



# Chemistry and pharmacological diversity of benzothiazepine—Excellent pathway to drug discovery

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## ABSTRACT

In this era of sporadic advancement in science and technology, a substantial amount of intervention is being set in motion to reduce health-related diseases. Discoveries from researchers have pinpointed the usefulness of heterocyclic compounds, amongst which benzothiazepine (BTZ) derivatives have been synthesized for their various pharmacological activities. This also contributes to their undeniable application in therapeutic medicine for the development of efficacious drugs. BTZs are compounds with a benzene ring fused with a thiazepine ring. This work contains several methods that have been used to synthesize 1,3-, 1,4-, 1,5-, and 4-1-benzothiazepine derivatives. In addition, up-to-date information about the crucial pharmacological activities of BTZ derivatives has been reviewed in this present study to appreciate their druggable potential in therapeutic medicine for drug development. Drug design and development have further been simplified with the implementation of computer aided approaches to predict biological interactions which can help in the design of several derivatives. Hence, the structural activity relationship (SAR), ADMET and the molecular docking studies of BTZ derivatives were discussed to further establish their interactions and safety in biological systems. This present work aims to expound on the reported chemistry and pharmacological propensity of BTZ moiety in relation to other relevant moieties to validate their potential as excellent pharmacophores in drug design and development.

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## 1. Introduction

Several organic compounds have been synthesized with the sole aim of developing a novel alternative that can help to treat various diseases [1–3]. The search for new alternatives is not just important but is a necessity as the problem of drug resistance becomes more prominent. Due to abuse, incomplete dosage, and application of antibiotics on agricultural produce over a long duration, some microbes become resistant after much exposure as a result of gene mutation [4,5]. Over the years, some of the research carried out has shown the rise of different drug-resistant species like *P. falciparum* in malaria, *Candida auris* in fungal infection, *Staphylococcus aureus*, *Klebsiella pneumonia* in bacterial infections, *Mycobacterium*

*tuberculosis* strains in tuberculosis, and strain of *N. gonorrhoeae* in gonorrhoea [6–9]. The level of resistance from these microbes has further increased the mortality rate of infants and adults. Malaria, Tuberculosis, and diarrhea are part of the causes of death worldwide this past year. It was estimated in 2018 that about 1.5 million people died as a result of tuberculosis and in 2020 about 627,000 people died due malaria worldwide,[10–12] while in 2016 about 1.6 million deaths were recorded for diarrheal disease globally [13,14].

It has been established that heterocyclics possess properties that make them relevant in drug design and synthesis [2,15–17]. More so, the presence of different heteroatoms within the heterocycle confers unique properties on them. The common heteroatoms include sulphur, nitrogen, oxygen, and phosphorus (S, N, O, P respectively) but are not limited to this [18–20]. Amongst the numerous heterocyclic scaffolds, those containing nitrogen, and sulphur molecules have gained attention as they are applied for their medicinal properties. They continue to remain relevant not only in medicinal chemistry but in pharmaceuticals, agriculture,

Abbreviations: ADMET, Absorption, Distribution, Metabolism, Excretion, and Toxicity.

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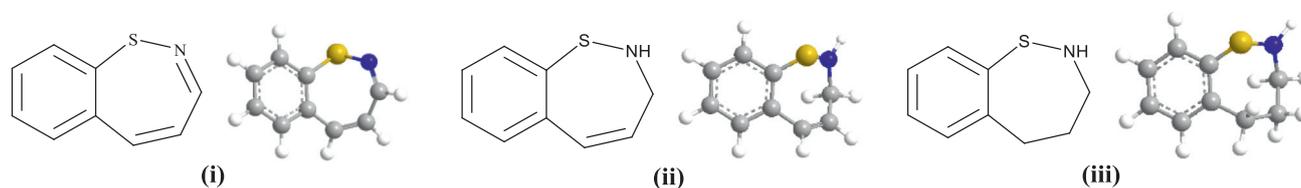


Fig. 1. Different forms of the benzothiazepine ring.

Table 1  
Heterogeneous catalyzed reaction for 1,4-benzothiazepine derivative.

**1**

+

**2**

+

**3**

EtOH  
r.t. 1 h  
NBC (0.025g)

**4a-e**

Entry	Catalyst	Catalyst amount (g)	Time (h)	Yield of 8 (%)	Yield of 13 (%)
1	Baker's yeast	0.5	24	20	25
2	Fe <sub>3</sub> O <sub>4</sub>	0.025	24	30	45
3	Free lipase (ANL)	0.1	5	65	75
4	Fe <sub>3</sub> O <sub>4</sub> NPs@lipase	0.01	1	60	60
5	Fe <sub>3</sub> O <sub>4</sub> NPs@lipase	0.015	1	72	75
6	Fe <sub>3</sub> O <sub>4</sub> NPs@lipase	0.025	1	95	95
7	Fe <sub>3</sub> O <sub>4</sub> NPs@lipase	0.030	1	95	95
8	Fe <sub>3</sub> O <sub>4</sub> NPs@lipase	0.04	1	95	95

and industry [2,3,19]. Some of these heterocyclic compounds are applied in medicine and relevant fields such as antibiotics, alkaloids, vitamins, amino acids, hemoglobin, and pigments. Benzothiazepine is a thiazepine derivative that contains a benzene ring and a seven-membered heterocyclic scaffold that is fused [21–24]. Benzothiazepines are classified under calcium channel blockers as they are used as cardiovascular agents which are useful in the treatment of hypertension. Various classes of benzothiazepine exist namely: 1,2-, 1,3-, 1,4-, 1,5-, and 4,1-benzothiazepines based on the positions of their heteroatoms (sulphur and nitrogen) on the thiazepine ring [25–27]. More so, benzothiazepines (i) can also exist as a dihydrobenzothiazepine (ii) or tetrahydrobenzothiazepine (iii) when the thiazepine ring is deficient in one or two double bonds (Fig. 1) [26].

Over time, the radar has moved from the synthesis of benzothiazepine moiety to the synthesis of substituted benzothiazepine. This substituted benzothiazepine are mainly achieved by incorporating functional groups or moieties with known activity to further increase the overall effectiveness when applied. They are usually solids observed as white, yellow, or green in color when synthesized. The therapeutic functions of benzothiazepine and its derivatives have made them a potential anticancer, antidiabetic, anti-inflammatory, antiviral agent, antimarial agent, CNS depressant, antiplatelet aggregator, anti-cholinesterases inhibitor, anticonvulsant agent, Ca<sup>2+</sup> channel antagonist, and vasodilator [25,26,28]. They are also applicable as corrosion inhibitors,[29] and antiviral agents in agriculture [17]. Some of the common examples include diltiazem, tianeptine, thiazesim, quetiapine, and clothiapine. This review aims to expound on the reported chemistry and pharmacological propensity of benzothiazepine derivatives to validate their potential as excellent pharmacophores in drug design and development.

## 2. Chemistry

### 2.1. Synthesis of benzothiazepine derivatives

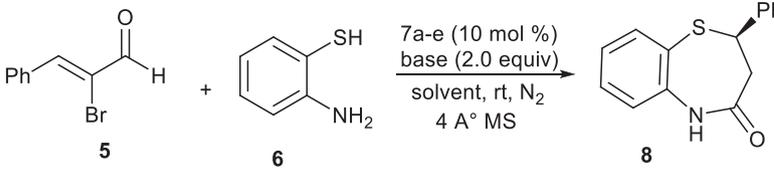
Several methods have been employed in the synthesis of benzothiazepine derivatives which are evolving from conventional methods to greener methods that uses mild reaction conditions and green solvents or exclude solvents. One or more spectroscopic method (<sup>1</sup>H and <sup>13</sup>C-NMR, FT-IR, Ultraviolet-Visible (UV-vis), X-ray crystallography and Mass Spectroscopy) were used in ascertaining the purity and formation of the synthesized compounds [30,31].

#### 2.2.1. Heterogeneous catalysis

(a) In the synthesis of 1,4-benzothiazepine derivatives (4), coumarin derivatives (1), 2-aminothiophenol (2), and alkyl isocyanides (3) were reacted together using a nano-biocatalyst (NBC) made from a lipase extracted from *Aspergillus niger* bonded on Fe<sub>3</sub>O<sub>4</sub> nanoparticle (Table 1). The appropriate catalyst was selected by employing different catalyst and varying the amount used. The overall product yield for the reaction was 95% (Table 1). The biocatalyst was preferred because it affords a large surface area for the reaction to be carried out upon and its easily recoverable using magnet [32].

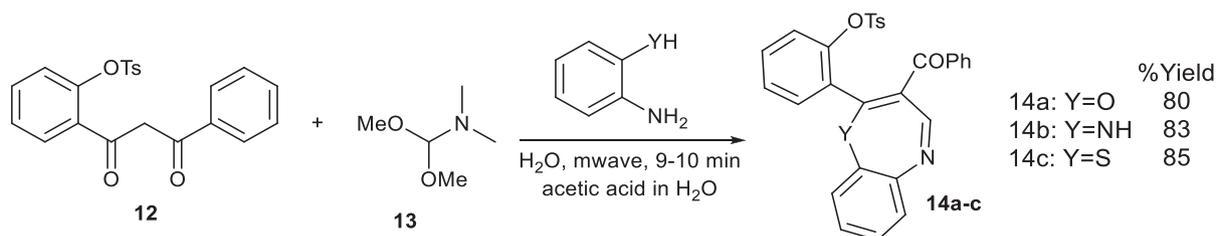
(b) Fang and co-workers reported the reaction between  $\alpha$ -bromoal (5) and 2-aminobenzenethiol (6) in the presence of an organocatalyst (7e) which gave an enantioselective N-H- free 1,5-benzothiazepine derivative (8) (Table 2). This synthesis proceeded through a one-step reaction unlike the common methods with two steps. The catalyst and solvents were varied to afford the optimal conditions for the reaction with a 63% yield and 94% enantiomeric excess (ee) (Table 2). The product (8) had a R configuration which was influenced by the stereochemistry of compound (5) and the

**Table 2**  
Asymmetric synthesis of 1,5-benzothiazepines derivative.



Entry	Catalyst	Solvent	Base	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	7a	PhMe	NaOAc	40	78
2	7b	PhMe	NaOAc	22	90
3	7c	PhMe	NaOAc	18	79
4	7d	PhMe	NaOAc NaOAc	trace	-
5	7e	PhMe	NaOAc NaOAc	43	94
6	7e	Mesitylene	NaOAc	30	92
7	7e	DCM		trace	-
8	7e	THF		trace	-
9	7e	PhMe	DIPEA	trace	-
10	7e	PhMe	TBuOK	trace	-
11	7e	PhMe	CsOAc	37	93
12	7e	PhMe	LiOAc	31	93
13c	7e	PhMe	NaOAc	63	94

<sup>a</sup>Isolated yields based on 5. <sup>b</sup>Ee values were determined by HPLC analysis. c20 mol % 7e was used. Mes = 2,4,6-(CH<sub>3</sub>)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>; ee = enantiomeric excess; DIPEA = N,N-diisopropylethylamine.



**Scheme 1.** Microwave synthesis of 1,4 benzothiazepine derivative.

product was further explored for the synthesis of (R)-thiazesim which is an antidepressant [33].

(c) In other studies, Meninno and co-workers synthesized 1,5-benzothiazepine derivatives (11) from  $\alpha,\beta$ -unsaturated N-acyl pyrazoles (9), and 2-aminothiophenol (10) using a minute quantity of takemoto's catalyst (VII) (Table 3). The reaction was regioselective, this was made possible by the effectiveness of compound (9). After optimization, 97% yield with 80% ee was reported and the product in this reaction can also be employed as a precursor for synthesizing (R)-thiazesim [34].

### 2.2.2. Microwave-aided approach

(a) Kendre and co-workers described the synthesis of 1,4-benzothiazepine analog (14) in the presence of acetic acid in water by microwave irradiation using 2-aminothiophenol and 1,3-diketone (12) with N,N-dimethylformamide dimethylacetal (13)

(Scheme 1). The product yield was 85%, and it showed better activity against *Bacillus subtilis*, *Pseudomonas aeruginosa*, than when the thiazepine ring was replaced with an oxazepine/diazepine ring [35].

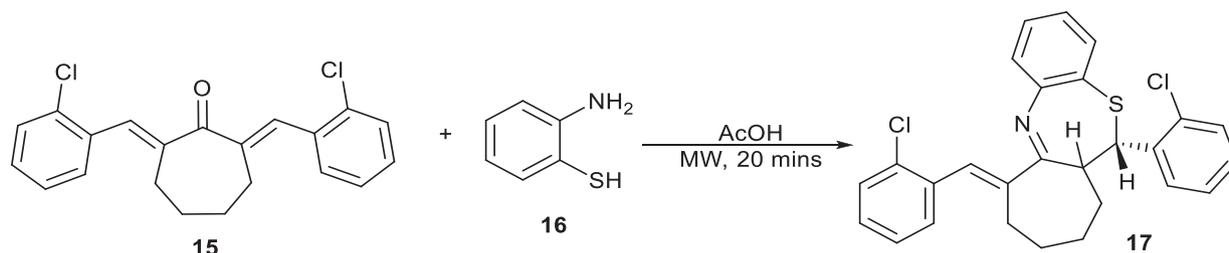
(b) In another microwave synthesized reaction between cycloheptanone derivative (15) and o-aminothiophenol (16) using AcOH as a catalyst for 20 min, a 1,4-benzothiazepine analog (17) was derived (Scheme 2). The reaction was carried out under thermal heat and microwave heat. It was observed that the microwave method was more promising with a shorter reaction time of 20 min and a higher yield of 89% as compared to the thermal method with 5 h reaction time and 73% yield [36].

(c) Therapeutically active compounds from 1,5-benzothiazepine scaffold (19) and (20) were synthesized from 6-oxocholest-4-ene (18) and 2-aminobenzenethiol under microwave irradiation (Scheme 3). Density functional theory was employed to determine

**Table 3**  
Asymmetric synthesis of 1,5-benzothiazepine scaffold.

Entry	Catalyst	T [°C] /Additive	t1(t2) [h]	Yield [%] <sup>a</sup>	ee [%] <sup>b</sup>
1	I	rt	92	85	52
2	I	40°C	14(11)	81	66
3	I	rt/silica gel	1.5(4)	82	76
4	-	rt	72	30	-
5	-	rt/silica gel	5	85	-
6	II	rt/silica gel	1.5(4) 1.5(4)	85	-61
7	III	rt/silica gel	2(4)	81	-61
8	IV	rt/silica gel		80	-81
9	V	rt/silica gel	2.5(4)	75	-76
10	VI	rt/silica gel	14(4)	95	-64
11	VII	rt/silica gel	0.5(4)	97	-80
12	VIII	rt/silica gel	4.5(4)	71	66

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>3</sub> as an internal standard. <sup>b</sup>Determined by HPLC on a chiral stationary phase. Negative sign indicates the enantiomeric excess (ee) for the opposite enantiomer.

**Scheme 2.** Microwave synthesis of 1,4-benzothiazepine derivative.

the theoretical spectroscopic results for the products and when compared to the experimental results it was similar making it easy to design compounds similar to the precursor [37].

### 2.2.3. Ultrasound-aided synthesis

Amongst the green methods of synthesis, the use of ultrasound is gaining recognition as it offers a short reaction time with a better product yield and purity when compared to conventional methods.

(a) A 1,5-benzothiazepine derivatives (23a-i) were synthesized by Pawar et al., (2018) using a combination of 2-aminothiophenol (22) and substituted chalcones (21) with ferrous sulphate as a catalyst at 40 °C (Scheme 4). The various substituted benzothiazepine derived had varied yields and reaction times with p-methyl benzaldehyde (d) giving an excellent yield [38].

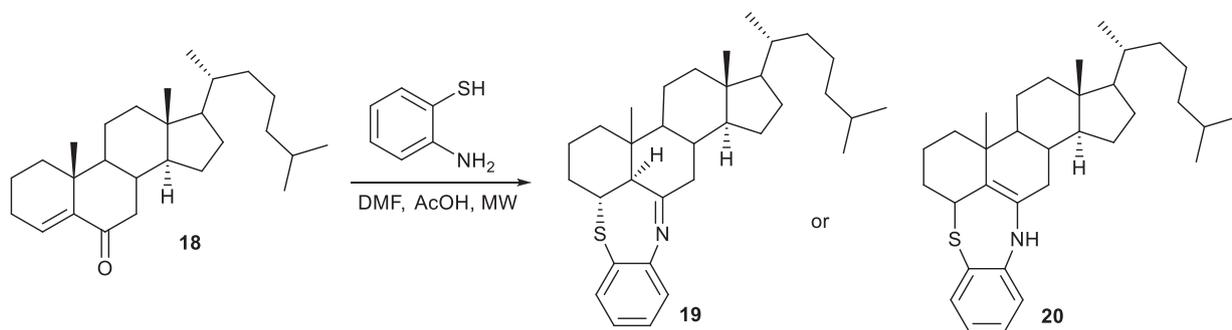
(b) Also, Ghodke and co-workers prepared twelve novel 1,5-benzothiazepine derivatives (26j-u) by dissolving chalcones (24) and 2-aminobenzenethiol (25) into dimethyl formamide (DMF) at room temperature under ultrasonic irradiation (Scheme 5). The

chalcones were made from aldehydes and different ketones while zirconium oxychloride was employed as the catalyst and the yield ranged from 60% to 90% for various derivatives [31].

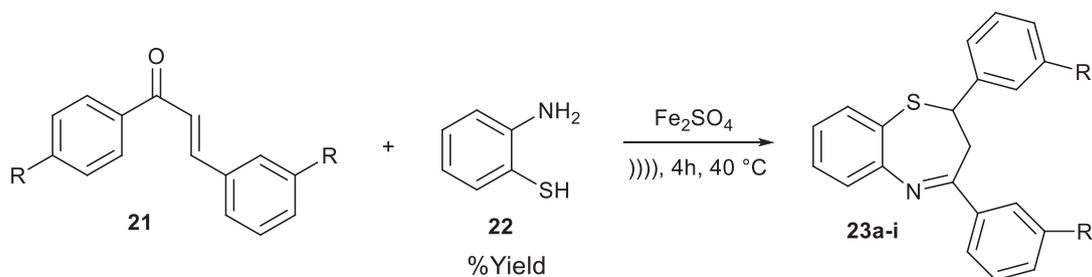
(c) Similarly, the synthesis of 1,5-benzothiazepine derivatives (29v-b') were carried out by condensing a series of chalcones (27) on 2-aminobenzenethiol (28) using different solvents under ultrasound irradiation and PEG-400 performed better with excellent yield (Scheme 6). The reaction proceeded at room temperature with a yield ranging from 86% to 93% for the various derivatives [39].

### 2.2.4. Solvent-free system

(a) Farghaly and co-workers synthesized new 1,5-benzothiazepine derivatives (32a-f) from 1,3-diaryl-2-propenones (30a-f) and 2-amino-thiophenol (31) under a solvent-free system employing H-ferrierite zeolite as catalyst (Scheme 7). The final stage involved a ring closure with the elimination of water and the product was of high purity as well as good yield [30].

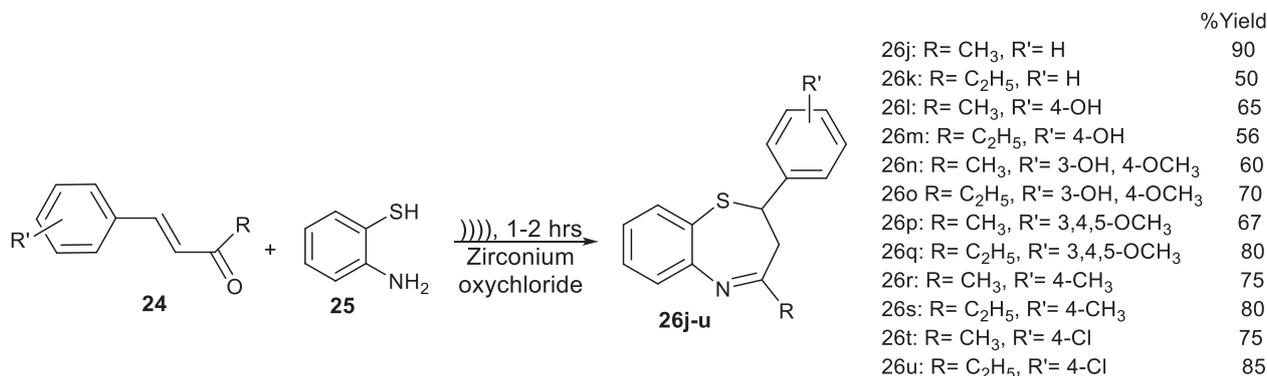


Scheme 3. Microwave synthesis of 1,5-benzothiazepine.



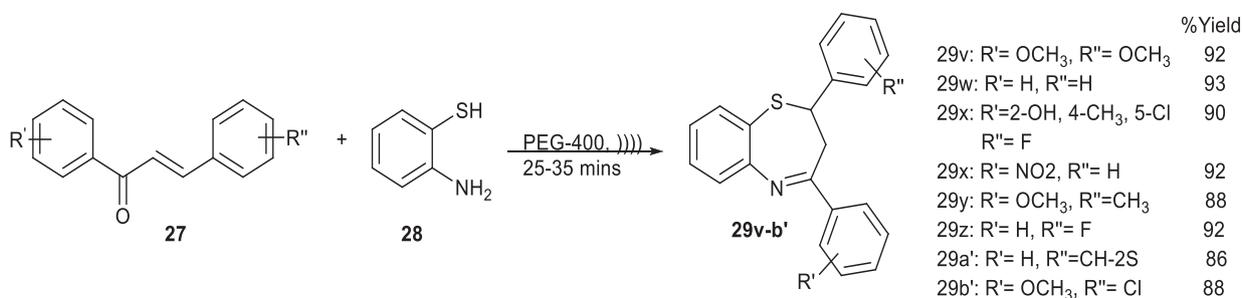
	%Yield
23a: R= <i>p</i> -Chloro Benzaldehyde	90
23b: R= <i>p</i> -Fluoro Benzaldehyde	91
23c: R= <i>p</i> -Methoxy Benzaldehyde	90
23d: R= <i>p</i> -Methyl Benzaldehyde	96
23e: R= <i>p</i> -Bromo Benzaldehyde	80
23f: R= <i>o</i> -Fluoro Benzaldehyde	85
23g: R= <i>p</i> -Nitro Benzaldehyde	94
23h: R= 2-thiophene aldehyde	60
23i: R= 2-furalanaldehyde	65

Scheme 4. Ultrasonic synthesis of 1,5-benzothiazepine.



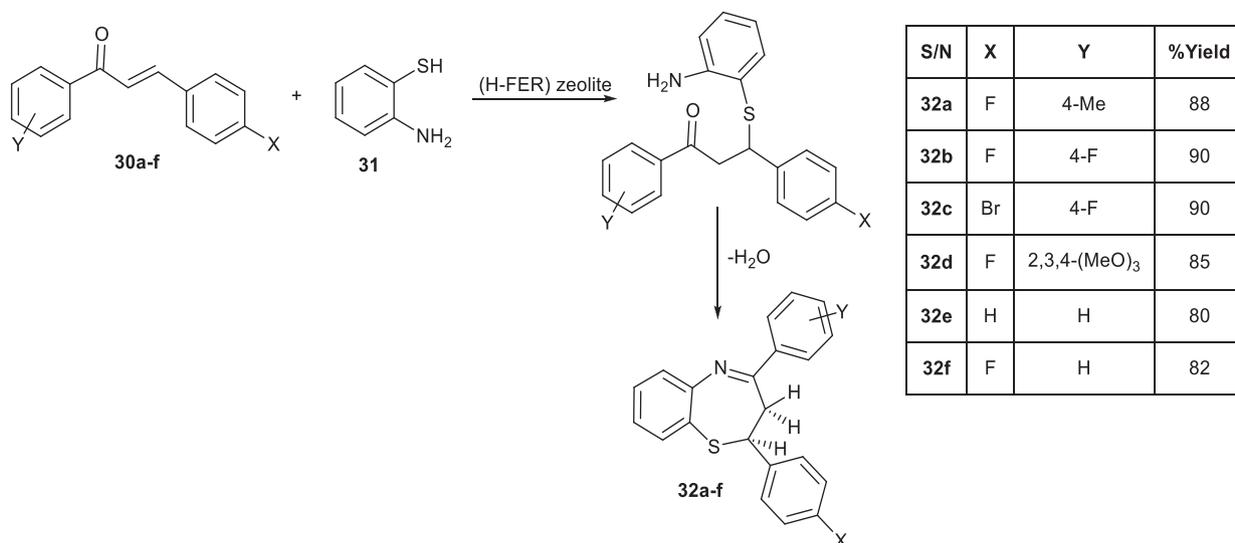
	%Yield
26j: R= CH <sub>3</sub> , R'= H	90
26k: R= C <sub>2</sub> H <sub>5</sub> , R'= H	50
26l: R= CH <sub>3</sub> , R'= 4-OH	65
26m: R= C <sub>2</sub> H <sub>5</sub> , R'= 4-OH	56
26n: R= CH <sub>3</sub> , R'= 3-OH, 4-OCH <sub>3</sub>	60
26o: R= C <sub>2</sub> H <sub>5</sub> , R'= 3-OH, 4-OCH <sub>3</sub>	70
26p: R= CH <sub>3</sub> , R'= 3,4,5-OCH <sub>3</sub>	67
26q: R= C <sub>2</sub> H <sub>5</sub> , R'= 3,4,5-OCH <sub>3</sub>	80
26r: R= CH <sub>3</sub> , R'= 4-CH <sub>3</sub>	75
26s: R= C <sub>2</sub> H <sub>5</sub> , R'= 4-CH <sub>3</sub>	80
26t: R= CH <sub>3</sub> , R'= 4-Cl	75
26u: R= C <sub>2</sub> H <sub>5</sub> , R'= 4-Cl	85

Scheme 5. Ultrasonic synthesis of 2,4-substituted 1,5-benzothiazepine.

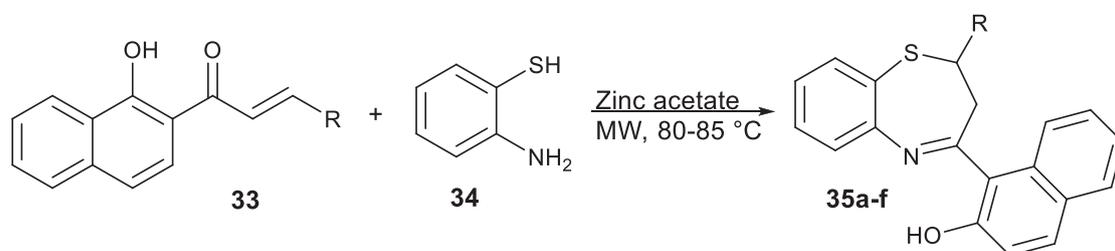


	%Yield
29v: R'= OCH <sub>3</sub> , R''= OCH <sub>3</sub>	92
29w: R'= H, R''=H	93
29x: R'=2-OH, 4-CH <sub>3</sub> , 5-Cl R''= F	90
29x: R'= NO <sub>2</sub> , R''= H	92
29y: R'= OCH <sub>3</sub> , R''=CH <sub>3</sub>	88
29z: R'= H, R''= F	92
29a': R'= H, R''=CH-2S	86
29b': R'= OCH <sub>3</sub> , R''= Cl	88

Scheme 6. Ultrasonic synthesis of 1,5-benzothiazepine.



**Scheme 7.** Solvent-free synthesis of 1,5-benzothiazepine derivatives.



S/N	35a	35b	35c	35d	35e	35f
R						
%Yield	72	88	78	61	70	60

**Scheme 8.** Synthesis of 1,5-benzothiazepine derivatives.

(b) The synthesis of 2, 4-substituted-1,5-benzothiazepine (35) was achieved by reacting 2-aminothiophenol (33) with 1, 3-substituted- prop-2-en-1-one (34) using a catalytic amount of zinc acetate (Scheme 8). The mixture was then placed in the microwave for 2–3 min to afford a yield of 60–88% for the various derivatives [40].

#### 2.2.5. Combinatorial method

(a) An interesting combination of 2-acetylbenzofuranes (38) and different benzaldehydes (39) yielded  $\alpha,\beta$ -unsaturated carbonyl compounds (40). This intermediate further reacted with ATP through thia-Michael addition and cyclo condensation reaction to give 22 substituted 1,5-benzothiazepine derivatives with a benzofuran part (41) (Scheme 9). It was also observed that the benzofuran moiety increased the pharmacological properties of the synthesized compound. The intermediate (38) was a product of a ring closure reaction of chloroacetone (37) and salicylaldehyde (36). Several reaction steps gave different compounds with their various derivatives with yields ranging from 60% to 90% [41].

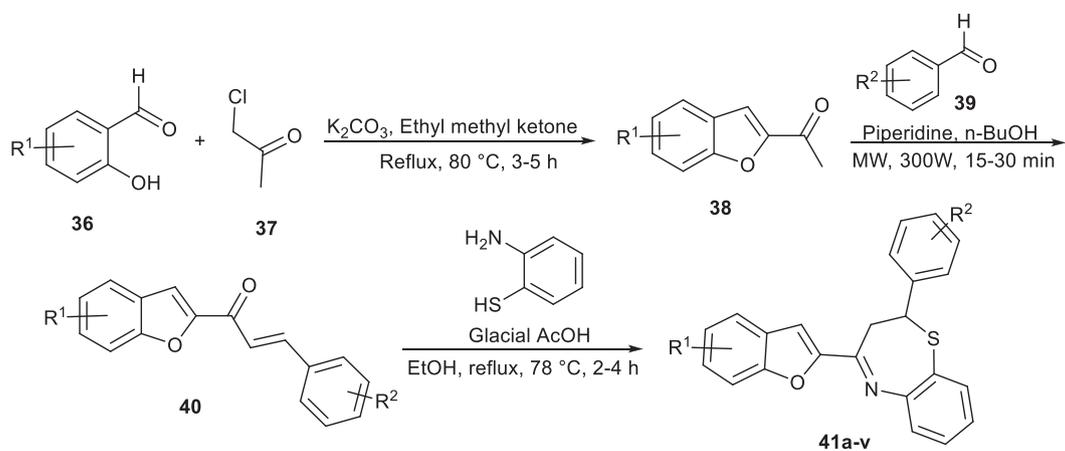
#### 2.2.6. Synthesis via intramolecular cyclization

(a) The formation of 1,3-benzothiazepine derivative (44) was achieved by reacting diphenylphosphoryl thioamide (42) and fluoro-hydroxyl(phenyl)iodosylate (4-F-HTIB) (43) under room temperature at a very short reaction time (Scheme 10). The reaction proceeded through direct intra-molecular dehydrogenative C–S bond formation to give a product yield of 85% [27].

(b) A new compound with a 4,1-benzothiazepine template (48) was synthesized using Boc-protected p-chloroaniline (45) which underwent ortho-lithiation to give an intermediate (46) which was further reacted with (47) in an intermolecular nucleophilic reaction (Scheme 11) [42].

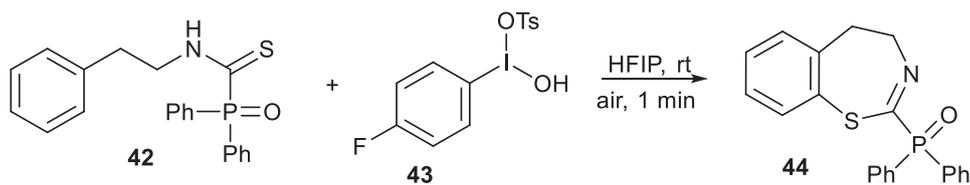
#### 2.2.7. Complex catalyzed reaction

(a) Yin and co-workers carried out asymmetric hydrogenation using Rh/Zhaophos complex as the catalyst to synthesize 1,5-benzothiazepines (50a–o) from a sulphur-coordinated medium-sized ring of unsaturated NH lactams (49) (Scheme 12). When the activity of the sulphur atoms was compared to bisphosphine ligand which is commer-

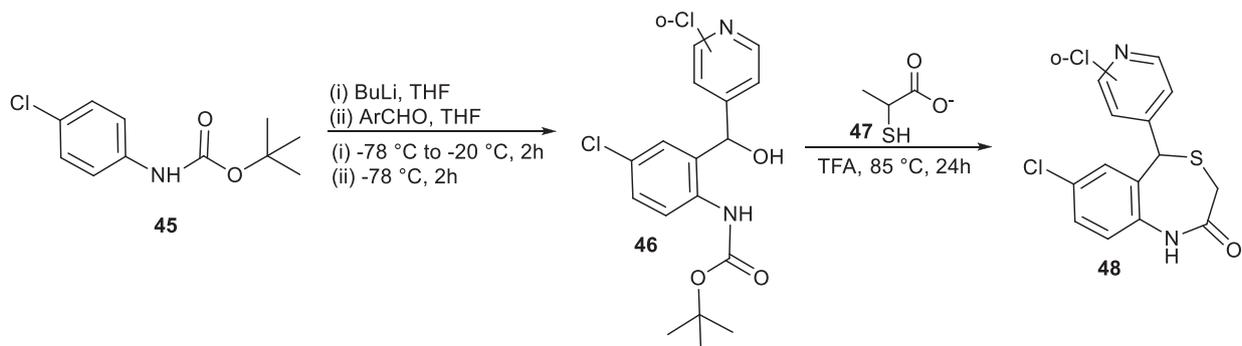


S/N	R <sup>1</sup>	R <sup>2</sup>	%Yield	S/N	R <sup>1</sup>	R <sup>2</sup>	%Yield
41a	H	4-OH	79	41l	5-Br	3-OCH <sub>3</sub>	73
41b	H	2-OCH <sub>3</sub>	72	41m	5-Br	4-OCH <sub>3</sub>	75
41c	H	3-OCH <sub>3</sub>	80	41n	5-Br	4-CH <sub>3</sub>	72
41d	H	4-OCH <sub>3</sub>	90	41o	5-Br	2-F	83
41e	H	1-Naphthyl	86	41p	5-Br	3-NO <sub>2</sub>	72
41f	H	3-Indolyl	80	41q	5-Br	1-Naphthyl	85
41g	7-OCH <sub>3</sub>	H	80	41r	5-Br	3-Indolyl	80
41h	7-OCH <sub>3</sub>	4-OH	89	41s	5-NO <sub>2</sub>	H	90
41i	5-Br	H	80	41t	5-NO <sub>2</sub>	2-F	78
41j	5-Br	4-OH	70	41u	5-NO <sub>2</sub>	1-Naphthyl	73
41k	5-Br	2-OCH <sub>3</sub>	75	41v	5-NO <sub>2</sub>	3-Indolyl	85

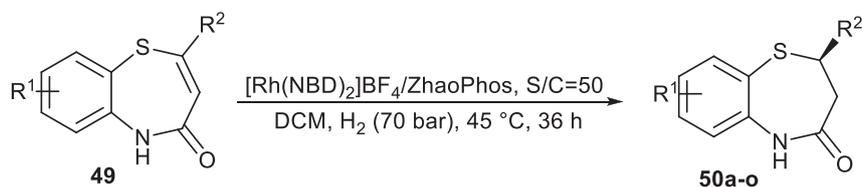
Scheme 9. Combinatorial synthetic route for 1,5-benzothiazepine derivatives.



Scheme 10. Synthesis of 1,3-Benzothiazepines derivative.

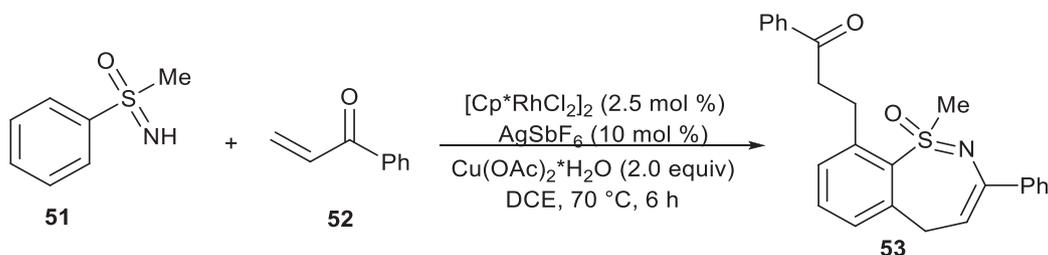


Scheme 11. Synthesis of 4,1-Benzothiazepines derivative.



S/N	R <sup>1</sup>	R <sup>2</sup>	%Yield	S/N	R <sup>1</sup>	R <sup>2</sup>	%Yield
50a	H	2-Ph	95	50i	H	<i>p</i> -F-Ph	82
50b	5-Me	2-Ph	91	50j	H	<i>p</i> -Cl-Ph	89
50c	5-Bn	2-Ph	97	50k	H	<i>p</i> -CF <sub>3</sub> -Ph	81
50d	7-F	2-Ph	96	50l	H	<i>p</i> -CO <sub>2</sub> Me-Ph	92
50e	7-Cl	2-Ph	85	50m	H	<i>p</i> -OMe-Ph	90
50f	7-Me	2-Ph	93	50n	Cl	<i>p</i> -OMe-Ph	92
50g	6-Me	2-Ph	90	50o	H	Me	95
50h	8-OMe	2-Ph	81				

**Scheme 12.** Rh-catalyzed reaction route of 1,5-Benzothiazepine derivatives.



**Scheme 13.** Synthesis of the 1,2-Benzothiazepine 1-Oxides derivative using Rh-catalyst.

cially used it was discovered that the sulfur atoms did not cause inhibition [43].

- (b) Wen and co-workers successfully synthesized 1,2-benzothiazepine 1-oxides (53) from phenyl vinyl ketone (52) and [4 + 3] cyclization of S-methyl-S-phenylsulfoximine (51) employing rhodium as a catalyst to give 89% product yield (Scheme 13) [44].

### 2.2.8. Other synthesis routes

- (a) Li and co-workers reported the synthesis of pyridine incorporated into 1,5-benzothiazepine derivatives (58a-z) through a three-step 1,3-dipolar cycloaddition reaction. The first intermediate (55a-z) was derived by reacting aromatic aldehyde and hydroxyacetophenone (54), then it was further reacted with 2-aminothiophenol to produce the second intermediate (56a-z). The second intermediate was finally reacted with a pyridine moiety (57) to give the final product (Scheme 14) [17].
- (b) In another reaction, Afzal and co-workers synthesized a chloropyrazine conjugated 1,5-benzothiazepine derivatives (62a-t) by first preparing a chalcone intermediate (61) from chloropyrazine-based chalcones (59) and heteroaryl aldehyde (60). The intermediates (61a-t) were then reacted with

2-aminothiophenol under given conditions to give products with good yields (Scheme 15) [16].

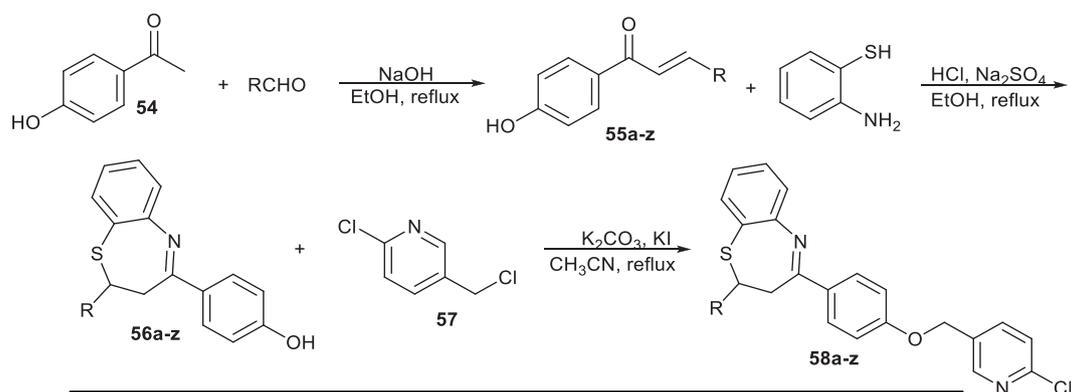
- (c) Lokeshwari and co-workers reported the synthesis of furan attached to 1,4 benzothiazepine ring (66a-h) from chalcone intermediates (65a-h) and 2-aminobenzenethiol in acidic conditions (Scheme 16). The chalcones were produced from 1-(furan-2-yl)ethanone (63), and various aromatic aldehydes (64a-h) [15].

## 3. Pharmacology properties of benzothiazepine Scaffolds

### 3.1. Biological activities

#### 3.1.1. Antitumor activity

A synthesized 1,4-benzothiazepine derivative (67) was screened and results showed a level of inhibition on the cancer cell lines at IC<sub>50</sub> = 1.48 μM for HeLa, 1.94 μM for A549, 1.52 μM for HT29, and 1.47 μM for MCF-7 when compared to Colchicine (Fig. 2). It was also preferred due to its low cytotoxicity [22]. The anti-tumor activity of dioxoles conjugated 1,4-benzothiazepines was described and results showed that compound (68) exhibited strong activity with IC<sub>50</sub> = 8.23 mM and 16.22 mM against the two human cancer cells Ec9706 and Eca109 respectively, better than 5-Fluorouracil with IC<sub>50</sub> of 23.26 [45].



S/N	R	%Yield	S/N	R	%Yield	S/N	R	%Yield
58a	Ph	58	58j	3,4-di-OCH <sub>3</sub> -Ph	55	58s	4-Cl-Ph	57
58b	4-CH <sub>3</sub> -Ph	52	58k	2-Cl-Ph	56	58t	3-F-Ph	52
58c	thiophen-2-yl	58	58l	2-Br-Ph	50	58u	2,4-di-Cl-Ph	51
58d	4-OCH <sub>3</sub> -Ph	56	58m	3-Br-Ph	52	58v	3,4-di-Cl-Ph	55
58e	4-NO <sub>2</sub> -Ph	51	58n	2-OCH <sub>3</sub> -Ph	56	58w	2,6-di-Cl-Ph	54
58f	4-OCF <sub>3</sub> -Ph	59	58o	2-F-Ph	56	58x	2-Cl-6-F-Ph	49
58g	4-Br-Ph	54	58p	3-OCH <sub>3</sub> -Ph	54	58y	3-NO <sub>2</sub> -Ph	53
58h	furan-2-yl	61	58q	4-CF <sub>3</sub> -Ph	57	58z	naphthalen-1-yl	51
58i	4-F-Ph	54	58r	2-CF <sub>3</sub> -Ph	53			

**Scheme 14.** A 1,3 dipolar cycloaddition synthetic route for 1,5-benzothiazepine derivatives.

### 3.1.2. Anti-malarial activity

In search of a better alternative for the treatment of malaria which has increased the mortality rate in children and adults, the results from discoveries have been reported. A carbazole-based 1,4-benzothiazepine (69) had inhibitory activity on the Plasmodium falciparum strain with an IC<sub>50</sub> of 0.75 µg/mL (Fig. 3) [46].

### 3.1.3. Antibacterial activity

The efficacy of benzothiazepine in inhibiting bacterial strain is no longer farfetched. Several studies have reported the potency of benzothiazepine in inhibiting the growth of microbes.

Studies showed that triazolo[1,5]benzothiazepine derivative (70) exhibited notable inhibitory properties against Enterobacter cloacae, Escherichia coli, and Staphylococcus aureus [47]. The antimicrobial activity of 1,4-benzothiazepine containing 1,3,4-oxadiazoles moiety (71) was found to inhibit the growth of Pseudomonas aeruginosa at MIC = 62.5 µg/mL (Fig. 4) [48].

### 3.1.4. Antifungal activity

The antifungal property of 1,4-benzothiazepine derivatives (72) bearing an aryl sulfonate moiety was tested against Aspergillus flavus, Aspergillus niger, and Fusarium oxysporium amongst other synthesized compounds and was found to have the highest zone of inhibition of 18, 22, 18 mm respectively [35]. Several synthesized 2,3/2,5-dihydro-1,5-benzothiazepines (73) were tested against Candida albicans, and from observations, the 2,5-dihydro-1,5-benzothiazepines derivatives were twice better in activity than the reference drug used [49]. Also, it was reported that a 1,5-benzothiazepine (74) containing benzofuran moiety possessed a

strong activity against Aspergillus brasiliensis and A. niger with an inhibition zone of 20 and 23 mm respectively as compared to the standard drug (Fig. 5) [41].

### 3.1.5. Anti-cancer activity

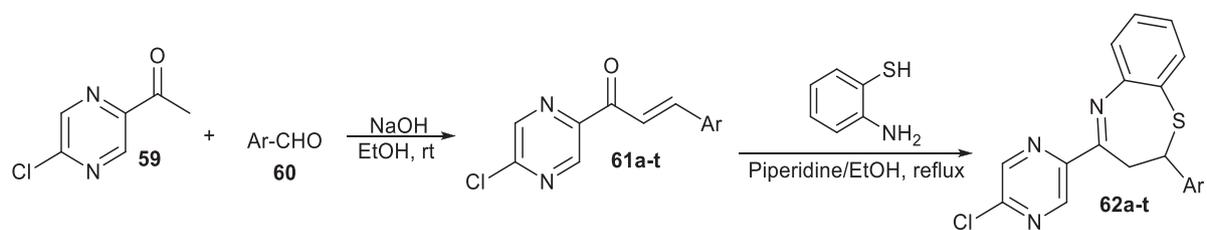
In recent times, research efforts have been made to discover novel drugs for cancer treatment. Amongst these findings includes piperazine conjugated 1,4 benzothiazepine derivatives (75) reported to inhibit the growth of colon carcinoma cells, leukemia cells, and breast cancer cells at IC<sub>50</sub> of 10, 12, 39 µM. A proposed mechanism will be through the inhibition of sirtuin protein [50]. Similarly, a 1,5-Benzothiazepine derivative (76) was effective against MCF-7, DU-145 and HT-29 cell lines with IC<sub>50</sub> of 27 µg/mL, 16 µg/mL and 28 µg/mL (Fig. 6) [51].

### 3.1.6. Anti-protozoal activity

Studies have shown that 1,5-benzothiazepine derivatives make impressive scaffolds for diverse compounds. The amoebicidal activity of a synthesized ferrocenylthiazepine derivative (77) was investigated using trophozoites of the strain HM1: IMSS. The compound was found to have an IC<sub>50</sub> = 7.5 µM while that of metronidazole which is mostly recommended for humans had IC<sub>50</sub> = 6.8 µM [50]. A 1,4-benzothiazepine derivative (78) was tested against Giardia lamblia which causes diarrheal disease in humans and it was inhibited with an IC<sub>50</sub> = 2.74 µg/mL (Fig. 7) [48].

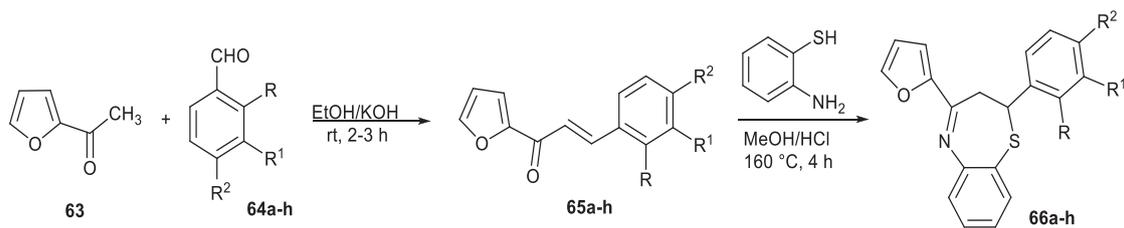
### 3.1.7. Anti-diabetic activity

Efforts to reduce elevated blood glucose levels as further propelled researchers in this field to source effective alternatives. From



S/N	Ar	%Yield	S/N	Ar	%Yield
62a	Ph	90	62k	4-di-Me-NO <sub>2</sub> -Ph	91
62b	4-Cl-Ph	95	62l	3,4-OMe-Ph	81
62c	4-F-Ph	92	62m	3,4,5-tri-OMe-Ph	75
62d	4-NO <sub>2</sub> -Ph	83	62n	2-pyridinyl	65
62e	2,4-di-F-Ph	79	62o	3-pyridinyl	58
62f	2,4-di-Cl-Ph	88	62p	4-pyridinyl	66
62g	4-OH-Ph	63	62q	2-thienyl	69
62h	4-Me-Ph	79	62r	2-furfuryl	80
62i	4-OMe-Ph	66	62s	2-pyrrolyl	75
62j	3-OMe-4-OH-Ph	73	62t	5-pyrazolyl	82

**Scheme 15.** Synthetic route for chloropyrazine conjugated 1,5-benzothiazepine derivatives.



S/N	R	R <sup>1</sup>	R <sup>2</sup>	%Yield	S/N	R	R <sup>1</sup>	R <sup>2</sup>	%Yield
66a	H	H	H	75	66e	H	H	OCH <sub>3</sub>	49
66b	H	H	Cl	68	66f	H	H	NO <sub>2</sub>	63
66c	H	H	F	76	66g	H	OCH <sub>3</sub>	OH	74
66d	H	H	Br	80	66h	H	OCH <sub>2</sub> O	OCH <sub>2</sub> O	66

**Scheme 16.** Synthetic route for furan attached to 1,4-benzothiazepine ring.

recent research, 1,4-benzothiazepine derivative (79) displayed impressive activity comparable to metformin and CGP37157 and the activity was traced to the electronegative substitution of benzothiazepine nucleus at the 7' position and that phenyl ring at the 2' position (Fig. 8) [28].

### 3.1.8. Antioxidant activity

Antioxidants help to inhibit oxidation or scavenge free radicals like oxygen, halogens, hydrogen peroxide, and nitric acid that may cause damage to the cells. Diltiazem (80) was employed in re-

ducing oxidative stress in human umbilicus vein endothelial cells (Fig. 9) [52].

### 3.1.9. Anti-inflammatory and analgesic activity

Anti-inflammatory agents are important in the body, as they have pain-relieving abilities. A new [1,4] benzothiazepine incorporated furan analogs (81) showed appreciable anti-inflammatory and ATPase inhibitory activities, making it a potential anti-ulcer drug (Fig. 10) [15].

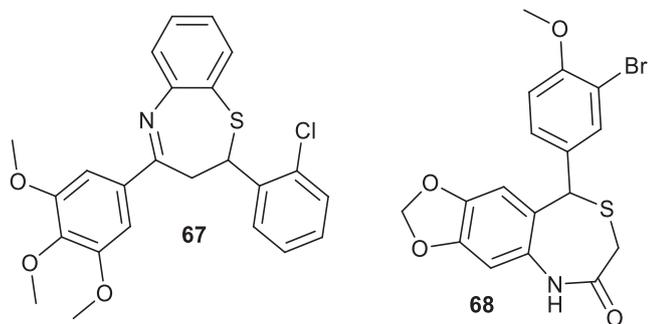


Fig. 2. Structures of benzothiazepine with anti-tumor properties.

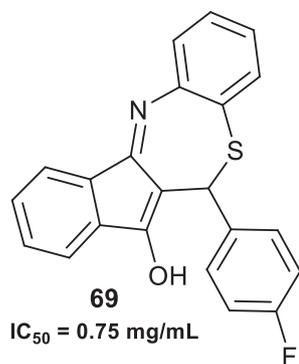


Fig. 3. Structures of benzothiazepine with anti-malaria properties.

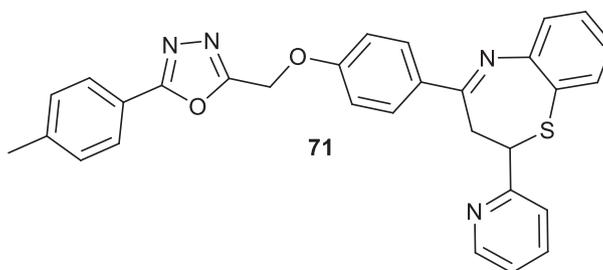
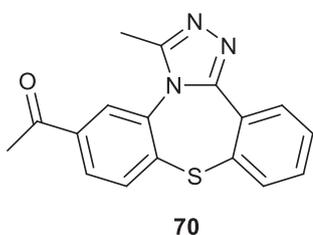


Fig. 4. Structures of benzothiazepine with anti-bacterial properties.

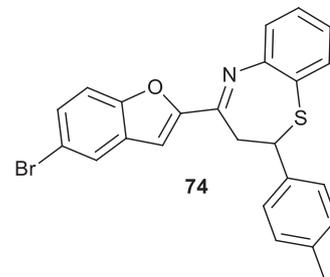
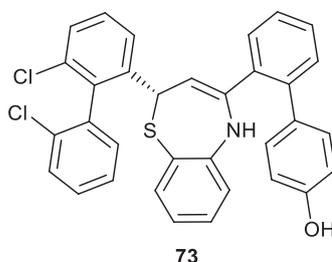
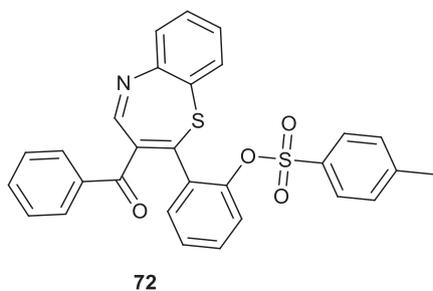


Fig. 5. Structures of benzothiazepine with anti-fungal properties.

### 3.1.10. Anti-leishmanial activity

The leishmanicidal activity of oxadiazoles conjugated 1,4-benzothiazepine (82) against *Leishmania mexicana* was reported and the results ( $IC_{50}$  of 0.65  $\mu\text{g/mL}$ ) were comparable to miltefosine (Fig. 11) [48].

### 3.2. Structure-activity relationship study

The SAR study was done on anti-viral agent 1,5-benzothiazepine derivatives (83) and it was deduced that when the R group was 3-Br-Ph and 3,4-di-Cl-Ph groups it was more effective and has a protective activity than ningnanmycin. While when R was 4-OCH<sub>3</sub>-Ph, 2-Br-Ph, and 3-OCH<sub>3</sub>-Ph, the activity was poor. In summary, the electron-withdrawing group present in the phenyl group of the target compound made it highly effective against the tobacco mosaic virus (Fig. 12) [17].

A similar observation was reported by Kadnor & Skelke, (2019) for the antimalarial and antimicrobial activities of the 1,5-benzothiazepine derivatives (84). In the presence of electron-withdrawing groups such as Cl and Br substituents on the aromatic ring, there was an increase in the various activities. Also, the carbazole group attached to the compound increases its antimicrobial activity. In other studies, it was observed that the substitution with electron-withdrawing groups confers stronger activities on the benzothiazepine derivatives than electron-donating groups (Fig. 13) [16].

### 3.3. ADMET studies on benzothiazepine derivatives

The need to ascertain the safety and drug-likeness of a synthesized compound has made it necessary to carry out several tests to confirm its compatibility as a drug candidate.

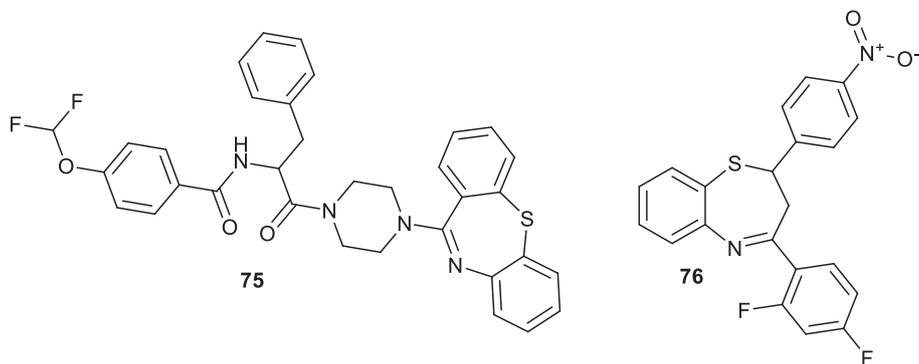


Fig. 6. Structures of benzothiazepine with anti-cancer properties.

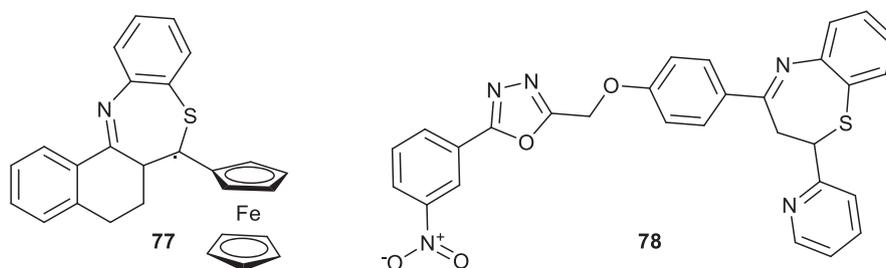


Fig. 7. Structures of benzothiazepine with anti-protozoal properties.

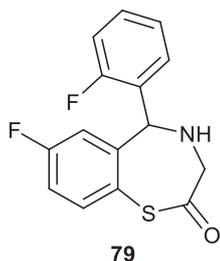


Fig. 8. Structures of benzothiazepine with anti-diabetic properties.

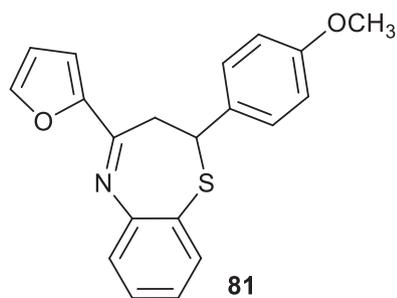


Fig. 10. Structures of benzothiazepine with anti-inflammatory properties.

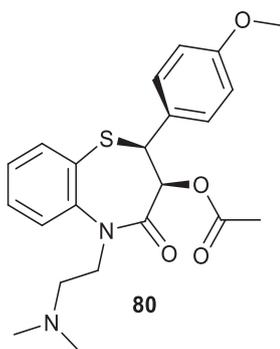


Fig. 9. Structures of benzothiazepine with anti-oxidant properties.

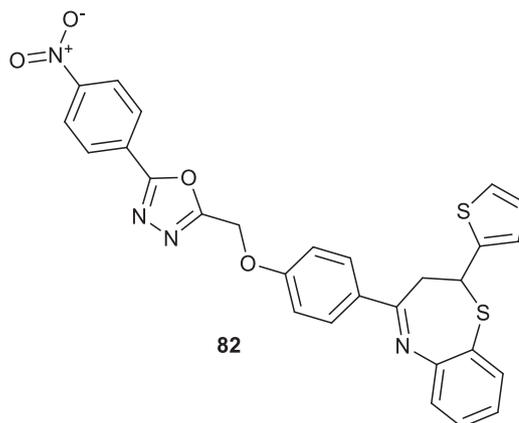


Fig. 11. Structures of benzothiazepine with anti-leishmanial properties.

In different studies, a novel 1,5 derivative (76) and 1,4-benzothiazepine-2-one derivative (79) were synthesized and tested as an anti-cancer agent [51] and anti-diabetic agent [28]. The compounds meet the lipinski's rule of five with molecular weight less than 500, hydrogen bond donor less than 5, and octanol/water partition coefficient logP less than 5. Hence the compounds were easily soluble and effective as a drug candidate. The *in silico* ADME studies carried out predicted that the compounds have no level of carcinogenicity nor tumorigenicity [28,51].

Diltiazem (80) is a calcium blocker that is administered orally in an extended-release and intravenously. It is sold under the brand name Cardizem, absorption takes place in the gastrointestinal tract [52,53]. Diltiazem is distributed to the liver, plasma, and intestine for further metabolism to take place. The metabolism of diltiazem

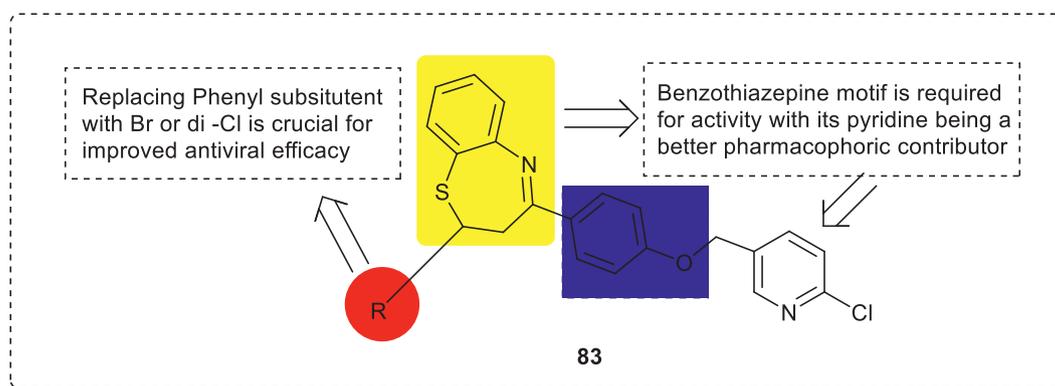


Fig. 12. SAR of 1,5-benzothiazepine derivatives containing pyridine moiety the antiviral activity.

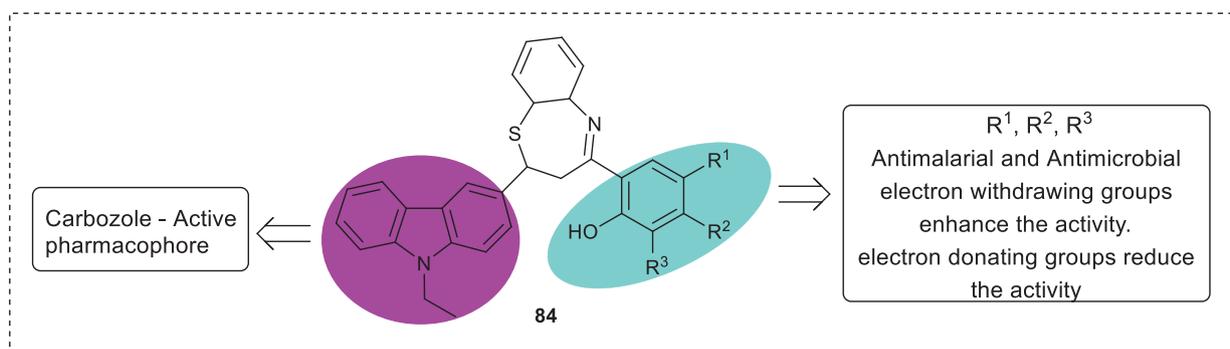


Fig. 13. SAR of carbazole incorporated 1,5-benzothiazepine the antimalarial and antimicrobial activity.

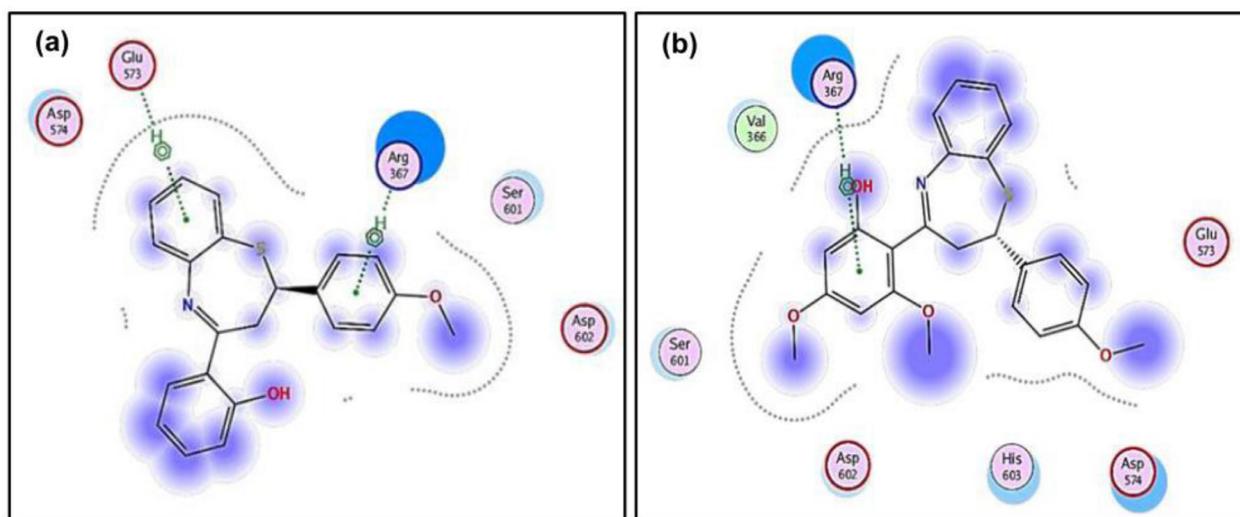


Fig. 14. 2D ligand interaction of compounds (a) 85 and (b) 86 against helicase of Zika virus protein [56].

takes place in the body when administered orally, it was reported that conversion of the drug to N-demethylation, O-demethylation, and deacetylation takes place in the liver, plasma, and intestine by the appropriate enzymes [53,54]. Diltiazem has a plasma elimination half-life ranging from 3-4.5 h for oral and intravenous administration, there might be an increase in half-life if the dose increases or hepatic impairment [53,54]. Similarly, extended-release

pills if administered once or multiple times might have a half-life between 6 and 9 h, the drug can be eliminated through the bile and kidney. Clinical tests were conducted for 24 months on rats using a dose of 100 mg/kg per day, reports showed no level of carcinogenicity, no mutagenic response in mammalian cells nor signs of impaired fertility [53,55]. Overdose of this drug can cause several diseases like hypotension, bradycardia, heart block, and car-

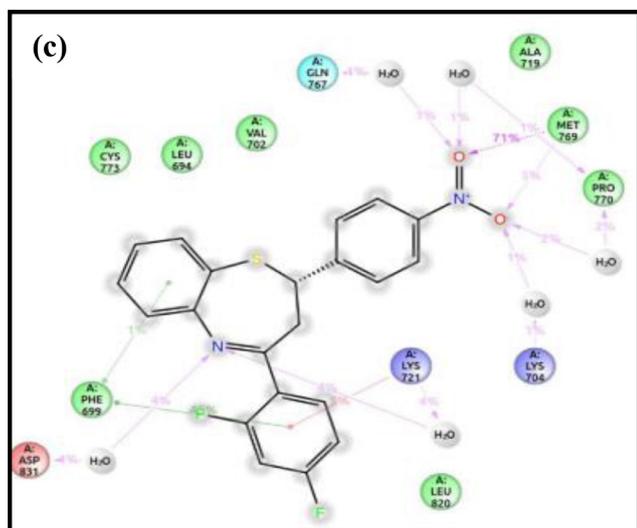


Fig. 15. 2D ligand interaction (c) of compound 87 against EGFR kinase domain [51].

diac failure with signs like lightheadedness and fatigue which can lead to death at its extreme [53]. Also, it was observed that there were possibilities of skeletal abnormalities, risk of stillbirths, embryo, and fetal lethality when the diltiazem dose is more than the daily prescribed intake for humans in experimental animals [53].

#### 3.4. Molecular modeling and binding study

Docking studies help in the prediction of the binding affinity of drug-like molecules to a specific protein. Some of the advantages include the cost-effectiveness, short time, and little energy required when compared to experimental determined biological activity.

Frimayanti, Nasution, & Etavianti (2021) carried out molecular docking studies of benzothiazepine-chalcone derivatives. It was predicted that compounds 85 and 86 were active inhibitors against helicase of Zika virus protein (PDB ID: 5GJB) with binding affini-

ties of  $-4.9291$  and  $-4.6490$  kcal/mol, respectively (Fig. 14). The derivatives were reported to be stable and they formed hydrogen bonds with Glu573, and Arg367, through van der Waals bonds. The compounds had the lowest binding energy making them more stable and efficient [56].

In another studies, Prasada and co-workers designed novel 1,5-benzothiazepine derivatives and carried out a docking studies to ascertain their anti-cancer potential. The epidermal growth factor receptor (EGFR) kinase domain was the target protein as it aids the growth of many tumor which includes cancer. Results predicted showed that compound 87 was more active in inhibiting the activity of receptor with binding energy of  $-9.71$  kcal/mol and this resonated with the experimental values done on three cancer cell lines (Fig. 15) [51].

Similarly, the anti-tumor potential of some 1,4-benzothiazepine bearing diaryl derivatives were predicted through the docking studies and using Tubulin (PDB ID: 4O2B) as the target protein. Tubulin gives rise to microtubules through polymerization and this microtubules plays a role in mitosis. Compound 88 was predicted to be a more potent inhibitor for the target and when the experimental tests were carried out on various cancer cell lines it inhibited their growth appreciably (Fig. 16) [22].

#### 4. Conclusion

The various benzothiazepine derivatives reported in this work have proven to be pharmacologically active and efficient which makes them potential drug candidates as various synthetic routes can be employed in synthesizing these molecules. Greener synthetic routes are encouraged alongside optimization of reaction conditions like the substrate, substituent, enzymes, solvent, and temperature to reduce costs, reduce pollution, and save energy. The SAR studies of the benzothiazepine analogs revealed that the positions of the substituents on the analogs had appreciable effects on their activities and this can help to design more active derivatives. The drug-likeness of some the derivatives were also reported to give an insight into their pharmacokinetic properties. Further research can be carried out to discover potential drug candidates with huge benefits that can remedy challenges like drug resistance faced in the pharmaceutical sector.

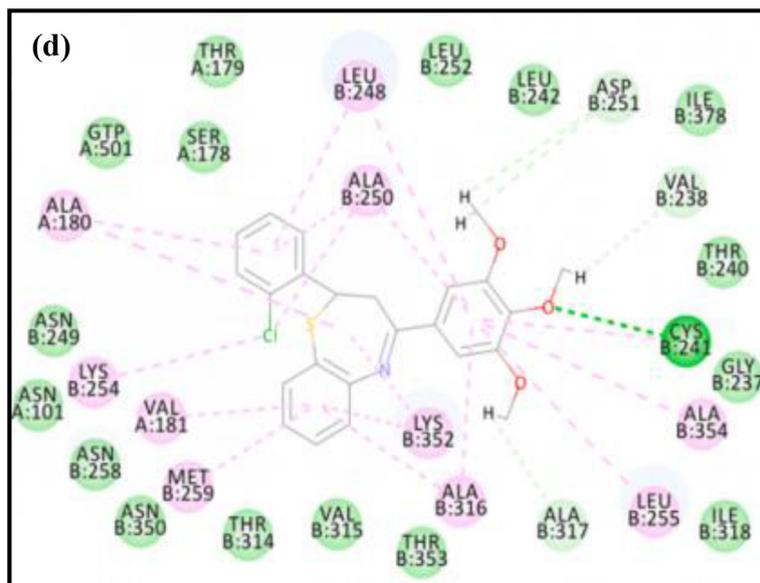


Fig. 16. 2D ligand interaction (d) of compound 88 against Tubulin.

## Author's contribution

O.O.A. conceived the review; T.A.O wrote the original draft and the final manuscript; O.O.A, G.O.O, E.F.O., and E.A proofread, and edited the manuscript.

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## Declaration of Competing Interest

The authors declare no potential conflict of interest concerning the research, authorship, and/or publication of this article.

## Data availability

No data was used for the research described in the article.

## References

- C Cabrele, O. Reiser, The modern face of synthetic heterocyclic chemistry, *J. Org. Chem.* 81 (21) (2016) 10109–10125, doi:10.1021/acs.joc.6b02034.
- SG Zlotin, AM Churakov, IL Dalinger, et al., Recent advances in synthesis of organic nitrogen–oxygen systems for medicine and materials science, *Mendeleev Commun.* 27 (6) (2017) 535–546, doi:10.1016/j.mencom.2017.11.001.
- L. Yet, Introduction, in: *Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis*. First, John Wiley & Sons, Inc., 2018, pp. 1–14.
- C Nsanabana, D Djalle, PJ Guérin, D Ménard, JJ. González, Tools for surveillance of anti-malarial drug resistance: an assessment of the current landscape, *Malar. J.* 17 (1) (2018) 1–16, doi:10.1186/s12936-018-2185-9.
- CA Michael, D Dorney-Howes, M. Labbate, The antimicrobial resistance crisis: causes, consequences, and management, *Front Public Heal.* 2 (SEP) (2014) 1–8, doi:10.3389/fpubh.2014.00145.
- MA Olszewska, A Gedas, M. Simões, Antimicrobial polyphenol-rich extracts : applications and limitations in the food industry, *Food Res. Int.* 134 (2020) 109214 August 2019, doi:10.1016/j.foodres.2020.109214.
- NJ. White, Antimalarial drug resistance, *J. Clin. Invest.* 113 (8) (2004) 1084–1092, doi:10.1172/jci200421682.
- AK Farha, QQ Yang, G Kim, et al., Inhibition of multidrug-resistant foodborne *Staphylococcus aureus* biofilms by a natural terpenoid (+)-nootkatone and related molecular mechanism, *Food Control* 112 (January) (2020) 107154, doi:10.1016/j.foodcont.2020.107154.
- S Muthupandian, B Ramachandran, H. Barabadi, The prevalence and drug resistance pattern of extended spectrum  $\beta$  – lactamases (ESBLs) producing Enterobacteriaceae in Africa, *Microb. Pathog.* 114 (2018) 180–192, doi:10.1016/j.micpath.2017.11.061.
- N Gebreselassie, R Hutubessy, J Vekemans, S den Boon, T Kasaeva, M. Zignol, The case for assessing the full value of new tuberculosis vaccines, *Eur. Respir. J.* 55 (3) (2020) 1902414, doi:10.1183/13993003.02414-2019.
- C Abbafati, KM Abbas, M Abbasi-Kangevari, et al., Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019, *Lancet* 396 (10258) (2020) 1223–1249, doi:10.1016/S0140-6736(20)30752-2.
- A Monroe, NA Williams, S Ogoma, C Karema, F. Okumu, Reflections on the 2021 World Malaria Report and the future of malaria control, *Malar. J.* 21 (1) (2022) 1–6, doi:10.1186/s12936-022-04178-7.
- J Wolf, PR Hunter, MC Freeman, et al., Impact of drinking water, sanitation and handwashing with soap on childhood diarrhoeal disease: updated meta-analysis and meta-regression, *Trop. Med. Int. Heal.* 23 (5) (2018) 508–525, doi:10.1111/tmi.13051.
- A Prüss-Ustün, J Wolf, J Bartram, et al., Burden of disease from inadequate water, sanitation and hygiene for selected adverse health outcomes: an updated analysis with a focus on low- and middle-income countries, *Int. J. Hyg. Environ. Health* 222 (5) (2019) 765–777, doi:10.1016/j.ijheh.2019.05.004.
- DM Lokeshwari, ND Rekha, B Srinivasan, HK Vivek, AK. Kariyappa, Design, synthesis of novel furan appended benzothiazepine derivatives and in vitro biological evaluation as potent VRV-PL-8a and H+/K+ ATPase inhibitors, *Bioorg. Med. Chem. Lett.* 27 (14) (2017) 3048–3054, doi:10.1016/j.bmcl.2017.05.059.
- AB Shaik, RR Bhandare, S Nissankararao, BVS Lokesh, S Shahanaaz, M Mukhlesur Rahman, Synthesis, and biological screening of chloropyrazine conjugated benzothiazepine derivatives as potential antimicrobial, antitubercular and cytotoxic agents, *Arab. J. Chem.* 14 (2) (2021) 102915, doi:10.1016/j.arabj.2020.102915.
- T Li, J Zhang, J Pan, Z Wu, D Hu, B. Song, Design, synthesis, and antiviral activities of 1,5-benzothiazepine derivatives containing pyridine moiety, *Eur. J. Med. Chem.* 125 (2017) 657–662, doi:10.1016/j.ejmech.2016.09.069.
- CG Arya, M Chandrakanth, K Fabitha, et al., Coumarin – benzimidazole hybrids: a review on diverse synthetic strategies, *Results Chem.* 4 (September) (2022) 100631, doi:10.1016/j.rechem.2022.100631.
- SE Hooshmand, AZ. Halimehjani, Nitroalkenes in diverse synthesis of heterocyclic compounds with two or three heteroatoms: recent advances, *Targets Heterocycl. Syst.* 22 (2018) 119–137, doi:10.17374/targets.2019.22.119.
- AK Guha, S Sarmah, AK. Phukan, Effect of substituents at the heteroatom on the structure and ligating properties of heterocyclic carbene, silylene, germlyene and abnormal carbene: a theoretical study, *Dalt. Trans.* 39 (2010) 7374–7383, doi:10.1039/c003266b.
- E Vatankhah, M Akbarzadeh, A Jabbari, K Saadat, A. Shiri, Synthesis and characterization of various novel derivatives of dipyrimido[4,5-b:4',5'-e][1,4]thiazepine and their theoretical evaluation as 15-Lipoxygenase Inhibitor, *Polycycl. Aromat. Compd.* 43 (1) (2023) 288–301, doi:10.1080/10406638.2021.2014536.
- B Wang, LR Wang, LL Liu, et al., A novel series of benzothiazepine derivatives as tubulin polymerization inhibitors with anti-tumor potency, *Bioorg. Chem.* 108 (2021) 104585 December 2020, doi:10.1016/j.bioorg.2020.104585.
- García-Casas P, Arias-Del-Val J, Alvarez-Ilлера P, et al. The neuroprotector benzothiazepine CGP37157 extends lifespan in *C. elegans* worms. Published online 2019, doi:10.3389/fnagi.2018.00440
- CE Gutteridge, BW Sadowski, SM Hughes, et al., Synthesis of substituted benzothiazepine compounds with medicinal potential, *Int. J. Org. Chem.* 10 (03) (2020) 123–134, doi:10.4236/ijoc.2020.103009.
- V Devi, G Singh, V. Monga, Recent advances in the synthetic chemistry of 1, 5-benzothiazepines : a minireview, *J. Heterocycl. Chem.* 57 (9) (2020) 3255–3270, doi:10.1002/jhet.4062.
- KAM. El-Bayouki, Benzo[1,5]thiazepine: synthesis, reactions, spectroscopy, and applications, *Org. Chem. Int.* 2013 (2013) 1–71, doi:10.1155/2013/210474.
- W.S. Guo, H. Gong, Y. Zhang, L. Wen, M. Li, Fast construction of 1,3-benzothiazepines by direct intramolecular dehydrogenative C – S bond formation of thioamides under metal-free conditions, *Org. Lett.* 20 (2018) 6394–6397, doi:10.1021/acs.orglett.8b02697.
- VK Srivastav, M. Tiwari, Synthesis and evaluation of antihyperglycemic activity of 1,4-benzothiazepine-2-one derivatives in alloxan induced diabetic rats, *Indian J. Pharm. Sci.* 83 (5) (2021) 1033–1043, doi:10.36468/pharmaceutical-sciences.857.
- T Sasikala, K Parameswari, S. Chitra, Synthesis and corrosion inhibition study of benzothiazepine derivatives on mild steel in acid medium, *Orient J. Chem.* 32 (2) (2016) 1215–1222, doi:10.13005/ojc/320248.
- TA Farghaly, Hassaneen HME. H-ferrierite zeolite: as an effective and reusable heterogeneous catalyst for synthesis of 1,5-benzothiazepine under solvent free condition and 1,3-dipolar cycloaddition in water, *Arab. J. Chem.* 10 (2017) S3255–S3262, doi:10.1016/j.arabj.2013.12.024.
- Ghodke M, Wagh S, Nikalje AP, Seijas Vázquez J. Ultrasound assisted synthesis of 2, 4-substituted 1, 5- benzothiazepine derivatives. In: Proceedings of the 23rd International Electronic Conference on Synthetic Organic Chemistry. Vol 3. MDPI; 2019:6704. doi:10.3390/ecsoc-23-06704
- R Baharfar, S. Mohajer, Synthesis and characterization of immobilized lipase on Fe3O4 nanoparticles as nano biocatalyst for the synthesis of benzothiazepine and spirobenzothiazine chroman derivatives, *Catal. Lett.* 146 (9) (2016) 1729–1742, doi:10.1007/s10562-016-1797-3.
- C Fang, T Lu, J Zhu, K Sun, D. Du, Formal [3 + 4] Annulation of  $\alpha$ ,  $\beta$  -unsaturated acyl azoliums: access to enantioenriched N – H – free 1,5-benzothiazepines, *Org. Lett.* 19 (13) (2017) 3470–3473, doi:10.1021/acs.orglett.7b01457.
- S Meninno, C Volpe, A. Lattanzi, Catalytic enantioselective synthesis of protecting-group-free 1, 5- benzothiazepines, *Chem. A Eur. J.* 23 (19) (2017) 4547–4550, doi:10.1002/chem.201700837.
- BV Kendre, MG Landge, SR. Bhusare, Synthesis and biological evaluation of some novel pyrazole, isoxazole, benzoxazine, benzothiazepine and benzodiazepine derivatives bearing an aryl sulfonate moiety as antimicrobial and anti-inflammatory agents, *Arab. J. Chem.* 12 (8) (2019) 2091–2097, doi:10.1016/j.arabj.2015.01.007.
- AF Kassem, EMH Abbas, NT Al-Qurashi, TA. Farghaly, New azoloazine derivatives as antimicrobial agents: Synthesis under microwave irradiations, structure elucidation, and antimicrobial activity, *J. Heterocycl. Chem.* 57 (2) (2020) 611–620, doi:10.1002/jhet.3792.
- MJ Alam, AU Khan, M Alam, S. Ahmad, Spectroscopic (FTIR, FT-Raman, 1H NMR and UV-vis) and DFT/TD-DFT studies on cholestenol [4,6-b,c]-2',5'-dihydro-1',5'-benzothiazepine, *J. Mol. Struct.* 1178 (2019) 570–582, doi:10.1016/j.molstruc.2018.10.063.
- P Pawar, VS Shivankar, YA Gaikwad, SS Patil, GC. Wadhawa, ferrous-sulphate-catalysed-synthesis-of-1-5benzothiazepines-using-sonication-method, *J. Biol. Chem. Chron.* 4 (2) (2018) 95–98 <https://www.eresearchco.com/articles/ferrous-sulphate-catalysed-synthesis-of-1-5benzothiazepines-using-sonication-method.pdf>.
- CG Devkate, SS Kola, DD Gaikwad, MIM. Siddique, Ultrasound promoted one pot synthesis of 1,5-benzothiazepines using polyethylene glycol (Peg-400), *Int. Res. J. Pharm.* 9 (11) (2018) 182–185, doi:10.7897/2230-8407.0911280.
- RK. Malik, Synthesis of novel 1,5 - benzothiazepines as CNS agents, *Acta Cienc Indica XLIII* (2) (2017) 235–240 [http://www.acta.co.in/acta-bo/files/published\\_general/5cd904c76cde3-134-C017.pdf](http://www.acta.co.in/acta-bo/files/published_general/5cd904c76cde3-134-C017.pdf).
- M Mostofi, G Mohammadi Ziarani, N Lashgari, Design, synthesis and biological evaluation of benzofuran appended benzothiazepine derivatives as inhibitors of butyrylcholinesterase and antimicrobial agents, *Bioorg. Med. Chem.* 26 (12) (2018) 3076–3095, doi:10.1016/j.bmc.2018.02.049.
- L Viejo, M Rubio-Alarcón, RL Arribas, et al., Synthesis and biological assessment of 4,1-benzothiazepines with neuroprotective activity on the Ca2+ over-

- load for the treatment of neurodegenerative diseases and stroke, *Molecules* 26 (2021) 4473, doi:[10.3390/molecules26154473](https://doi.org/10.3390/molecules26154473).
- [43] C Yin, T Yang, Y Pan, J Wen, X. Zhang, Rh-catalyzed asymmetric hydrogenation of unsaturated medium-ring NH lactams: highly enantioselective synthesis of N-unprotected 2,3-dihydro-1,5-benzothiazepinones, *Org. Lett.* 22 (3) (2020) 920–923, doi:[10.1021/acs.orglett.9b04478](https://doi.org/10.1021/acs.orglett.9b04478).
- [44] J Wen, H Cheng, G Raabe, C. Bolm, Rhodium-catalyzed [4 + 3] annulations of sulfoximines with  $\alpha,\beta$ -unsaturated ketones leading to 1,2-benzothiazepine 1-oxides, *Org. Lett.* 19 (21) (2017) 6020–6023, doi:[10.1021/acs.orglett.7b03106](https://doi.org/10.1021/acs.orglett.7b03106).
- [45] L Wu, X Yang, Q Peng, G. Sun, Synthesis and anti-proliferative activity evaluation of novel benzo[d][1,3] dioxoles-fused 1,4-thiazepines, *Eur. J. Med. Chem.* 127 (2017) 599–605, doi:[10.1016/j.ejmech.2017.01.021](https://doi.org/10.1016/j.ejmech.2017.01.021).
- [46] VA Kadnor, SN. Shelke, Synthesis, antimicrobial and antimalarial activity of 1,4-benzothiazepine and pyrazoline derivatives incorporating carbazole moiety, *Bulg. Chem. Commun.* 51 (2) (2019) 234–241, doi:[10.34049/bcc.51.2.4921](https://doi.org/10.34049/bcc.51.2.4921).
- [47] A Sharma, D Kishore, B. Singh, An expedient method for the synthesis of 1,2,4-triazolo-fused 1,5-benzodiazepine, 1,5-benzoxazepine, and 1,5-benzothiazepine Scaffolds: a novel seven-membered ring system of biological interest, *J. Heterocycl. Chem.* 55 (3) (2018) 586–592, doi:[10.1002/jhet.3060](https://doi.org/10.1002/jhet.3060).
- [48] P Navin, P Sarvil, P Amit, et al., Synthesis and biological evaluation of newer 1,3,4-oxadiazoles incorporated with benzothiazepine and benzodiazepine moieties, *Z. Naturforsch - Sect. C J. Biosci.* 72 (3–4) (2017) 133–146, doi:[10.1515/znc-2016-0129](https://doi.org/10.1515/znc-2016-0129).
- [49] S Pant, P Godwal, K. Sanju, Syntheses and Studies of 8-Substituted-2-(2-Chlorophenyl)/3-chlorophenyl)-4-(4-hydroxyphenyl/phenyl)-2,3/2,5-dihydro-1,5-benzothiazepines, *Asian J. Chem.* 33 (11) (2021) 2653–2656, doi:[10.14233/ajchem.2021.23369](https://doi.org/10.14233/ajchem.2021.23369).
- [50] JJ Sánchez García, Y Toledano-Magaña, M Flores-Alamo, et al., Polycyclic ferrocenyl(dihydro)thiazepine derivatives: diastereo-selective synthesis, characterization, electrochemical behavior, theoretical and biological investigation, *J. Inorg. Biochem.* 166 (2017) 141–149, doi:[10.1016/j.jinorgbio.2016.09.002](https://doi.org/10.1016/j.jinorgbio.2016.09.002).
- [51] CMMR Prasad, RP Yejella, S. Rehman, C Rajeswari, SH. Basha, Novel series of 1,5 Benzothiazepine skeleton based compounds as anti-cancer agents – In silico and MTT assay based study, *J. PeerScientist* 1 (2) (2018) 1–10, doi:[10.5281/zenodo.3372436](https://doi.org/10.5281/zenodo.3372436).
- [52] L Zhou, M Yang, S Zuo, et al., Diltiazem inhibits the oxidative stress induced by angiotensin II through growth hormone secretagogue receptor type 1a in human umbilicus vein endothelial cells, *Biomed. Pharmacother.* 89 (2017) 76–82, doi:[10.1016/j.biopha.2017.02.022](https://doi.org/10.1016/j.biopha.2017.02.022).
- [53] L Rodríguez Padial, G Barón-Esquívias, A Hernández Madrid, D Marzal Martín, V Pallarés-Carratalá, A de la Sierra, Clinical experience with diltiazem in the treatment of cardiovascular diseases, *Cardiol. Ther.* 5 (1) (2016) 75–82, doi:[10.1007/S40119-016-0059-1](https://doi.org/10.1007/S40119-016-0059-1).
- [54] P Manitpisitkul, CR Curtin, K Shalayda, SS Wang, L Ford, D. Heald, Pharmacokinetic interactions between topiramate and diltiazem, hydrochlorothiazide, or propranolol, *Clin. Pharmacol. Drug Dev.* 3 (5) (2014) 378–387, doi:[10.1002/cpdd.107](https://doi.org/10.1002/cpdd.107).
- [55] XQ Yan, ZG Chen, RL Wang, et al., Pharmacokinetics of diltiazem hydrochloride delay-onset sustained-release pellet capsules in healthy volunteers, *Brazil. J. Pharm. Sci.* 49 (1) (2013) 29–38, doi:[10.1590/S1984-82502013000100004](https://doi.org/10.1590/S1984-82502013000100004).
- [56] N Frimayanti, MR Nasution, E. Etavianti, Molecular docking and molecular dynamic simulation of 1,5-benzothiazepine chalcone derivative compounds as potential inhibitors for Zika virus helicase, *J. Ris. Kim.* 12 (1) (2021) 44–52.