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Synthesis and biological activities of 1,4-benzothiazine derivatives: An overview

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Abstract: The aim of present review is to collate literature work reported by various researchers to provide an overview of the available methodologies for the synthesis and diverse biological activities exhibited by 1,4-benzothiazines. This review highlights recent reports on various routes of synthesis and biological studies *viz.* antibacterial activity, antifungal activity, antihypertensive activity, calcium antagonist, anti-inflammatory activity, antioxidant, antimalarial activity, antitumor activity, antiproliferative activity, anti-hepatitis C virus activity, central nervous system stimulating activity, potassium channel opener activity, antihyperlipidemic activity, cardiovascular activity, 15-lipoxygenase inhibitors, anti-allergic activity *etc.* of 1,4-benzothiazine derivatives.

Keywords: 2-Aminothiophenol, 1,4-benzothiazine, biological activities.

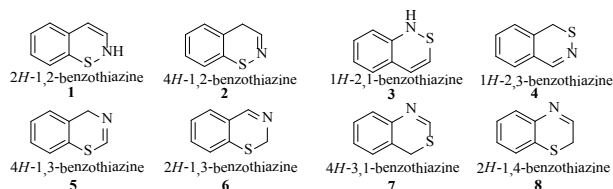
INTRODUCTION

Of the total chemical compounds registered, about one half contain heterocyclic systems. Heterocyclic compounds are important, not only because of their abundance, but because of their chemical, biological and technical importance. Heterocycles count among their number many natural products, such as vitamins, hormones, alkaloids, antibiotics, as well as pharmaceuticals, herbicides, dyes, and other products of technical importance like antiaging drugs, corrosion inhibitors, sensitizers,

stabilizing agents, etc. In current years, there has been a growing interest in the synthesis of various heterocyclic compounds because most of the compounds with biological nature are imitative from heterocyclic structures.

Among various heterocyclic compounds containing nitrogen and sulphur as heteroatoms, benzothiazines constitute an important class of highly applicable bioactive molecules as they exhibit interesting biological properties and used as a key structural motif [1]. The benzothiazine is a heterocyclic compound in which benzene

ring is fused to the 6-membered thiazine ring through carbon-carbon linkage. Thiazines are six-membered heterocyclic systems containing both nitrogen and sulphur in the same ring. Depending upon the position of sulphur and nitrogen atoms in the ring, benzothiazines exist as the following structural isomers:



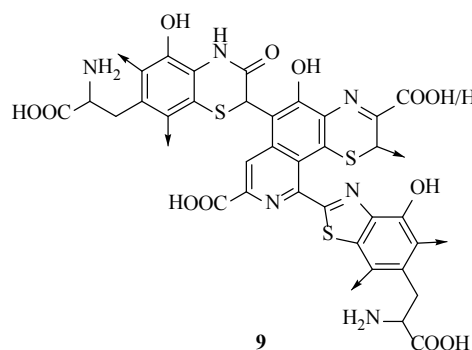
Amongst them, 1,4-benzothiazines constitute an important category which received increasing attention worldwide due to their wide spectrum biological activities [2–4]. The biological activity of several 1,4-benzothiazines is similar to that of phenothiazines due to the presence of a fold along the nitrogen-sulphur axis, featuring the same structural specificity [5–9]. 1,4-Benzothiazines are a class of medicinally important heterocyclic compounds which are used extensively in drug design [10]. 1,4-Benzothiazines also find use as antimalarial, antimicrobial, antihypertensive, calcium antagonist, anti-inflammatory, anti-HIV, antioxidant, ATP-sensitive potassium channel opener, antitumor, antihyperlipidemic and central nervous system (CNS) stimulating agents, *etc.*

However, the aim of the present article is to provide an overview on the synthesis and biological activities of 1,4-benzothiazine derivatives in order to unfold a new window of opportunities that may be available for new drug discovery from this scaffold [11].

Natural occurrence of 1,4-benzothiazine

Pheomelanin is a class of melanin which occurs naturally in the human red hair and skin as a major oligomeric nucleus [12]. Pheomelanin is thought to be engendered by the interception of

dopaquinone with cysteine which results in the incorporation of a 1,4-benzothiazine monomer into the polymer [13]. Pheomelanin (**9**) which contains the 1,4-benzothiazine nucleus is particularly concentrated in the lips, glands of the penis, nipples and vagina [14]. Further, the two most abundant trichochromes (dimers of benzothiazines) were isolated from red chicken feathers [15]. Pheomelanins are also known to act as potent photosensitizers leading to reactive oxygen species (ROS) production [16].



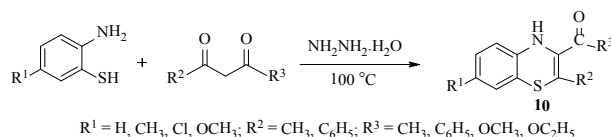
The arrows denote the directions where the polymer continues

An overview of the different methods of synthesis and biological activities of 1,4-benzothiazines is given as follows:

METHODS OF SYNTHESIS OF 1,4-BENZOTHAZINES

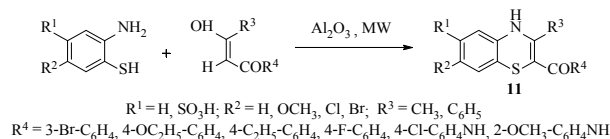
In general, 1,4-benzothiazines are obtained from the compounds having suitable carbon fragments as discussed below:

1. Synthesis from 1,3-dicarbonyl compounds
Munde *et al.* (2003) [17] synthesized substituted 1,4-benzothiazines (**10**) by the condensation of 2-aminothiophenols with 1,3-dicarbonyl compounds under solvent free conditions (Scheme 1).



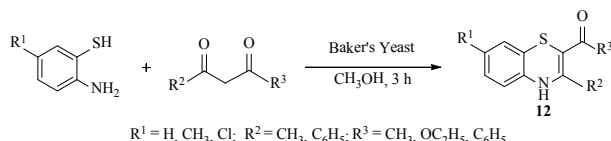
Scheme 1

Gupta *et al.* (2011) [18] synthesized substituted 4*H*-1,4-benzothiazines (**11**) by the condensation of 2-aminothiophenols with β -diketones using basic alumina and microwave irradiation (Scheme 2).



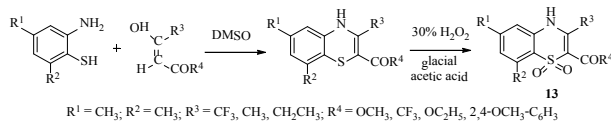
Scheme 2

Pratap *et al.* (2011) [19] carried out the synthesis of 1,4-benzothiazines (**12**) by oxidative cyclocondensation of 2-aminothiophenols with 1,3-dicarbonyl compounds using biocatalyst baker's yeast at ambient temperature in methanol (Scheme 3).



Scheme 3

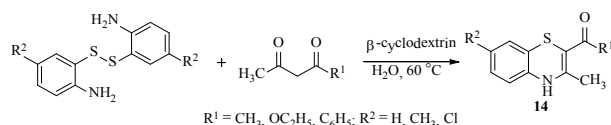
Gautam *et al.* (2012) [20] synthesized 4*H*-1,4-benzothiazine sulfone derivatives (**13**) via condensation and oxidative cyclization of substituted 2-aminothiophenol with 1,3-dicarbonyl compounds in dimethylsulfoxide (DMSO) and further oxidation using 30% hydrogen peroxide (H_2O_2) in glacial acetic acid (Scheme 4).



Scheme 4

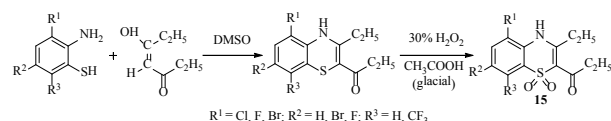
Londhe *et al.* (2015) [21] reported the synthesis of 2,3-disubstituted 1,4-benzothiazines (**14**) by cyclocondensation of 1,3-dicarbonyl compounds with substituted 2-(2-(2-aminophenyl)disulfanyl)benzenamines under supramolecular catalysis of β -cyclodextrin in water at neutral

pH (Scheme 5).



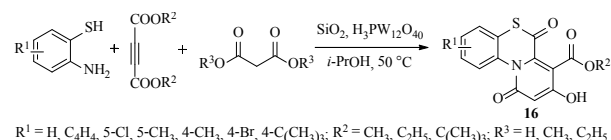
Scheme 5

Gautam *et al.* (2015) [22] prepared 4*H*-1,4-benzothiazines (**15**) by the reaction of substituted 2-aminothiophenols with 1,3-dicarbonyl compounds in DMSO and further oxidation by 30% H_2O_2 in glacial acetic acid (Scheme 6).



Scheme 6

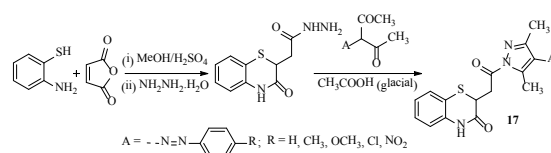
Samzadeh-Kermani *et al.* (2016) [23] reported the heteropoly acid (HPA, $\text{H}_3\text{PW}_{12}\text{O}_{40}$) catalyzed synthesis of 1,4-benzothiazine derivatives (**16**) by the reaction of 2-aminothiophenol, acetylenic esters and malonate esters in isopropyl alcohol at 50 °C for 7 h (Scheme 7).



Scheme 7

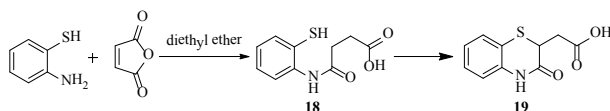
2. Synthesis of 1,4-benzothiazine derivatives from maleic anhydride

Dabholkar and Gavande (2011) [24] synthesized 1,4-benzothiazine derivatives (**17**) by the reaction of 2*H*-4*H*-2-hydrazinocarbonyl methyl-3-oxo-1,4-benzothiazine with acetyl acetone derivatives in presence of glacial acetic acid under ultrasonication (Scheme 8).



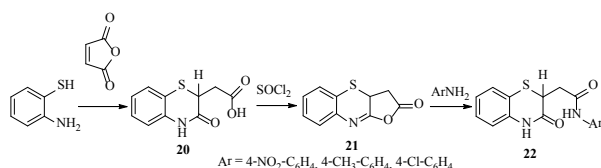
Scheme 8

Dabholkar and Gavande (2011) [25] synthesized 1,4-benzothiazine-2-acetic acid (**19**) by the reaction of 2-aminothiophenol with maleic anhydride in diethyl ether *via* the formation of *o*-mercaptomaleanilic acid (**18**) intermediate (Scheme 9).



Scheme 9

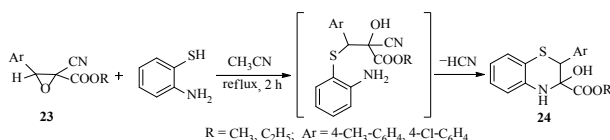
Gajbhiye and Goel (2013) [26] carried out the synthesis of *N*-aryl-2-(3-oxo-1,4-benzothiazine-2-yl)acetamide derivatives (**22**). The condensation of 2-aminothiophenol with maleic anhydride yielded 2,3-dihydro-3-oxo-(2*H*)-1,4-benzothiazine acetic acid (**20**) that upon reaction with thionyl chloride gave (2*H*)-oxo-3,3a-dihydrofuro[3,2-*b*][1,4]-benzothiazine (**21**) which was further reacted with substituted anilines to afford the corresponding amides (**22**) (Scheme 10).



Scheme 10

3. Synthesis from α -cyano- β -alkoxy carbonyl epoxide

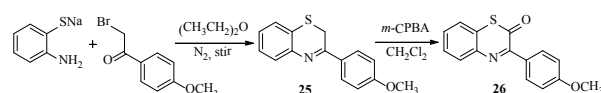
Saadouni et al. (2014) [27] synthesized 1,4-benzothiazines (**24**) by the reaction of 2-aminothiophenol with α -cyano- β -alkoxy carbonyl epoxides (**23**) in the presence of acetonitrile (CH₃CN) (Scheme 11).



Scheme 11

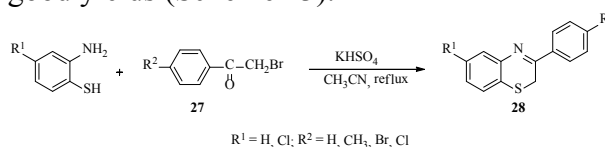
4. Synthesis from α -halo ketones, acids and esters

Sabatini et al. (2008) [28] carried out the reaction of sodium-2-aminothiophenolate with 2-bromo-1-(4-methoxyphenyl)ethanoate at room temperature using diethyl ether as solvent to afford an intermediate (**25**), which upon subsequent treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in presence of dichloromethane at room temperature for 30 min yielded 3-(4-methoxyphenyl)-2*H*-1,4-benzothiazin-2-one (**26**) in high yield (Scheme 12).



Scheme 12

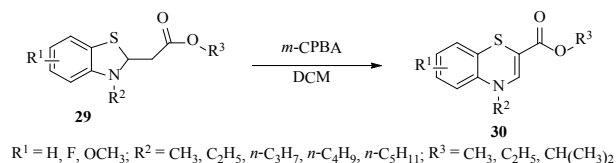
Baghernejad et al. (2011) [29] have reported the synthesis of 3-aryl-2*H*-benzo[1,4]thiazines (**28**) by condensation of 2-aminothiophenols and 2-bromo-1-phenylethanones (**27**) in acetonitrile (CH₃CN) using catalytic amount of KHSO₄ in good yields (Scheme 13).



Scheme 13

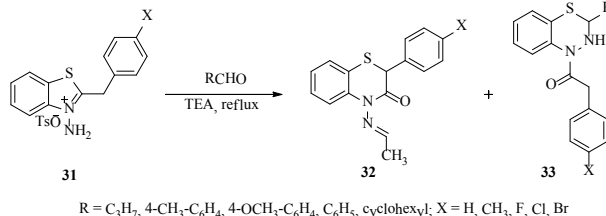
5. Synthesis from ring expansion reaction of benzothiazolines

Pi et al. (2009) [30] synthesized the 2-substituted-*N*-alkylated-1,4-benzothiazines (**30**) by treatment of benzothiazolylacetates (**29**) with *m*-chloroperbenzoic acid (*m*-CPBA) *via* oxidative ring expansion process (Scheme 14).



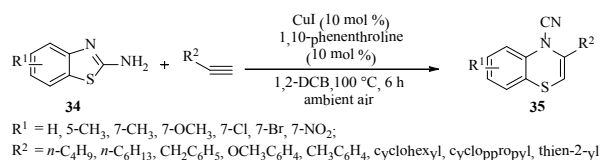
Scheme 14

Filak *et al.* (2009) [31] prepared substituted 1,4-benzothiazines (32) and (33) by the reaction of *N*-amino-2-benzylbenzothiazolium salt (31) with aldehydes in the presence of TEA (triethyl amine) (Scheme 15).



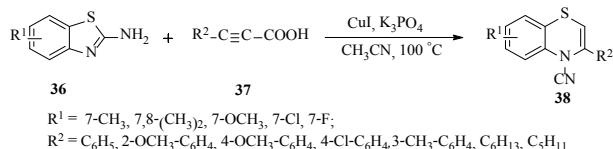
Scheme 15

Mitra *et al.* (2014) [32] carried out the synthesis of a series of substituted benzo[*b*][1,4]thiazine-4-carbonitriles (35) by copper-catalyzed coupling of 2-aminobenzothiazoles (34) and terminal alkynes in the presence of ambient air followed by intramolecular cyclization (Scheme 16).



Scheme 16

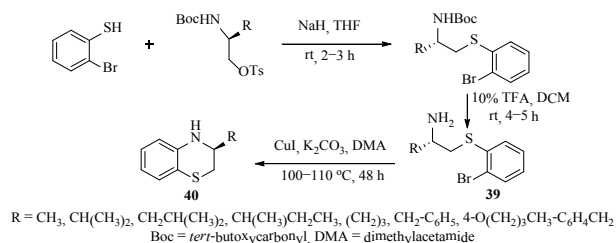
Qiu *et al.* (2015) [33] reported a one-pot synthesis of 1,4-benzothiazines (38) by the reaction of 2-aminobenzothiazoles (36) with alkynyl carboxylic acids (37) through decarboxylative coupling, nucleophilic ring-opening reaction and intramolecular hydroamination processes (Scheme 17).



Scheme 17

6. Synthesis from catalytic intramolecular amination

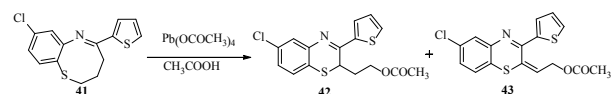
Parai and Panda (2009) [34] carried out the synthesis of 3,4-dihydro-2*H*-1,4-benzothiazine derivatives (40) *via* a copper-catalyzed intramolecular *N*-aryl amination reaction on substituted (2-bromophenylthio)ethanamines (39) (Scheme 18).



Scheme 18

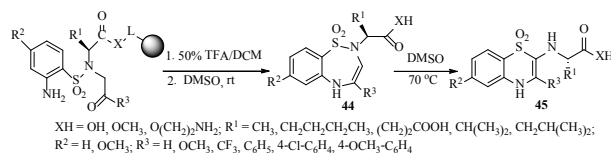
7. Synthesis from ring contraction of benzothiadiazepine

Press *et al.* (1980) [35] reported the ring contraction of 8-chloro-3,4-dihydro-5-(2-thienyl)-2*H*-1,6-benzothiazocine (41) by lead tetra-acetate to yield 1,4-benzothiazines (42) and (43) in the ratio 1.4:1 (Scheme 19).



Scheme 19

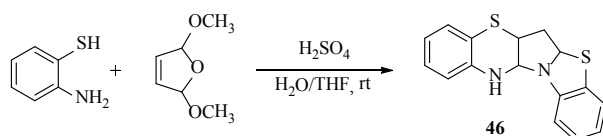
Fulopova *et al.* (2015) [36] reported the polymer supported synthesis of 4*H*-benzo[*b*][1,4]-thiazine-1,1-dioxides (45) *via* ring contraction of 2,5-dihydro[*f*][1,2,5]thiadiazepine-1,1-dioxides (44) under mild reaction conditions involving carbon-sulphur bond formation process (Scheme 20).



Scheme 20

8. Synthesis from 2,5-dihydro-2,5-dimethoxyfuran

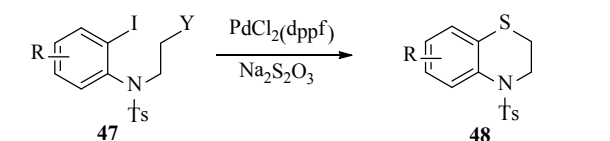
Jaafar *et al.* (2014) [37] carried out the synthesis of 1,4-benzothiazine derivatives (**46**) by the reaction of 2,5-dihydro-2,5-dimethoxyfuran with an excess of 2-aminothiophenol in a tetrahydrofuran (THF)/H₂O mixture in the presence of a catalytic amount of conc. H₂SO₄ at room temperature (Scheme 21).



Scheme 21

9. Synthesis from Pd-catalyzed double C-S bond formation

Qiao *et al.* (2013) [38] synthesized substituted 1,4-benzothiazine derivatives (**48**) by coupling reaction of *N*-(2-iodophenyl)-*N*-(2-substitutedethyl)-4-methylbenzenesulfonamide derivatives (**47**) in the presence of Na₂S₂O₃·5H₂O and PdCl₂(dppf) as catalyst (Scheme 22).

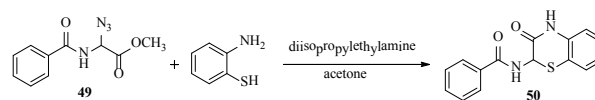


R = CN, NO₂, CH₃, OCH₃, COCH₃; Y = I, Br, Cl, OTs, OMs
dppf = 1,1'-bis(diphenylphosphino)ferrocene; Ts = tosyl; Ms = mesyl

Scheme 22

10. Synthesis by *S*-alkylation with methyl α -azidoglycinates

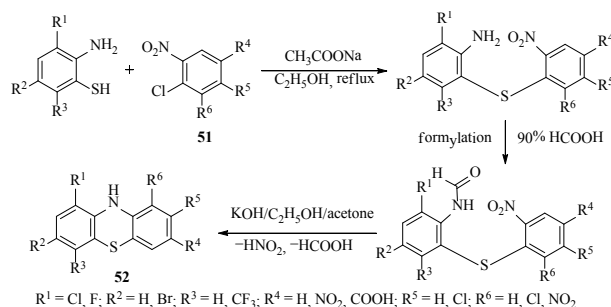
Mabrouk *et al.* (2010) [39] reported a one-pot regioselective synthesis of *N*-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-yl)benzamide (**50**) by the reaction of 2-aminothiophenol with azide derivatives (**49**) in the presence of diisopropylethylamine in acetone (Scheme 23).



Scheme 23

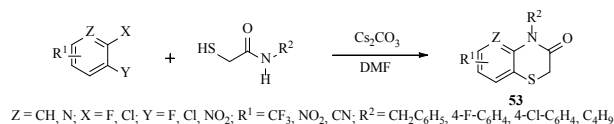
11. Synthesis via Smiles rearrangement

Gautam *et al.* (2009) [40] carried out the reaction of substituted halonitrobenzene (**51**) with 2-aminobenzenethiols to form intermediate, 2-(nitrophenylthio)anilines, which upon formylation followed by Smiles rearrangement afforded a series of novel 1,2,4,5,6,7-hexasubstituted 10*H*-phenothiazines (**52**) (Scheme 24).



Scheme 24

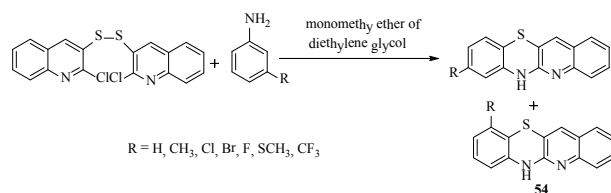
Zhao *et al.* (2012) [41] synthesized benzo[1,4]thiazin-3(4*H*)-one derivatives (**53**) via Smiles rearrangement (Scheme 25).



Scheme 25

12. Synthesis from 2,2-dichloro-3,3'-diquinolinyldisulfide

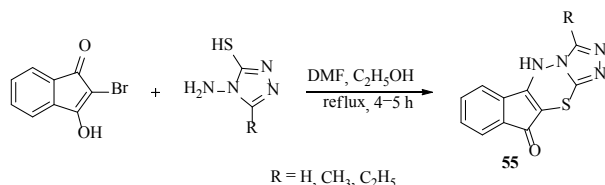
Jelen *et al.* (2013) [42] carried out the synthesis of a series of 1,4-benzothiazine derivatives (**54**) by the reaction of 2,2'-dichloro-3,3'-diquinolinyldisulfide with substituted anilines in the presence of monomethyl ether of diethylene glycol (Scheme 26).



Scheme 26

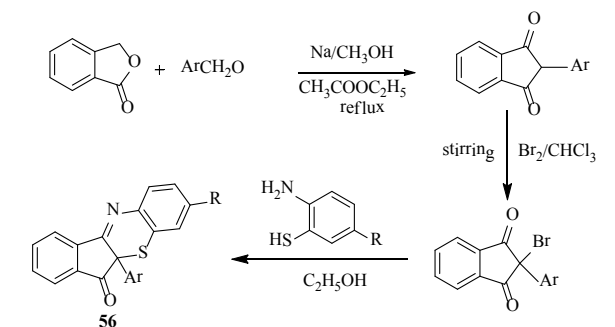
13. Synthesis from indandione

Dabholkar *et al.* (2013) [43] carried out the synthesis of 3-substituted-[(1,2,4)triazolo[4,5-*b*]indeno(2,3-*e*)]-1,3,4-thiadiazines (**55**) by the reaction of 2-bromoindandione with substituted triazoles in ethanol/DMF under reflux for 4–5 h (Scheme 27).



Scheme 27

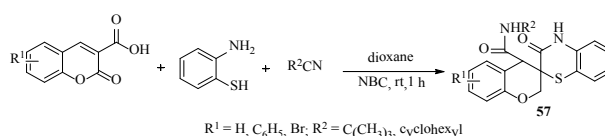
Mor *et al.* (2016) [44] synthesized tetracyclic 1,4-benzothiazines (**56**) by two-step procedure that involves reaction of phthalide with 4-substituted benzaldehydes in the presence of sodium methoxide and ethylacetate using methanol as solvent to yield 2-aryl-1*H*-indene-1,3(2*H*)-diones, which upon bromination in Br₂/chloroform afforded the corresponding 2-aryl-2-bromo-1*H*-indene-1,3(2*H*)-diones. Further, the condensation of 2-aryl-2-bromo-1*H*-indene-1,3(2*H*)-diones and 2-aminothiophenols in refluxing ethanol for 8–13 h resulted in the formation of tetracyclic 1,4-benzothiazines (**56**) (Scheme 28).



Scheme 28

14. Synthesis by using heterogeneous catalyst

Baharfor *et al.* (2016) [45] carried out the synthesis of spiro 1,4-benzothiazine derivatives (**57**) by the reaction of coumarin-3-carboxylic acid derivatives, alkyl isocyanide and 2-aminothiophenol in the presence of nano biocatalyst (NBC) using dioxane as solvent under stirred conditions at room temperature. In this reaction, heterogeneous nano biocatalyst was recovered and reused for the next run of the reaction without significant loss in the product (Scheme 29).



Scheme 29

BIOLOGICAL ACTIVITIES OF 1,4-BENZOTHAZINES

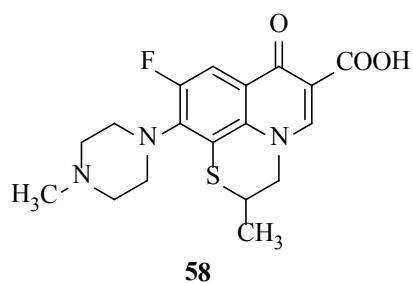
Multi-drug resistance is one of the major instant extortions to human health today [46,47]. Epideminological studies have also revealed that emergence of new diseases has occurred at alarming rates in the recent time [48]. On the basis of various studies, chemists have found 1,4-benzothiazines to be highly expeditious building blocks in medicinal research. Some important biological activities possessed by

1,4-benzothiazines are described as follows:

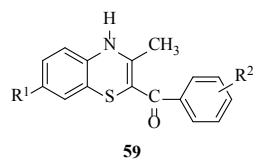
1. Antibacterial activity

Despite the problem of multi-drug resistance, 1,4-benzothiazines are known to be good antibacterial agents [49].

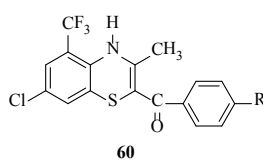
Cecchetti et al. (1993) [50] reported a series of 2-substituted-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzothiazine-6-carboxylic acids and amongst them derivative (**58**) was found to be the most active compound with minimum inhibitory concentration (MIC) value of 0.25 µg/mL against *Escherichia coli* and *Klebsiella pneumonia*.



Rathore et al. (2006) [51] synthesized 7-chloro-5-trifluoromethyl/7-fluoro/7-trifluoromethyl-4H-1,4-benzothiazines and found that the derivatives (**59**) and (**60**) showed high antibacterial activity against *Bacillus subtilis*, *Bacillus mega* and *Escherichia coli* as determined by zone of inhibition method.



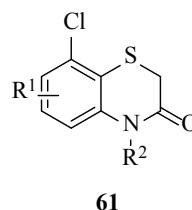
R¹ = F, CF₃; R² = *m*-Br, *p*-Cl



R = C₂H₅, Br

Yang et al. (2011) [52] synthesized benzo[*b*][1,4]thiazin-3(4*H*)-one derivatives (**61**), and assayed *in vitro* for their antibacterial activity against Gram-positive bacteria such as *Staphylococcus aureus*, *Bacillus subtilis* and *Micrococcus luteus*, and Gram-negative bacteria like *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*. Most compounds exhibited MIC

values in the range of 16–64 µg/mL, however, all the tested benzo[*b*][1,4]thiazin-3(4*H*)-ones (**61**) displayed activity lower than those of the reference drugs ampicillin, streptomycin and ceftazidime.

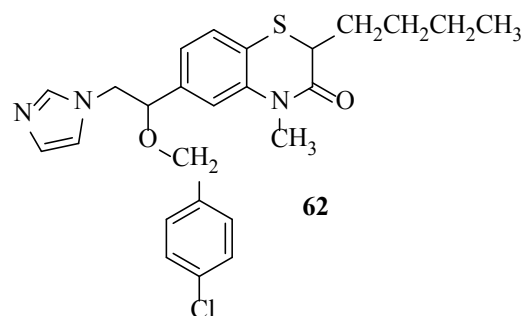


R¹ = 5-chloro, 6-chloro, 7-chloro, 8-chloro

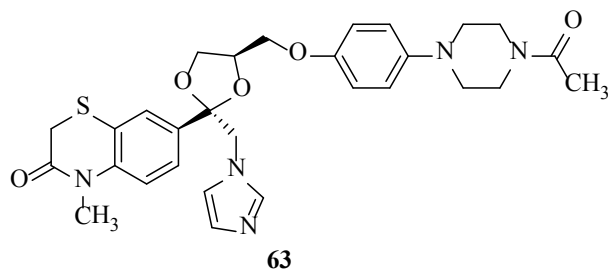
R² = *n*-hexyl, cyclohexyl, benzyl, tetrahydrofuran-2-yl methyl

2. Antifungal activity

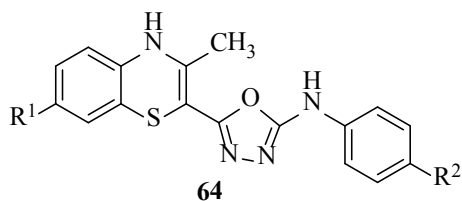
Schiaffella et al. (2005) [53] synthesized a series of 1,4-benzothiazines derivatives. The compound (**62**) competed favorably with the fluconazole reference drug against *Candida albicans* and *Candida krusei*.



Schiaffella et al. (2006) [54] reported 1,4-benzothiazine derivatives with structure similar to that of ketoconazole (KTZ) in order to obtain more potent inhibition of CYP51 enzyme of *Candida albicans* and best activity was reported in the racemic *trans* analogue (**63**).

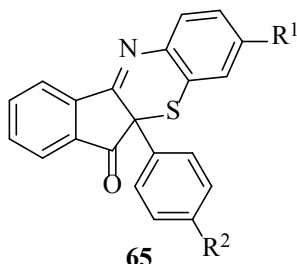


Khairnar *et al.* (2012) [55] carried out the synthesis of a series of 5-(3-methyl-7-substituted-4*H*-1,4-benzothiazine-2-yl)-*N*-aryl-1,3,4-oxadiazol-2-amines (**64**) and reported them to possess potent *in vitro* antifungal activities.



$R^1 = \text{H, CH}_3, \text{OC}_2\text{H}_5, \text{Cl, Br}; R^2 = \text{H, CH}_3, \text{OCH}_3, \text{Cl, Br}$

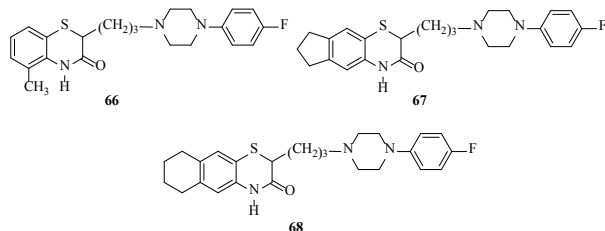
Mor *et al.* (2012) [56] carried out the synthesis of a series of 10a-phenylbenzo[*b*]indeno[1,2-*e*] [1,4]thiazin-11(10a*H*)-ones (**65**) and reported them to possess potent *in vitro* antifungal activities against fungi viz. *Aspergillus fumigates* and *Candida albicans*.



$R^1 = \text{H, CH}_3, \text{OCH}_3, \text{Br}; R^2 = \text{H, CH}_3, \text{OCH}_3, \text{Cl}$

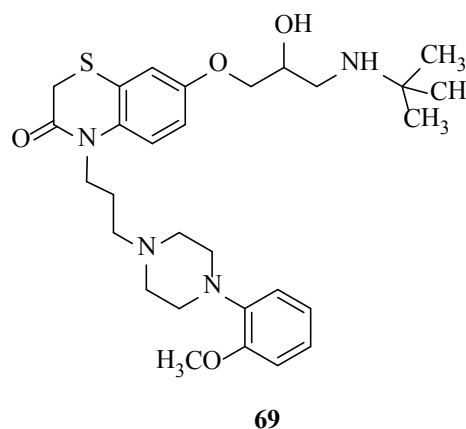
3. Antihypertensive activity

Kajino *et al.* (1991) [57] synthesized a series of substituted 2*H*-1,4-benzothiazin-3(4*H*)-one derivatives and evaluated them for antihypertensive activity in spontaneously hypertensive rats. The derivatives (**66–68**) showed potent antihypertensive effects.



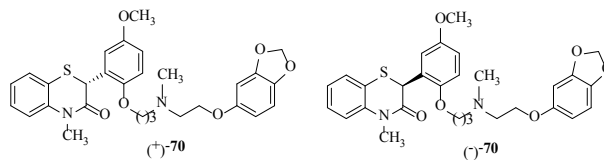
Cecchetti *et al.* (2000) [58] synthesized a

series of compounds having a piperazine moiety linked to the benzothiazine nucleus and evaluated them for *in vitro* α -adrenoceptor affinity by radioligand receptor binding assays. The derivative (**69**), in particular, exhibited the highest α_1 -AR affinity ($K_i = 1.3 \text{ nM}$) as well as the highest α_1 -selectivity ($\alpha_2/\alpha_1 = 407$) coupled with good but not selective β -AR affinities.



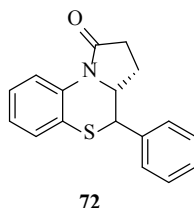
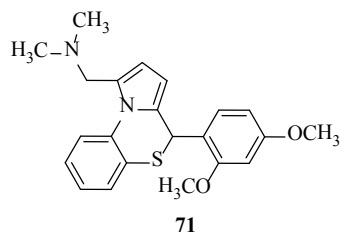
4. Calcium antagonist

Fujita *et al.* (1990) [59] synthesized a series of 1,4-benzothiazine derivatives and evaluated them for calcium antagonist activity. The Ca^{2+} antagonistic activity of derivative (+)-**70** was found about 7 times more than (-)-**70**. However, *in vitro* study showed low cardioselectivity of (+)-**70** compared to verapamil and diltiazem suggesting that (+)-**70** would show less adverse effects due to cardiac inhibition than diltiazem and verapamil in therapeutic use.

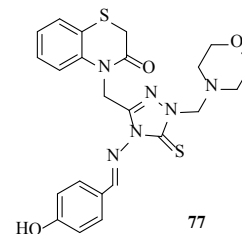
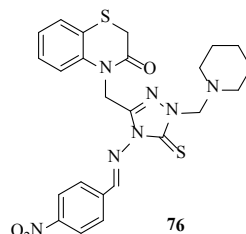


Campiani *et al.* (1995) [60] carried out the synthesis of a series of pyrrolo[2,1-*c*] [1,4]-benzothiazine derivatives and evaluated them for Ca^{2+} antagonist activity by using an isolated guinea pig left atrium. Two of the tested compounds (**71**) and (**72**) were identified as potent calcium antagonists selective for cardiac

over vascular tissue as compared to reference calcium antagonists verapamil and *cis*-(+)-diltiazem.

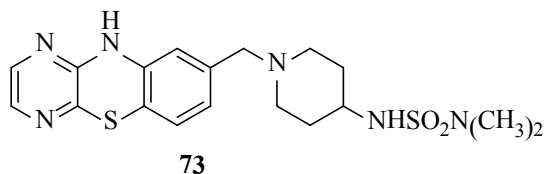


possess anti-inflammatory activity comparable to that of indomethacin.

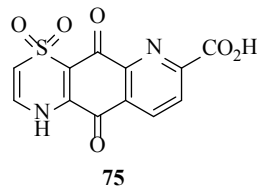
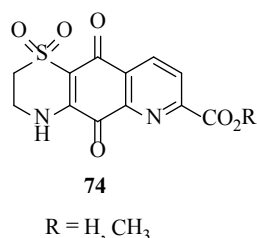


5. Anti-inflammatory activity

Kaneko *et al.* (2002) [61] synthesized a series of 10*H*-pyrazino[2,3-*b*][1,4]-benzothiazines. Among them the derivative *N*-[1-(10*H*-pyrazino[2,3-*b*][1,4]-benzothiazin-8-ylmethyl)-piperidin-4-yl]-*N,N'*-dimethylsulfamide (**73**) exhibited the potent inhibitory activities against neutrophil migration in a murine interleukin-1 (IL-1) induced paw inflammation model.



Pearce *et al.* (2007) [62] isolated tricycles thiazine containing quinolinequinone alkaloids (**74** & **75**) from the New Zealand Ascidian *Aplidium* species which were found to be used as anti-inflammatory drugs.

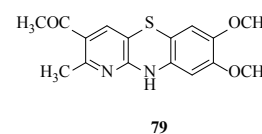
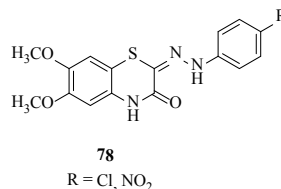


Gowda *et al.* (2011) [63] synthesized 4-[(4-amino-5-sulfany-1*H*-1,2,4-triazol-3-yl)methyl]-2*H*-1,4-benzothiazin-3(4*H*)-one Schiff and Mannich bases derivatives and evaluated for their anti-inflammatory and analgesic activity. The compounds **76** and **77** were found to

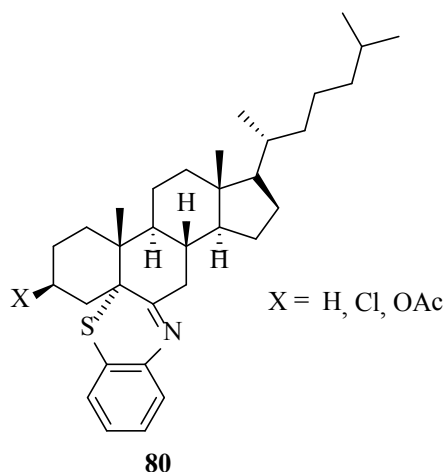
6. Antitumor activity

The benzothiazine core within the phenothiazine system played a significant role in antitumor drug chemotherapy.

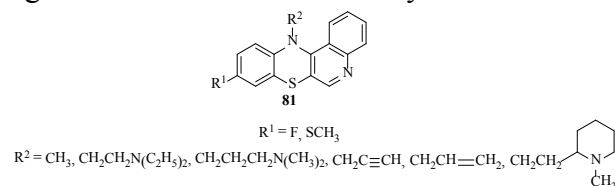
Abbas *et al.* (2010) [64] synthesized 2-(arylhydrazono)-6,7-dimethoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**78**) and 3-acetyl-7,8-dimethoxy-2-methyl-10*H*-pyrido-[3,2-*b*][1,4]benzothiazine (**79**) which were found to be active against HCT-116 cell line more than that of HEPG2 and MCF cell lines.



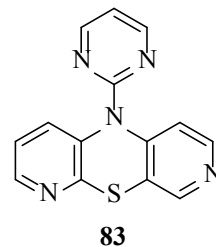
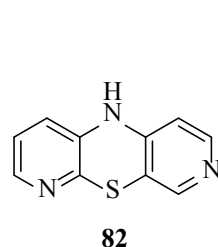
Shamsuzzaman *et al.* (2014) [65] carried out the synthesis of 5*α*-cholestano[5,6-*b*]benzothiazines (**80**) and screened them for *in vitro* anticancer activity against four human cancer cell lines; SW480 (colon adenocarcinoma cells), A549 (lung carcinoma cells), HepG2 (hepatic carcinoma cells) and HeLa (cervical cancer cells) using MTT assay. All the derivatives displayed a noticeable increase in anticancer activity, and in particular, derivative (R = H) showed potential anticancer activity with IC₅₀ = 13.73 μM against HeLa cells, comparable to Doxorubicin (IC₅₀ = 12.52 μM) against the same cells.



Pluta *et al.* (2016) [66] carried out *in vitro* assay of tetracyclic phenothiazines (**81**) using cultured human breast cancer MCF-7 and MDA-MB-231, glioblastoma SNB-19 cell lines using cisplatin as a reference. The MDA-MB-231 cells were found to very sensitive for most compounds and exhibited good activity with $IC_{50} < 10 \mu\text{g/mL}$. The derivative 9-fluoro-12-(1-methyl-2-piperidylethyl)quinobenzothiazine was found most active with $IC_{50} < 7 \mu\text{g/mL}$ against all cell lines under study.

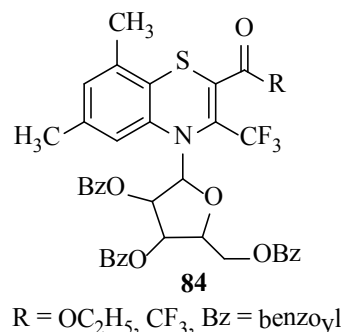


Mlodawska *et al.* (2016) [67] investigated the *in vitro* anticancer activity of 3,6-diazaphenothiazines derivatives using cultured glioblastoma SNB-19, melanoma C-32 and breast cancer MCF-7 cells lines and cisplatin as a reference drug. But, the parent compound 10*H*-3,6-diazaphenothiazine (**82**) was found 10 times more active against all tumor lines with $IC_{50} = 0.46\text{--}0.72 \mu\text{g/mL}$ than the reference drug cisplatin. Similarly, compound 10-(2-(pyrimidinyl)-3,6-diazaphenothiazine (**83**) was found more reactive against breast cancer MCF-7 cell line with $IC_{50} = 0.73 \mu\text{g/mL}$ in relation to cisplatin.

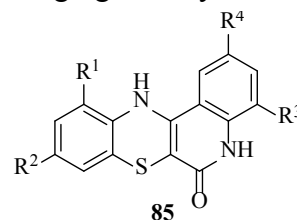


7. Antioxidant activity

Gautam *et al.* (2012) [20] synthesized substituted *N*-(2,3,5-tri-*O*-benzoyl- β -*D*-ribofuranosyl)benzothiazine derivatives (**84**) which showed much better activity in DPPH assay than their phenothiazine bases against *Coagulase negative Staphylococci*.



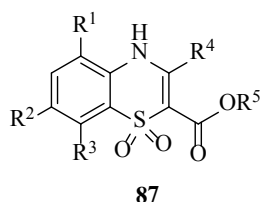
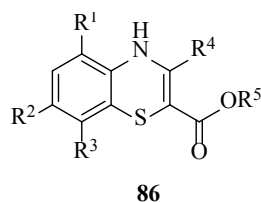
Kumar *et al.* (2013) [68] synthesized a series of quinolinobenzothiazines (**85**) and evaluated for their antioxidant (LPO and GSH) and radical scavenging activities (DPPH and ABTS assays). The compounds given below showed strong radical scavenging activity in DPPH assays.



$R^1 = \text{H}, \text{OCH}_3$; $R^2 = \text{H}, \text{CH}_3$; $R^3 = \text{H}, \text{CH}_3, \text{OCH}_3$; $R^4 = \text{H}, \text{CH}_3$

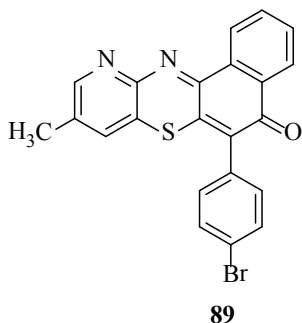
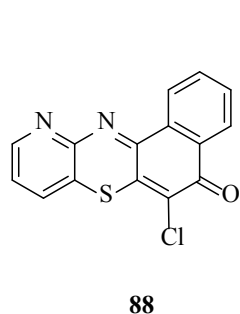
Garg *et al.* (2014) [69] synthesized 4*H*-1,4-benzothiazine compounds (**86** & **87**) and screened for antioxidant activity by 1,1-diphenyl-2-picrylhydrazyl (DPPH•)

radical scavenging assay and 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS•+) radical cation decolorization assay. All these have exhibited moderate to higher activity against the test assay.

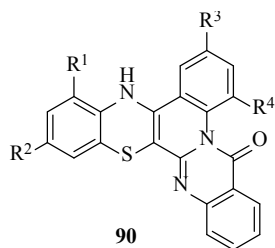


$R^1 = \text{F, Cl}; R^2 = \text{H, Cl, Br}; R^3 = \text{H, OCH}_3, \text{NO}_2;$
 $R^4 = \text{CH}_3, \text{C}_2\text{H}_5; R^5 = \text{C}_2\text{H}_5, \text{OCH}_3, \text{OCH}(\text{CH}_3)_2$

Engwa *et al.* (2016) [70] reported a series of tetracyclic and pentacyclic non-linear phenothiazine derivatives and evaluated them for *in vitro* and *in vivo* antioxidant activity. The compound 6-chloro-11-azabenzothiazine-5-one (88) and 6-(4-bromophenyl)-10-methyl-11-azabenzothiazine-5-one (89) exhibited very high percentage inhibition of hydrogen peroxide (97.17–99.99%) comparable to that of the reference compound ascorbic acid.



Sharma *et al.* (2016) [71] reported a series of quinazolinoquinolinobenzothiazinones (90) and evaluated them for antioxidant and radical scavenging activities. The antioxidant activity was measured by estimating reduced glutathione (GSH) and lipid peroxidant (LPO) in the livers of Swiss albino mice. Some derivatives have displayed significant antioxidant activity as construed by the results of DPPH• and ABTS•+ assays.

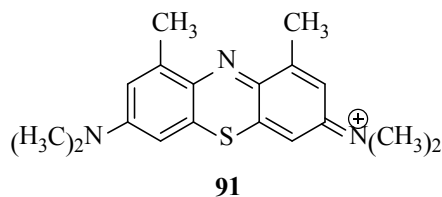


$R^1 = \text{H, OCH}_3; R^2 = \text{H, CH}_3;$
 $R^3 = \text{H, CH}_3; R^4 = \text{H, OCH}_3$

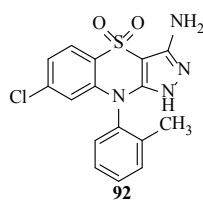
8. Antimalarial activity

Malaria is a tropical infectious disease which possesses serious problem to human health. It is caused primarily by a protozoan *Plasmodium falciparum*.

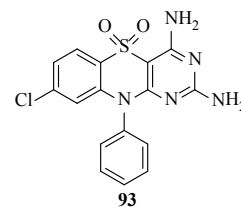
Vennerstrom *et al.* (1995) [72] carried out the synthesis of thiazine dye methylene blue (91) which was reported as a highly selective antimalarial agent.



Barazarte *et al.* (2009) [73] reported a series of phenyl substituted pyrazolo and pyrimido benzothiazine dioxide derivatives and evaluated for their activity to inhibit β -hematin formation, hemoglobin hydrolysis and *in vivo* antimalarial efficacy in rodent *Plasmodium berghei*. 3-Amino-7-chloro-9-(2-methylphenyl)-1,9-dihydropyrazolo-[4,3-*b*]benzothiazine 4,4-dioxide (92) and 2,4-diamino-8-chloro-10H-phenyl-pyrimido-[5,4-*b*]benzothiazine 5,5-dioxide (93) were found to be the most promising as inhibitors of hemoglobin hydrolysis, however, not as efficient as chloroquine.



% Inhibition = 92.32 ± 1.1

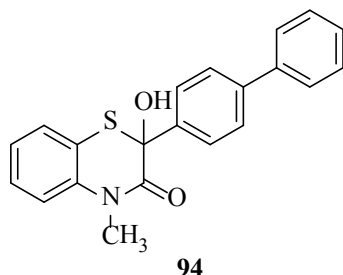


% Inhibition = 83.72 ± 2.13

9. Antihyperlipidemic activity

Hyperlipidemia is high level of cholesterol in the body. Cholesterol is a fat (also called a lipid) that the human body needs to work properly but high cholesterol level can increase a person's chance of getting heart disease stroke and other problems.

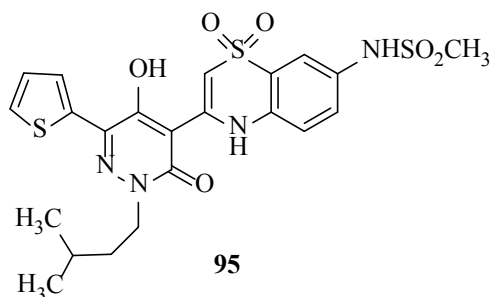
Matralis *et al.* (2011) [74] synthesized 1,4-benzothiazine (**94**) with biphenyl substitution at C-2 position and reported as a highly antihyperlipidemic agent.



10. Anti-hepatitis C virus activity

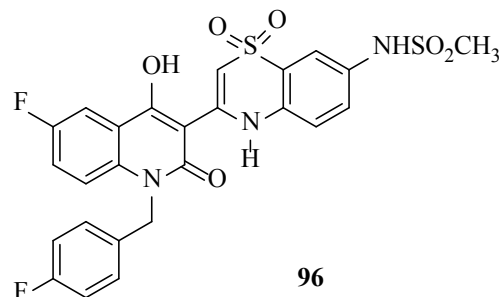
Hepatitis C virus (HCV) is a major source of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer [75,76].

Ellis *et al.* (2008) [77] carried out the synthesis of 4-(1,1-dioxide-1,4-dihydro-1,4-benzothiazine-3-yl)-5-hydroxy-2H-pyridazin-3-one derivative (**95**) which was reported to display potent inhibitory activities in biochemicals and replicon assays ($IC_{50} < 10 \mu M$) as well as good stability towards human liver microsomes.



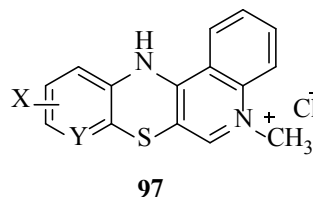
Vicente *et al.* (2009) [78] reported a series of

benzothiazine-substituted quinolinediones and evaluated them as inhibitors of HSCV polymerase NS5B. The compound (**96**) was found to show significant improvement in both enzyme and replicon potency (NS5B $IC_{50} = 0.005 \mu M$; Replicon $EC_{50} = 0.014 \mu M$).



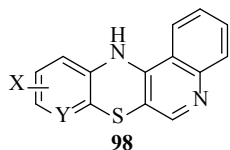
11. Antiproliferative activity

Zieba *et al.* (2010) [79] investigated 5-alkyl-12(*H*)-quino-[3,4-*b*][1,4] benzothiazinium salts (**97**) *in vitro* using cultured HCT116 and LLC cells lines but the derivative (**97**, X = 10-NH₂, Y = CH) demonstrated the highest antiproliferative activity overall towards the cell lines under study ($IC_{50} = 2.3 \pm 0.3$ – $4.7 \pm 0.7 \mu g/mL$) as compared to the reference doxorubicin ($IC_{50} = 3.3 \pm 0.2$ – $3.7 \pm 0.3 \mu g/mL$).

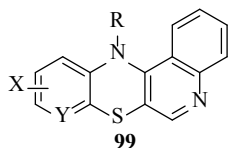


X = H, 9-CH₃, 11-CH₃, 9-F, 9-Cl, 9-Br, 9-OH, 10-OH, 11-OH, 9-NH₂, 10-NH₂, 11-NH₂; Y = CH, N

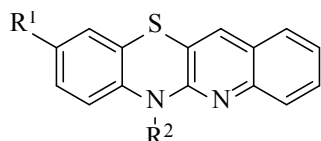
Zieba *et al.* (2013) [80] synthesized 12(*H*)-quino[3,4-*b*][1,4]benzothiazines (**98**) and (**99**) which were evaluated for their *in vitro* antiproliferative activity against two cancer cell lines SNB-19 and C-32 using cisplatin as a reference. Most of the studied azaphenothiazine derivatives demonstrated activity against both the cell lines investigated ($IC_{50} = 5.6$ – $12.4 \mu g/mL$).



X = H, 9-F, 9-CH₃; Y = CH, N; R = (CH₂)₂NC₃H₁₀, (CH₂)₃N(CH₃)₂



Jelen *et al.* (2013) [42] reported a series of tetracyclic quino[3,2-*b*]benzo[1,4]thiazines (**100**) and tested their effects on phytohemagglutinin A (PHA)-induced proliferative response of human peripheral blood mononuclear cells (PBMC) and lipopolysaccharide (LPS)-induced tumor necrosis factor alpha (TNF- α) production by these cells. The compounds (**100a–100c**) exhibited growth inhibition of leukemia L-1210 cells, colon cancer SV-948 cells and epidermal carcinoma A-341 cells comparable to that of cisplatin.

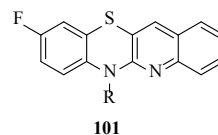


100a, R¹ = Cl; R² = (CH₂)₄NHCOCH₃

100b, R¹ = Cl; R² = (CH₂)₃NHCONH(CH₂)₂Cl

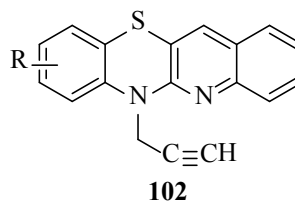
100c, R¹ = CH₃; R² = (CH₂)₄NHCONH(CH₂)₂Cl

Jelen *et al.* (2015) [81] reported a series of 6-Substituted 9-fluoroquino[3,2-*b*]benzo[1,4]thiazines (**101**) which exhibited differential cytotoxic as well as antiproliferative actions against human peripheral blood mononuclear cells (PBMC) stimulated with phytohemagglutinin A (PHA). Additionally, they suppressed lipopolysaccharide (LPS)-induced tumor necrosis factor alpha (TNF α) production by whole blood human cell cultures. Among them compound with propargyl group at position 9 showed strong suppressive actions on growth of L1210, SW948, A-431 and CX-1 tumor cell lines which were close to those of the reference drug cisplatin.



R = CH₃, CH₂CH₂N(C₂H₅)₂, CH₂CH₂CH₂N(CH₃)₂, CH₂CH(CH₃)CH₂N(CH₃)₂, CH₂C $\equiv$ CH, CH₂CH=CH₂, H₂CH₂C-N, H₂CH₂C-N, CH₂CH₂-N

Jelen *et al.* (2016) [82] reported a series of tetracyclic 6-propargylquinobenzothiazine derivatives (**102**) which demonstrated strong antiproliferative actions against human peripheral blood mononuclear cells (PBMC) stimulated with phytohemagglutinin A (PHA), greatly suppressed lipopolysaccharide (LPS)-induced TNF- α production by whole blood human cell cultures, and displayed low cytotoxicity. Amongst them, three propargylquinobenzothiazines with the bromine, trifluoromethyl, and methylthio groups at position 9 exhibited comparable actions to cisplatin against the L-1210 and SW-948 tumor lines.

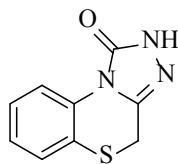


R = H, 8-Cl, 9-Cl, 9-Br, 9-CF₃, 9-OCH₃, 9-SCH₃, 10-Cl

12. Central nervous system (CNS) stimulating activity

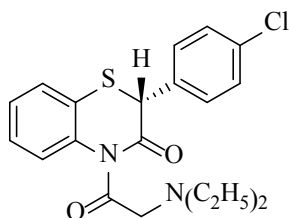
Benzothiazine derivatives have shown activities both as CNS stimulating and muscle relaxant.

Junnarkar *et al.* (1992) [83] studied the neuropsychopharmacological profile of 2,4-dihydro[1,2,4]triazolo[3,4-*c*][1,4]benzothiazin-1-one (IDPH-791) and compared its activity with muscle relaxant, Mephesisin. All the conducted tests revealed that this compound was safer and had long duration of action than Mephesisin.



IDPH-791

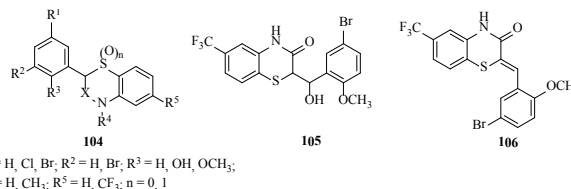
Kobayashi *et al.* (1997) (84) reported T-477 ((*R*)-(+)-2-(4-chlorophenyl)-2,3-dihydro-4-diethylaminoacetyl-4*H*-1,4-benzothiazine) (**103**) an analogue of diltiazem as a neuroprotective agent which exerts neuroprotection of brain neurons from ischemic neuronal damage through its inhibitory action on brain Ca^{2+} channels.



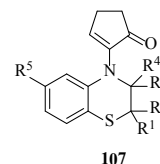
103

13. Potassium channel opener activity

Calderone *et al.* (2008) [85] carried out the synthesis of a series of 1,4-benzothiazine derivatives (**104–106**) targeted for the large-conductance calcium activated potassium channels (BK) which were targeted for the large-conductance potassium channels. The *in vitro* functional characterization of BK channel opening activity was also duly assessed by measuring the relaxation of isolated rat aortic rings precontracted with KCl 20 mM. The compound **104** bearing $\text{R}^1 = \text{Br}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{OCH}_3$; $\text{R}^4 = \text{H}$; $\text{R}^5 = \text{CF}_3$; $\text{X} = \text{CO}$; $n = 0$) displayed the highest potency (Maximal vasorelaxing effect (E_{max}) = $77 \pm 5\%$; Vasorelaxant potency ($\text{pIC}_{50} = 7.40 \pm 0.12$)) superior to that of reference BK-activator NS-1619.



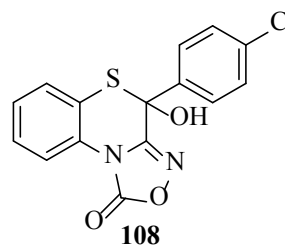
Martelli *et al.* (2013) [86] synthesized a series of 4-(1-oxo-2-cyclopentenyl)-1,4-benzothiazine derivatives (**107**) and evaluated for their vasorelaxing effects on rat aortic rings and membrane hyperpolarization in human vascular smooth muscle cells with potency superior to the reference levromakalim (LCRK). The derivative with $\text{R}^1 = \text{R}^2 = \text{CH}_3$; $\text{R}^3 = \text{R}^4 = \text{H}$; $\text{R}^5 = \text{COCH}_3$ exhibited the high level of potency.



$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{H, CH}_3$; $\text{R}^5 = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{NH}_2, \text{COCH}_3, \text{NHCOCH}_3, \text{SO}_2\text{N}(i\text{-Bu})_2$

14. Cardiovascular activity

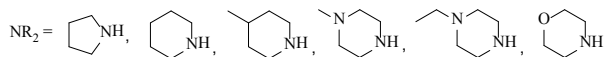
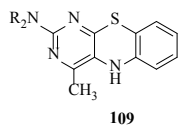
Budriesi *et al.* (2002) [87] investigated the cardiovascular characterization of 4-hydroxy-4-phenylbenzo[*b*][1,2,4]oxadiazolo[4,3-*d*][1,4]thiazin-1(4*H*)-one (**108**) which is found more active as a negative inotropic agent and more selective with regard to the chronotropic and vascular activity than the reference drug diltiazem.



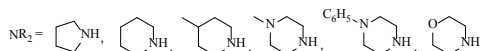
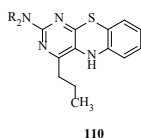
15. 15-Lipoxygenase inhibitors

Bakavoli *et al.* (2008) [88] synthesized a series of 2-substituted pyrimido[4,5-*b*][1,4]benzothiazines (**109**) and evaluated their enzyme inhibitory activity on 15-lipoxygenase

(15-LOX). The derivative having a 4-methylpiperazin-1-yl substituent with $IC_{50} = 18 \mu M$ was the most potent inhibitor of soybean 15-LOX.

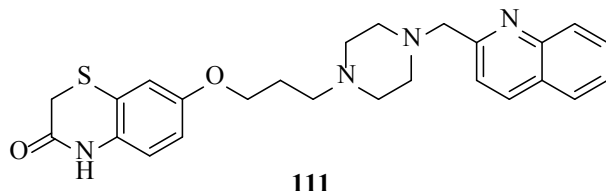


Nikpour *et al.* (2013) [89] synthesized 2-substituted 4-*n*-propyl pyrimido[4,5-*b*][1,4] benzothiazines (**110**) and evaluated them as soybean 15-LOX inhibitors. Among them, 2-(4-methyl piperazinyl) analog displayed the best soybean 15-LOX inhibition activity with $IC_{50} = 8.9 \pm 0.4 \mu M$.



16. Anti-allergic activity

Timmerman *et al.* (1999) [90] synthesized a 1,4-benzothiazine derivative, 7-{3-[4-(2-quinolinylmethyl)-1-piperazinyl]propoxy}-2,3-dihydro-4*H*-1,4-benzothiazin-3-one(VUF-K-8788)(**111**) and its pharmacological properties were investigated *in vitro* and *in vivo* in guinea pigs and rats by **Toshiaki *et al.* (2001)** [91]. It was found to be a potent and selective histamine H_1 -receptor antagonist without anticholinergic or anti-serotonin activity.



CONCLUSION

The present review highlights that a continuous explorative study of 1,4-benzothiazine cannot

be overemphasized. Much research has been carried out with a view to improve benzothiazine based drugs and to avoid the adverse effects. An overview of the synthesis and biological activities of 1,4-benzothiazine derivatives has been accredited herein. There are various methods accessible in designing of expeditious 1,4-benzothiazine pharmacophores which may serve as great opening to new drug discovery and development in the chemotherapy world.

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