.20 Hz), 7.19-7.23 (m, 2H, J= 25.28 Hz – C₆H₅ of benzthiazole ring), 7.28-7.34 (m, 6H, -C₆H₅ of benzene ring), 8.14 (s, 1H, -N-CHO); ¹³C NMR (100 MHz, CDCl₃): 163.72 (-CHO), 122.20, 125.35, 126.81, 127.00, 128.66, 128.74, 128.78, 129.17, 131.38, 136.72, 137.31, 132.29, 63.92, 40.20, 38.95.

2.4.2.2. 2-(4-Chlorophenyl)-4H-benzo[b][1,4]thiazine-4-carbaldehyde (106b; Ar= p-Cl-C₆H₄):

Orange colored solid; m.p: 209 °C; yield: 42% (Method A), 78% (Method B); m/z 287 (M + H⁺), 289 (3:1); ¹H NMR (DMSO, 400 MHz): δ= 7.15-7.28 (m, 2H, -C₆H₅ofbenzothiazole ring), 7.31-7.36 (m, 4H, –C₆H₅ of benzene ring), 7.44-7.47 (d, 1H, J=8.48 Hz), 7.55-7.60 (t, 1H, –C₆H₅ of benzothiazolering, J= 8.44Hz), 7.65 (s, 1H, =CH), 8.17 (s, 1H, N-CHO).

2.4.2.3. 2-(4-Bromophenyl)-4H-benzo[b][1,4]thiazine-4-carbaldehyde (106c; Ar= p-Br-C₆H₄):

Orange colored solid; m.p: 223 °C; yield: 45% (Method A), 80% (Method B); m/z 332.96, 334; ¹H NMR (DMSO, 400 MHz): δ= 7.15-7.19 (q, 3H, J= 5.12Hz, J= 4.12 Hz, –C₆H₅ of benzothiazole ring), 7.22-7.38 (m, 3H, –C₆H₅ of benzene ring),7.45-7.60(m, 2H, –C₆H₅ of benzothiazole ring, – C₆H₅ of benzene ring), 7.71 (s, 1H, =CH), 8.14 (s, 1H, -N-CHO); ¹³C NMR (100 MHz, CDCl₃): 163.88 (-CHO), 142.13, 136.44, 133.12, 132.42, 130.03, 127.57, 119.54, 119.27, 119.23, 118.81, 117.83, 116.57, 116.34, 78.48, 40.19, 38.94.
2.4.2.4. 2-p-Tolyl-4H-benzo[b][1,4]thiazine-4-carbaldehyde (106d; Ar= p-H$_3$CO-C$_6$H$_4$): Orange colored solid; m.p: 215°C; yield: 48% (Method A), 73% (Method B); m/z 283 (M + H$^+$); $^1$H NMR (CDCl$_3$, 400 MHz): δ= 3.27 (s, 3H, -OCH$_3$), 7.15- 7.22 (m, 1H, -C$_6$H$_5$ of benzothiazole ring), 7.24-7.26 (m, 1H, -C$_6$H$_5$ of benzothiazole ring), 7.34-7.58 (m, 4H, -C$_6$H$_5$ of benzene ring), 7.60 (s, 1H, =CH), 7.92-8.11 (t, 2H, J= 5.68 Hz, -C$_6$H$_5$ of benzothiazole ring), 8.28 (s, 1H, -N-CHO).

2.4.2.5. 2-(4-Phenyl)-4H-benzo[b][1,4]thiazine-4-carbaldehyde (106e; Ar= p-H$_3$C-C$_6$H$_4$): Orange colored solid; m.p: 222 °C; yield: 47% (Method A), 72% (Method B); m/z 267 (M + H$^+$); $^1$H NMR (CDCl$_3$, 400 MHz): δ= 2.37 (s, 3H, -CH$_3$), 7.04-7.07 (m, 1H, -C$_6$H$_5$ of benzothiazole ring), 7.11-7.20 (m, 1H, -C$_6$H$_5$ of benzothiazole ring), 7.30-7.32 (d, 2H, J= 8.12Hz, 7.43-7.45 (t, 4H, J= 6.84Hz, -C$_6$H$_5$ of benzene ring), 7.68 (s, 1H, =CH), 8.20 (s, 1H, -N-CHO).

2.5. Computational Studies

Theoretical chemistry, a mathematical description of chemistry. Computational theoretical chemistry computes electronic structures, properties, interactions etc. of the molecules through simulated experimental results. Computational chemistry Further, with and integration in chemical, mathematical and computing skills many chemical problems could be solved. The term "Computational Chemistry" first emerged in 1970. A book “Computers and Their Role in the Physical Sciences” on the subject relates computational chemistry with reality and experimental chemistry" [Fernbach and Taub, 1970]. During said era ('70s), numerous new methods integrated with emerging discipline of computational chemistry. A Journal of Computational Chemistry, published in 1980 has been through enough to explain the physical, theoretical aspects of molecules along with their coordination, interactions.
Computational chemistry helps to have an insight into the molecular geometries, rates of reactions, equilibria positions, spectra, and other physical properties with the tools viz. molecular mechanics, ab initio, semi empirical and density functional methods, and molecular dynamics. An important feature of the computational remains theoretical (or structural) modelling part, known as molecular modeling. In the latter, simulations of the chemical reactions and processes are carried over at the atomic level in the virtual space (computer). Further, with an advancement in the molecular modeling, probable molecular structures, thermo-chemistry, spectroscopy, conformational search and energy of a compound could be determined. This technique has provided the chemists a room to understand the envisaged strategies before the actual run of the experiments that has proved to be quite economical.

The basis of computational chemistry has been the quantum and classical mechanics, statistical physics and thermodynamics as these model the atoms and molecules with mathematics. Through computational study and development of algorithms, it has been possible to correlate all important molecular properties i.e. stabilities, reactivates and electronic properties to the molecular structure. The most important numerical approaches in the computational chemistry has been empirical, semi-empirical, \textit{ab-initio} and DFT methods.

2.6. Biological activities

2.6.1. Methodology for antioxidant activity (DPPH radical scavenging activity)

As per the mechanism reported in the literature, autooxidation of unsaturated lipids was due to the presence of free radicals [Allen, 1996; Frankel, 1980]. The antioxidant potential of an
synthesised compounds can be calculated by using DPPH (1,1-diphenyl-2-picryl hydrazyl) radical scavenging activity [Tailor et al., 2014; Kalaisezhiyen et al., 2015; Kandhasamy et al., 2013; Sadhu et al., 2003]. The notable feature of antioxidants were that these donate hydrogens from phenolic hydroxy groups and also interfere in the oxidation process of free radical chain present in the lipids. As the structure of DPPH depicts that it contains stable free radicals along with odd number of electrons which proves to be useful for determining antioxidant properties of different compounds. The synthesized compounds exhibited antioxidant activity when screened against the DPPH scavenging activity. The activity was performed with the help of the method given by Yalcinnas Cavusoglu [Yalcin et al., 2010]. Free radical DPPH was used as a reagent and ascorbic acid as a standard in this experiment. 100μL (1mg/ml) of the synthesised compounds or standard ascorbic acid in methanol was taken in each test tube.

The required amount of DPPH was dissolved in methanol to make it 0.004% (weight/volume) ratio. In each test tube, 3ml of DPPH solution was added with the help of pipette to maintain accuracy. For the blank, equal amount i.e 3ml of DPPH was added in pure methanol to prepare solution. After the addition, all the samples including blank were incubated at room temperature in dark for 30 minutes. The absorbance was recorded at 517nm against blank. The readings for inhibition were taken in triplicates and the average absorbance were used for further calculation. The percentage inhibition was calculated by using the following equation

\[
\%[\text{DPPH radical}] = \left(\frac{\text{Ac} - \text{As}}{\text{Ac}}\right) \times 100
\]

where, As = absorbance of the sample and Ac = absorbance of the control.

2.6.2. Antimicrobial activity

Agar Diffusion Method
The antimicrobial activity of newly synthesized compounds was determined by agar diffusion method [Threlfall et al., 1999; Walker et al., 2000] by comparing the inhibition zones of sensitive micro-organisms produced by known concentrations of synthesized compounds and the broad spectrum antibiotics as reference standards.

Agar medium for anti-bacterial activity was prepared by dissolving peptone (10 g), NaCl (10g), yeast extract (5g) and agar (20 g) in 1000 ml of distilled water with slow heating and stirring to dissolve the medium completely. Similarly, for anti-fungal activity, Czapek-Dox agar media was prepared from sucrose (30g), sodium nitrate (2g), K₂HPO₄ (1 g), MgSO₄. 7H₂O (0.5 g), KCl (0.5g), FeSO₄ (0.01 g), agar (20 g). It was sterilized in autoclave at 15 PSI and 121 °C for 15 minutes. The sterilized medium was immediately poured into petri dishes to form a uniform layer (2 mm to 5 mm thick). The petri dishes were stored in incubator so, that no appreciable growth of the micro-organisms was observed before the dishes were used. Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at 37°C for 18-48hrs. Solutions of synthesized compounds 50 mg/mL) and reference substances were prepared that were presumed to be of equal concentration. The solutions of 10μL synthesized compound and reference standard were applied to the surface of the medium (6 mm in diameter) in triplicate, in cavities prepared in the agar. Negative controls were prepared by using dimethyl sulphoxide (DMSO), which was employed to dissolve the test compounds. Gentamycin, Amphotericin with the 50 mg/mL concentration were used as reference standards to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37 °C for 24 to 48 hours. Antibacterial activities of synthesized compounds were calculated quantitatively (bio assay) by measuring the diameter of zone of inhibition (mm) and compared with the reference standards.
(measured the diameters with a precision of at 0.1 mm). All bacterial strains were cultured on their respective medium for further bacterial propagation.

2.7. Result and Discussion

The six membered heterocycles especially 1,4-benzothiazines, owing to the presence of nitrogen, carbon and sulfur linkage have attained an important place due to their wide range of applications in different fields like pharmaceutical, medicinal field, therapeutic, agricultural etc. [Souza et al., 2010]. Various derivatives of 1,4-benzothiazines reported in the literature possess numerous biological activities viz. antibiotic, anticancer, antiviral, antifungal, antimicrobial, and antiparkinson, anti-inflammatory, antihypertensive, anti-tumor, anti-aldosoreductase, anti-rheumatic, anti-arrhythmic, anti-HIV activities, anti-allergic properties [Kumar et al., 2008; Parai et al., 2009; Li et al., 2013; Saadouni et al., 2014; Meng et al., 2013]. Even some of these moieties have been known to be better antipyretics and analgesics in comparison with aspirin [Shahwar et al., 2013]. A well-known anti-psychotic drug, phenothiazine comprises of benzothiazine as the core nucleus [Dabholkar et al., 2011]. It has been reported that a slight change in the substituents of 1,4-benzothiazine derivatives can cause a significant change in their activities [Dabholkar et al., 2011]. In view of above, various synthetic methodologies have been developed to synthesise 1,4-benzothiazines and their derivatives viz. cyclocondensations and ring transformations [Parai et al., 2009; Li et al., 2013; Pi et al., 2009]. In the present investigations a green synthetic pathway has been discussed for the synthesis 1,4-benzothiazine derivatives along with the X-ray crystallographic data. The present work has been divided into two parts:
a) Base induced ring transformations through the reactions of N-methylbenzothiazolium cations and its derivatives with α-haloketones.

b) Base induced ring transformations of 3-phenacylbenzothiazolium cations.

One pot synthesis of 4H-1,4-benzothiazines has been carried from ionic liquid based N-methylbenzothiazolium and the derivatives of phenacyl bromide in basic medium (Scheme-39). On stirring N-methylbenzothiazolium iodide with p-bromophenacyl bromide, an orange colored solid with mp: 170 °C in 51% (Method A) and 75% (Method B) has been obtained. With M+ at m/z 346, 348 (1 : 1) (100%), it shows an absorption band 1660 cm⁻¹ (C=O) in IR. Its ¹H NMR exhibits signals at 3.07 (s, 3H, N–CH₃), 6.52–6.54 (d, 1H, –C₆H₅ of benzothiazole ring, J= 8.0 Hz), 6.73 (s, 1H, =CH), 6.85–6.86 (m, 2H, –C₆H₅ of benzothiazole ring), 6.92–6.96 (m, 1H, –C₆H₅ of benzothiazole ring), 7.40–7.42 (m, 2H, –C₆H₅ of benzene ring), 7.53–7.56 (m, 2H, –C₆H₅ of benzene ring) while in ¹³C NMR of the isolated product shows signals at δ 186.9 (C=O), 149.3, 139.0, 137.0, 131.5, 129.9, 127.5, 127.2, 125.8, 125.3, 122.2, 113.3, 106.7 (C₆H₅), 40.4 (=CH). From the above data, the structure (4-bromophenyl)(4-methyl-4H-benzo[b][1,4]thiazin-2-yl)methanone (104c; R= -H, X= -Br) has been assigned to the compound.

Similarly, the other 1,4-benzothiazine derivatives (104a,b,d-i) have been synthesized. As above, the structure of the synthesized 4H-1,4-benzothiazines has been established through spectral data (¹H,¹³C NMR, Mass, IR). The singlet in ¹H NMR of the products at δ 6.53 confirms the hydrolytic cleavage of C-S and alternate cyclization to 1,4-benzothiazine ring. The singlet due to three protons between δ 3- 4 shows N-CH₃ in the species, [additional singlets at δ 3.8 (3H), δ 2.3 (3H), δ 2.51 (3H) in (104d), (104e) and (104h) correspond to methoxy and methyl group, respectively], whereas the multiplet between δ 6-8 confirms the presence of aromatic
protons in the product. The peak in $^{13}$C NMR between δ 180-190 ppm [(104b), (104d), (104g)] shows the presence of C=O in the compounds. Besides, the above peaks in $^1$H and $^{13}$C NMR, the $M^+$ in mass spectrometry corresponds to the molecular weight of the compounds, however (104b) show $M^+$, m/z at 302.1; 304.1 (3:1) which indicates the presence of chlorine in the said compounds. Similarly, $M^+$, m/z at 313 and 327 confirms the structure of compounds (104f) and (104h), respectively (Table-1).

The parent ion peak of 104c has been observed at m/z 346, 348 (1:1). The fragmentation of the compound has also been carried out using Chem Biodraw Ultra 8.0 and the respective peaks has been matched with the peaks obtained from GC-Ms spectrum. The fragment ion, m/z 190.035 appeared after the elimination of phenyl ring, m/z 77.0391 and bromide ion, m/z 78.91 from parent ion peak 346. Further, the ion fragment, m/z 27.99 due to CO gets removed from 190.035 to give another fragment at m/z 162.035 which showed corresponding molecular peak at m/z 162 in the GC-MS spectrum. This fragment at m/z 162.03 further gets dissociated by the elimination of –CH₃ peak, m/z 15.0235 that gives another $M^+$ peak at 145.022. From the latter, a fragment ion, m/z 57.9877 gets removed to give another fragment ion at m/z 93, which finally undergoes dissociation into molecular ions of m/z 78 and 16 corresponding to phenyl ring and NH$_2$ (Figure 1).
Figure 1. Fragmentation pattern of compound (104c)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
<th>Mass Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>104a</td>
<td>3.06 (s, 3H, N–CH$_3$), 6.51–6.53 (d, 1H, –C$_6$H$_5$ of benzothiazole ring, $J = 8.0$ Hz), 6.77 (s, 1H, =CH), 6.83–6.88 (m, 2H, –C$_6$H$_5$ of benzothiazole ring), 6.92–6.96 (m, 1H, –C$_6$H$_5$ of benzothiazole ring), 7.39–7.43 (q, 2H, –C$_6$H$_5$ of benzene ring, $J = 15.7$ Hz, $J = 6.9$ Hz),</td>
<td></td>
<td>267 (M$^+$)</td>
</tr>
<tr>
<td>104b</td>
<td>7.45–7.49 (m, 1H, –C₆H₅ of benzene ring), 7.52–7.54 (t, 2H, –C₆H₅ of benzene ring, J= 6.8 Hz)</td>
<td>186.9 (C=O), 149.3, 139.0, 137.0, 131.5, 129.9, 127.5, 127.2, 125.8, 125.3, 122.2, 113.3, 106.7 (C₆H₅), 40.4 (=CH)</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>104c</td>
<td>3.08 (s, 3H, N–CH₃), 6.53–6.55 (d, 1H, –C₆H₅ of benzothiazole ring, J = 8.0 Hz), 6.74 (s, 1H, =CH), 6.86–6.87 (d, 2H, –C₆H₅ of benzothiazole ring, J= 4.2 Hz), 6.93–6.97 (m, 1H, –C₆H₅ of benzothiazole ring), 7.38–7.40 (d, 2H, –C₆H₅ of benzene ring, J = 8.2 Hz), 7.47–7.50 (d, 2H,–C₆H₅ of benzene ring, J= 8.3 Hz)</td>
<td>301.1 (M + H⁺) 346; 348 (1 : 1) (M + H⁺)</td>
<td></td>
</tr>
<tr>
<td>104d</td>
<td>3.07 (s, 3H, N–CH₃), 3.85 (s, 3H, –OCH₃), 6.51–6.53 (d, 1H, –C₆H₅ of benzothiazole ring, J = 7.9 Hz), 6.80 (s, 1H, =CH), 6.84–6.90 (m, 2H, –C₆H₅ of benzene ring), 6.92–7.38 (m, 2H, –C₆H₅ of benzene ring)</td>
<td>187.3 (C=O), 161.9, 148.8, 139.6, 130.6, 130.4, 127.5, 127.1, 125.5, 122.4, 113.6, 113.0, 106.9 (C₆H₅), 55.4 (C–OCH₃), 40.2 (=CH)</td>
<td>297 (M + H⁺)</td>
</tr>
</tbody>
</table>
104e 6.96 (m, 3H, –C₆H₅ of benzothiazole ring), 7.53–7.57 (m, 2H, –C₆H₅ of benzene ring) 2.39 (s, 3H, –CH₃), 3.0 (s, 3H, N–CH₃), 6.51–6.53 (d, 1H, –C₆H₅ of benzothiazole ring, J = 8.0 Hz), 6.79 (s, 1H, =CH), 6.84–6.87 (t, 2H, –C₆H₅ of benzothiazole ring, J = 5.0 Hz), 6.91–6.96 (m, 1H, –C₆H₅ of benzothiazole ring), 7.20–7.26 (t, 2H, –C₆H₅ of benzene ring, J = 15.7 Hz), 7.44–7.46 (d, 2H, J = 7.9 Hz, –C₆H₅ of benzene ring) 281 (M + H⁺)

104f 3.68 (s, 3H, N–CH₃), 6.84–6.86 (d, 1H, –C₆H₅ of benzothiazole ring, J = 9.0 Hz), 7.01 (s, 1H, =CH), 7.66–7.67 (d, 1H, –C₆H₅ of benzothiazole ring, J = 2.6 Hz), 7.83–7.86 (q, 1H, –C₆H₅ of benzothiazole ring, J = 11.6 Hz, J = 6.3 Hz), 7.56–7.61 (m, 3H, –C₆H₅ of benzene ring), 7.47–7.51 (m, 2H, –C₆H₅ of benzene ring) 313 (M + H⁺)

104g 3.14 (s, 3H, N–CH₃), 6.84–6.86 (d, 1H, –C₆H₅ of benzothiazole ring, J = 9.0 Hz), 7.05 (s, 1H, =CH), 7.53–7.55 (q, 2H, –C₆H₅ of benzene ring) 186.0 (C=O), 149.6, 145.2, 143.9, 130.3, 128.5, 124.09, 123.57, 121.13, 113.89 (C₆H₅), 40.08 (=CH) 346 (M⁺)
<table>
<thead>
<tr>
<th>Compound</th>
<th>Signals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>104h</strong></td>
<td>3.10 (s, 3H, N–CH₃), 6.50–6.52 (d, 1H, –C₆H₅ of benzothiazole ring, J = 8.00 Hz), 6.64 (s, 1H, =CH), 7.43–7.45 (q, 2H, –C₆H₅ of benzene ring, J = 8.44 Hz, J = 4.84 Hz), 7.57–7.60 (q, 2H, –C₆H₅ of benzene ring, J = 8.44 Hz, J = 4.80 Hz), 7.65–7.66 (d, 1H, –C₆H₅ of benzothiazole ring, J = 2.52 Hz), 7.79–7.82 (q, 1H, –C₆H₅ of benzothiazole ring, J = 11.44 Hz, J = 6.32 Hz)</td>
</tr>
<tr>
<td><strong>104i</strong></td>
<td>2.51 (s, 3H, –CH₃), 3.36 (s, 3H, N–CH₃), 6.83–6.85 (d, 1H, –C₆H₅ of benzothiazole ring, J = 9.12 Hz), 7.01 (s, 1H, =CH), 7.65–7.66 (d, 1H, –C₆H₅ of benzothiazole ring, J = 2.60 Hz), 7.83–7.86 (q, 1H, –C₆H₅ of benzothiazole ring, J = 11.60 Hz, J = 6.28 Hz), 7.50–7.52 (d, 2H, –C₆H₅ of benzene ring, J = 8.08 Hz), 7.28–7.30 (d, 2H, –C₆H₅ of benzene...</td>
</tr>
</tbody>
</table>
Lastly, the structure of 104c has been confirmed on the basis of single X ray diffraction and DFT studies. To validate the structure, analytical and calculated results have been correlated and the values have been observed to be in good coherence with each other which confirms the structure of compound (104c).

From the reactions of N-methylbenzothiazolium iodide or N-methyl-6-nitrobenzothiazolium iodide and the α-haloketone carried out in different concentrations of bases (sodium hydroxide, sodium carbonate etc.) it has been established that 5% (3.7 equivalent) NaOH was optimum concentration of the base which provided the products in good yields.

The reaction proceeds through the initial nucleophilic attack of the hydroxide ion at C(2) of N- methylbenzothiazolium iodide or N-methyl-6-nitrobenzothiazolium iodide to form a pseudobase (103a) which undergoes hydrolytic C (2) -S cleavage to give (103b) that further reacts with phenacyl bromide to form (103c). The latter, under the given reaction conditions generates α-thiocarbanion (103d) which finally undergoes cyclisation along with removal of H2O to give the target molecule (104) (Scheme-40).

\[ \text{Ultrasonication} \]

\[ \begin{align*}
\text{(103)} \\
R= -\text{H; -NO}_2
\end{align*} \]
X = -H, -Cl, -Br, -OCH₃, -CH₃

Scheme 39

Scheme 40

b) Base induced ring transformations 3-phenacylbenzothiazolium cations.

3-(4-Bromophenacyl)benzothiazolium bromide when stirred in 3% NaOH solution, it provides a solid, M⁺ m/z 332.96, 334 (1:1) with m.p 223 °C in 45% (Method A), 80% (Method B). In ¹H NMR, it shows signals at δ 7.15-7.19 (q, 3H, J= 5.12Hz, J= 4.12 Hz, –C₆H₅ of benzothiazole ring), 7.22-7.38 (m, 3H, –C₆H₅ of benzene ring), 7.45-7.60(m, 2H, –C₆H₅ of benzothiazole ring, –C₆H₅ of benzene ring), 7.71 (s, 1H, =CH), 8.14 (s, 1H, -N-CHO) and in ¹³C NMR, it exhibits signals at 163.88 (-CHO), 142.13, 136.44, 133.12, 132.42, 130.03, 127.57, 119.54, 119.27, 119.23, 118.81, 117.83, 116.57, 116.34, 78.48, 40.19, 38.94. From the above data a structure 2-(4-
bromophenyl)-4H-benzo[b][1,4]thiazine-4-carbaldehyde (106c; Ar= p-Br-C₆H₄) has been assigned to the compound.

The another series of 1,4-benzothiazines compounds (106a,b,d) has also been synthesized using same reaction conditions (Scheme-41). The structure of the compounds have elucidated by similar spectroscopic techniques as used for 106c. The singlet between δ 7.1-7.8 confirms the presence of =CH in the structure of compounds (106a,b,d) and the multiplets between δ 7—8 shows the presence of phenyl ring. Further, peak at δ 8.1-8.2 clearly shows N—CHO group in all the compounds (106). Besides that, the peak at δ 163-165 in ¹³C NMR confirms the presence of –CHO group. In addition to the above peaks, the molecular ion peaks at m/z 254, 287, 283 corroborates the structure of the synthesized compounds (106a), (106b), (106d), respectively (Table-2).

The reaction proceeds with initial attack of the OH⁻ on C-2 of the appended benzothiazolium cation 105 followed by its scission and alternate cyclisation to give 106 (Scheme-42).

\[
\text{CH}_2\text{COAr} \quad \xrightarrow{\text{Ultrasound, 3\% NaOH}} \quad \text{CHO} \quad \text{Ar}
\]

(105) \hspace{1cm} (106)

Ar= -C₆H₅, p-Cl -C₆H₄, p-Br -C₆H₄, p-CH₃O-C₆H₄, p-H₃C-C₆H₄

Scheme 41
Table-2. Spectral data of the synthesised compounds (106a-e)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
<th>Mass Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>106a</td>
<td>7.10 (s, 1H, =CH), 7.14-7.16 (d, 1H, –C$_6$H$_5$ of benzothiazole ring, J= 8.20 Hz), 7.19-7.23 (m, 2H, J= 25.28Hz –C$_6$H$_5$ of benzothiazole ring), 7.28-7.34 (m, 6H, – C$_6$H$_5$ of benzene ring), 8.14 (s, 1H, -N-CHO)</td>
<td>163.72 (-CHO); 122.20, 125.35, 126.81, 127.00, 128.66, 128.74, 128.78, 129.17, 131.38, 136.72, 63.92, 40.20, 38.95</td>
<td>254 (M $^+$)</td>
</tr>
</tbody>
</table>

106b | 7.15-7.28 (m, 2H, –C$_6$H$_5$ of benzothiazole) | | 287 (M + H$^+$) |
ring), 7.31-7.36 (m, 4H, -C_6H_5 of benzene ring), 7.44-7.47 (d, 1H, J=8.48 Hz), 7.55-7.60 (t, 1H, -C_6H_5 of benzothiazole ring, J=8.44Hz), 7.65 (s, 1H, =CH), 8.17 (s, 1H, N-CHO)

106c
7.15-7.19 (q, 3H, J=5.12Hz, J= 4.12 Hz, -C_6H_5 of benzothiazole ring), 7.22-7.38 (m, 3H, -C_6H_5 of benzene ring), 7.45-7.60 (m, 2H, -C_6H_5 of benzothiazole ring, -C_6H_5 of benzene ring), 7.71 (s, 1H, =CH), 8.14 (s, 1H, -N-CHO)

163.88 (-CHO), 142.13, 136.44, 133.12, 132.42, 130.03, 127.57, 119.54, 119.27, 119.23, 118.81, 117.83, 116.57, 116.34, 79.06, 78.48, 40.19, 38.94

332.96 (M + H^+)

106d
3.27 (s, 3H, -OCH_3), 7.15- 7.22 (m, 1H, -C_6H_5 of benzothiazole ring), 7.24-7.26 (m, 1H, -C_6H_5 of benzothiazole ring), 7.34-7.58 (m, 4H, -C_6H_5 of benzene ring), 7.60 (s, 1H, =CH), 7.92-8.11 (t, 2H, J= 5.68 Hz, -C_6H_5of benzothiazole ring), 8.28(s, 1H, -N-CHO)

283 (M + H^+)

106e
2.37 (s, 3H, -CH_3), 7.04-7.07 (m, 1H, -C_6H_5 of benzothiazole ring), 7.11-7.20 (m, 1H, -C_6H_5 of benzothiazole ring), 7.30-7.32 (d, 2H, J=8.12Hz, 7.43-7.45 (t, 4H, J= 6.84Hz, -C_6H_5

267 (M + H^+)
of benzene ring), 7.68 (s, 1H, =CH), 8.20 (s, 1H, -N-CHO)

For an authentic comparison, the reactions as mentioned in a and b have been carried out by both conventional and greener routes. Employing the latter, i.e. through ultrasonication the yield of the product enhanced and a substantial reduction in reaction time has been observed (Table 3).

Table 3. Comparative data of Conventional and greener method

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Conventional method</th>
<th>Ultrasonication method</th>
<th>Solvents for Ultrasonication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reaction time /Yield (%)</td>
<td>Reaction time /Yield (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Hrs/ min) /Solvent</td>
<td>(Hrs/ min)</td>
<td></td>
</tr>
<tr>
<td>104a</td>
<td>4hrs 30 min. 50 / DMF</td>
<td>25 min 70 Methanol</td>
<td></td>
</tr>
<tr>
<td>104b</td>
<td>4Hrs 20 min 53/ DMF</td>
<td>20 min 72 Methanol</td>
<td></td>
</tr>
<tr>
<td>104c</td>
<td>4Hrs 20 min 51/ DMF</td>
<td>20 min 75 Methanol</td>
<td></td>
</tr>
<tr>
<td>104d</td>
<td>4Hrs 15 min 54/ DMF</td>
<td>25 min 72 Methanol</td>
<td></td>
</tr>
<tr>
<td>104e</td>
<td>4Hrs 15 min 58/ DMF</td>
<td>25 min 78 Methanol</td>
<td></td>
</tr>
<tr>
<td>104f</td>
<td>4Hrs 30 min 56/ DMF</td>
<td>15 min 76 Methanol</td>
<td></td>
</tr>
<tr>
<td>104g</td>
<td>4Hrs 25 min 49/ DMF</td>
<td>20 min 78 Methanol</td>
<td></td>
</tr>
<tr>
<td>104h</td>
<td>4Hrs 20 min 47/ DMF</td>
<td>25 min 82 Methanol</td>
<td></td>
</tr>
<tr>
<td>104i</td>
<td>4Hrs 30 min 40/ DMF</td>
<td>15 min 80 Methanol</td>
<td></td>
</tr>
<tr>
<td>106a</td>
<td>2Hrs 25 min 43/ DMF</td>
<td>20 min 75 Ethanol</td>
<td></td>
</tr>
<tr>
<td>106b</td>
<td>2Hrs 20 min 42/ DMF</td>
<td>20 min 78 Ethanol</td>
<td></td>
</tr>
</tbody>
</table>
2.7.1. Computational Details

The optimized molecular geometry, $^1$H and $^{13}$C NMR calculations have been performed with the Gaussian 09W [Frisch et al., 2009] by DFT methods with B3LYP (Beck three parameter Lee-Yang-Parr) exchange correlation functional, which combines the hybrid exchange functional of Becke [Becke, 1988], with the gradient-correlation functional of Lee et al [Lee et al., 1988]. The 6-31G (d) basis set has been used for calculation in the gas phase of the structure (104c). The optimized geometry with the 6-31G (d) basis set has been used in the $^1$H and $^{13}$C NMR calculations using DFT to characterize all stationary points as minima. The calculated geometrical parameters viz. bond lengths and bond angles have been compared with the experimental geometrical parameters obtained from single crystal X-ray data of compound (104c). The optimized structural parameters using B3LYP/6-31G (d) have been listed in Table 4 along with an optimized structure with atom number in Figure 2. Table 4 show that the optimized parameters were in good agreement with X-ray crystal structure. The optimized bond length of C (11)-S and C (9)-N was 1.796 Å and 1.368, respectively. However, actual bond lengths of C (11)-S and C (9)-N was 1.773 and 1.361. The optimized bond angles for C (9)-N(1) - C(10) and C (7) –C (8) -S(1) were 123.1 and 118.2 respectively whereas, actual bond angles were 123.1 and 114.4. The largest difference between calculated and experimental bond lengths and bond angles have been about -0.04 at S (1) –C (8) and -3.8° in C (7) –C (8)–S (1), respectively.

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>106c</td>
<td>2Hrs 15 min</td>
<td>45/ DMF</td>
<td>25 min</td>
<td>80</td>
<td>Ethanol</td>
</tr>
<tr>
<td>106d</td>
<td>2Hrs 30 min</td>
<td>48/ DMF</td>
<td>23 min</td>
<td>73</td>
<td>Ethanol</td>
</tr>
<tr>
<td>106e</td>
<td>2Hrs 20 min</td>
<td>47/ DMF</td>
<td>22 min</td>
<td>72</td>
<td>Ethanol</td>
</tr>
</tbody>
</table>
The slight deviation in single crystal X-ray data and the computed geometrical data could be due to the crystal packing interactions in the solid state and this deviation has not been observed in optimized geometry of a molecule in the gas phase.

Shielding tensors of structure of compound (104c) have been computed within the GIAO approach. By applying the similar methods and 6-31G (d) basic set has been used for geometrical optimization. It has been essential to optimize the geometry of TMS and chloroform molecule in order to express the chemical shift in ppm. $^1$H and $^{13}$C NMR spectra were calculated by 6-31G (d) basis set for structure of compound (104c). The equation, $\delta_i = \sigma_{TMS} \sigma_i$ has been used to convert the calculated isotropic shielding constants $\sigma_i$ to chemical shifts relative to TMS. The experimental and calculated $^1$H and $^{13}$C NMR chemical shifts (ppm) of compound (106c) has been enlisted in Table 5. Due to the availability of only a single value for the hydrogen atoms of CH$_3$ groups in experimental $^1$H NMR, an average chemical shift values have been used.

For the $^1$H NMR of compound (104c), the calculated singlet of =C-H comes at $\delta =$ 13.1556 in comparison to experimental value which has been at $\delta =$ 6.5332. The average calculated chemical shift of the N-CH$_3$ protons comes at 3.5888 ppm whereas the experimental chemical shift has been 3.07 ppm. The calculated C=O chemical shift in the $^{13}$C NMR spectrum comes at 165.9 whereas in the experimental spectrum the peak has been at 187.5 ppm. The carbon attached to the nitrogen atom in the experimental and calculated $^{13}$C NMR gives peaks at 36.2 ppm and 52.6 ppm, respectively. The correlation value for the calculated and experimental $^{13}$C NMR chemical shifts comes at 0.995 (Figure 3). The experimental $^{13}$C NMR chemical shifts show good correlation which confirms the structure of compound (104c). The optimized structure of
compound (104c) didn’t show any negative frequencies in the frequency optimized calculation which automatically confirms that the global minimum or equilibrium geometry has been found. The calculated energy of the optimized structure of the compound (104c) was -3716.03 a.u. and the dipole moment was 5.63 debye with the point group C1.

![Optimized structure of 1,4-benzoazine (104c)](image)

**Figure 2:** Optimized structure of 1,4-benzoazine (104c)

**Table 4.** Selected experimental and calculated bond parameters of compound (104c).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Compound (104c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental</td>
</tr>
<tr>
<td><strong>Bond Length (Å)</strong></td>
<td></td>
</tr>
<tr>
<td>Br-C(1)</td>
<td>1.901</td>
</tr>
<tr>
<td>S(1)-C(8)</td>
<td>1.770</td>
</tr>
<tr>
<td>S(1)-C(11)</td>
<td>1.773</td>
</tr>
<tr>
<td>O(1)-C(7)</td>
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<tr>
<td>N(1)-C(9)</td>
<td>1.361</td>
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<td>N(1)-C(10)</td>
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<tr>
<td>N(1)-C(12)</td>
<td>1.464</td>
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<tr>
<td>C(2)-C(3)</td>
<td>1.378</td>
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<tr>
<td>C(11)-C(16)</td>
<td>1.389</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.370</td>
</tr>
</tbody>
</table>

**Bond Angles (°)**
<table>
<thead>
<tr>
<th>Bond</th>
<th>Experimental NMR</th>
<th>Calculated NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(8)-S(1)-C(11)</td>
<td>99.9</td>
<td>101.4</td>
</tr>
<tr>
<td>C(9)-N(1)-C(10)</td>
<td>122.4</td>
<td>123.1</td>
</tr>
<tr>
<td>C(9)-N(1)-C(12)</td>
<td>118.3</td>
<td>118.4</td>
</tr>
<tr>
<td>C(10)-N(1)-C(12)</td>
<td>118.8</td>
<td>118.4</td>
</tr>
<tr>
<td>C(9)-C(8)-S(1)</td>
<td>122.0</td>
<td>123.4</td>
</tr>
<tr>
<td>C(7)-C(8)-S(1)</td>
<td>114.4</td>
<td>118.2</td>
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<tr>
<td>C(11)-C(10)-N(1)</td>
<td>120.9</td>
<td>121.7</td>
</tr>
<tr>
<td>C(13)-C(10)-N(1)</td>
<td>121.1</td>
<td>119.2</td>
</tr>
<tr>
<td>C(8)-C(9)-N(1)</td>
<td>127.2</td>
<td>123.1</td>
</tr>
</tbody>
</table>

**Table 5.** Experimental and calculated $^1$H and $^{13}$C NMR chemical shifts of compound (104c)
2.7.2. Single crystal X-ray diffraction study and structural description

An X-ray diffraction study has been carried out using an X Calibur EOS OXFORD Diffractometer at 293 (2) K. The structure has been solved using a SHELX-97 software package. The non-hydrogen atoms have been refined with anisotropic parameters. Compound (104c) crystallizes in a monoclinic system with the refinement of 0.0587. The crystal had space group P2₁/n and cell formula units 4. The cell length of the crystal a, b, c have been 11.7172 (19), 9.2242 (17) and 13.153 (2) respectively, and angles were α= 90°, β= 93.150° (16) and γ= 90°. Graphite monochromator radiation of type Moka with wavelength of 0.71073 was used for the diffraction study. The bond angle of O1-C7-C8 was 118.7 (4)° shows that C7 to be sp² hybridized and the bond length of O1-C7 was 1.243 (7) Å depicts its double bond character. Similarly, the bond length of C9-C8 at 1.345 (6) Å also points at a double bond between C9 and C8. The ortep diagram of compound (104c) [(4-Bromophenyl)(4-methyl-4H-benzo[b][1,4]thiazin-2-yl)methanone] has been shown in Figure 4, the crystal close packing along the a, b, c coordinates (Figure 5) and the structural data has been given in Table-6.
Figure 4. ORTEP diagram of compound

Table 6: Structural data of compound (104c)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCDC No.</td>
<td>1050855</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>$C_{16}H_{12}BrNOS$</td>
</tr>
<tr>
<td>Formula mss</td>
<td>346.24</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>293</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/n</td>
</tr>
<tr>
<td>$a$, $b$, $c$ (Å)</td>
<td>11.7172(19) 9.2242(17) 13.153(2)</td>
</tr>
<tr>
<td>$\alpha$, $\beta$, $\gamma$ (°)</td>
<td>90, 93.150(16), 90</td>
</tr>
<tr>
<td>Volume (Å³)</td>
<td>1419.5(4)</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
</tr>
<tr>
<td>Density (calc)/ gcm-3</td>
<td>1.620</td>
</tr>
<tr>
<td>$\mu$ (MoKa) [ /mm ]</td>
<td>3.0</td>
</tr>
<tr>
<td>Crystal Size [mm]</td>
<td>0.13 x 0.18 x 0.24</td>
</tr>
</tbody>
</table>
Figure 5. Three dimensional crystal close packing of the compound (104c).
2.7.3. Absorption Spectra

The absorption spectra of compounds (104c), (104d), (104g) and (104i) has been recorded in chloroform and DMSO [Figure 6 and Figure 7]. The spectra reveals that the maximum absorption for the above said compounds appear within the ranges of 180-200 nm and 290-300 nm owing to the presence of C=O in the compounds. These absorptions have been attributed to the \(\pi-\pi^*\) and \(n-\pi^*\) transitions. Another absorption peak occurs in the range of 390-460 nm has been due to benzothiazine chromophore. Similar absorption peaks in the spectra indicate similar structures all the compounds. The shift in absorption spectra of compounds (104g) and (104h) towards higher wavelength i.e red shift has been noticed due to the presence of \(-\text{NO}_2\) group in these compounds. Similar transitions \(\pi-\pi^*\) and \(n-\pi^*\) have been observed in compounds (104 a-i) due to presence of 1,4-benzothiazine core moiety and carbonyl group.

2.7.4. Fluorescence

The emission spectra of compounds (104c), (104d), (104g) and (104i) have been shown in Figure 8, whereas the emission and excited wavelength have been given in Table 7. The emission spectra of compounds (104c), (104d), (104g) and (104i) show peaks at 373 nm, 577nm, 421 nm and 321nm, respectively. So, these compounds represent the single fluorescence emission band which makes these compounds fluorescence active. The spectrum in Figure 8 shows that compound (104c) and (104d) were more fluorescence active in comparison to compound (104g) and (104i).

**Table 7.** Maximum excitation and emission wavelength of compound (104c), (104d), (104g), (104i) in CHCl₃ solvents.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>CHCl₃</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\lambda_{ex}$</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>104(c)</td>
<td>268</td>
</tr>
<tr>
<td>104(d)</td>
<td>457</td>
</tr>
<tr>
<td>104(g)</td>
<td>291</td>
</tr>
<tr>
<td>104(i)</td>
<td>296</td>
</tr>
</tbody>
</table>

**Figure 6.** UV-vis absorption spectra of compounds (104c), (104d), (104g) and (104i) in chloroform
Figure 7. UV-vis absorption spectra of compounds (104c), (104d), (104g) and (104i) in DMSO
Mechanism of free radical scavenging activity

The DPPH free radical scavenging method has been employed for the evaluation of antioxidant potential. The antiradical power by the above said method could easily be measured. Due to presence of odd electrons in DPPH free radical, the blank show the absorbance at 517nm. The synthesized compounds with different concentrations (mg/ml) were added into the 3 mL DPPH (0.004%) solution. After incubation of half an hour, the colour of the solution decolourizes from dark purple to light colour viz. yellow sometimes or light purple. This decolourization been due to the number of captured unpaired electrons from the added compound. When odd electrons of DPPH get paired with hydrogen radical obtained from synthesized compounds, a stable reduced DPPH-H gets formed due to which colour of DPPH solution changes. When absorbance of aliquots were recorded, the absorbance decreases from 517nm, which indicates the
disappearance of odd electrons from the solution and formation of diamagnetic spin paired molecule [Matthaus, 2002].

The antioxidant potential of the synthesized compounds has been summarized in Table 8. The chemical structure of the organic compounds strongly influence the bioactive behaviour of that particular compound. In the series of synthesized 4H-1,4-benzothiazines bearing N-CH₃, show considerable antioxidant activity. The presence of halogen group in the compounds (104b), (104c), (104f) and (104g) sharply enhances the antioxidant activity. Compound (104c) with strong reducing power shows maximum antioxidant activity. The compounds (104f), (104g), (104h) and (104i) shows less antioxidant activity in comparison to compounds (104a-e) as these contain −NO₂ group (deactivating group) [Figure 9].

**Table 8. Antioxidant potential of syntheised compounds (104a-i).**

<table>
<thead>
<tr>
<th>Test samples</th>
<th>% Radical Scavenging Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1mg/ml</td>
</tr>
<tr>
<td>(104a)</td>
<td>20.01</td>
</tr>
<tr>
<td>(104b)</td>
<td>25.22</td>
</tr>
<tr>
<td>(104c)</td>
<td>26.99</td>
</tr>
<tr>
<td>(104d)</td>
<td>18.09</td>
</tr>
<tr>
<td></td>
<td>17.78</td>
</tr>
<tr>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>(104e)</td>
<td></td>
</tr>
<tr>
<td>(104f)</td>
<td>17.33</td>
</tr>
<tr>
<td>(104g)</td>
<td>18.07</td>
</tr>
<tr>
<td>(104h)</td>
<td>19.03</td>
</tr>
</tbody>
</table>

Ascorbic Acid 58.42% - - - 

Figure 9. Antioxidant potential of compounds (104a-h).
2.7.6. Antimicrobial Activity

Nine newly synthesized samples have been assayed for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* bacterial strains and for antifungal activity against *Aspergillus niger, Candida albicans* by agar diffusion method. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at concentrations of 100 µg/mL and 500 µg/mL. The results have been recorded for each tested compound as the average diameter of inhibition zones of bacterial growth surrounding the well (in millimetres) (Table 9). Standard antibacterial *Gentamycin* and antifungal *Amphotericin* have been employed as control drugs to evaluate the potency of the tested compounds under the same conditions. The results of antimicrobial activities reveal that all the tested compounds except (104f) and (104d) show promising antibacterial and antifungal activities. Compound (104b), (104c), (104b) and (104c) exhibit discrete antibacterial activity, even better than the standard drug, against *Staphylococcus aureus* and *Escherichia coli*. When electron withdrawing group like –Cl, -Br attached to the heterocyclic ring enhances the antimicrobial activity. While, –NO₂ in compounds (104f-104i) decreases the antimicrobial activity (figure-10). While, in series with compounds by intermolecular cyclization shows promising antibacterial activity along with moderate antifungal activity.

Table 9. Antimicrobial activity of the synthesised compounds (104a-i).

<table>
<thead>
<tr>
<th>Entry</th>
<th><em>S. aureus</em></th>
<th><em>E.coli</em></th>
<th><em>C. albicans</em></th>
<th><em>A. niger</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The synthesized compounds (106a-e) have been evaluated for their antibacterial and antifungal activity against *Staphylococcus aureus* and *E.Coli* bacterial strains while, for antifungal activity these have been tested against *Aspergillus niger* and *Candida albicans* by agar diffusion method (already described). The results of antimicrobial activities reported in (Table 10) reveal that all the tested compounds show moderate antibacterial and antifungal activities.

<table>
<thead>
<tr>
<th>Zone of inhibition (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 µg/mL</td>
</tr>
<tr>
<td>(104a)</td>
</tr>
<tr>
<td>(104b)</td>
</tr>
<tr>
<td>(104c)</td>
</tr>
<tr>
<td>(104d)</td>
</tr>
<tr>
<td>(104e)</td>
</tr>
<tr>
<td>(104f)</td>
</tr>
<tr>
<td>(104g)</td>
</tr>
<tr>
<td>(104h)</td>
</tr>
<tr>
<td>Gentamycin</td>
</tr>
<tr>
<td>Amphotericin</td>
</tr>
</tbody>
</table>

**Compound (106a-e)**

The synthesized compounds (106a-e) have been evaluated for their antibacterial and antifungal activity against *Staphylococcus aureus* and *E.Coli* bacterial strains while, for antifungal activity these have been tested against *Aspergillus niger* and *Candida albicans* by agar diffusion method (already described). The results of antimicrobial activities reported in (Table 10) reveal that all the tested compounds show moderate antibacterial and antifungal activities.
Whereas, compounds (106b) and (106c) exhibit good antibacterial activity against \textit{S. aureus} and \textit{E. coli}. Further, compound (106e) exhibits good antifungal activities (Figure 11).

\textbf{Table 10.} Antimicrobial activities of compounds (10a6-e).

<table>
<thead>
<tr>
<th>Compds.</th>
<th>\textbf{Antimicrobial activity}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>\textit{S. aureus}</td>
</tr>
<tr>
<td>Entry</td>
<td>(\mu g/mL)</td>
</tr>
<tr>
<td>100</td>
<td>500 (\mu g/mL)</td>
</tr>
<tr>
<td>106a</td>
<td>5.24</td>
</tr>
<tr>
<td>106c</td>
<td>8.27</td>
</tr>
<tr>
<td>106d</td>
<td>3.16</td>
</tr>
<tr>
<td>106e</td>
<td>8.27</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>9.88</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 10. Pictorial representation of antimicrobial and antifungal activity of compound (104a-i).
Figure 11. Pictorial representation of antimicrobial and antifungal activity of compound (106a-e).

The above investigations reveal that derivatives of 1,4-benzothiazines could be procured from the reaction of N- methylbenzothiazolium iodide with α-haloketones in the basic medium and base induced ring transformations of N- phenacylbenzothiazolium cations in good yields. Hence, It is concluded that in basic medium, appropriately appended benzothiazolim cation could yield corresponding 1,4-benzothiazine derivatives in a single step. Moreover, reactions through ultrasonication proved to be better protocol than conventional methodology (stirring at room temperature, refluxing at high temperature). Further, to ascertain the singularity and structure of the product, single X-ray and DFT study were carried out respectively. Consonant with the literature, synthesis of 1,4-benzothiazines exhibit considerable biological activity that gets
enhanced on the introduction of electron withdrawing group [Narang et. al, 2016; Malik et. al, 2013].

References


Deligne, P. 1986. Circulatory effects of neuroleptics used in anesthesia. Cardiovascular actions of anesthetics and drugs used in anesthesia. 1: 103- 140.


