Fused 1,5-Benzothiazepines from \( o \)-Aminothiophenol and its Derivatives as Versatile Synthons\(^1\)

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Abstract

This review describes the reactions of \( o \)-aminothiophenol and its derivatives as building blocks for the synthesis of poly-functionalised 1,5-benzothiazepines with pharmacological interest. Annelated 1,5-benzothiazepines were prepared by a cyclocondensation reaction of \( o \)-aminothiophenol and its derivatives with carbonyl and other functionalities. In case of carbonyl function this reaction takes place by a nucleophilic addition, followed by a cyclisation and concomitant elimination of water. The objective of this survey is to provide a comprehensive account of the synthesis of various 1,5-benzothiazepines derivatives and their potential to develop better chemotherapeutic agents.

Keywords: \( o \)-aminothiophenol, chalcones, cyclocondensation, green synthesis, 1,3-dipolar cycloadditions.

1. Introduction

\[ R = (a) \text{H}, (b) 4-\text{Cl}, (c) 4-\text{MeO}, (d) 4-\text{CF}_3, \\
\text{(e) 5-\text{Me}, (f) 5-\text{MeO}, (g) 5-\text{F}, (h) 5-\text{EtO},} \\
\text{(i) 5-\text{CF}_3, (j) 3-\text{Br}, (k) 3-\text{CF}_3, (l) 3,4-\text{Me}_2} \]

The hybrid nature of the \( o \)-aminothiophenol motif (1) containing two different donor functions within the same molecule, highlights its usefulness as a ligand in coordination chemistry. In addition, \( o \)-aminothiophenol-containing compounds have been used as ligands for biomimetic models of the active sites of enzymes such as Fe and Ni based oxidases.\(^1,2\) Applications of \( o \)-aminothiophenol and its derivatives include antitrypanosomal, antimalarial treatments\(^3\) (Figure 1a, b) and in the synthesis of GW 7647 as an agonist of PPAR \( \alpha \) (Figure 1c).\(^4\) Surprisingly,

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\(^1\) This article is dedicated to my beloved teacher and researcher Dr Y. D. Reddy, Retired Professor of Chemistry, NIT-Warangal, India who left for his heavenly abode on 9th November 2013.

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very little has been reviewed on the versatility of \( o \)-aminothiophenols and its derivatives as fundamental synthetic building blocks in heterocyclic synthesis. In spite of the fact that there appeared voluminous literature on the synthesis, toxicity, occupational health hazards, industrial and environmental pollution of \( o \)-aminothiophenol and its derivatives, in recent times a detailed account on the reactions with carbonyl group and other functionalities is not reported till now. This necessitated us to review and highlight the current reactions in the field of 1,5-benzothiazepines. Consequently, this review attempts to present the work encompassing synthetic versatility of \( o \)-aminothiophenol and its derivatives as building blocks for the preparation of a wide range of 1,5-benzothiazepines.

2. Methods of the Preparation of 1,5-Benzothiazepine System and Its Related Derivatives

The present review summarizes the methods for preparing benzothiazepines and related annulated thiazepines. The preparative methods include ring closure reactions, aromatizations and ring transformations. Several reviews have focused on the synthesis, reactions, medicinal chemistry, biological properties of 1,5-benzothiazepines as they are privileged scaffolds in drug discovery. The presence of benzothiazepines moiety in natural products and pharmaceuticals determines their potential use as antipsychotic agents, for example quetiapine (trade name, seroquel) (Figure 2a), the angina relieving calcium channel blocker diltiazem (Figure 2b), the inhibitor of the lipoprotein disorders GW 577 (Figure 2c), the hypertensive agent clentiazem (Figure 2d) and the GABA blocker thiazesim (Figure 2e). Recently, a family of 1,5-benzothiazepine derivatives has been reported as potent and selective bradykinin receptor antagonists as JMV 1645 (Figure 2f). The present review is divided into 7 sections based on the type of reaction or nature of benzothiazepine formed or employed.

1. 1,5-Benzothiazepines based on bielectrophiles
2. Chalcones based synthesis
3. Green synthesis
4. Mannich Base derivatives
5. 1,3-Dipolar cycloaddition
6. Flurobenzothiazepines
7. Miscellaneous

One of the most widely employed methods for the preparation of 1,5-benzothiazepines involves the reaction of \( o \)-aminothiophenol (\( o \)-ATP, 1) with \( \alpha,\beta \)-unsaturated esters, \( \alpha,\beta \)-unsaturated ketones or chalcones both under acidic and basic conditions. Although in all reactions between a dinucleophile (\( o \)-aminothiophenol) with a dielectrophile

Figure 2. Examples of 1,5-benzothiazepine derivatives with interesting biological properties.
of the type discussed in scheme, two compounds can be formed,\(^{25}\) since only benzothiazepines were isolated it was assumed that the reaction starts by the 1,4-Michael addition of the SH on the –C=C– double bond followed by the condensation of the NH\(_2\) on the carbonyl group.

2.1. 1,5-Benzothiazepines Based on Bielectrophiles

2.2. Baylis–Hillman Derivatives

The Baylis–Hillmann adducts are utilized very well as building blocks for the synthesis of natural products and biologically active molecules.\(^{26}\) Murugan et al.\(^{27}\) reported the synthesis of dihydro-benzothiazepin-4-ones using Baylis–Hillman chemistry. A variety of (Z)-2-(bromomethyl)-3-arylprop-2-enaoates (2a–j) prepared from the corresponding Baylis–Hillman adduct were treated with \(\sigma\)-aminothiophenol (1) in the presence of potassium \(\sigma\)-butoxide in THF at r.t. giving \(S\)-alkylated acrylates 3a–j in good yields. The crude intermediates 3a–j were treated with \(p\)-toluenesulfonic acid in xylene under reflux conditions to give the (Z)-3-arylidene-2,3-dihydrobenzo[b][1,4]thiazepin-4(5\(H\))-ones (4a–j) in 65–71% yield. The formation of seven-membered benzothiazepinone can be rationalized by selectively tethering the sulfur atom of the \(\sigma\)-aminothiophenol (1) with allylic carbon, which is attached to the bromine atom of the compound 2, at one end and at the other end by tethering the nitrogen atom of the \(\sigma\)-aminothiophenol with carbonyl carbon present in the bromo derivative of the Baylis–Hillman adducts 2\(^{29}\) as shown in Scheme 1.

2.3. Allene-1,3-dicarboxylates-cyclophilic Reactions

\(\sigma\)-Aminothiophenol (1) reacts with dimethyl allene-1,3-dicarboxylate (5) to give first the Michael adduct 6. The cyclization reaction of thioenol ether 6 at 200 °C gave the 1,5-benzothiazepinone 7 in 48% yield.\(^{29}\) A consideration of Baldwin’s rules\(^{30}\) and vector analysis suggests that the 7-exo-trig cyclization is favored over 5-exo-trig process for the formation of thiazepines in preference to thiazoles (Scheme 2).

2.4. \(\beta\)-Propiolactone / \(\beta\)-Butyrolactone as a Precursor

4,5-Differently substituted / \(\sigma\)-aminothiophenols (1) are conveniently converted into 2,3-dihydro-1,5-benzothiazepin-4(5\(H\))-ones (8a–l) by a reaction with \(\beta\)-propiolactone or \(\beta\)-butyrolactone in anhydrous pyridine followed by the treatment with \(\text{Ac}_2\text{O}\). The lower reactivity of \(\beta\)-butyrolactone results in the poorer yields of benzothiazepines 8a–l (30–80%).\(^{31}\) The yields of 1,5-benzothiazepine derivatives depend also upon both the nature and position of the substituent. The electron withdrawing substituents were also found to decrease the yield to some extent, which could be attributed to the retarded formation of the amino acid intermediate due to the decreased nucleophilicity of the sulfur atom. The presence of an electron releasing group at 5-position affects the reactivity of 1 in agreement with previous observa-

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**Scheme 1.** Synthesis of dihydrobenzothiazepin-4-ones 4a–j.

\[
\begin{align*}
4: \quad & (a) \quad R = H \ (71\%); \\
& (b) \quad R = 4-\text{NO}_2 \ (67\%); \\
& (c) \quad R = 2, \quad 4-\text{Cl}_2 \ (67\%); \\
& (d) \quad R = 4-\text{Et} \ (68\%); \\
& (e) \quad R = 4-\text{Pr} \ (66\%); \\
& (f) \quad R = 2-\text{Cl} \ (67\%); \\
& (g) \quad R = 3-\text{Cl} \ (65\%); \\
& (h) \quad R = 4-\text{Cl} \ (71\%); \\
& (i) \quad R = 2-\text{Me} \ (67\%); \\
& (j) \quad R = 4-\text{Me} \ (70\%)
\end{align*}
\]

**Scheme 2.** Synthesis of 1,5-benzothiazepinone 7.

\[
\begin{align*}
& (i) \quad \text{MeOH, 20 °C, 8h; } \\
& (ii) \quad 200 °C, 60 \text{ min}
\end{align*}
\]
tions on similar reactions.\textsuperscript{32} When 4-methoxy-2-amino
benzenethiol was used, the lowest yields of the corresponding benzothiazepinones \textit{8c,8k} were obtained (Scheme 3).

2. 5. π Acceptors as Reactants

The condensation of \textit{o}-aminothiophenol (1) with π
acceptors such as tetracyanoethylene (9) in ethyl acetate
at r.t. furnishes 4-aminobenzo[\textit{b}]\textit{{[1,4]}}thiazepine-2,3-di-
carbonitrile (10) in 77\% yield.\textsuperscript{33} Interestingly, upon the
reaction of 1 with 1-(dicyanomethylen)acenaphthen-2-one
(11) in acetonitrile under reflux conditions for 5 h benzot-
hiazepine derivative 12 was obtained in 70\% yield\textsuperscript{34}
(Scheme 4).

2. 6. Thiazepinopyridazine Derivatives

The reaction of 4-benzoyl-5,6-diphenylpyridazine-
3-(2\textit{H})-one (13) with \textit{POCl}_3 at 100 °C gave the chlorina-
ed product 4-benzoyl-3-chloro-5,6-diphenylpyridazine
(14). The condensation of chloro derivative 14 with \textit{o}-aminothiophenol (1) in ethanol gave thiazepinopyridazine
derivative 15 in 85\% yield\textsuperscript{35} (Scheme 5).

\begin{center}
\textbf{Scheme 3. Synthesis of 2,3-dihydro-1,5-benzothiazepin-4-ones 8a–l.}
\end{center}

\begin{center}
\textbf{Scheme 4. Synthesis of benzothiazepine derivatives 10,12.}
\end{center}

\begin{center}
\textbf{Scheme 5. Synthesis of thiazepinopyridazine derivative 15.}
\end{center}
2.7. Sonogashira Coupling-isomerization Reaction

The reaction of 1-phenylpropynol (16) and electron poor (hetero) aryl halides 17a-d under reaction conditions of the Sonogashira coupling in a boiling mixture of THF and Et₃N gave the in situ generated enone as Michael acceptor. The subsequent addition of 5-trifluoromethyl / o-aminothiophenol (1) as a suitable 1,4-dinucleophile component and acetic acid to the reaction mass, gave the beige to yellow 2,3-dihydro[1,4]thiazepines, 36 18a-f in 38–85% yield (Scheme 6).

2.8. Heterocyclization of 4-Aryl-3-nitrobut-3-en-2-ones

Reaction of 4-aryl-3-nitrobut-3-en-2-ones37 (19) with o-aminothiophenol (1) occurred at 18–20 °C in methanol to give crystalline 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines (22a–c) in 81–98% yield.38 The process may follow nucleophilic addition pattern with a subsequent heterocyclization of S-adducts 20,21 (Scheme 7).


Scheme 7. Synthesis of 2-aryl-4-methyl-3-nitro-1,5-benzothiazepines 22a–c.

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2. 9. Phenylazo-benzothiazepines

Abd ElLatif et al.\(^{39}\) have reported the synthesis of polysubstituted-1,5-benzothiazepine using as the key intermediates hydrazono derivatives 23 and 30. Phenylhydrazono-malononitrile (23a) and phenylhydrazono ethyl cyanoacetate (23b) reacted with o-aminothiophenol (1) in the presence of piperidine in ethanol under reflux conditions to give 2-amino-3-phenylazo-1,5-benzothiazepine derivatives 26 and 28 in 62–85% yield. The 4-amino-2-imino-3-phenyl-hydrazo-1,5-benzothiazepine (25a) seems to be formed via a nucleophilic addition of the –SH group of 1 to the –CN function of 23a (Y = CN) to yield the intermediate similar to 24 (Scheme 8). Further cyclization through a similar addition of the NH\(_2\) to the second –CN function finally yielded 25a which could isomerise to 2,4-diamino-3-phenylazo-1,5-benzothiazepine (26a) in 85% yield. In the case of 23b (Y = CO\(_2\)Et), it seems that the reaction proceeds via elimination of water from the intermediate 24 resulting in the formation of 4-ethoxy-2-imino-3-phenylhydrazo-1,5-benzothiazepine (27) which might be present as 2-amino-4-ethoxy-3-phenylazo-1,5-benzothiazepine (28). The formation of compound 29 was ruled out based on spectral and elemental analytical data. However, the phenylhydrazonoacetylacetone (30a) underwent condensation with o-aminothiophenol (1) in the presence of piperidine in ethanol very easily to yield the key intermediate 31 (Y = COMe), which in turn loses another molecule of water from the intermediate 32 to yield 2,4-dimethyl-3-phenylazo-1,5-benzothiazepine (33) in 70% yield. On the other hand, phenylhydrazonoethylacetoacetate (30b) (Y = CO\(_2\)Et) condensed with 1 to yield the corresponding 2-hydroxy-4-methoxy-3-phenylazo-1,5-benzothiazepine (34) via loss of ethanol directly from the intermediate 31 (Y = CO\(_2\)Et) (Scheme 8).

2. 10. 3-Ethoxycarbonyl-1,5-benzothiazepine Derivatives

The Knoevenagel condensation of aromatic aldehydes 35 with ethyl acetoacetate (36) in dry benzene catalysed by piperidine under reflux conditions gave 3-benzylidene ethyl acetoacetate (37). The Michael addition of o-aminophenol (1) to the compound 37 yielded the corresponding ethyl acetoacetate derivative 38. The intramo-
lecular cyclization of 38 followed by a dehydration at pH 3–4 in acetic acid / methanol provided 2,3/2,5-dihydro-4-methyl-2-aryl-3-ethoxycarbonyl-1,5-benzothiazepines (39a–e) in 20–33% yield. The synthesized compounds were tested for their antimicrobial activities by standard disc diffusion method. The assayed collection included the following microorganisms: C. albicans (ATCC 10231), S. aureus (ATCC 25923), S. epidermidis (ATCC 26069) and E. coli (ATCC 44753) using disk diffusion methods. Fluconazole was used as a standard drug against fungi and vancomycin against bacteria. In the disc diffusion method, sterile paper discs (φ 6 mm) impregnated with compounds dissolved in DMSO at conc. of 12.5, 50, 100, 200 μg / disc were used. Preliminary study of the assay revealed that substituent on the phenyl rings had a large effect on the antimicrobial activity; compound 39e exhibited the greatest antimicrobial activity (Scheme 9).

2. 11. 3-Hydroxy-tetrahydro -1,5-benzothiazepines

The reaction of o-aminothiophenol (1) with various 2-(1-haloalkyl)oxiranes (40) provides cis and trans isomers of 1,5-benzothiazepines 42. The stereochemical outcome of these reactions depends on the configuration of the starting oxirane 40. The oxiranes were first reacted with o-aminothiophenol (1) in the presence of triethylamine to give the hydroxy precursors 41. The cyclization of the precursor occurred in the presence of KOH to give benzothiazepines 43. The alkyl or aryl substitution can be

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</table>

Scheme 10. Synthesis of 3-hydroxytetrahydro-1,5-benzothiazepines 43a–f.
introduced at the position 3 ($R^2$) and 4 ($R^3$) by properly choosing starting 2-(1-haloalkyloxiranes) $R_4$. The stereochemistry at C-4 and C-3 was confirmed by NOESY spectroscopy and analysis of the vicinal coupling constants. It is noteworthy that the reaction proceeded in a stereospecific manner ($i.e.$, syn $R_4$ gave cis $R_3$ and anti $R_4$ gave trans $R_3$). These results suggest the reaction proceeded via the oxirane intermediate $R_2$ (Scheme 10).

2. 12. Quinobenzothiazepines

One-pot synthesis of quino[2,3-$b$][1,5]benzothiazepines was described by the condensation of 2-chloroquinoline-3-carboxaldehydes $R_1$–$d$ with $o$-aminothiophenol (1) in DMF and in the presence of dry potassium carbonate at r.t. in 40–81% yield. The intermediary imines could not be isolated and the reduction of benzothiazepines $R_4a$–$c$ with lithium aluminum hydride in ether gave the corresponding 11,12-dihydro derivatives $R_4a$–$c$ in 80–90% yield. The tetracyclic derivative $R_4$ could derive from the base promoted formation of a Schiff base. The probable driving force for the reaction which leads to $R_4$ is the base catalysed displacement of the chlorine in $R_1$ by the sulfur atom of 1, although the initial formation of an imine cannot be ruled out (Scheme 11).

2. 13. $\alpha$-Oxoketene / $\alpha$-Cyanoketene Thioacetals as Synthons

The reaction of $\alpha$-oxo / cyanoketene S,S-acetals with $o$-aminothiophenol (1) in the presence of ethanol and triethylamine as a catalyst under reflux conditions gave 1,5-benzothiazepine derivatives $R_4a$–$c$. The reaction of benzothiazepine $R_4$ with hydrazine, phenylhydrazine or hydroxylamine in ethanol gave the corresponding azolobenzothiazepines $R_5a$–$c$ in 66–85% yield. Reaction of compound $R_4$ with malononitrile afforded pyrano[4,3-$b$]benzothiazepines $R_5$, which underwent cyclization into pyrido[4,3-$b$][1,5]benzothiazepine $R_6$. Also reaction of compound $R_4$ with ethyl cyanoacetate afforded pyrano[4,3-$b$]benzothiazepin-3-one $R_7$. The reaction pathway was assumed to proceed via a nucleophilic addition of an active methylene at the ethylenic bond of the thiazepine ring with an elimination of the MeSH molecule followed by the enolization and cyclization to the desired pyrano-benzothiazepine derivatives (Scheme 12).

![Scheme 11. Synthesis of quino2,3-b1,5benzothiazepine derivatives 45,46a-c.](image)

![Scheme 12. Synthesis of azolo / pyrano / pyridobenzothiazepines 51a–c,52–54.](image)
3. Preparation of 1,5-Benzothiazepines from Chalcones

Chalcones are the principal precursors for the biosynthesis of flavonoids and isoflavonoids. A three carbon α,β-unsaturated carbonyl system constitutes chalcones. Chalcones are the condensation products of aromatic aldehydes with acetophenones in the presence of a catalyst. These compounds are of high interest, due to their use as intermediates in the synthesis of a series of heterocyclic compounds, such as benzothiazepines, the pyrazolines and flavones. Although there are several methods available for the synthesis of chalcones the most important of them is by Claisen–Schmidt condensation performed in an acidic or basic medium under homogeneous conditions. The various types of benzothiazepines synthesized by employing chalcones are illustrated in Schemes 13–15 and are summarized in Table 1 (Schemes 16–19).

3.1. 2,4-Diaryl-1,5-benzothiazepines

The Claisen–Schmidt condensation of various substituted acetophenones with aromatic aldehydes in the presence of ethanol and KOH gave (E)-1-(5-substituted-2-hydroxyphenyl)-3-(4-substituted phenyl)prop-2-en-1-ones (chalcones) (57a–h). The chalcones on reaction with o-aminothiophenol (1) under reflux conditions in ethanol in the presence of glacial AcOH gave 1,5-benzothiazepine derivatives (58a–h) in 58–71% yield (Scheme 13). All the synthesized compounds were screened for their in vitro antimicrobial activity against Gram-positive organisms P. aeruginosa and S. aureus and Gram-negative organism E. coli using Gentamicin and Cefixime as a reference standard by paper disc diffusion method. All the tested compounds were evaluated at 50–100 μg/mL concentration. The microbial data revealed that 58e has shown better activity for Gram positive bacteria S. aureus ATCC 259223 (13–17 mm) (Scheme 13).

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Scheme 13. Synthesis of 2,4-diaryl-1,5-benzothiazepines 58a–h.

3.2. 1,2-Diaryl-1,5-benzothiazepines

The Claisen–Schmidt condensation of various substituted acetophenones with aromatic aldehydes in the presence of ethanol and KOH gave (E)-1-(5-substituted-2-hydroxyphenyl)-3-(4-substituted phenyl)prop-2-en-1-ones (chalcones) (57a–h). The chalcones on reaction with o-aminothiophenol (1) under reflux conditions in ethanol in the presence of glacial AcOH gave 1,5-benzothiazepine derivatives (58a–h) in 58–71% yield (Scheme 13). All the synthesized compounds were screened for their in vitro antimicrobial activity against Gram-positive organisms P. aeruginosa and S. aureus and Gram-negative organism E. coli using Gentamicin and Cefixime as a reference standard by paper disc diffusion method. All the tested compounds were evaluated at 50–100 μg/mL concentration. The microbial data revealed that 58e has shown better activity for Gram positive bacteria S. aureus ATCC 259223 (13–17 mm) (Scheme 13).

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<th>58</th>
<th>R₁</th>
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Scheme 13. Synthesis of 2,4-diaryl-1,5-benzothiazepines 58a–h.

Scheme 14. Synthesis of 1,5-benzothiazepine derivative 62.

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3.2. α-Substituted α,β-Enone as a Reactant

The reaction of cyclopropyl phenyl ketone (59), 4-chlorobenzaldehyde (60) and diethylamine in the presence of diethylaluminium iodide as the Lewis acid followed by Hofmann elimination of the formed intermediate pyrroolidinium salt with KOr-Bu gave the α-substituted-α,β-enone in 60% yield with E/Z ratio of 85:15.55 The reaction of α,β-enone 61 with o-aminothiophenol (1) in toluene in the presence of p-TSA gave the 1,5-benzothiazepine scaffold 62 in 45% yield. LC/MS analysis and NMR experiments indicated the formation of only one diastereoisomer, which was determined by NOESY experiments to be anti (Scheme 14).

3.3. cis-(±)-1,5-Benzothiazepines

Rao et al.56 have reported the synthesis of 1,5-benzothiazepines by cyclocondensation reaction of α-aminothiophenol (1) with diethylamine in the presence of 3a.

Table 1. Examples of 1,5-benzothiazepine derivatives by chalcones

<table>
<thead>
<tr>
<th>Scheme 16: 2,3-Diaryl-1,5-Benzothiazepines: (i) DMF, Al2O3 (basic), MWI, 90 °C, 7 min</th>
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</thead>
<tbody>
<tr>
<td>68 (a) R1 = R2 = R3 = R4 = H (78%); (b) R1 = Cl, R2 = R3 = R4 = H (82%); (c) R1 = Cl, R2 = R3 = R4 = H (84%);</td>
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<tr>
<td>(d) R1 = F; R2 = R3 = R4 = H (83%); (e) R1 = R2 = R3 = R4 = H, R1 = F (86%); (f) R1 = R2 = R3 = R4 = H, R1 = Cl (80%);</td>
</tr>
<tr>
<td>(g) R1 = R2 = R3 = R4 = H, R1 = MeO (89%); (h) R1 = R2 = R3 = H, R1 = MeO (81%); (i) R1 = R2 = R3 = H, R1 = Br (89%)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Scheme 17: Microwave mediated synthesis: (i) Benzene, AcOH (cat), MWI, 6 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>69 (a) R1 = R2 = R3 = H ; (b) R1 = MeO, R2 = R3 = H ; (c) R1 = MeO, R2 = R3 = H ;</td>
</tr>
<tr>
<td>(d) R1 = R2 = R3 = MeO ; (e) R1 = Cl, R2 = R3 = H ; (f) R1 = Cl, R2 = R3 = MeO</td>
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</tbody>
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<tr>
<th>Scheme 18: Benzoimidazolyl-benzothiazepines: (i) MeOH, AcOH (cat), reflux, 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 R = (a) H (67%); (b) MeO (61%); (c) 4-MeO (58%); (d) 3-Br (66%); (e) 2-Cl (61%); (f) Me2N (58%);</td>
</tr>
<tr>
<td>(g) 3-NO2 (65%); (h) 2-OH (66%); (i) 3-OH-4-MeO (63%); (j) 3,4-(MeO)2 (69%)</td>
</tr>
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</table>

Scheme 16: 2,3-Diaryl-1,5-Benzothiazepines: (i) DMF, Al2O3 (basic), MWI, 90 °C, 7 min

Scheme 17: Microwave mediated synthesis: (i) Benzene, AcOH (cat), MWI, 6 min

Scheme 18: Benzoimidazolyl-benzothiazepines: (i) MeOH, AcOH (cat), reflux, 4 h

Scheme 19: Piperazinyl-diazenyl-1,5-benzothiazepines: (i) DMF, AcOH, reflux, 9 h

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hiophenol (1) with Michael acceptors. The Friedel–Crafts acylation of benzene / substituted benzene with chloroacetyl chloride in the presence of aluminium chloride gave the phenacyl chloride 63 which underwent etherification with 4-nitrophenol in the presence of sodium carbonate in ethanol medium to give nitroether derivative 64. α-(4-Nitrophenoxy)chalcones 65 were obtained by a condensation reaction of 64 with arylaldehydes in the presence of NH$_4$OAc in EtOH. The cyclocondensation of chalcones 65 with o-aminothiophenol (1) in the presence of piperidine and dry toluene under reflux conditions gave the cis-(±)-2,4-diaryl-3-(4-nitrophenoxy)-1,5-benzothiazepines (66a–f) in 50–70% yield (Scheme 15).

4. Green Synthesis

Green chemistry with its twelve principles would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the number of the stages of the synthetic routes and minimize waste as far as practically possible. In this way, organic synthesis will be part of the effort for sustainable development. Green chemistry is also interested for research and alternative innovations on many practical aspects of organic synthesis. The various types of benzothiazepines synthesized by employing the green principles are illustrated in Schemes 20–24 and summarized in Table 2 (Schemes 25–30).

4.1. Ionic Liquid Mediated Regioselective Synthesis

The reaction between o-aminothiophenol (1) and methyl-(±)-trans-3-(4-methoxy / benzyloxyphenyl)glycinate (75a,b) under N$_2$ atmosphere at 60 °C in the presence of ionic liquid 1-butyl-3-methylimidazolium bromide ([BMIM][Br]) gave (+)/(-)-cis-2-(4-methoxy/benzyloxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (78a–h) as major products. The corresponding trans stereoisomer 81a–h were obtained as minor products in each case (Scheme 20). The stereochemistry (i.e. cis and trans) of compounds 78a–h and 81a–h was determined from the $^1$H NMR vicinal coupling constant data.

In the ionic liquid, the oxirane opens stereoselectively, followed by a subsequent cyclization resulting in the formation of products. The stereoselectivity and overall yield with glycidate 75b is better than with glycidate 75a because of the better electron donating ability of 75b (due to benzyloxy substituent), thereby resulting in increased carbocationic character of the benzylc carbon in the transition state. This observation is in agreement with an earlier report. The total yields of compounds 78 and 81 and the cis/trans ratio were dependent on the electron withdrawing effect of the substituents attached to o-aminothiophenols 1. The total yields of compounds 78 and 81 follow the order 7-CF$_3 >$ 9-CI > 8-CI > 7-CI > H and 7-CF$_3 >$ 8-CI > H when the reaction was carried out with the corresponding substituted o-aminothiophenol (1) and glycidates 75a and 75b, respectively.

4.2. Microwave Irradiation

The reaction of chalcones 82a–c with o-aminothiophenol (1) in the presence of silica-sulfuric acid without solvent under microwave irradiation for 1–2 min at 105–110 °C (2450 MHz, 800 W modified Amana domestic microwave oven) afforded 2-aryl-2,3-dihydro-4-(thiophen-2-yl)-1,5-benzothiazepine derivatives (85a–c) in 82–89% yield. The reaction may involve two pathways: (a) conjugate addition of the sulfhydryl to the α,β-unsaturated carbonyl group of 82a–c leading to the intermediate formation of the thia-Michael adduct 83, which upon a subsequent intramolecular nucleophilic attack by the NH$_2$ group on the carbonyl carbon followed by the dehydration forms the 2,3-dihydro-1,5-benzothiazepine 85a–c (path a) or (b) condensation of the amino group of 1 with carbonyl group of 82a–c leading to the intermediate formation of aza-diene 86, which upon a subsequent intramolecular conjugate addition by the sulfhydryl group forms the isomeric 2,5-dihydro-1,5-benzothiazepines 88a–c (path b). The reaction products 85a–c that are assumed to be formed via path a were identified by their
Scheme 20. Ionic liquid mediated regioselective synthesis of 1,5-benzothiazepines 78a-h.

(i) [BBIM]Br, N₂, 60 °C, 6-8 h

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<tr>
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<td>d</td>
<td>9-Cl</td>
<td>MeO</td>
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Scheme 21. Synthesis of 4-thiophenyl-1,5-benzothiazepines 85a-c.

(i) silica sulfuric acid, MWI, 1-2 min

85 Ar = (a) p-F-C₆H₄ (85%)
(b) p-CN-C₆H₄ (82%)
(c) 2-Thienyl (89%)

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analytical and spectral data. The other possible isomeric structures 88a–c were excluded based on their IR and 1H NMR spectral data (Scheme 21).

4. 3. Solid Phase Synthesis Approach

The reaction of Wang bromide resin 89 and ketone 90 in the presence of Cs₂CO₃ and NaI in DMF at 50 °C for 5 h gave the corresponding anchored ketone 91 in a quantitative yield. In the next step the formation of chalcone 92 was readily achieved by adding an excess of the desired ketone 91 to the anchored aldehyde (or vice versa) in THF / MeOH and using freshly prepared NaOMe as a base at r.t. The resin supported chalcone 92 was reacted with o-aminothiophenol in ethanol or THF in the presence of a few drops of AcOH at 60 °C for 5 h giving the resin bound 1,5-benzothiazepine derivatives. TFA cleavage in DCM at r.t. for 1 h gave the 1,5-benzothiazepine 93 in a total yield of 60–80 % (Scheme 22).

The synthesis of 1,5-benzothiazepines using tetrabutylammonium tribromide [TBATB] as a phase transfer catalyst (PTC) in water, sodium dodecylsulfate (SDS) in water, Al₂O₃ nano particles as inorganic solid support, microwave irradiation in the presence of 2-methoxyethanol, DMF as examples of alternative and environmentally benign reaction conditions are summarized in Schemes 23–27 (Table 2).

5. Mannich Base Derivatives

Mannich bases were at first used to improve water solubility of compounds currently in use, but later they were used to enhance the activity of some compounds with dialkylamino methyl groups. The Mannich reaction plays a key role in synthesis giving easy access to nitrogen containing compounds. Their functionalization towards various possible activities is still under investigation. Since numerous heterocyclic aromatic tricycles, including pyrrolobenzodiazepines and pyrrolobenzoxazepines bearing a basic side chain have been found to possess psychotropic activity, Kumar and Kaur et al. aimed at the synthesis of 3-(dimethylamino)methyl derivatives of 1,5-benzothiazepines in order to assess if any biological property could be ascribed to this series of compounds.

5. 1. Benzthiazepine Derivatives as Anticonvulsant Agents

The reaction of 4-hydroxyacetophenones and substituted benzaldehyde in the presence of KOH in methanol gave the corresponding substituted 4-hydroxy chalcones 102a–e in 80–90% yield. The cyclization of chalcones 102a–e with o-aminothiophenol (1) in the presence of glacial acetic acid in methanol under reflux conditions gave 4-(4'-hydroxyphenyl)-2-(substituted phenyl)-2,3-dihydro-1,5-benzothiazepines 103a–e in 68–78% yield. The Mannich reaction of 1,5-benzothiazepine derivatives 103 with various substituted anilines in the presence of formaldehyde in methanol under reflux conditions gave a series of 4-(4'-hydroxyphenyl)-2-(3-substituted phenyl)-3-(4-substituted phenylaminomethylene)-2,3-dihydro-1,5-benzothiazepines 104a–i in 68–78% yield. All the synthesized compounds 104a–i were screened in vivo for their anticonvulsant activity against maximal electroshock induced seizures at a dose of 30 mg / kg i.p.; All compounds 104a–i exhibited potent anticonvulsant activity 40–90 %. However, compound 104f (having 4-methoxy-phenylaminomethylene substitution...
at the third position of benzothiazepine ring) have shown most potent activity of 90% against MES test which is more potent than the standard drug phenytoin sodium (Scheme 28).

### 5.2. Benzothiazepinylpyridine Derivatives

2-Acetylpyridine was reacted with various substituted aromatic aldehydes to yield 2-(substituted benzylidenechalconyl)pyridines (105a–c), which on cyclisation with o-ami-
Chandrasekhar: Fused 1,5-Benzothiazepines from o-Aminothiophenol

In the presence of glacial AcOH, o-aminothiophenol (1) gave 2-[(2-substituted phenyl)-2,3-dihydro-1,5-benzothiazepin-4-y1]pyridines (106a–c) in 76–82% yield. Compounds 106a–c further undergo Mannich reaction with various substituted anilines in methanol to afford 2-[2-(substituted phenyl)-3-(substituted phenylaminomethyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]pyridines (107a–h) in 68–85% yield (Scheme 29). All the synthesized compounds 106a–c and 107a–h were tested for their anticonvulsant activity. Anticonvulsant activity was determined by supramaximal electroshock seizure pattern tests (SMES). This activity was performed by following the method of Toman et al. in albino rats. The effect of unknown compounds was compared with the standard drug phenytoin sodium and the LD50 was determined in albino rats weighing 100–120 g of either sex by the method of Smith. The results show that compounds having 2,3-dichlorophenyl moiety at the 3rd position of benzothiazepine ring (i.e., compounds 107e and 107h) exhibited more potent anticonvulsant activity than the reference drug.

Some more examples of this category of 1,5-benzothiazepine derivatives synthesized using the methodology discussed in reaction Schemes 28 and 29 are summarized in the Table 3 (Schemes 30–33).

6. 1,3-Dipolar Cycloaddition Reactions

The field of 1,3-dipolar cycloaddition chemistry developed dramatically during the past twenty-five years turning out to be a general method for the synthesis of five-membered heterocyclic rings containing the pyrroline structural unit. Recently, a lot of new compounds containing various heterocyclic rings, such as oxadiazole, imidazole and triazole annelated to the 1,5-benzothiazepine ring were synthesized by numerous research groups. It is well documented that the pharmacological activity could be increased when an additional heterocyclic ring is fused to the heptatomic nucleus. Taking this into con-

(i) AcOH (cat), MeOH, reflux, 5 h; (ii) MeOH, reflux, 6 h

122 (a) R = 3-MeO, R1 = 4'-Cl (42%); (b) R = 2-Cl, R1 = 4'-Cl (70%); (c) R = 4-Cl, R1 = 4'-Cl (68%);
(d) R = 2-OH, R1 = 4'-Cl (54%); (e) R = 4-OH, R1 = 4'-Cl (52%); (f) R = 3-MeO, R1 = 4'-MeO (67%);
(g) R = 2-Cl, R1 = 4'-MeO (53%); (h) R = 4-Cl, R1 = 4'-MeO (44%); (i) R = 2-OH, R1 = 4'-MeO (55%)

Scheme 28. Synthesis of 2,4-diaryl-1-(4-substituted phenylaminomethylene)-1,5-benzothiazepines 104a–i.

(i) EtOH, AcOH; (ii) MeOH, HCHO

107 (a) R = 4-OH, R1 = H (70%); (b) R = 4-OH, R1 = 2'-Cl (68%);
(c) R = 4-OH, R1 = 2'-MeO (69%); (d) R = 4-MeO, R1 = H (76%);
(e) R = 4-MeO, R1 = 2,3-Cl2 (70%); (f) R = 4-MeO, R1 = 2-MeO (73%);
(g) R = 4-OH, R1 = 3-MeO, 2-Cl (71%); (h) R = 4-OH, R1 = 3-MeO, 2,3-Cl2 (85%)

Scheme 29. Synthesis of 1,5-benzothiazepinyl pyridine derivatives 107a–h.

Some more examples of this category of 1,5-benzothiazepine derivatives synthesized using the methodology discussed in reaction Schemes 28 and 29 are summarized in the Table 3 (Schemes 30–33).
Table 3. Examples of 1,5-benzthiazepine derivatives by Mannich reaction

Scheme 30: Benzothiazepinyl indoles 110a–g: (i) AcOH, reflux, 4 h; (ii) MeOH, HCHO, Ar’NH₂, reflux, 6 h.

Scheme 31: N-substituted benzothiazepinylphenothiazepines 113a–m (i) MeOH, AcOH, reflux, 8 h; (ii) MeOH, HCHO, reflux, 6 h.

Scheme 32: 4-Methyl-1,5-benzothiazepinyl derivatives 116a–h: (i) AcOH, reflux, 4 h; (ii) MeOH, HCHO, R₇N₂, reflux, 6 h.
6.1. Oxadiazolo-benzothiazepines

The 1,5-benzothiazepine derivatives 117a–i were synthesized according to the previously reported methodology.88 The reaction between 1,5-benzothiazepine derivatives 117a–i and benzonitrile oxide 118 generated in situ from benzohydroximinoyl chloride (119) and Et3N in DCM leads to 3a,4-dihydro-1-phenyl-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepines (120a–i) in 37–68% yield.89 The oxadiazole ring is fused at the “d” edge of the heptatomic nucleus and the cycloaddition reaction has been found to be regiospecific and affords a single regiosomer according to the FMO approach. The stereochemistry of the synthesized compounds was unambiguously determined by NOE measurements in combination with the analysis of proton coupling constants and previous studies.88 The 5-substituent occupies a quasi-equatorial position in the predominant confirmation and the substituent at C-3a occupies a nearly axial position. The anticonvulsant properties of these derivatives 120a–i were evaluated in DBA/2 mice, which were genetically susceptible to sound-induced seizures.90 DBA/2 mice were exposed to auditory stimulation following intraperitoneal administration of drugs at the concentration of 0.1 mL / 10 g body weight of mouse. Auditory stimulation (12–16 kHz, 109 dB) was applied for 60 s or until tonic extension occurred. The results were compared with the activity shown by clinically useful anticonvulsant 1,5-benzothiazepines such as clobazam and desmethylclobazam, ED50 values were calculated by the method of probits analysis.91 The 5-(4-bromophenyl)-1,3-diphenyl derivative 120b, the most active compound of the series, is over 20 times more active than the parent benzothiazepine 117b and shows an activity comparable to clobazam and is better than desmethylclobazam (Scheme 33).

![Scheme 33. Synthesis of oxadiazolo-benzothiazepines 120a-i,121.](image)

![Scheme 34. Synthesis of 1,5-benzothiazepine derivatives 127a-h by cycloaddition reactions.](image)
6.2. Cycloaddition Reactions

The conjugated system of Ar–N=–N=Ar of 1,5-benzothiazepine is non-planar and the –C=N– bond in this system is more rigid than that in other systems. Roma et al. reported\(^9^2\) the cycloaddition reaction of the –C=N– bond of 1,5-benzothiazepines 123 with α-carbonyl ketene and the seven-membered heterocyclic tricyclic systems 127 were obtained. The reaction of α,β-unsaturated ketones 122 and α-aminothiophenol (1) in methanol in the presence of piperidine gave the 2,3-dihydro-1,5-benzothiazepines 123 in 80–95% yield. The reaction of 1,5-benzothiazepines 123 with 2-diazo-1,3-diphenyl-1,3-propanedione (124) in xylene at 100 °C afforded (4a,6-diaryl-2,3-diphenyl)-4a,5,6,12-tetrahydro-1H-1,3-oxazino[3,2-d][1,5]benzothiazepin-1-ones (127) in high yields\(^9^3\) (Scheme 34). All seven-membered rings in these heterocyclic compounds take the slightly distorted boat-like conformation and cis-fused 1,3-oxazinoone rings take the half-chair confirmation.

7. Fluoro Benzothiazepines

The chemistry of heterocyclic compounds with incorporated fluorine atoms is a rather promising area of

Table 4: Examples of 1,5-benzthiazepine derivatives by 1,3-dipolar cycloaddition reaction

| Scheme 35: Hexahydro-oxadiazolo-pyrido-benzothiazepines 133a–j: (i) MeOH, AcOH, piperidine, reflux, 30 min, r.t., 12 h; (ii) Et3N, DCM, r.t., 48 h. | Ref 94 |
| Scheme 36: Triazolo-benzothiazepines 137a–l: (i) MeOH, AcOH (cat), reflux 4 h, r.t., 12 h; (ii) DCM, Et3N, r.t., 72 h. |  |

Chandrasekhar: *Fused 1,5-Benzothiazepines from α-Aminothiophenol* ...
Table 5. Examples of 1,5-benzthiazepine derivatives by 1,3-dipolar cycloaddition reaction

Scheme 37: Oxadiazolo-1,5-benzothiazepine-containing 2-phenyl-1,2,3-triazole 140a–h: (i) EtOH, AcOH (cat), reflux 6 h, r.t., 12 h; (ii) DCM, Et3N, r.t., 72 h.

Scheme 38: Tricyclic 1,5-Benzothiazepines 142: (i) MeOH, AcOH (cat), reflux 8 h; (ii) DCM, Et3N, r.t., 24 h.

Scheme 39: Tetrahydro-1,2,4-triazolo/oxadiazolo-benzothiazepine 145a–f: (i) EtOH, AcOH (cat), reflux 6 h; (ii) DCM, Et3N, r.t., 48 h.

Scheme 40: Oxadiazolo-1,5-benzothiazepine 148a–d: (i) MeOH, AcOH (cat), reflux 12 h; (ii) DCM, Et3N, r.t., 4 days.

Chandrasekhar: Fused 1,5-Benzothiazepines from o-Aminothiophenol
Table 6. Examples of 1,5-benzthiazepine derivatives prepared by cycloaddition reaction

| Scheme 41: \(N\)-protected amino-\(\beta\)-lactam-1,5-benzothiazepine derivatives 151: (i) DCM, Et₃N, 72 h, r.t. | Ref 100 |
| Scheme 42: \(\alpha\)-Phenyl-\(\beta\)-lactam derivatives of 1,5-benzothiazepines 153a–d: (i) Benzene, Et₃N, 48 h, r.t. | Ref 101 |
| Scheme 43: \(\alpha\)-amino-\(\beta\)-lactam derivatives of 1,5-benzothiazepines 155a–l: (i) DCM, Et₃N, 72 h, r.t. | Ref 102 |
| Scheme 44: \(\alpha\)-(N-protected amino)-\(\beta\)-lactam-1,5-benzothiazepines 157: (i) DCM, Et₃N, 72 h, r.t. | Ref 103 |

research that has been fast developing for the last two decades.\textsuperscript{104,105} The introduction of fluorinated moieties into organic molecules brings important physicochemical modifications which often allow pertinent modulations of pharmacokinetic properties of molecules. In particular, the increased lipophilicity of trifluoromethylated compounds could favor the transmembrane permeation allowing a better biodispensibility of trifluoromethylated drugs.\textsuperscript{106} Thus, fluorine containing compounds have found wide application in medicinal chemistry; in particular, 20% of the currently developed pharmaceuticals contain fluorine atoms in their structure.\textsuperscript{107}

7.1. Trifluorobenzothiazepines

\(\beta\)-Trifluoromethyl-\(\beta\)-chloroacroleins 158 on the reaction with \(\alpha\)-aminothiophenol (1) in the presence of triethylamine and in THF at r.t. for 3 h gave benzothiazepine 162 in 30% yield. In a basic medium, such as in the presence of sodium hydride, the tetrahedral intermediate 159 is probably formed.\textsuperscript{108} The competition between the rate of intramolecular cyclization of the tetrahedral intermediate (159\(\rightarrow\)163) and the elimination of the chloride anion (159\(\rightarrow\)160) depends on the nucleophilicity of the amino group. Owing to the poor nucleophilicity of the amino group of 159, the elimination of the chloride anion occurs, resulting in the formation of 162.
(159→160→162, yield 30%). The benzothiazepine 162 was also obtained by cyclization of the iminothiol 161 (Scheme 45).

7.2. Trifluoromethylated Enones as Reactants

The reaction between β-trifluoromethylated enones 164a–e and o-aminothiophenol (1) in toluene in the presence of molecular sieves under reflux conditions, gave the fluorinated 1,5-benzothiazepines 165a–e in good yields. The two steps required for the formation of the thiazepine ring are equilibrium between Michael / retro-Michael reaction and ketone / imine formation. Consequently, if 164 is electrophilic enough to react with 1, these equilibrium should be simply displaced by favoring the formation of the imine. With this logic and reaction conditions the other 1,5-benzothiazepines were obtained with excellent yields (Scheme 46).

7.3. Fluorinated Benzothiazepine Fused β-Lactam Derivatives

The reaction of 3/4/5-differently substituted o-aminothiophenols 1 and 3-(substituted benzoyl)-2-propionic acid 166 in the presence of Montmorillonite KSF under microwave irradiation gave 2-carboxy-2,3-dihydro-1,5-benzothiazepines 167a–i in 70–82% yield. The reaction of 1,5-benzothiazepines 167 with chloroacetyl chloride in the presence of K2CO3 under microwave irradiation in the absence of any solvent gave the β-lactam derivatives, namely azeto[2,1-d][1,5] benzothiazepine derivatives 168a–i in 75–85% yield. Structures of all β-lactam fused benzothiazepine derivatives have been elucidated by elemental analyses and spectral data. The synthesized compounds were screened for antifungal activity against three pathogenic fungi, namely Rhizoctonia solani (causing root rot of okra), Fusarium oxysporum (causing wilt of mustard) and Collectotrichum capsici (causing leaf spot and fruit rot of chili) using pot trial method. In the pot trial experiments it was found that compounds having

(i) molecular sieves, 4 Å, toluene, reflux, 72 h

165 Ar = (a) (40%) ; (b) (63%) ; (c) (46%) ; (d) (75%)

Scheme 46. Synthesis of aryl / heteroaryl trifluorobenzothiazepines 165a–d.
alkoxy (OR) and trifluromethyl (CF₃) groups showed maximum germination (76–80%) indicating that it is the most effective in controlling the growth of the pathogen. “Baynate” and “Thiran”, recommended as standard fungicides as seed dressers to control this disease are also having –N–C–S– linkage similar to the synthesized compounds (Scheme 47).

8. Miscellaneous 1,5-Benzothiazepines

8.1. Aryl-phenylindeno-benzothiazepines

The condensation of 3-phenylindan-1-one (169) and the appropriate p-substituted benzaldehydes in NaOH / ethanol gave 2-(E)-benzylidene / p-substituted benzylidene-3-phenylindan-1-ones (170) in excellent yields.¹¹² Condensation of equimolar quantities of 2-(E)-benzylidene / p-substituted benzylidene-3-phenylindan-1-ones (170) with o-aminothiophenol / 5-substituted-2-aminobenzenethiols (1) in toluene using TFA as the catalyst furnished 11-p-substituted phenyl-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepines (171a–l) in 70–83% yields.¹²⁴ The in vitro antibacterial activity of the synthesized 1,5-benzothiazepines 171a–l was tested against two Gram-positive bacteria, viz. B. subtilis (MTCC 441), S. aureus (MTCC 7443), two Gram-negative bacteria, viz. E. coli (MTCC42) and P. aeruginosa (MTCC7952), using serial dilution technique and minimum inhibitory concentrations (MIC) were

![Scheme 47. Fluorinated benzothiazepine fused β-lactam derivatives 168a–i.](image)

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Scheme 48. Synthesis of aryl-phenylindeno-benzothiazepines 171a–l.
determined as described in the literature. Penicillin and streptomycin were used as reference compounds and MIC were determined in terms of μmol/mL. The antimicrobial data indicated that compounds 171d–f, 171i–l exhibited very promising antibacterial activity (Scheme 48).

8. 2. Acyl Benzothiazepines

The Knoevenagel condensation of various aromatic aldehydes 172a–j with propanedioic acid in the presence of pyridine and piperidine under reflux conditions gave the 3-substituted acrylic acids 173a–j in 56–95% yield. The cyclization of the resulting acids 173a–j with o-aminothiophenol (1) without any solvent at 180 °C for 6 h gave the key intermediates of 2,3-dihydro-1,5-benzothiazepine-4(5H)-one 174 analogs in moderate yields after recrystallization. The electrophilic substitution of alkyl or acyl halides in the presence of NaH at –10 °C for 30 min gave the N-alkyl, aromatic alkyl or acylbenzothiazepine analogs 175a–s in 15–95% yield.115 It is worth noting that the unfavorable attack of C-3 position could be avoided under this reaction conditions and as a result high yields of 80–95% were obtained116 (Scheme 49).

8. 3. trans-7-Aryl-benzopyranobenzothiazepines

Reaction of 4-chromanone 176 with various aromatic aldehydes 177a–i in the presence of AcOH and HCl at 0 °C gave the trans-3-arylidenyl derivatives of chroman-4-ones in 80–96% yield. The absence of cis-3-arylindinyl compounds was ascertained by HPLC. The reaction of arylidenes 178a–i and o-aminothiophenol (1) in 1:1 (v/v) solution of ethanol / toluene in the presence of a strong acid, such as TFA with conc. HCl for 2 h gave trans-7-aryl-6H-6a,7-dihydro[1]benzo-pyran[3,4-c][1,5]benzothiazepines117 (181a–i) in 87–97% yield. These reactions did not require the usual work up since the products 181a–i precipitated from the reaction medium in pure state upon standing. The mechanism involves reaction of 178 with 1 by a Michael type addition to give the adduct 179, which then undergoes an intramolecular nucleophilic addition of the amino group to the carboxyl moiety to give intermediate 180. This intermediate then undergoes dehydration to give 181. The structures of 181a–i were confirmed by 1H NMR, 13C NMR spectroscopy and in the case of 181a and 181g by X-ray crystallography (Scheme 50).

8. 4. Benzopyrano-benzothiazepinones

3-Formylchromones 182 reacted with o-aminothiophenol (1) in the presence of p-toluenesulfonic acid in benzene under reflux conditions for 30 min giving 5a,11-dihydro[1]benzo-pyran[2,3-b][1,5]benzothiazepin-13-ones (184a–c) in 78–81% yield. Prolonged heating of the reaction mixture led to the dihydro products 184 being formed in admixture with the corresponding dehydrogenated compounds 185 reflecting the ease with which the more conjugated product is formed from the dihydro com-

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Scheme 49. Synthesis of acylbenzothiazepines 175a–s.

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The cyclization stage proceeds via an intramolecular 1,4-nucleophilic addition process which leads to the 7-membered ring rather than the alternative 5-membered ring. This conclusion is in agreement with the Baldwin prediction that the 7-endo-trig process is favored whereas the 5-endo-trig is not. The dehydrogenation reaction of dihydro derivatives with chloroanil in xylene under reflux conditions gave the benzopyrano[2,3-b][1,5]benzothiazepine-13-ones in high yields (Scheme 51).

8.5.4-Fluorophenyl-6-phenyl[1]benzopyrano[3,4-c][1,5]benzothiazepines

The condensation of 3-(4-fluorobenzylidene)-flavanone (flavindogenide) with 5-substituted o-aminothiophenols in toluene in the presence of catalytic amount of TFA under reflux conditions gave a series of 10-substituted-6a,7-dihydro-6H-7-(4-fluorophenyl)-6-phenyl[1]benzopyrano[3,4-c][1,5]benzothiazepines in 58–68% yield. The protonation of...
the carbonyl carbon in flavindogenide causes a drift of electrons from α,β-unsaturated carbon to the carbonyl carbon. As a result, vinyl carbon becomes poorer in electron density and is prone to a nucleophilic attack by sulfhydryl electrons. This results in the formation of an intermediate, which immediately further reacts with the amino group. The dehydrative cyclization accompanied by the elimination of a protonated water molecule results in the formation of –C=N– bond. All synthesized compounds were screened for their antimicrobial activity against the bacteria *E. coli* and *Alteromonas tetraodonis* (GFC) at the conc. of 100 μg / disc using the filter paper disc method 122 with bacitracin as the reference standard. The compounds 188a, 188b, 188f showed higher relative activity (activity index = 1.14–1.28) against *E. coli*, whereas against GFC the compound 188f was found to be of higher relative activity (activity index = 1.28) (Scheme 52).

8. 6. Enantiomerically Pure
1,5-Benzothiazepines and Benzothiazolyl-2-methylacrylic Acids

The reaction of itaconic acid or dimethylitaconate with o-aminothiophenol (1) in THF gave the Michael adducts 189a,b in 70–74% yield. The carbodiimide induced regioselective intramolecular dehydrative cyclization of the diacid 189a gave the seven membered benzothiazepinyl acetic acid 190a in 88% yield. The benzothiazepinyl acid 190a was converted to its methyl and ethyl esters 190b,c. The formation of the seven membered benzothiazepine 190a was confirmed by X-ray crystallographic data, ruling out the possibility of a formation of an eight membered compound, benzothiazozone 203. From these observations of the reaction of itaconic anhydride (191) with o-aminothiophenol (1), it is clear that a chemoselective Michael type addition of the thiol takes place first to form the unisolable intermediate 192, the amine moiety of which condenses in an intramolecular fashion with the adjacent anhydride carbonyl to furnish the benzothiazepine 190a. Herein, an addition of the thiol to a –C=C– double bond on an anhydride system before the anhydride ring opening with an amine moiety is an example of a delicately balanced selectivity.

The reaction of itaconic anhydride (191) with natural (−)-menthol in the presence of p-TSA in toluene under azeotropic removal of water gave dimethyl itaconate (193) in 80% yield. The stereoselective reaction of o-aminothiophenol (1) with the chiral diester 193 in glacial acetic acid gave the chiral adduct 194a in 82% yield. The reaction was moderately stereoselective and a mixture of two diastereomers in nearly 7:3 ratio were formed as evidenced from 1H NMR data. The adduct 194a upon the acid catalysed hydrolysis gave the diacid 195a in 86% yield. The carbodiimide (EDCI) induced regioselective ring closure of 195a yielded the 1,5-benzothiazepinyl-1,3-acetic acid (196a) in 88% yield. The reaction of 196a with (+)-(R)-phenylethylamine gave the two diastereomers 197 and 198 in 90% yield, which led to the final separation of the two enantiomers 196a. The mixture of diastereomers 197 and 198 was easily separated by flash chromatography to obtain pure 197 and 198 with quantitative recovery of 197:198 (70:30).123 The single isomer 194b upon the hydrolysis followed by the ring closure gave the desired enantiomERICALLY pure 1,5-benzothiazepinylacetic acid (196b) in 76% yield (Scheme 53).

The reaction of o-aminothiophenol disulfide (199) with 2.2 equiv. of itaconic anhydride (191) in THF at r.t. afforded the dicarboxylic acid 200 in 81% yield. The triphenyl phosphate induced reductive cleavage of the S–S bond in the diacid 200 formed the unsoluble interme-
diary acid 201, which by an in situ intramolecular dehydration cyclization furnished the 2-benzothiazo-2-yl methyl acrylic acid (202) in 84% yield. The expected benzothiazocine 203 was not obtained, indicating the reluctance for the intramolecular Michael type addition of thiol in 201 to form the eight membered heterocycle (Scheme 53).

8. 7. 1,5-Benzothiazepines and 1,4-Benzothiazines

The condensation of dehydroacetic acid (DHA) (204) with benzaldehydes or their heterocyclic analogs in chloroform in the presence of piperidine\textsuperscript{124} gave α,β-unsaturated ketones 205. In the second step, compounds

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205 reacted with o-aminothiophenol (1) in EtOH / AcOH to afford dihydro-1,5-benzothiazepines 208 and/or dihydro-1,4-benzothiazines 209 in 76–86% yield. Both kinds of molecules can be formed from the same kind of intermediate by a 7-endo-trig and 6-exo-trig mechanism. This is a formal representation and does imply whether the N–C or S–C bond is formed first. The formation of the seven membered ring in the case of a phenyl substituent and that of the six membered ring in the case of pyridine as an example of an electron withdrawing substituent that include o-nitro and p-nitrophenyl groups, is illustrated in 207. In the case of pyridine, the protonation of the pyridine nitrogen should catalytically even increase its electron withdrawing properties. Thus, based on the structures of aldehydes or reaction conditions, the products 208,209 are formed (Scheme 54).

### 7. Conclusions

The data presented in this review clearly demonstrate the high synthetic potential of o-aminothiophenol (1) and its derivatives. Many biologically active 1,5-benzothiazepine derivatives have been obtained on the basis of reactions of these reagents and carbonyl compounds and other functional groups.

### 8. References

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V pregledu so predstavljene reakcije o-aminotiofenola in njegovih derivatov kot gradnikov za sintezo polifunkcionalnih 1,5-benzotiazepinov s farmakološko pomembnimi lastnostmi. Pripojeni 1,5-benzotiazepini so bili pripravljeni s ciklo-kondenzacijskimi reakcijami o-aminotiofenola in njegovih derivatov s spojinami, ki vsebujejo karbonilne in druge funkcionalne skupine. V primeru, ko reagirajo karbonilne skupine, reakcije potekajo z nukloefilno adicijo, ki ji sledi ciklizacija s hkratno eliminacijo vode. Namen tega prispevka je zagotoviti celosten pregled nad sintezami različnih 1,5-benzotiazepinskih derivatov in prikazati njihov potencial za razvoj boljših kemoterapevtikov.