Review Article
Benzo[1,5]thiazepine: Synthesis, Reactions, Spectroscopy, and Applications

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This review article deals with synthesis and reactions of benzo[1,5]thiazepines and the related derivatives and their applications, biological activity as well as spectroscopic data. Most of the reported data on the methods of synthesis, chemical reactions, and biological activity of these heterocycles published over the last ten years are reviewed in this paper.

1. Introduction

1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine and one of the three possible benzo-condensed derivatives, namely, 1,4-, 4,1- and 1,5-benzothiazepines. The parent 1,5-benzothiazepine, itself, has not hitherto been described in the literature for its pharmacological properties. However, its 2,4-disubstituted derivatives and many hydrated derivatives have been synthesized. The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets. The first molecule of 1,5-benzothiazepine used clinically was diltiazem, followed by clenitazem, for their cardiovascular action. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim and quetiapine fumarate. Moreover, 1,5-benzothiazepine moiety is a privileged class of pharmacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities such as anticonvulsant, Ca^{2+} channel antagonist, antianginal, anti HIV, squalene synthetase inhibitor, V_{2} arginine vasopressin receptor antagonist, and HIV-1 reverse transcriptase inhibitor [1–3].

The methods for the preparation of 1,5-benzothiazepines can be divided into two major groups, namely, the construction of a seven-membered heteroring from the elements of open chains, and reactions involving ring expansion.

2. Nomenclature and Way of Numbering

1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine. According to the IUPAC nomenclature, the benzo[1,5]thiazepine structures IA or IB may be named as (Z)-2,3-dihydrobenzo[b][1,4]thiazepine or (Z)-2,3-dihydro-substituted-benzo[b][1,4]thiazepine. Also, the substituted-benzo[1,5]thiazepines structure IIA or IIB may have the name: 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine or 2,3,4,5-tetrahydro-substituted-benzo[b][1,4]thiazepine (see Figure 1).

3. Preparation of 1,5-Benzothiazepine System and Its Related Derivatives

3.1. Thiophenol and Its Derivative Approaches

3.1.1. Solid Phase Synthesis: Claisen-Schmidt Condensation of 3-Hydroxyacetophenone with Different Substituted Aldehydes and o-Aminothiophenol. The solution phase synthesis of 2,3-dihydro-1,5-benzothiazepines 4 and 5 was carried out by heating under reflux of α,β-unsaturated ketones 3 (obtained from reaction of an aldehyde and the acetophenones 2) with o-aminothiophenol in dry acidic MeOH in the presence of drops of glacial CH_{3}COOH. Also, the synthesis of 2,3-dihydro-1,5-benzothiazepines 9 was carried out on Wang
Solution phase synthesis of 2,3-dihydro-1,5-benzothiazepines (4 : a–d; 5 : a–g)

Solid phase synthesis of 2,3-dihydro-1,5-benzothiazepines 9 (a–p)

Scheme 1: Solid phase synthesis: Claisen-Schmidt condensation of 3-hydroxyacetophenone with different substituted aldehydes and o-aminothiophenol.

3.1.2. Reactions of Polyfluorinated Chalcones with o-Aminobenzenethiol and Its Zinc Salt. Chalcone 10a on heating under reflux with 2 moles of o-aminothiophenol produced equal amounts of the benzo[ b ][1, 5]thiazepine 11a

resin using chalcones 8 as precursors which in turn were synthesized on the same solid support through Claisen-Schmidt condensation of 3-hydroxyacetophenone 6 with different substituted aldehydes 7 [4] (Scheme 1).
Scheme 2: Reactions of polyfluorinated chalcones with o-aminobenzethiol and its zinc salt.

(5% yield) and 3-(2-aminophenylthio)-3-(perfluorophenyl)-1-phenylpropan-1-ol 12a. Reaction of 10b with o-aminothiophenol (2-moles) afforded 1,5-benzothiazepine 11b in 88% yield. When a threefold excess of the reactant was used in the reaction of 10c with o-aminothiophenol the benzo[b][1,5]thiazepine 11c was afforded (80% yield). To reveal the sequence step of formation of benzothiazepines, the thia-adducts 12a–c were synthesized by the reaction of chalcones 10a–c with o-aminothiophenol in MeOH at 20°C for 3–6 h. The thia-adduct 12a under reflux in MeOH in presence of HCl underwent partial ring closure to form benzothiazepine 11a and partially 12a transformed into chalcone 10a; however, the most part of 12a remains unchanged. The adduct 12b under the same reaction conditions was completely consumed and the reaction mixture contained chalcone 10b, 1-(4-(2-aminophenylthio)-2,3,5,6-tetrafluorophenyl)-3-phenylprop-2-en-1-one 13 together with thebenzo[b][1,5]thiazepines 11b,d. Also, the same reaction of the adduct 12c under reflux formed a complicated mixture of products containing chalcone 10c, thia-adducts 12c,d, and benzothiazepines 11c,e [5] (Scheme 2).

3.1.3. Reaction of Gem-Acetyl- and Gem-Benzoylnitrostyrenes with o-Aminothiophenol. The chemical behavior of nitrogen ketones was investigated via reactions of gem-acetyl- and gem-benzoylnitrostyrenes 14–19 with o-aminothiophenol. These reactions proceed successfully at equimolar ratio of reagents under very mild conditions at 18–20°C in methanol, in the absence of a catalyst, in 10–20 min, to
form new compounds 20–24, respectively. However, while the gem-acetyl-nitro-styrenes 14–16 afford 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines 20–22, from the gem-benzoinitrostyrenes 17–19 linear S-adducts 23–25 were obtained in 80–98% yield. Apparently, the reaction of o-aminophenol with gem-acetyl-nitro-styrenes 14–19 lead initially to the formation of an adduct at the multiple C=C bond (AdN), which was isolated in the case of compounds with the benzoyl group 23–25, and the adducts obtained from the gem-benzoinitrostyrene 14–16 immediately suffers heterocyclization. This may be due to the difference in activity of carbonyl groups in the benzoyl and acetyl function of the addition products. Probably, the attack of amino group on the benzoyl carbonyl group in the adducts 23–25 is difficult compared to the acetyl analogs due to steric and electronic factors.

In order to obtain nitrobenzotheazepine structures with phenyl substituent at the C4 atom, the linear S-adducts 23 and 24 when heated under reflux in EtOH in the presence of methanolic HCl for 1–3 h 2-aryl-3-nitro-4-phenyl-2,5-dihydro-1,5-benzothiazepines 26 and 27, were obtained, respectively [6] (Scheme 3).

3.1.4. Cyclocondensation Reaction of (E)-N-(4-(3-(2-Chloro-5, 6,7,8-substituted-quinolin-3-yl)acryloyl)phenyl)-methylbenzo-nesulfonamide with 2-Aminobenzothiazepine in Ethanol in Presence of Bi-Catalyst. The 2-chloro-substituted quinoline chalcones 30 were prepared from condensation of 4-methyl sulphonamido acetonaphone 28 and quinoline-3-carbaldehyde 29 in alcoholic KOH. Cyclo-condensation of the chalcones 30 with o-aminophenol in the presence of a bicatalyst afforded the benzothiazepines 31 in good yield [7] (Scheme 4).

3.1.5. Cyclocondensation of 1-(4-(Methylsulfonyl)phenyl)-2-tosyl-3-(3,4,5-trisubstituted phenyl)prop-2-en-1-ones with 2-Aminophenol in Refluxing Toluene Using Catalytic Amounts of Trifluoroacetic Acid. Condensation of 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone 32 and 4-methyl sodium benzene sulfinate 33 gave 1-(4-(methylsulfonyl)phenyl)-2-tosylethanone 34. Claisen-Schmidt condensation of 34 with aryl aldehydes in the presence of piperidine in CH$_2$Cl$_2$ gave the intermediates 1-(4-(methylsulfonyl)phenyl)-2-tosyl-3-(3,4,5-trisubstituted-phenyl)prop-2-en-1-ones 35a–f in excellent yields. Cyclo-condensation of 35a–f and o-aminophenol in refluxing toluene using CF$_3$COOH catalyst gave better yields of 2-(substituted phenyl)-3-[(methyl phenyl) sulfonyl][[(methyl sulfonyl) phenyl]-2,3-dihydro-1,5-benzothiazepines 36a–f (Method A). Also, the neat cyclo-condensations of the chalcones 35 supported on silica-gel with o-aminophenol occurred rapidly at 80°C and gave better yields of the desired tri-substituted 1,5-benzothiazepines 36a–f (Method B) [8] (Scheme 5).

3.1.6. Cyclo-Condensation Reaction of the Phenolic $\beta$-Diketones with o-Aminotheophenol. Cyclo-condensation of the Phenolic $\beta$-diketones 37a–d with o-aminophenol proceeded under oxidation to give oxygen-bridged 1,5-benzothiazepines 39a–d in a reasonable yield, whereas the respective compounds 38a–d and 40a–d were not detected [9] (Scheme 6).
Scheme 4: Cyclocondensation reaction of (E)-N-(4-(3-(2-chloro-5,6,7,8-substituted-quinolin-3-yl)acryloyl)phenyl)-methylbenzenesulfonamide with 2-aminothiophenol in ethanol in presence of bi-catalyst.

3.1.7. Thermal Reaction of (Z)-1,3-Diphenyl-2-(1H-1,2,4-triazol-1-yl)prop-2-en-1-one with o-Aminothiophenol in the Presence of CF$_3$COOH. 1-Phenyl-2-(2H-1,2,3-triazol-2-yl)ethanone 41 when heated under reflux with benzaldehyde and catalytic amount of piperidine gave 1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl)prop-2-en-1-one 42. The latter triazole upon thermal reaction with o-aminothiophenol and CF$_3$COOH for 5-6 h yielded 1,5-benzothiazepine containing 1,2,4-triazole moiety 43 (43$^\dagger$ tautomeric form in solvent) in 72.7% yield [10] (Scheme 7).

3.1.8. Reaction of 1-(2-Phenyl-2H-1,2,3-triazol-4-yl)-3-(p-substituted-phenyl)prop-2-en-1-ones with o-Aminothiophenol, in EtOH under Reflux in the Presence of CF$_3$COOH. 1-(2-Phenyl-2H-1,2,3-triazol-4-yl)-3-(p-substituted-phenyl)prop-2-en-1-ones 44a–d (prepared from the desired aromatic aldehydes and 1-(2-phenyl-2H-1,2,3-triazol-4-yl)ethanone) on reaction with o-aminothiophenol, in EtOH under reflux in the presence of CF$_3$COOH gave 2,3-dihydro[1,5]benzothiazepines 45a–e in good yield (Scheme 8) [11] (Scheme 8).

3.1.9. Thermal Reaction of (E)-1-(2-Phenyl-2H-1,2,3-triazol-4-yl)-3-(p-substituted-phenyl)prop-2-en-1-ones with o-Aminobenzethiol in Presence of CF$_3$COOH. The $\alpha$,$\beta$-unsaturated carbonyl compounds 48a–c were prepared by a condensation reaction of 4-acetyl-2-phenyl-1,2,3-triazole 46 with substituted aldehydes 47a–c. Preparation of the carbonyls 48d,e using the same method failed and instead gave Michael type addition products 50d,e as major compounds. Successful preparation of 48d and e was fulfilled via dropping of 4-acetyl-2-phenyl-1,2,3-triazole 46 into solutions of the aldehydes 47d,e in EtOH slowly. The triazoles 48a–e upon heating with o-aminothiophenol in presence of CF$_3$COOH in ethanol (5-6 h) afforded the
Scheme 5: Cyclocondensation of 1-[(4-methylsulfonyl)phenyl]-2-tosyl-3-(3,4,5-trisubstituted-phenyl)prop-2-en-1-ones with o-aminothiophenol in refluxing toluene using catalytic amounts of trifluoroacetic acid.
Scheme 6: Cyclo-condensation reaction of the phenolic \( \beta \)-diketones with o-aminothiophenol.

Scheme 7: Thermal reaction of (Z)-1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl)prop-2-en-1-one with o-aminothiophenol in presence of \( \text{CF}_3\text{COOH} \).

\( \text{(E)}-4\text{-}(2\text{-phenyl}-2H-1,2,3-triazol-4-yl)-2\text{-}(p\text{-substituted-phenyl})2,3\text{dihydrobenzo}[1,5]\text{thiazepines 49a}–\text{e in good yield} \) [12] (Scheme 9).

3.1.10. Reaction of Chalcones with 2-Aminothiophenol Derivatives in the Presence of Fluoroboric Acid Adsorbed on Silica-Gel (HBF\(_4\)–SiO\(_2\)). When chalcones of type 51 were treated with o-aminothiophenol in the presence of fluoroboric acid adsorbed on silica-gel (HBF\(_4\)–SiO\(_2\)) selective thia-Michael addition to the \( \alpha,\beta \)-unsaturated carbonyl moiety took place to form the corresponding adducts 52 in excellent yields. The latter adducts when heated under reflux in MeOH/HBF\(_4\)–SiO\(_2\) gave the corresponding 2,3-dihydro-1,5-benzothiazepines 53 in high yields through a one-pot cycloaddition reaction [13] (Scheme 10).

3.1.11. Reaction of 3-(2-Phenoxyquinolin-3-yl)-1-p-substituted-prop-2-en-1-ones with o-Aminothiophenol in Ethanol Using Acetic Acid as Catalyst. 2-Chloro-3-quinolinecarbaldehyde
**Scheme 8:** Reaction of 1-(2-phenyl-2H-1,2,3-triazol-4-yl)-3-(p-substituted-phenyl)prop-2-en-1-ones with o-aminothiophenol, in EtOH under reflux in the presence of CF₃COOH.

<table>
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<tr>
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<td>76</td>
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<tr>
<td>(b)</td>
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<td>(c)</td>
<td>Cl</td>
<td>80</td>
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<tr>
<td>(d)</td>
<td>NO₂</td>
<td>79</td>
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(i) (1) EtOH, NaOH (2%), stirring at r.t. (2-3 h); (2) neutralization to pH 7

(ii) Ethanol, stirring for 20–30 min, CF₃COOH, reflux for 5–6 h

**Scheme 9:** Thermal reaction of (E)-1-(2-phenyl-2H-1,2,3-triazol-4-yl)-3-(p-substituted-phenyl)prop-2-en-1-ones with o-aminobenzenethiol in the presence of CF₃COOH.

54 reacted with phenol in presence of an alkali to give 2-phenoxy-3-quinolinecarbaldehyde 55. The α,β-unsaturated ketones 56a–c were synthesized via Claisen-Schmidt condensation between the phenoxy derivative 55 and 1-arylthionones. Equimolar quantities of 56a–c and o-aminothiophenol in ethanol using CH₃COOH as catalyst afforded satisfactory yields of the 1,5-benzothiazepine derivatives 57a–c [14] (Scheme 11).
One-pot synthesis of 2,3-dihydro-1,5-benzothiazepines 53.

HBF₄-SiO₂-catalysed one-pot synthesis of 2,3-dihydro-1,5-benzothiazepines by reaction of 1,3-diaryl-2-propenones with o-aminothiophenol

<table>
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<td>4</td>
<td>81</td>
</tr>
<tr>
<td>(b)</td>
<td>H</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>(c)</td>
<td>Cl</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>(d)</td>
<td>H</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>(e)</td>
<td>H</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>(f)</td>
<td>OMe</td>
<td>6</td>
<td>87</td>
</tr>
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</table>

(a) 1,3-Diaryl-2-propanone in MeOH treated with o-aminothiophenol in the presence of HBF₄-SiO₂; (b) Isolated yield of 2,3-dihydro-1,5-thiazepines after chromatographic purification.

Scheme 10: Reaction of chalcones with o-aminothiophenol derivatives in the presence of Fluoroboric acid adsorbed on silica-gel (HBF₄-SiO₂).

Scheme 11: Reaction of 3-(2-phenoxyquinolin-3-yl)-1-p-substituted-prop-2-en-1-ones with o-aminothiophenol in ethanol using acetic acid as catalyst.

Scheme 12: Thermal Reaction of 5-Aryl-2,4-bis(arylmethylidene) Dihydro-3-thiophenones and o-Aminothiophenol in Acetic Acid Compared to Same Reaction Performed under Solvent-Free Microwave Irradiation. The benzothiazepines 58 were synthesized in 55–91% yields upon heating under reflux 5-aryl-2,4-bis(arylmethylidene) dihydro-3-thiophenones 60 with o-aminothiophene in a 1:1.5 molar ratio in CH₃COOH for 45–60 min.

For comparison, when the thiophenone 60 and o-aminothiophenol in the same molar ratio and CH₃COOH...
catalyst were thoroughly mixed and irradiated while stirring in a microwave oven for 2-3 min at maximum 84°C; the benzothiazepine derivatives were afforded in moderate yields (42-62%). Therefore, the reaction under microwave irradiation proceeded rapidly but led to a lower yield of the desired benzothiazepine products compared with the thermal reaction.

The tandem reaction leading to 58 presumably proceeds through an initial Michael addition of o-aminophenol to 5-aryl-2,4-bis(aryl)methylene)dihydro-3-thiophenones affording 61 with concomitant condensation to afford 63 either directly from 62 or through 59. Presumably, the aromatic stability of the thiophene ring provides the impetus for the isomerization of 63 to furnish 58. It is pertinent to note that thieno-benzothiazepine 64, a regioisomer of 58, forming 63 is envisaged to trigger the isomerization of 59 in the presence of acetic acid [15] (Scheme 12).

### 3.1.13. Improved Synthesis of 1,5-Benzothiazepines Using Ceric Ammonium Nitrate (CAN).

Reaction of chalcone 65a with o-aminophenol at 60–65°C in the absence of ceric ammonium nitrate (CAN) catalyst did not proceed after extensive long reaction times (8–10 h) with lower yield of the desired 1,5-benzothiazepine. Meanwhile, upon using 2 mol or 6 mol% of CAN catalyst, the conversion to 1,5-benzothiazepine was 70% and 85% yield, respectively. Continuation of subsequent condition optimization revealed that 10 mol% of CAN catalyst was sufficient to complete the reaction and the best result obtained 66a in ethanol after ultrasonic irradiation was 93% without any undesirable side product being observed. Therefore, attempts were continued to examine this reaction generality through reactions of several substituted homocyclic 65b–h and heterocyclic 65i–k chalcones with o-aminophenol. The obtained results were compatible with various substituents such as F, NO2, Cl, CH3, and OCH3 and no competitive nucelophilic cleavage was observed for the substrate having an aryl, CH3 or OCH3 groups. Also, the case of electron donating substituents resulted in longer reaction times, and the electron withdrawing substituents required shorter time for the complete reaction. Moreover, no significant substituent effects were observed in case of heteroaryl aldehydes. Generally, this method offers significant advantages over the other methods including the fact that (i) the reaction is simple to execute; (ii) the 1,5-benzothiazepine products are isolated in good to excellent yields; (iii) the work-up is simple; (iv) the reaction time is short (32–38 min); (v) the 1,5-benzothiazepines are obtained in excellent purity [16] (Scheme 13).


To prove that the ultrasonic irradiation plays an important role in the synthesis of 1,5-benzothiazepines a model optimum experimental conditions for the reaction of chalcones of type 69 (prepared from 4-(phenylthio)benzaldehyde 68 and o-hydroxy acetophenones 67) reaction of chalcone 69a with o-aminothiophenol in EtOH was tried. The results indicated that 30 min and a temperature of 65°C were sufficient to obtain high yield of the 1,5-benzothiazepine product 70a (93%). In comparison, upon using conventional method, the yield of 70a was 57% after heating 4-5 h at 65°C. Similarly, the thiazepines 70b–g were synthesized in good yield from 69b–g and o-aminophenol in EtOH under ultrasonic irradiation method. A proposed mechanism was outlined for the synthesis of the thiazepines via [1, 4] and [1, 2] addition of o-aminophenol to the chalcones 69 under ultrasonic irradiation [3] (Scheme 14).

### 3.1.15. Thermal Reaction of 1-(2,4-Disubstituted-phenyl)-3-(p-substituted-phenyl)prop-2-en-1-ones with 2-Aminothiophenol in the Presence of a Catalytic Amount of Nanocrystalline Al2O3. Reaction of 1-(2,4-disubstituted-phenyl)-3-(p-substituted-phenyl)prop-2-en-1-ones 71a–h with o-aminothiophenol (2.5:1 molar ratio) in the presence of a catalytic amount of nanocrystalline Al2O3 in water, while stirring at room temperature for the appropriate time afforded the corresponding 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines in good to excellent yield. This reaction was found compatible with various electron-donating and electron-withdrawing substituents, and assumed to start by 1,4-Michael addition of the SH on the C=C bond followed by the condensation of the NH2 on the carbonyl group. It is worthy to note that using nanocrystalline Al2O3 is preferable than commercially available bulk Al2O3 or basic Al2O3 due to its increased catalytic activity and could be reused for four cycles without loss of activity and selectivity [17] (Scheme 15).

### 3.1.16. MW-Assisted Condensation Reactions of o-Aminothiophenol with Carboxyl Compounds in the Presence of Erbium (III) Triflate.

Condensation reactions of simple ketones (acetoacetone, acetoacetonitrile, p-nitro- and p-methoxy acetophenones) with 6a o-aminothiophenol in presence of erbium (III) triflate (Er(OOTf)3) catalyst while stirring at room temperature for 3 h gave no 1,5-benzothiazepine products 73 or 74a–c. These reactions in fact lead to the corresponding Schiff bases without further cyclization to form the desired 1,5-benzothiazepine. In contrast, the stirred reaction of chalcone 75a with o-aminophenol using Er(OOTf)3 under solvent-free microwave-assisted condensation process, (1000 W) for 30 min. at room temperature led to the cyclized 1,5-benzothiazepines 76a as fair yield product. Whereas very good results were obtained for the more reactive substrates 75b and c (highly electron rich), confirming the synthesis of...
Mechanism for formation of thienothiazepines 58

Scheme 12: Thermal reaction of 5-aryl-2,4-bis(aryl methylidene) dihydro-3-thiophenones and o-aminothiophenolinacetic acid compared to same reaction performed under solvent-free microwave irradiation.
NH2

<table>
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<td>H</td>
<td>32</td>
<td>8-9</td>
</tr>
<tr>
<td>(b)</td>
<td>H</td>
<td>p-F</td>
<td>30</td>
<td>6-8</td>
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<td>(c)</td>
<td>p-NO2</td>
<td>H</td>
<td>328</td>
<td>8-9</td>
</tr>
<tr>
<td>(d)</td>
<td>p-OMe</td>
<td>p-OMe</td>
<td>37</td>
<td>8-10</td>
</tr>
<tr>
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<td>p-CH3</td>
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<td>(j)</td>
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US: ultrasonic irradiation

Scheme 13: Improved synthesis of 1,5-benzothiazepines using ceric ammonium nitrate (CAN).

1,5-benzothiazepine derivatives 76b,c in excellent yields [18] (Scheme 16).

3.1.17. Reaction of Various Hydroxyl Chalcones with o-Aminothiophenol in the Presence of Gallium (III) Triflate. Reactions of o-aminothiophenol and the hydroxy chalcones 77a–h in the presence of water-tolerant strong Lewis acid catalyst Ga(OTf)3 (10 mol%) lead to the 1,5-benzothiazepines 78a–h in moderate to excellent yields. The ortho-OH group of chalcones is crucial for this unprecedented condensation process.

A proposed reaction mechanism involves at first, Ga(OTf)3 catalyst and o-hydroxychalcone I form complex II, which further reacts with III to afford complex IV and then V after losing H2O. Then the XH group attacks the C=C bond and lead to the formation of thiazepine 78. The o-hydroxy group in chalcone structure has the following two important roles: (i) it involved in the formation of stable complex III by chelating with Ga(OTf)3 and facilitates the dehydration process to from complex V; (ii) the presence of this group caused the α,β-unsaturated carbonyl to be more reactive toward the addition of XH [19] (Scheme 17).

3.1.18. Reaction of 4-(4-Fluoro-2-methylphenyl)-4-oxobut-2-enolic Acids with 2-Aminobenzenethiols in the Presence of Lanthanum-Containing Y Zeolite (LaY), While Stirring, under Solventless Conditions. Stirring of o-aminothiophenol derivatives and the α,β-unsaturated ketones 79 at room temperature in the presence of Lanthanum-containing Y zeolite (LaY) zeolite catalyst, under solvent less conditions gave 8-substituted-2-carboxy-2,3-dihydro-1,5-benzothiazepines 80a–f in good to excellent yield. As an initial attempt, a variety of experimental reaction conditions were examined by changing catalyst, reaction medium (MW irradiation, conventional, and stirring), and temperature.

It was found that more acidic LaY zeolite was the best choice of catalyst for the preparation of 2-carboxy-2,3-dihydro-1,5-benzothiazepine 80a. This can suggest that the acid sites on zeolite work as active sites for this reaction. For checking the catalyst amount’s effect on reaction conditions the reaction was tried via different amounts of catalyst and 2g of catalyst amount was sufficient for activation of 80a product synthesis; higher amount of the catalyst produced lesser yield.

It was also, observed that MW irradiation using different monomode reactor with focused rays and a much more homogeneous electromagnetic field and classical heating gave lower yield with higher reaction time compared to reactions realized under stirring conditions and interphase catalysis. In view of all these observations and results, the other 1,5-benzothiazepines 80b–f were synthesized via reaction of hydroxychalcones 79 and o-aminothiophenol using LaY zeolite under stirring at 100°C [20] (Scheme 18).
Scheme 14: Reaction of 1-(2-hydroxy-3,4,5-trisubstituted-phenyl)-3-(4-(phenylthio)phenyl)prop-2-en-1-ones with o-aminothiophenol in ethanol under ultrasonic irradiation via a [4 + 3] annulation.

3.1.19. Reaction of 1,3-Diaryl-2-propenones with 2-Aminothiophenol in the Presence of Substoichiometric Amount of Cyanuric Chloride. Cyanuric chloride 2,4,6-trichlorotriazine (TCT) catalyst was employed for preparation of several 1,5-benzothiazepine derivatives via reaction of various kinds of 1,3-diaryl-2-propenones 81 with o-aminothiophenol. When this reaction was carried out in the absence of cyanuric chloride 2,4,6-Trichlorotriazine (TCT), thin layer chromatography (TLC) and $^1$H NMR spectra of the reaction mixture showed a combination of starting materials.
A plausible mechanism for 1,5-benzothiazepines

**Scheme 15**: Thermal reaction of 1-(2,4-disubstituted-phenyl)-3-(p-substituted-phenyl)prop-2-en-1-ones with o-aminothiophenol in the presence of a catalytic amount of nanocrystalline Al₂O₃.

and corresponding thia-Michael adducts were formed, the expected benzo[1,5]thiazepines were afforded in very poor yield. Upon repeating the reaction in the presence of TCT catalyst (5 mol%), between 80 and 90 °C, the expected benzothiazepine derivatives 82a–l were obtained in high yield, whether bearing electron-withdrawing groups (such as halide or nitro) or electron-donating groups (such as the alkyl group). It is worthy to note that the *in situ* generated HCl (from cyanuric chloride) efficiently catalyzed the reaction and act as protic acid to activate the carbonyl oxygen for forming a carbo-cation. So, subsequent intramolecular nucleophilic attack by the NH₂ group on the carbo-cation followed by dehydration forms the desired 1,5-benzothiazepines 82. Also, doing the reaction under dry reaction conditions in the presence of MS 4 Å was met with failure, a matter which indicated that the “incipient” moisture plays an important role for HCl generation *in situ* from TCT catalyst [21] (Scheme 19).

3.1.20. Microwave-Assisted Reaction of 2-Aminothiophenol and 1,3-Substituted-prop-2-en-1-ones in the Presence of Zinc Acetate. One pot efficient facile, solvent-free microwave-assisted green synthesis of 1,5-benzothiazepine derivatives 86 has been approved via cyclo-condensation of o-aminothiophenol and 1,3-substituted-prop-2-en-1-ones 85a–h (prepared via Claisen-Schmidt condensation of acetophenone or substituted acetophenone 83 or 84 in ethanol in the presence of 40% KOH) via using zinc acetate as an eco-friendly catalyst. The thiazepine products 86a–h were synthesized in shorter reaction time and better yields as compared with their corresponding prepared via conventional synthesis (4–6.5 hr; 63–70% yield) [22] (Scheme 20).

3.1.21. Microwave Irradiation of 1,3-Substituted-prop-2-en-1-one with o-Aminothiophenol in the Presence of Zinc Acetate in Solvent-Free Conditions. Reaction of 1,3-substituted-prop-2-en-1-ones 89a–f (prepared from acetylated α-naphthol 87 and the corresponding aromatic aldehyde 88 in basic medium) with o-aminothiophenol under microwave irradiation for 2-3 minutes at 80–85 °C in the presence of eco-friendly catalyst zinc acetate, solvent-free conditions afforded the 1,5-benzothiazepines 90a–f in good yield and short reaction time. Upon repeating the reaction, using conventional method by mixing of the acetylated α-naphthol with various aldehydes in ethanol in the presence of 40% KOH, heating under reflux for the proper time the benzothiazepine.
products 90a–f were formed in a comparative long reaction time and low yield [23] (Scheme 21).

3.1.22. Mannich Condensation Reaction of Substituted 1,8-Naphthyridines and Substituted 2-Amino thiophenols in the Presence of Crystalline Bi(NO$_3$)$_3$·5H$_2$O Catalyst under MW Irradiation and Comparison with or without Adding Any Solid Support as Well with Its Performing under Thermal Conditions. The Mannich condensation of substituted 1,8-naphthyridines 91a–d and substituted o-amino thiophenol derivatives in the presence of crystalline Bi(NO$_3$)$_3$·5H$_2$O catalyst under Microwave irradiation for about 8-9 min at an interval of 1 min at 160 W gave 1,5-benzothiazepine[7, 6-b]-1,8-naphthyridines 92a–j in good to excellent yields. The reaction proceeds through condensation of amino group with aldehydic group of 1,8-naphthyridines; it is the sulfur atom that reacts with the carbon next to the chlorine at C$_2$ of 1,8-naphthyridines, which resulted in the desired 1,5-benzothiazepines 92a–j. For comparison, the reaction was also carried out without adding any support under neat condition, which could be expected to be the most economic method. Unfortunately, lower yields (5–56% yield) were obtained. Therefore, the Bi(NO$_3$)$_3$·5H$_2$O is the most effective solid for the synthesis of 1,5-benzothiazepine[7, 6-b]-1,8-naphthyridines 92a–j, whereas acidic alumina, basic alumina, neutral alumina, and molecular sieves (5 Å) were ineffective in giving products in good yields.

Moreover, this reaction when performed under reflux (10–12 h) in MeOH as a solvent, the yields were significantly lower than those obtained using the MW method. So, this simple, practical, and very regioselective method for the synthesis of 1,5-benzothiazepine[7, 6-b]-1,8-naphthyridines derivatives was presented using the inexpensive, oxygen and moisture-tolerant, and easily available Bi(NO$_3$)$_3$·5H$_2$O catalyst [24] (Scheme 22).

3.1.23. Reaction of 3-(Benzo[d][1,3]dioxol-5-yl)-1-(substituted-phenyl)prop-2-en-1-ones with o-Amino-thiophenol in the Presence of Silica Gel at 80°C for 3 h under Solvent-Free Conditions. 3-(Benzo[d][1, 3]dioxol-5-yl)-1-(substituted-phenyl)prop-2-en-1-ones 93a–f on reaction with o-amino thiophenol in

<table>
<thead>
<tr>
<th></th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Yield of 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>H</td>
<td>H</td>
<td>45</td>
</tr>
<tr>
<td>(b)</td>
<td>H</td>
<td>o-OH</td>
<td>83</td>
</tr>
<tr>
<td>(c)</td>
<td>p-Ome</td>
<td>o-OH</td>
<td>98</td>
</tr>
</tbody>
</table>
Proposed mechanism for Ga(OTf)$_3$-catalyzed reaction of 2-hydroxychalcones with o-aminothiophenol.

**Scheme 17**: Reaction of various hydroxyl chalcones with o-aminothiophenol in the presence of gallium (III) triflate.
Synthesis of 8-substituted-2-carboxy-4-(4-fluoro-2-methylphenyl)-2,3-dihydro-1,5-benzothiazepines (80a–f) using La Y zeolite (a)

<table>
<thead>
<tr>
<th>Reaction time (min)</th>
<th>Yield (b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 8-OCH₃</td>
<td>8</td>
</tr>
<tr>
<td>(b) 8-CH₃</td>
<td>10</td>
</tr>
<tr>
<td>(c) 8-Cl</td>
<td>12</td>
</tr>
<tr>
<td>(d) 6-Cl</td>
<td>10</td>
</tr>
<tr>
<td>(e) 6-Br</td>
<td>13</td>
</tr>
<tr>
<td>(f) 6-F</td>
<td>15</td>
</tr>
</tbody>
</table>

(a) 100 wt % catalyst used that means the substrate catalyst weight ratio is 1:1.
(b) Isolated yields.

Scheme 18: Reaction of 4-(4-fluoro-2-methylphenyl)4-oxobut-2-enoic acids with o-amino thiophenol derivatives in the presence of Lanthanum-containing Y zeolite (LaY), while stirring, under solventless conditions.

Synthesis of 1,5-benzothiazepines 82 using cyanuric chloride.

Preparation of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines 82 (a)

<table>
<thead>
<tr>
<th>81,82</th>
<th>R¹</th>
<th>R²</th>
<th>Time (h)</th>
<th>Isolated yield (c) (%) of 82</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>H</td>
<td>H</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>(b)</td>
<td>p-OCH₃</td>
<td>H</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>(c)</td>
<td>p-allyloxy</td>
<td>H</td>
<td>5</td>
<td>86</td>
</tr>
<tr>
<td>(d)</td>
<td>p-OH</td>
<td>H</td>
<td>5</td>
<td>81</td>
</tr>
<tr>
<td>(e)</td>
<td>o-OH</td>
<td>H</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>(f)</td>
<td>H</td>
<td>p-OCH₃</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>(g)</td>
<td>H</td>
<td>p-Cl</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>(h)</td>
<td>H</td>
<td>m-NO₂</td>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>(i)</td>
<td>p-Cl</td>
<td>p-OCH₃</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>(j)</td>
<td>p-Cl</td>
<td>o-Cl</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>(k)</td>
<td>o-OH</td>
<td>Ar = Thinly</td>
<td>6</td>
<td>79</td>
</tr>
<tr>
<td>(l)</td>
<td>o-OH</td>
<td>p-OH</td>
<td>5</td>
<td>82</td>
</tr>
</tbody>
</table>

(a) Reaction conditions: 2-aminothiophenol (10 mmol); 1,3-diaryl-2-propenones (10 mmol), TCT (0.5 mmol); 80 °C; neat. (b) 82j is a new product and other thiazepines are known and prepared by other methods.
(c) Isolated yield.

Scheme 19: Reaction of 1,3-diaryl-2-propenones with o-aminothiophenol in the presence of sub-stoichiometric amount of cyanuric chloride.

the presence of silica gel at 80°C for 3 h, under solvent-free conditions. 2-(benzo[d][1, 3]dioxol-5-yl)-4-(substituted-phenyl)-2,3-dihydro-benz[1, 5]thiazepine derivatives 94a–f were afforded in good yield. The latter thiazepines probably involves the intermediate [95] which was formed by 1,2- and 1,4- type addition of o-aminothiophenol with chalcones 93a–f. The sulfur atom being more nucleophilic in nature than the nitrogen atom attacks the β-carbon of chalcones 93 and gives intermediate [95] that easily undergoes dehydration in a nonaqueous medium [25] (Scheme 23).
3.1.24. Comparative MW Irradiation and Thermal Reactions of \(\beta\)-Benzoyl Arylic Acid with \(\alpha\)-Aminothiophenols and Chloroacetyl Chloride over the Basic Alumina as Inorganic Solid Support. \(\beta\)-Benzoyl arylic acid 96 reaction with 5-substituted-\(\alpha\)-aminothiophenol derivatives and 2-chloroacetyl chloride 98 under MW irradiation over basic alumina (as inorganic solid support) in absence of any solvent occurred in 5-6 min gave only the desired azeto-benzothiazepines 99 in excellent yield.

The basicity of alumina is sufficient to cause this cycloaddition reaction and the 1,5-benzothiazepines 97 were formed in situ, as intermediates, by reaction of \(\beta\)-benzoyl arylic acid 96 and 5-substituted \(\alpha\)-aminothiophenol derivatives under MW irradiation.

When a solution of Et_3N in benzene was added drop wise into a solution of 2-chloroacetyl chloride and 1,5-benzothiazepine 97 in benzene mixture of azeto-[2, 1-d][1, 5]-benzothiazepines 99, the ring contracted 2-substituted 2,3-dihydro-3-phenyl-\(N\)-acetyl-2-styrylbenzothiazole 100 was obtained in fair yields. Presumably, the low yield of azeto-[2, 1-d][1, 5]-benzothiazepine 99 is due to the competitive ring contraction with “Staudinger reaction” under the reaction conditions. The yield could be improved to 30% if a solution of 2-chloroacetyl chloride 98 in benzene was added drop wise into a solution of benzothiazepine and Et_3N in benzene. Although the ring contraction could be inhibited under this additional mode, the yield of 99a was still low when 1.5 equivalents of 98 were used and a new byproduct 101 was obtained. Upon applying 3.0 equivalents of 98 to improve the yield, the desired azeto[2, 1-d][1, 5]benzothiazepines 99 were not obtained, but the yield of the by-product 101 was improved slightly. Another trial involved first the formation of diketenes through addition of Et_3N to a solution of 98 in benzene and subsequent addition of the 1,5-benzothiazepine 99a into the resulting reaction mixture which resulted only in the 1,3-oxazine derivative 101 in low yield. On the other hand, under microwave irradiation the desired azeto[2, 1-d][1, 5]-benzothiazepine 99a was formed as the only product with
Scheme 21: Microwave irradiation of 1,3-substituted-prop-2-en-1-one with o-aminothiophenol in presence of zinc acetate in solvent-free conditions.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Yield (%)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>C₆H₅</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>(b)</td>
<td>o-OHC₆H₄</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>(c)</td>
<td>p-OHC₆H₄</td>
<td>78</td>
<td>67</td>
</tr>
<tr>
<td>(d)</td>
<td>p-OCH₃C₆H₄</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>(e)</td>
<td>Furfuryl</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>(f)</td>
<td>Thienyl</td>
<td>60</td>
<td>58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Yield (%)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>R=R=R=H</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>(b)</td>
<td>R=R=CH₃</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>(c)</td>
<td>R=R=Cl</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>(d)</td>
<td>R=R=CH₃, R₁=R₂=R₃=H</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>(e)</td>
<td>R=R=Cl, R₁=R₂=R₃=H</td>
<td>72</td>
<td>65</td>
</tr>
</tbody>
</table>

3.1.25. Thermal (Short Time) Reaction of 1-Methyl-3,5-bis-(arylidene)-4-piperidones with o-Aminothiophenol in the Presence of a Catalytic Amount of Acetic Acid under Atmospheric Pressure. MW irradiation of o-aminothiophenol and 1-methyl-3,5-bis-(arylidene)-4-piperidones 102 (1:1 molar ratio) in the presence of CH₃COOH as a catalyst in silica bath (≈85°C) under atmospheric pressure for 4–10 min afforded 2-methyl-11-aryl-4-[((E)-arylmethylidene]-1,2,3,4,11,11-a hexahydropyrido[3,4-c][1,5]benzothiazepines 103 in excellent yield. The same reaction in either C₂H₅OH or MeOH at reflux with few drops of CH₃COOH took several hours with less than 30% conversion, while refluxing in CH₃COOH alone led to complete decomposition of the reaction mixture [27] (Scheme 25).

3.1.26. Thermal Reaction of (E)-3-(3,4-Disubstituted-phenyl)-1-(2-hydroxy-3,4,5-trisubstituted-phenyl)prop-2-en-1-ones with 2-Aminothiophenol under the Influence of Glacial Acetic Acid. Oxidative cyclisation of 3-(3,4-di-substituted-phenyl)-1-(2-hydroxy-3,4,5-tri-substituted phenyl)prop-2-en-1-ones 104a–j (prepared via Claisen-Schmidt condensation of

good yield. Similarly, products 99b–f were obtained in fair to good yield [26] (Scheme 24).
Scheme 23: Reaction of 3-(benzo[d][1,3]dioxol-5-yl)-1-(substituted-phenyl)prop-2-en-1-ones with o-aminothiophenol in the presence of silica-gel at 80°C for 3 h under solvent-free conditions.

<table>
<thead>
<tr>
<th>99</th>
<th>X</th>
<th>Time&lt;sup&gt;o&lt;/sup&gt; (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>12 + 3</td>
<td>90</td>
</tr>
<tr>
<td>(b)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10 + 5</td>
<td>87</td>
</tr>
<tr>
<td>(c)</td>
<td>Cl</td>
<td>12 + 6</td>
<td>83</td>
</tr>
<tr>
<td>(d)</td>
<td>Br</td>
<td>10 + 5</td>
<td>86</td>
</tr>
<tr>
<td>(e)</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>9 + 4</td>
<td>88</td>
</tr>
<tr>
<td>(f)</td>
<td>F</td>
<td>10 + 5</td>
<td>87</td>
</tr>
</tbody>
</table>

<sup>o</sup>Time (12 + 3) indicates first irradiation for 12 min, gives compound 97 (detected by TLC) and then further irradiation after adding chloroacetyl chloride for 3 min yields 99a.

Scheme 24: Comparative MW irradiation and thermal reactions of β-benzoyl acrylic acid with o-aminothiophenols and chloroacetyl chloride over the basic alumina as inorganic solid support.
various substituted acetoephones with aromatic aldehydes in the presence of EtOH/KOH using CuCl₂ at reflux in DMSO gave 3,6-dichloro-2-(4-fluorophenyl)-7-methyl-4H-chromen-4-one 105a–j in good yield. The chalcones 104a–j on treatment with o-aminothiophenol in the presence of CH₂COOH/MeOH provided 1,5-benzothiazepine derivatives 106a–j in good yield [28] (Scheme 26).

3.1.27. Intramolecular Cyclisation of 3-((2-Amino-4-pheny/substituted-phenyllthio)(phenyl)methyl)pentane-2,4-diones or -hexane-2,4-diones Followed by Dehydration in Acetic Acid/Methanol. Knoevenagel condensation of selected aromatic aldehydes with 2,4-pentanedione in dry benzene catalyzed by piperidine gave 3-arylidenedepentane-2,4-dione derivatives 109. Michael addition of o-aminothiophenol to medium yields (59–71%). Neither the yield nor course of reaction with o-aminothiophenol in the presence of aqueous KOH (60%) at room temperature afforded methylene-bis-chalcones 113. The latter chalcones on reaction with o-aminothiophenol, in EtOH in the presence of CH₃COOH at reflux for 4 h, gave methylene-bis-[1,5]-benzothiazepine derivatives 114a–g in good to excellent yields. The thiazepines 114a–g on condensation with α-bromoacetoephone, in the presence of anhydrous K₂CO₃/dry acetone and catalytic amount of KI, followed by cyclization in ethanolic KOH, gave methylene-bisbenzofuranoro-[1,5]-benzothiazepine derivatives 115a–g (yield% was not reported) and were purified by column chromatography using silica-gel (60–120 mesh)/petrol ether (60–80°C) [30] (Scheme 28).

3.1.28. Thermal Reaction of Methylene-bis-chalcones with o-Aminothiophenol in Ethanol in the Presence of Acetic Acid. Condensation of 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde 112 with methyl ketones in the presence of aqueous KOH (60%) at room temperature afforded methylene-bis-chalcones 113. The latter chalcones on reaction with o-aminothiophenol, in EtOH in the presence of CH₃COOH at reflux for 4 h, gave methylene-bis-[1,5]-benzothiazepine derivatives 114a–g in good to excellent yields. The thiazepines 114a–g on condensation with α-bromoacetoephone, in the presence of anhydrous K₂CO₃/dry acetone and catalytic amount of KI, followed by cyclization in ethanolic KOH, gave methylene-bisbenzofuranoro-[1,5]-benzothiazepine derivatives 115a–g (yield% was not reported) and were purified by column chromatography using silica-gel (60–120 mesh)/petrol ether (60–80°C) [30] (Scheme 28).

3.1.29. Reaction of Exocyclic α,β,γ,δ-Unsaturated Ketones with o-Aminothiophenol in a Mixture of Boiling Toluene and Acetic Acid. The exocyclic α,β,γ,δ-unsaturated ketones 116–123 when allowed to react with o-aminothiophenol in a mixture of boiling toluene and CH₃COOH the tetracyclic 1,5-benzothiazepines 124–131 were obtained in relatively good to medium yields (59–71%). Neither the yield nor course of the reaction was influenced by the presence of an electron donor or an electron acceptor o-substituent in the starting material. Replacement of the styryl group by a 2-(furan-2-yl)ethenyl-one slightly enhanced the yield of the formation of 1,5-benzothiazepines 130 and 131 (71 and 68% resp.) [31] (Scheme 29).
3.1.30. Reactions of Thiénylidene Malononitrile and o-Amino-thiophenol in the Presence of Catalytic Amount of Piperidine. o-Amino-thiophenol and thiénylidene malononitrile 132 (equimolecular ratios) upon heating under reflux in EtOH containing piperidine for 30 min gave 2-amino-3-cyano-4-(2-thienyl)[1,5]benzothiazepine 135 in good yield. Formation of 135 may proceed via the intermediate (133) which cyclized to afford the intermediate (134). The latter intermediate in turn tautomered to 2-amino-4,5-dihydrobenzothiazepine and released hydrogen under an aerobic oxidation to give 135. The latter thiazepine when reacted with ethyl cyanoacetate 136a and diethyl malonate 136b in CH₂COOH afforded pyridobenzothiazepine derivatives 138a,b. Elimination of ethanol from the cetate group gave the intermediate (137), subsequently cyclized via the addition of active methylene hydrogens to the cyano function yielding 4-amino-5-[2-thienyl]pyrido[6,5-b][1,5]benzothiazepine-1, 4-dihydropyridine-2-one derivatives 138a,b. To confirm the structure of type 138, compound 138b (X = CO₂C₂H₅) on boiling at reflux with hydrazine hydrate in ethanolic piperidine solution gave the pyrazolo[3,4'-4',3']pyrido[6,5-b]benzothiazepine derivatives 139 in satisfactory yield. Similarly, the azepine 135 reacted with malononitrile 140a and cyanothioacetamide 140b in acetic acid at a reflux temperature to give in each case the same product 141. In the case of malononitrile 140a 2 successive steps of a nucleophilic addition to the cyano functions yield 141; whereas in case of 140b, a condensation between the thione group of the amide and the amine of 135 released hydrogen sulfide was followed by a nucleophilic addition of the active methylene to the cyano function affording the same final product 141.

Also, reaction of 135 with arylidene malononitrile 142a-c afforded pyrido-benzothiazepine derivatives 146a-c. Formation of the latter thiazepines was explained via the intermediate (143), which cyclized via a nucleophilic addition of hydro-gen of arylidine to a cyano function of benzothiazepine to form dihydropyridine intermediate (144). The latter released hydrogen cyanide to give 145 and tautomered to form the final product 146.

Moreover, Compound 135 reacted easily with urea in AcOH to afford 2,4-diaminopyrimidobenzothiazepine 147 (65% yield) via cyclo-condensation addition reaction. Furthermore, reaction of 135 under reflux with triethylthioformate yielded the ethoxymethylidenamino derivatives 148 (61% yield), which on reaction with hydrazine hydrate afforded the corresponding pyrimidobenzothiazepine 149 (60%) via the elimination of ethanol followed by a nucleophilic addition to the cyano function.

Finally, the benzothiazepine 135 in EtOH reacted with trichloroacetanilide to give benzothiazepine 153 (60% yield). Compound 153 was suggested to be formed via the intermediate (150) which in turn cyclized to the pyrimidine.

Scheme 26: Thermal reaction of (E)-3-(3,4-disubstituted-phenyl)-1-(2-hydroxy-3,4,5-trisubstituted-phenyl)-prop-2-en-1-ones with o-aminothiophenol under the influence of glacial acetic acid.
Scheme 27: Intramolecular cyclisation of 3-((2-amino-4-phenyl substituted-phenyllthio)-(phenyl)methyl)pentane-2,4-diones or -hexane-2,4-diones followed by dehydration in acetic acid/methanol.

intermediate (151). In the reaction medium the C-2 of pyrimidine became relatively positive, easily accepted the hydroxide ion from water of intermediate (152) yielding the final benzothiazepine 153 (60% yield) [32–36] (Scheme 30).

3.1.3. Reaction of 3-[1-oxo-3-(Substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones with o-Aminothiophenol in the Presence of Piperidine. The chalcones 155a–g (derived from 3-acetyl coumarin derivatives 154 and the proper
aromatic aldehydes) when reacted with o-aminophenol in a mild acidic medium using weakly acidified ethanol gave 2-aryl-4-(2H-2-oxo-[1]-benzopyran-3-yl]-2,3-dihydro-1,5-benzothiazepines 156a–j in good to excellent yields. Meanwhile, upon heating the chalcones 155 under reflux in ethanol containing o-aminophenol and piperidine, the corresponding 2-aryl-4-[2H-2-oxo-[1]benzopyran-2-one-3-yl]-2,5-dihydro-1,5-benzothia-zepines 157a–g were obtained in good yield [37] (Scheme 31).

3.1.32. Reactions of Butoxy(trifluoromethyl)enones with o-Aminophenol or o-Amino-thiophenol Derivatives. Reactions of t-butoxy(trifluoromethyl)enones 158 with 1,2-diamines (o-phenylene diamine or 1,2-ethylenediamine) lead to 1,5-diazepines 159 and 160. In comparison, reaction of 158 with o-aminophenol derivatives or o-aminothiophenol, yielded 1,5-oxazepines or 1,5-thiazepines of type 161. Good results were obtained by using microwave irradiation. Meanwhile, upon carrying the same reaction in boiling xylene, the condensation leads to a mixture of products [38] (Scheme 32).

Scheme 30: Continued.
under microwave irradiation in an open vessel afforded the trans- and cis-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4-ones 163, 164. Varying the reaction time and power output as well as the nature of the solvent controlled the disastereo-selectivity of this reaction. Carrying out the process for 20 min at a power of 390 W in toluene led to a cis/trans ratio of 9:1 (yield: 74%). Raising the power to 490 W for 10 min involved an inversion of the ratio, that is, increasing dramatically the amounts of the trans-isomer (yield: 84%). The traditional one-pot preparation of racemic target compounds 163, 164 produced less than 30% yield at 160°C with prolonged reaction times.

1,3-Dihydro-3-(2-phenyl-2-oxoethylidene)indol-2-one 165 and o-aminothiophenol derivatives under thermal and microwave reaction conditions using ethylene glycol afforded spiro[benzo[8][1,4]thiazepine-2,3′-indolin]-2′-ones 166.

To enhance the anxiolytic activity of some azepine derivatives by the introduction of a trifluoromethyl group in the dia-, oxa- or thiazepine, trifluoroacetyl ketene acetals 167 were reacted with o-aminothiophenol derivatives in the presence of xylene, applying a multimode microwave oven (8–12 min at 980 W). Although this methodology uses microwave inert solvents (e.g., toluene or xylene), which are not serving in the energy transfer processes, it gave the 3-substituted 2-hydroxy-2-trifluoromethyl-1,5-benzothiazepine derivatives 168 in good yields, suggesting absorption of the microwaves by the reactants [33, 35, 36, 39] (Scheme 33).
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Scheme 31: Reaction of 3-[1-oxo-3-(substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones with o-aminothiophenol in the presence of piperidine.

3.1.34. Comparative Microwave-Assisted and Conventional Heating Reactions of N-[4-(2-oxo-2H-Chromen-3-yl) thiazol-2-yl]cinnamamide with o-Aminothiophenol in the Presence of Glacial Acetic Acid as Catalyst and Methanol. N-[4-(2-oxo-2H-Chromen-3-yl)-1,3-thiazol-2-yl]acetamide 170 (prepared from 3-(2-amino-1,3-thiazol-4-yl)-2H-chromen-2-one 169 by acetylation with acetyl chloride in chloroform) on reaction with various aldehydes 171a–j gave N-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] cinnamamide derivatives 172a–j in good yield. The latter derivatives on treatment with o-aminothiophenol in the presence of glacial CH₃COOH as catalyst and MeOH under MWI for afforded 2,3-dihydro-2-aryl-4-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-ylamino]1,5-benzothiazepine 173a–j. Higher yields of compounds 172a–j and 173a–j were realized at 500 watt for 2–2.5 min of microwave irradiation, whereas similar reactions of 173a–j under conventional heating (steam bath) at reflux gave poorer yields after much longer times [40] (Scheme 34).

3.1.35. Reaction of 1-(4-(4,6-bis(Phenylamino)-1,3,5-triazin-2-ylamino) phenyl)-3-(4-methoxyphenyl) prop-2-en-1-ones with o-Aminothiophenol in the Presence of a Few Drops of Glacial Acetic Acid. Reaction of 2,4,6-trichloro-1,3,5-triazine with aniline in acetone at 0–5°C gave 4,6-dichloro-N-phenyl-1,3,5-triazin-2-amine 174. Further reaction of 174 with aniline in acetonitrile at room temperature yielded 6-chloro-N², N⁴-diphenyl-1,3,5-triazine-2,4-diamine 175. The latter product
Scheme 32: Reactions of butoxy(trifluoromethyl)enone with \(o\)-aminophenol or \(o\)-aminothiophenol derivatives.

\[
\begin{align*}
\text{R}^1 &= \text{H, Me; } \text{R}^2 &= \text{H, Me, Cl, NO}_2, \text{ COPh; } \text{R}^3 &= \text{H, Cl} \\
Y &= \text{O, S, P = H}
\end{align*}
\]

Scheme 33: Microwave-assisted irradiation of \(o\)-aminobenzenethiol and the oxirane-2-carboxylate.
on reaction with (4-aminophenyl) ethanone gave 1-(4-(4,6-bis(phenylamino)-1,3,5-triazin-2-ylamino)phenyl)ethanone 176. 1-(4-(4,6-bis(phenylami-no)-1,3,5-triazin-2-ylamino)-3-(4-methoxyphenyl)propenone 177d was obtained from reaction of 176 with 4-methoxybenzaldehyde in good yield in DMF/KOH. Similarly, products 177a–d were synthesized using the appropriate aromatic aldehydes.

Reactions of 177a–d with o-aminothiophenol in the presence of few drops of glacial CH$_3$COOH yielded 1,5-benzothiazepines 178a–d in moderate yields (56–63%) [41–43] (Scheme 35).

3.1.36. Condensation Reactions of Enones with o-Aminothiophenol. The overall process for the formation of the hemiperfluoroenones 181 from perfluoroalkyl iodides and acylsilanes has been described previously [44, 45]. Depending on the experimental conditions, compounds 179 and 180 were isolated. The latter compounds are considered as useful synthons and regarded as equivalents of the enones 181. Condensation of o-aminothiophenol, with the enones 179 (or 180 or 181) provided the corresponding benzothiazepines 182a–c in good yields. In the carbohydrate series, the 1,5-benzothiazepines 182c was obtained as an epimeric mixture (D-xylo/L-arabino in a 85:15 ratio), indicating that a further C-4 epimerisation had occurred during the formation of the heterocycle [44–47] (Scheme 36).

3.1.37. Reaction of 1-(Benzo[d][1,3]dioxol-5-yl)-3-phenylpropane-1,3-diones with o-Aminothiophenol. 1-(Bnzo[d][1,3]dioxol-5-yl)-3-phenylpropane-1,3-diones 183a–l on reaction with o-aminothiophenol in pyridine under reflux for ~4 h, while stirring, afforded the 2,4-disubstituted 1,5-benzothiazepines 184a–l. The reaction is initiated by the nucleophilic attack of sulphhydril electrons on enolic carbon atom of the \( \beta \)-diketone followed by loss of water molecule. Therefore, amino group comes in vicinity of carbonyl group, by dehydration resulting into the cyclized products of type 184 [48] (Scheme 37).

3.1.38. Reactions of 2-Hydroxybenzal Acetophenone and 1-(1-Naphthyl)-3-(1-naphthyl)-2-propenone with o-Aminothiophen Derivatives. The absorbed ethanolic solutions of chalcones 187a,b (prepared from the aldehydes 185a,b and the ketones 186a,b under microwave irradiation on a suitable solid support Mont. KSF) when mixed with o-aminothiophenol derivatives (20% by weight of the reactants) and irradiated inside a MW oven for an appropriate time at 640 W yielded the benzothiazepine 188a–g in excellent yield.

When equimolar mixture of o-aminothiophenol derivatives and 2-hydroxybenzalaceto-phenone 187a in dry ethanol was saturated with dry HCl gas until boiling and heated under reflux for 6 h the benzothiazepine products 188a–g were synthesized (65–67% yield). Irradiation of the absorbed ethanolic solutions of 188a,b on clay fen (prepared from 2 g clay + 0.001 mol Fe (III) NO$_3$) inside a microwave oven for 6 min yielded 8-ethoxy-2,5-dihydro-1,5-benzothiazepine-1,1-dioxides 189a,b in good yields (88%) and no mono-oxide of type 190 was detected. The dioxides 189a,b were also obtained in satisfactory yield (conventional method) via dissolved
Scheme 35: Reaction of 1-(4-(4,6-bis (phenylamino)-1,3,5-triazin-2-ylamino)phenyl)-3-(4-methoxyphenyl) prop-2-en-1-ones with o-aminothiophenol in presence of a few drops of glacial acetic acid.

solutions of 188a,b in glacial CH₃COOH, H₂O₂ (30%) and the mixture was boiled under reflux for 10–12 h and no traces were detected for the expected benzothiazepines of type 190 [49] (Scheme 38).

3.1.39. Reaction of (E)-N-(2-(Allylsulfonyl)phenyl)-4-methyl-N-(prop-1-enyl)benzene Sulfonamide with o-Aminothiophenol in the Presence of Grubbs’ Second-Generation Catalyst. Ortho-aminothiophenol was Monoalkylated with allyl bromide and the amine subsequently protected with a tosyl group to afford N-(2-(allylthio)phenyl)-4-methylbenzenesulfonamide 191. Allylation of 191 readily afforded the sulfonamide 192. Surprisingly, ring-closing metathesis (RCM) on this substrate did not give the expected 8-membered 6-tosyl-5,6-dihydro-2H-benzo[bc]1,4-thiazocine 193 and attempted isomerization of the same substrate was also unsuccessful. Substrate 192 was thus oxidized to the corresponding sulfone 194 and the RCM successfully afforded the corresponding sulfon 195 in good yield. By applying the sequential isomerization-RCM strategy on compound 194 it was rather surprising to isolate N-(2-(allylsulfanyl)phenyl)-4-methyl-N-(prop-1-enyl) benzenesulfonamide 196 in which only the N-allyl group had been isomerized. Subsequently, when compound 196 was treated with Grubbs’s second-generation catalyst 197, the 7-membered 2,5-dihydro-1,5-benzothiazepine,1-dioxide 198 was obtained in fair yield; although the reaction was particularly slow [50] (Scheme 39).

3.1.40. Reaction of Substituted Chalcones with o-Amino-thiophenol: Formation of Benzothiazepines Depended on Chalcone Substituents. Reaction of chalcones 199 with o-a-phthiophenol in the presence of silica-gel that was carried out under solvent-free conditions afforded 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine 200 in one step in good yield. This reaction depended on the chalcone substituents. In the case of chalcones having NO₂ and OH groups,
the yields were lower (44–68%) than those of chalcones with the other substituents. It seems that low reactivity of chalcones having NO\textsubscript{2} and OH groups is due to these groups being absorbed more strongly on the surface of silica-gel than that of a carbonyl group in the same molecule. Meanwhile, chalcones 199 when reacted with \(\alpha\)-aminothiophenol in refluxing toluene, the chalcones with electron-donating substituents such as CH\textsubscript{3} and OCH\textsubscript{3} group, gave only \(\beta\)-phenyl-\(\beta\)-(2-aminophenylmercapto)-propiophenones of type 199A, whereas from chalcones with
electron-withdrawing substituents such as NO₂ group, only 1,5-benzothenazepines were formed. Therefore, the carbonyl group in chalcones having NO₂ or OH groups is less activated than that in chalcones with the other substituents [51, 52] (Scheme 40).

3.1.41. Synthesis of Fluorinated Azeto[2,1-d][1,5]benzothenazepine from 2-Carboxy-2,3-dihydro-1,5-benzothenazepine Using Conventional and Microwave-Assisted Reactions. A mixture of substituted ortho-amino-thiophenol derivatives, 3-(substituted benzoyl)-2-propionic acid 201 and montmorillonite KSF was dissolved in acetone, swirled for a while and excess solvent was removed under gentle vacuum. The obtained dry flowing powder was irradiated under microwave oven for short time. After completion of the reaction (monitored by TLC) and filtration of the recyclable inorganic solid support, the 2-carboxy-2,3-dihydro-1,5-benzothenazepines 202a–m were obtained in good yield [53] (Scheme 41).

3.1.42. Reactions of o-Amino-thiophenol Derivatives with Isatin and 3-Methyl-1-phenyl-2-pyrazolin-5-one under MW Irradiation in the Presence of Montmorillonite KSF. A neat mixture of isatin 203 and 3-methyl-1-phenyl-2-pyrazolin-5-one 204 placed on an alumina bath and irradiated...
Reagents and conditions: (i) allyl bromide, MeOH, NaOH, H₂O, rt, 2 h; (71%); (ii) TsCl, pyridine, CH₂Cl₂, 45°C, N₂, 24 h (99%); (iii) K₂CO₃, allyl bromide, acetone, rt, 24 h; (99%); (iv) 5% catalyst, toluene, 50°C, N₂, 48 h, complex mixture; (v) [RuCl₂(CO)(PPh₃)₃], toluene, 105°C, 24 h (84%); (viii) 5% catalyst, CHCl₃, rt, 24 h, then 45°C, 24 h (95%); (vi) 5% catalyst, 80°C, 24 h, 78 (41%) and 196 (59%).

Scheme 39: Reaction of (E)-N-(2-(allylsulfonyl)phenyl)-4-methyl-N-(prop-1-enyl)benzenesulfonamide with o-aminothiophenol in the presence of Grubbs' second-generation catalyst.

Scheme 40: Reaction of substituted chalcones with o-aminothiophenol: formation of benzothiazepines depended on chalcone substituents.

for 6–8 minutes gave 3-(3-methyl-5-oxo-1-phenyl-1H-pyrazol-4(5H)-ylidene)indolin-2-one 205 in quantitative yield. Conventional synthesis via heating 203 and 204 in EtOH afforded spiro[dipyrazolopyran3H-indol]-2H-one 206 as major product along with the indilone 205 and required a tedious work during isolation. Reactions of the intermediate 205 synthesized “in situ” with o-aminothiophenol derivatives were examined under MW irradiation using different solid supports including acidic, basic, or neutral alumina, silica, montmorillonite KSF, and K10. The montmorillonite K10 was found the most adaptable and simplest catalyst for synthesizing spiro[indole-pyrazolo][4,3-c][1,5]benzothiazepines 207a–e, since comparatively a higher yield (72–91%) was achieved in shorter reaction time (∼7 min.) by this method.

The best results obtained under microwave irradiation were extrapolated to conventional heating. Thus, in the case of compound 207a when the reaction was carried out using a preheated oil-bath under the same reaction conditions (time, temperature, pressure, and vessel) it did not occur and the reactants remained unchanged even on extended reaction times, suggesting that the effect of
microwave irradiation is not simply thermal process [54] (Scheme 42).

3.1.43. Microwave Thermal Reaction of Alkynone with o-Aminothiophenol. As a model reaction, p-chlorobenzoyl chloride 208b and phenyl acetylene 209a were first reacted under Sonogashira conditions for 1 h at room temperature to furnish the expected alkynone, and after the subsequent addition of o-aminothiophenol and acetic acid (upon varying reaction temperature under microwave irradiation and time) led to the formation of benzothiazepine 210b. This optimization of hetero-cyclisation clearly showed that dielectric heating is superior over conductive heating.

In comparison to the other known MCR synthesis of benzo[b][1,5]diazepines this result is just reverse. Although the Michael addition and cyclo-condensation were essentially completed after 10 min at 60°C in the microwave cavity for electronically diverse substitution and a reaction time of 30 min at 60°C was chosen as the optimal condition.

With these optimizations in hand, a series of acid chlorides 208, alkynes 209, and the o-aminothiophenol or 2-amino-4-chlorobenzenethiol derivatives were submitted to the coupling-addition/cyclo-condensation sequence to give various 2,4-disubstituted benzo[b][1,5]thiazepines 210a–n as yellow to brown or red solids or resins in fair to good yields [55] (Scheme 43).

3.1.44. Comparative Microwave-Assisted and Conventional Thermal Reactions of trans-5-Methyl-3-[p-(3'-aryl-acryl-1'-oyl)-phenyl]-3H-2-oxo-Δ4,1,3,4-oxadiazoles with o-Aminothiophenol. 4-Acetylphenylsydnone 211 (conveniently prepared from p-aminoacetoephone) when reacted with an aromatic aldehyde 212a–d in EtOH afforded trans-3-[p-(3'-aryl acryl-1'-oyl)] phenylsydnone 213a–d as predominant products (Claisen-Schmidt reaction). The trans isomer are favored, since in the transition state, two large substituents are not eclipsed and there is no interference with co-planarity of the enolate system. The trans 213a–d on bromination in Ac2O sydnone ring underwent 1,3-dipolar cycloaddition to give meso-3-[p-(2',3'-dibromo-3'-aryl-propion-1'-yl)-phenyl]-5-methyl-3H-2-oxo-Δ4,1,3,4-oxadiazole 214a–d. During cycloaddition reaction, chalcone moiety was also brominated. The dibromo derivative 214a–d on treatment with o-aminothiophenol did not form the target benzothiazepines 218a–d. Therefore, this method was not advantageous due to the bromination of chalcone moiety. Upon changing the strategy, product 211 was brominated in presence of CH3COOH to 4-bromo-3-(4'-acetyl)-phenylsydnone 215, which upon treatment with aromatic aldehydes 212a–d in EtOH afforded trans-4-bromo-3-[p-(3'-aryl-acryl-1'-oyl)] phenylsydnone 216a–d. The latter compounds upon heating in the presence of Ac2O at 135°C or under microwave irradiation sydnone ring underwent 1,3-dipolar cycloaddition along with the elimination of bromine as acetyl bromide to afford exclusively trans 5-methyl-3-[p-(3'-aryl-acryl-1'-oyl)] phenyl]-3H-2-oxo-Δ4,1,3,4-oxadiazoles 217a–d. Nucleophilic addition of sulfhydryl electrons of o-aminothiophenol on Cα of 217a–d, is followed by intramolecular dehydrative cyclisation to afford the final benzothiazepine products 218a–d (MW: 84–90% yield, time 8–11 min.; thermal: 49–62% yield, time: 175–190 min.). Upon comparing the synthesis by microwave assisted method with the conventional method, it was observed that the reaction progressed very fast with excellent yield in the

<table>
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<th>Scheme 41: Synthesis of fluorinated azeto[2,1-d][1,5]benzothiazepine from 2-carboxy-2,3-dihydro-1,5-benzothiazepine using conventional and microwave-assisted reactions.</th>
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Scheme 42: Reactions of o-aminothiophenol derivatives with isatin and 3-methyl-1-phenyl-2-pyrazolin-5-one under MW irradiation in presence of montmorillonite KSF.

Scheme 43: Microwave thermal reaction of alkynone with o-aminothiophenol.
former. Microwave irradiation facilitates polarization of the molecule under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state [56] (Scheme 44).

3.1.45. Noncatalytic Reaction of Nitro Enones with o-Aminobenzenethiol. Reactions of nitro enones 219–221 with o-aminobenzenethiol occurred very readily at 18–20 °C in methanol (without a catalyst) and completed in 10–20 min. Crystalline 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines 222–224 separated in excellent yields (98–81%) and diastereoisomerically pure. Presumably, the process of this reaction follows nucleophilic addition pattern with subsequent heterocyclization of S-adducts [57] (Scheme 45).

3.1.46. Reaction of 2-(Bromomethyl)-1-sulfonylaiziridines with 2-Aminothiophenol in THF in the Presence of K₂CO₃: A Regio- and Stereocontrolled Synthesis of trans-2-Phenyl- and trans-4-(phenyl or propyl)-3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines. 2-(Bromomethyl)aziridines 226a–c were prepared from ally sulfonamides 225. Aziridination of allylic alcohols 227 afforded the corresponding 2-(hydroxymethyl)-1-tosylaziridines and subsequently sulfonylated to 2-(sulfonyloxymethyl) aziridines 228a–c. Treatment of 2-(bromomethyl) aziridines 226 with 1.2 equiv of o-aminothiophenol provided 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines 230 in good yield. The presence of the corresponding acyclic intermediates 229 could be confirmed by means of ¹H NMR spectroscopy, implying that the formation of benzothiazepines 230 proceeds through initial attack of the sulfur atom of...
Scheme 45: Noncatalytic reaction of nitro enones with o-aminobenzanethiol.

3.1.47. Intramolecular Cyclization through Dehydration of Ethyl 2-(2-Aminophenylthio)-4-oxo-4-p-substituted-phenylbutanoate via Heating. 2-Enoic acids 235a-f were prepared by treating different substituted benzene with commercially available maleic anhydride in the presence of anhydrous AlCl₃. When these acids reacted with C₂H₅OH, then conjugate addition with o-aminophenol leads to ethyl 2-(2-aminophenylthio)-4-oxo-4-p-substitutes-phenylbutanoate 237a-f passing with the enoates 236a-f. On heating in ethanol, 237a-f underwent intramolecular cyclization through dehydration to afford the thiazepines 238a-f (yield unreported) [59] (Scheme 47).

3.1.48. Reactions of 3-(2-Chlorophenyl)-1-(4-chlorophenyl)-2-propenone and 3-(2-Chlorophenyl)-1-(2-thienyl)-2-propenone with 5-Substituted-2-aminobenzenethiols in the Presence of Dry HCl Gas and in Dry Ethanol. When equimolar quantities of 3-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propen-one 240a, 3-(2-chlorophenyl)-1-(2-thienyl)-2-propenone 240b (prepared from reactions of o-chlorobenzaldehyde and the proper ketones 239a or b) reacted with 5-substituted-2-aminobenzenethiol derivatives in the presence of dry HCl gas and in dry EtOH the 2-(2-chlorophenyl)-4-(4-chlorophenyl)/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines 241a-l were afforded in 68–58% yield.

It was established that such reactions take place in two steps. In the first step, nucleophilic attack by the sulfhydryl electrons of 5-substituted-2-aminobenzenethiols takes place on the activated β-carbon atom of the α,β-unsaturated carbonyl compounds to give Michael-adduct type intermediates, which simultaneously undergo dehydrative cyclization to give final products in the second step. The formation of the intermediate and/or cyclized product was found to depend significantly on the reaction conditions. Also, the cyclized products were obtained in a single step in maximum yields in an acidic medium, that is, in methanol/ethanol saturated with dry hydrogen chloride gas [60] (Scheme 48).

3.1.49. Reactions of 6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5H-benz[a]cyclohepten-5-ones with 2-Aminothiophenol in Dry (EtOH/HCl Gas). 6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5H-benz[a]cyclohepten-5-one 243a was obtained by the condensation of 2,3-dimethylbenzocyclohepten-5-one 242a with appropriate aldehyde. Compound 243a reacted with o-aminophenol in dry ethanol and dry HCl gas (passed with the reaction mixture until its saturation). The usual workup gave 2,3-dimethyl-8-phenyl-6,7,7a,8-tetrahydro-5H-9-thia-14-azadibenzo[a,b]heptalenone 244a (in 63% yield) along with a small amount of a dimer 245 as a side product. Under analogous conditions, the reaction of 6-arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one 243b-l with 2-aminophenol in ethyl alcohol afforded 1,5-benzothiazepine derivatives 244b-l, respectively (55–65% yield) [61–63] (Scheme 49).

3.1.50. Thermal Condensation of o-Aminobenzenethiol Derivatives with Methyl trans(±)-3-(4-methoxyphenyl)glycidate in Xylene. Synthesis of (±)-cis-2-(4-methoxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones 247
Scheme 46: Reaction of 2-(bromomethyl)-1-sulfonylaziridines with 2-aminothiophenol in THF in the presence of K₂CO₃: A regio- and stereocontrolled synthesis of trans-2-phenyl- and trans-4-(phenyl or propyl)-3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines.
was carried out by the condensation of o-aminothiophenol derivatives with methyl trans(±)-3-(4-methoxyphenyl)glycidate 246 in xylene at 160°C for 16–20 hours under nitrogen atmosphere. Treatment of 247 with dimethylsulphate afforded (±) cis-2-(4-methoxyphenyl)-3-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones 248, on treatment with chloroacetylchloride gave (±) cis-2-(4-methoxyphenyl)-3-methoxy-2,3-dihydro-1,5-benzothiazepin-4-(chloroacetyl)-ones 249, which in turn afforded (±) cis-2-(4-methoxyphenyl)-3-methoxy-2,3-dihydro-1,5-benzothiazepin-4-[5(4′-met-hylpiperazino-1′)acetyl]-ones 250 on reaction with N-methylpiperazine. Compounds 248 upon treatment with hexamethyldisilazane produced the corresponding trimethylsilyl derivatives 251 which when stirred with sugar, namely, β-D-ribofuranosyl-1-acetate-2,3,5-tribenzoate, in vacuo at 155–160°C for 10 hours gave the corresponding nucleosides 252 [64, 65] (Scheme 50).

3.1.5.1. Multicomponent Reaction (MCR) of the Intermediates Benzylidenepyrazolinones with o-Aminothiophenol under Microwave Irradiation Using Montmorillonite K10 and through a Neat Reaction. Montmorillonite K10 is the most adaptable support for synthesizing the substituted benzothiazepines 257, since a comparatively higher yield was achieved in a shorter time. The reaction has also been performed under neat conditions under microwave irradiation, where 2-phenyl-benzothiazole 260 was formed exclusively instead of the expected product pyrazolo[4,3-c][1,5]benzothiazepines 257. When the same reaction was carried by heating 255 and aminothiophenol derivatives in EtOH and CH₃COOH low yield (15%) of products 257 was obtained instead of 259. The formation of 257 was explained by involving the intermediacy of 256 instead of 258. The mechanistic pathway of the reaction of benzylidenepyrazolinones 255 with aminothiophenol derivatives involves the formation of intermediate Michael adduct 256 via nucleophilic attack of the sulphydryl group on the β-carbon atom of the double bond of 255 which is rendered electrophilic due to vinyl-carbonyl conjugation (i.e., when substituents are present in an α,β-unsaturated ketone, only the nucleophilic addition of the mercapto group to the β-carbon atom takes place, followed by condensation of the carbonyl group with the aromatic primary amine to give a seven-membered ring system) and leads to the formation of the benzothiazepines 257. Formation of intermediate 256 was confirmed by its isolation during the course of the reaction. It was also synthesized separately using isopropanol and their further conversion to final product and was found to be identical with benzothiazepine 257 synthesized using montmorillonite KSF. Formation of intermediate 256 rules out the possibility of the formation of product 259.

In order to develop a facile procedure for the synthesis of 257, it was carried out the improved synthesis of key intermediates 255a–c in solvent-free conditions (neat) under microwave irradiation by irradiating a mixture of p-substituted benzaldehyde 254a–c and 3-methyl-1-phenyl-2-pyrazolin-5-one 253 for 1–2 min to give 255a–c. Therefore, it was used as such for further reaction with 2-aminothiophenol derivatives. Hence, this condition was extended for one-pot synthesis of 257 but surprisingly, the product isolated was identified as 2-phenyl-benzothiazole 260 instead of the expected benzothiazepine 257. The formation of 260 can be explained by the mechanism which involved losses of pyrazolone moiety 253 from the intermediate 256. Intramolecular
nucleophilic attack by a lone pair of nitrogen on the electrophilic carbon in (261) leads to the dihydro intramEDIATE 262, which is readily oxidized to the corresponding 2-arylbenzothiazoles 260. The reaction was investigated also via MCR of 253, 254, and aminothiophenol derivatives under microwave irradiation using montmorillonite K10 and through a neat reaction. The results showed the formation of the pyrazolo[4, 3-c][1, 5]benzothiazepines 259 under microwave irradiation, in low yield, coupled with inorganic supports and the synthesis of 2-phenyl-benzothiazole 260 in neat conditions.

Finally, the results obtained under microwave irradiation were compared to conventional heating. The reaction in the case of compounds 257a has been carried out using a preheated oil bath under the same conditions as under microwaves (time, temperature, vessel, and solid support). It has been found that reactants remained unchanged up to 7 min, while traces of mixture of product were obtained when the reaction time was extended to 7-8 h [66] (Scheme 51).

### 4. Miscellaneous Approaches

#### 4.1. Solid-Phase Synthesis of 3,5-Disubstituted 2,3-Dihydro-1,5-benzothiaepin-4(5H)-ones. A synthetic pathway to benzothiazepines was described. Starting with a nucleophilic aromatic substitution of the benzoic acid 263 after immobilization of 264. The nitro group was reduced by tin (II) chloride. Reductive alkylation of 265 gave 266, which in turn reacted with aldehydes 267 and sodium cyanotriborohydride 268 to afford the secondary anilines 269. Intramolecular cyclisation formed the 3,5-disubstituted 2,3-dihydro-1,5-benzothiaepin-4(5H)-ones 270. In this pathway, N-α-Fmoc-S-trityl-l-cysteine coupled to p-methylbenzhydryl amine resin, the trityl group was cleaved and the benzoic acid 263 was connected to give 271.

A similar pathway to benzothiazepines was described previously [62]. N-α-Fmoc-S-trityl-l-cysteine was coupled to p-methylbenzhydrylamine resin, the trityl group was cleaved and the benzoic acid 263 was connected. The protected amine...
272 was deprotected and reductively alkylated. Cyclization of 273 resulted in the benzothiazepine skeleton 274. The nitro group was reduced and coupled to the carboxylic acid [62, 67, 68] (Scheme 52).

4.2. Intramolecular Acylation of 1-(2-Carboxymethylthiophenyl)-2H-imidazol-2-ones in Polyphosphoric Acid. The starting benzothiazolones 276a and b were obtained by alkylation of 2(3H)-benzothiazolones 275a and b with chloroacetone in DMF at room temperature in the presence of dry K2CO3 and benzyltriethylammonium chloride (TEBA-Cl). Under these conditions, the alkyl derivatives 276a and b were prepared for a more short time and in higher yields. Imidazolones 277a–k, were obtained as a result of a ring transformation of 3-(2-oxopropyl)-2(3H)-benzothiazolones 276a and b upon treatment with primary amines. In this case, the reaction was carried out in aqueous media, instead of perchloric acid, using 6–10 fold excess of the amine. To prevent a possible partial oxidation of the thiol group to disulfide, the products 277a–k were immediately used in the next step without isolation and further purification. Alkylation reaction of 277a–k with chloroacetic acid proceeded smoothly upon reflux in aqueous NaOH for 30–60 min. The resulting 1-(2-carboxymethylthiophenyl)-2H-imidazol-2-ones 278a–k are stable compounds and were isolated with good to excellent yields (63–86%). Intramolecular acylation of compounds 278a–k in polyphosphoric acid (PPA) at 110–120°C gave benzothiazepines 279a–k in 47–83% yield. The intramolecular acylation, described in this work, is a convenient and easily adjustable method for the synthesis of 1,5-benzothiazepines, containing an annelated imidazole ring substituted at 2-, 3-, or 5-position [69] (Scheme 53).

4.3. Reactions of Azirinobenzothiazine with HBr (Heating) or with Trifluoride Etherate (at Room Temperature). Azirinobenzothiazine 281 was synthesized via cycloaddition of dichlorocarbene (generated by alkaline hydrolysis of chloroform or thermocatalytic decomposition of sodium trichloroacetate) to the C=N double bond of 3-phenyl-2H-1,4-benzothiazine 280. On heating 281 in concentrated...
The azirinobenzothiazine 281 on reaction with boron trifluoride etherate at room temperature gave the imidoyl chloride 284. This imidoyl chloride hydrolyzed more easily under purification on silica gel forming [1, 5]benzothiazepinone 285. After chromatography on silica gel, 28% of the dichlorobenzo[1, 5]thiazepine 284 and 44% of the monochlorobenzo[1, 5]thiazepine 285 were isolated; whereas

**Scheme 50:** Thermal condensation of α-aminobenzenethiol derivatives with methyl trans(±)-3-(4-methoxyphenyl)glycidate in xylene.
chromatography on alumina gave 83% of compound 284 and 13% of compound 285.

The benzothiazepine 284 contains two chlorine atoms, which could potentially be used for its modification via reactions with nucleophiles. When compound 284 was heated with sodium methoxide in methanol, and it was smoothly transformed into the corresponding methoxy derivative 286. Chloride 284 reacted also with morpholine to give amidine 287 in good yield [70, 71] (Scheme 54).

4.4. Reactions of 4-Methoxy-α-[4H-pyrrolo-3-pyridyl]thio]-phenyl Acetic Acid with Phosphorus Pentachloride. 4-Aminopyridine reacted with pivaloyl chloride at 0°C in the presence of Et₃N to form 4-pivaloylaminopyridine 288 in high yield. Double lithiation of 288 using 2.5 M n-butyllithium produced a white precipitate of the dilithio derivative. Reaction of this species with the electrophile tetraisopropylthiuram disulfide (TITD) produced 3-(N,N-diisopropylthiocarbamato)pyridine 289 in good yield (87%). Attempted removal of the pivaloyl group using 5 M HCl solution produced a 2-tert-butylthiazolo[5,4-c]pyridine 290 in 99% yield. The subsequent alkaline hydrolysis of 290 produced the disulfide 291. The 1,2-bis(4-(1H-pyrrol-1-yl)pyridin-3-yl)disulfane 292 was prepared by reaction of 2,5-dimethoxytetrahydrofuran with bis(2-amino-4-pyridyl)disulfane 291. The disulfane 292 was
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Scheme 52: Solid-phase synthesis of 3,5-disubstituted 2,3-dihydro-1,5-benzothiaepin-4(5H)-ones.

4.5. Reaction of (E)-1-(2-Hydroxyphenyl)-3-(p-substituted phenyl)prop-2-en-1-ones with 1-Amino-2-mercapto-5-phenyl-1,3,4-triazole in the Presence of a Catalytic Amount of Sodium Acetate in DMSO. One pot reaction of chalcones 296a–f under microwave irradiation (6–8 min, at 500 W with short interruptions of 30 sec to 1 min to avoid an excessive evaporation of the solvent) with 1-amino-2-mercapto-5-phenyl-1,3,4-triazole in the presence of a catalytic amount of sodium acetate in DMSO, underwent heterocyclization, afforded the corresponding 1,5-thiadiazepines 297a–f in good yields (92–80%). The formation of 297 probably involves the intermediates (298) which could produce 297a–f. The formation of the condensed heterocyclic compounds 297 by the dehydration of (298) could be favorable in a nonaqueous medium. A dipolar transition state is involved in the formation of intermediates (298) by the 1,2- and 1,4-addition to the carbonyl group and to the β-carbon atom of the α,β-unsaturated carbonyl system, followed by cyclization to give title 1,5-benzothiazepine 297 [73] (Scheme 56).

4.6. Synthesis of Indolo[3,2-b]-1,5-benzothiazepine-ones from Indoleanilides Substituted at C-2 and at C-3. Indoleanilides substituted at C-2 (300, 302, 304, 306): indole-2-carboxylic acid reduced with NaBH₄ in refluxing ethanol to give 3-mercapto-4H-pyrrolopyridine and the latter subsequently reacted with α-bromo-4-methoxyphenylacetic acid ethyl ester (obtained from 4-methoxyphenylacetic acid by an esterification reaction with absolute ethanol containing a catalytic amount of concentrated H₂SO₄, and then bromination with N-bromosuccinimide) to give ethyl 2-(2-(1H-pyrrol-1-yl)phenylthio)-2-(4-methoxyphenyl)acetate 293. Hydrolysis of ester group in 293 with 5% NaOH solution afforded 4-methoxy-α-[(4H-pyrrolo-3-pyridyl)thio] phenyl acetic acid 294. Intramolecular cyclization of the acid 294 using phosphorus pentachloride gave the target compound: 2-(4-Methoxyphenyl)pyrrolo[2,1-d]pyrrolo[2,3-c][1,5]thiazepine-3(2H)-one 295 [72] (Scheme 55).
Scheme 53: Intramolecular acylation of 1-(2-carboxymethylthiophenyl)-2H-imidazol-2-ones in polyphosphoric acid.

Scheme 54: Reactions of azirinobenzothiazine with HBr (heating) or with trifluoride etherate at room temperature.
Reagents and conditions: (a) pivaloyl chloride, Et₃N, anhydrous CH₂Cl₂, 0°C; (b) TTTD, 2.5M n-butyllithium, −78°C, anhydrous THF; (c) 5 M-HCl, reflux; (d) 5M NaOH, solid NaOH, reflux; (e) 2.5-dimethoxytetrahydrofuran, glacial acetic acid, 110°C; (f) i) NaBH₄, absolute EtOH, reflux, (ii) a-bromophenyl acetic acid ethyl ester, EtOH, rt; (g) 5% NaOH, MeOH, MeOH/THF (1:1), rt; (h) PCl₅, anhydrous CH₂Cl₂, rt, 60°C.

Scheme 55: Reactions of 4-methoxy-α-[(4H-pyrrolo-3-pyridyl)thio]phenyl acetic acid with phosphorus pentachloride.

Reagents and conditions: (a) pivaloyl chloride, Et₃N, anhydrous CH₂Cl₂, 0°C; (b) TTTD, 2.5M n-butyllithium, −78°C, anhydrous THF; (c) 5 M-HCl, reflux; (d) 5M NaOH, solid NaOH, reflux; (e) 2.5-dimethoxytetrahydrofuran, glacial acetic acid, 110°C; (f) i) NaBH₄, absolute EtOH, reflux, (ii) a-bromophenyl acetic acid ethyl ester, EtOH, rt; (g) 5% NaOH, MeOH, MeOH/THF (1:1), rt; (h) PCl₅, anhydrous CH₂Cl₂, rt, 60°C.

Scheme 55: Reactions of 4-methoxy-α-[(4H-pyrrolo-3-pyridyl)thio]phenyl acetic acid with phosphorus pentachloride.

Acid chloride and a 2-(alkylthio) aniline produced sulfides 299a–c in modest yields. Problems have been reported with reactions of indole carboxylic acids with thionyl chloride and use of the unstable acid chloride (and consequent low yield of amide) could be avoided by trimethylaluminum-catalyzed condensation of 2-(alkylthio)anilines and ethyl indole-2-carboxylate. For example, 299a was obtained in 92% yield by this approach. The method selected was typically based on solubility of the starting sulfide in the oxidation medium.

Monoalkylated compounds 302ab bearing a methyl substituent on the amide nitrogen were prepared, on replacing the aniline component with an N-methyl-2-(alkylthio) aniline followed by oxidation. Monoalkylated compounds bearing the methyl substituent on the indole 304ab were prepared from alkylthioanilines and N-methylindole carboxylic

Intermediates (298)
acid followed by oxidation. N,N′-Dimethylated compounds 306ab were prepared by dialkylation of amides (299ab) by catalytic phase transfer methylation followed by oxidation. Sulfide 299c decomposed under phase transfer conditions (retro-Michael) so compound 306c was prepared in low yield by reaction of 1-methyl-1H-indole-2-carboxylic acid chloride with 3-[(2-(methylamino)-phenylthio)propanenitrile followed by oxidation. When the sulfides were subjected to cyclization conditions (either activation by electrophilic species (TFAA) or thermally (refluxing in chloroform or p-xylene)) clear patterns of reactivity emerged when the sulfides were cyclized. Conditions for cyclization were either thermal (refluxing in chloroform or p-xylene) or electrophilic activation (TFAA). In successful reactions, tert-butyl sulfoxide derivatives cyclize thermally in refluxing chloroform; whereas ethyl sulfoxide derivatives cyclize thermally in refluxing chloroform or electrophilic activation (TFAA). Conditions for cyclization were either thermal (refluxing in chloroform or p-xylene) or thermally (refluxing in chloroform or p-xylene) for 3
dimethylated compounds 306abc were prepared by dialkylation of amides (299ab) by catalytic phase transfer methylation followed by oxidation. Sulfide 299c decomposed under phase transfer conditions (retro-Michael) so compound 306c was prepared in low yield by reaction of 1-methyl-1H-indole-2-carboxylic acid chloride with 3-[(2-(methylamino)-phenylthio)propanenitrile followed by oxidation. When the sulfides were subjected to cyclization conditions (either activation by electrophilic species (TFAA) or thermally (refluxing in chloroform or p-xylene)) clear patterns of reactivity emerged when the sulfides were cyclized. Conditions for cyclization were either thermal (refluxing in chloroform or p-xylene) or electrophilic activation (TFAA). In successful reactions, tert-butyl sulfoxide derivatives cyclize thermally in refluxing chloroform; whereas ethyl sulfoxide derivatives require higher temperatures (refluxing in p-xylene).

Compounds in which the amide site is methyalted (but still contain an indolic N–H) 302ab cyclize both thermally and with TFAA activation to 10,11-dihydro-10-methyl-12H-indolo[3,2-b]1,5-benzothiazepin-11-one 307. Dimethylated compounds 306abc react to give 10,11-dihydro-10,12-dimethylindolo[3,2-b]-1,5-benzothiazepin-11-one 308. Due to competing side reactions, yields of 308 from 2-propanenitrile compounds were inferior to both ethyl and tert-butyl sulfoxides and were not pursued further. In addition, 308 was synthesized from 309. Refluxing 309 in toluene using SiO₂ as catalyst gave 310, which upon catalytic phase transfer dimethylation gave a product chromatographically and spectroscopically identical to the cyclisation product 308. This clearly establishes the sites of attachment of the sulfur and carbonyl groups on the indole ring of the SES product. Catalytic phase transfer methylation of 307 also produced 308 (76%) confirming the structure of that product as well.

Indolenilides substituted at C-3. Reproducibility problems were encountered with the reported preparation of 3-indole carboxylic acid while preparing 311a, so the tert-butyl analogue 311b was prepared directly from indole and 2-(tert-butylthio)aniline in the presence of tri-phosgene and pyridine in 33% yield. Methylation and oxidation provided 314b. Cyclizations of sulfoxides 312a, 314ab, or the thio-compound 313ab were conducted under both thermal activation and TFAA activation. The product obtained from heating 314a under reflux for 15 h in p-xylene (67% yield after chromatography) proved to be identical to the benzothiazepine 308, the cyclization product from the 2-substituted indole sulfoxide.

As a conclusion both 2- and 3-indolenilides 306abc and 314a undergo cyclisation to produce the same product indolo[3,2-b]-1,5-benzothiazepin-11-one 308. For the 3-indolenilides, the possibility of indole substituent migration before or after cyclization was eliminated and a 3H-indolinium spirocyclic intermediate, with preferential migration of the amide-containing moiety from C-3 to C-2, via 315-316-317 is proposed to rationalize the rearrangement. Also, it was discovered that successful cyclisation in this series requires the absence of an amidad hydrogen in the compounds. The lack of cyclization of compounds containing an amidad hydrogen is attributed to N–H⋯O=S hydrogen bonding, a low energy trans-amide conformation, and a formidable rotational barrier to the cis-amide conformation, all of which enforce a molecular geometry that precludes the sulfur atom from achieving an orientation conducive to interaction with indole π-electrons. By extrapolation, if cyclized compounds containing an amidad hydrogen are synthethic targets, one should consider introducing an easily removable amidad alkyl substituent (e.g., benzyl) into the SES substrate [74] (Scheme 57).

4.7. Cyclization of 3-[5-[(alkylamino)phenyl]sulfanyl]-propanoic Acids with 1,3-Dicyclohexylcarbodiimide (DCC) at r.t. in THF. N₁-(Alkyl)-2-(alkylsulfanyl)-N⁴-phenyl-1,4-benzenediamines 319a–f were prepared in 87–97% yields by treatment of N₄-[(alkylimino]-2,5-cyclohexadien-1-ylideneanilines 318a–c with the corresponding R-mercaptoalkanoate esters. Also, 2H-1,4-benzothiazin-3(4H)-ones 321a–f prepared in 89–97% yields by intramolecular cycloadditions of compounds 319a–f on treatment with trifluoroacetic acid under reflux overnight. Alkyl 3-[(5-anilino-2-(alkyl-amino) phenyl)sulfanyl]-propanoates 322a–f were obtained in 86–92% yields by treatment of N₄-[(alkylimino]-2,5-cyclohexadien-1-ylideneanilines 318a–c with the corresponding β-mercaptoalkanoate esters. Cyclization of compounds 321a–f by heating with trifluoroacetic acid at 70°C was attempted. Compounds 321a–f failed to provide the desired cyclized benzothiazepines 322a–f under these reaction conditions. Refluxing of compounds 321d–f in chlorobenzene for 2 days led only to recovery of the starting materials. When Decalin was used as a solvent, decomposition of the starting materials occurred after heating at 190°C for 3 days. The synthesis of benzothiazepinones was tried by treating benzoquinone diimines 318a–c with 3-mercaptopropionic acid. It was envisioned that once the addition products, 3-[(5-anilino-2-(alkylamino) phenyl)sulfanyl] propanoic acids 323a–c were made, cyclization could be achieved upon addition of 1,3-dicyclohexylcarbodiimide (DCC). Intermediate compounds 323a–c, were isolated (but characterized only by 'H NMR) and further used in the final cyclization step to obtain the target benzothiazepines 322a–c. Treatment of the intermediates 323a–c with DCC and subsequent purification by flash column chromatography gave the desired benzothiazepines 322a–c in 81–97% yields [75] (Scheme 58).

4.8. Ring-Closure Reactions between α,β-Unsaturated Ketones and the Intermediate Samarium Diiodide (Kagan Reagent). Ring-closure reactions between α,β-unsaturated ketones and intermediates samarium diiodide (Kagan reagent) 325 (prepared from bis(o-nitrophenyl)disulfide 324 and SmI₂) took place readily to afford 2,3-dihydro-1,5-benzothiazepines 326. It was found that chalcones are more reactive than the new anionic species 325 than any other α,β-unsaturated ketones. It must be noted that α-aminothio phenols were less reactive toward aldehydes than the intermediates 325 [76] (Scheme 59).
Synthesis of 2-indoleanilides.
Reagents and conditions (compound number,% yield): (a) 2-ethylthioaniline, AlMe₃, toluene, reflux (299b 92%, 303a 84%); (b) SOCl₂, Et₂O, 2-(alkylthio)aniline, rt (299a 32%, 299b 71%, 303b 59%); (c) SOCl₂, Et₂O, N-methyl-2-(alkylthio)aniline, rt (301a 38%, 301b 79%, 305c 27%); (d) 50% NaOH, CH₃I, n-Bu₄NHSO₄, toluene (305a 82%, 305b 79%).

Confirmation of structures of 307 and 308.
Reagents and conditions: (a) 2,2’-diaminodiphenyldisulfide, NaH, DMF (93%); (b) SiO₂, toluene, reflux (63%); (c) n- Bu₄NHSO₄, 50% NaOH, CH₃I, toluene, reflux [from 307 (76%), from 12 (89%)].

Scheme 57: Continued.
5. Reactions

5.1. Staudinger Reaction of 2,4-Disubstituted 2,3-Dihydro-1,5-benzothiazepines with Cyclohexanecarboxylic Chloride in the Presence of Triethylamine in Anhydrous Benzene. The reaction of 2-(4-chlorophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine 327a with cyclohexanecarboxylic chloride in the presence of triethylamine when carried out using commercially available benzene as solvent afforded the amide 329a and not the β-lactam derivative 328a (<5% yield). Using sodium-dried benzene as solvent, the reaction also gave amide 329a as the major product together with a 16% yield of β-lactam 328a and some recovered 1,5-benzothiazepine 327a. A longer reaction time of 8 h increased the yield of β-lactam 328a to 27%; but with a more extended reaction time no further improvement of the yield was achieved. In the same way, the spirofused β-lactams 328b,c (34–54%) and amides 329b,c (16–38%) together with recovered starting materials were obtained from 1,5-benzothiazepines 327b,c. The lower yields of β-lactams 328 in the current cases are possibly due to steric hindrance of the disubstituted ketene, penta-methyleneketene. A proposed reaction mechanism for the formation of amides 329 was suggested as follows. Imines 327 (R1, R2, R3 = Ph, H, 4-XC6H4) reacted with pentamethyleneketene to form zwitterionic intermediates A, which undergo a conrotatory ring closure to form β-lactam derivatives 328. The zwitterionic intermediates A was not completely converted into β-lactams and reacted with water during workup to generate hemiaminal intermediates B, which, in turn, underwent ring opening forming the amides 329. Formation of β-lactams and amides is competitive in the Staudinger reaction with the weak electron-donating disubstituted ketene [77] (Scheme 60).

5.2. Ring Contraction of 1,5-Benzothiazepines. When 1,5-Benzothiazepines 330–339 were allowed to react with a mixture of acetic anhydride and pyridine afforded 3-acetyl-2,3-dihydro-2-phenyl-2-styrylbenzothiazoles 340–349 (83–61% yield) via ring contraction of the thiazepine ring. It is worth mentioning that the ortho-acetoxy group in the phenyl ring at position 2 of compounds 330–337 seemed to be without influence on the acetylation of the nitrogen atom and, therefore, on the course of the ring contraction leading to the formation of benzothiazoles 340–347. The above mentioned 3-acetyl-2,3-dihydrobenzothiazoles appeared to be convenient substrates to get newer insights into the scope and limitation of the utility of the dimethyldioxirane for a chemoselective oxidation of the sulfur atom of compounds with various sites of oxidation. Therefore, when compounds 340, 344–353 were allowed to react with isolated dimethyldioxirane (DMD) (in acetone solution) their 1,1-dioxides 354–364 were obtained as sole isolable product (78–94% yield) in each case [78] (Scheme 61).

5.3. Reactions between 2,4-Disubstituted 2,3-dihydro-1,5-benzothiazepines and Ketenes. Reaction of benzothiazepines 365 and 366 in the presence of Et3N showed different
Preparation of Alkyl 3-[(5-anilino-2-(alkylamino)phenyl)sulfanyl] propanoates (321a-f), 3-[(5-anilino-2-(alkylamino)phenyl)sulfanyl] propanoic acid 323a-c and 2,3-Dihydro-1,5-Benzothiazepin-4(5H)-ones (322a-c)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
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<td>90</td>
<td>322a</td>
<td>2-Methylpropyl</td>
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<td>H</td>
<td>89</td>
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<td>81</td>
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<td>Me</td>
<td>H</td>
<td>86</td>
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<td>Et</td>
<td>88</td>
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<td>H</td>
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<td>H</td>
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<td>Et</td>
<td>92</td>
<td>c</td>
<td>Me</td>
<td>70</td>
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</table>

Scheme 58: Cyclization of 3-[(5-anilino-2-(alkylamino)phenyl)sulfanyl] propanoic acids with 1,3-dicyclohexylcarbodiimide (DCC) at r.t. in THF.

reactivity with different substituents on 365 or 366, and several different products at different reaction temperatures have been obtained.

When the reaction was carried out at room temperature, reaction of 365 and 366 produced 367 as the major product, except that 369b was obtained as the major product in the reaction of 2-methyl substrate 365b with dichloroacetyl chloride. However, the reaction gave very complicated products when carried out at refluxed temperature. The product is a mixture of 367, 368, and 369, one or two of which are major products, and product 369 can only be obtained when reagent 366 is 366b. Compounds 367, 368, and 369 have been separated and characterized, among them, 368 and 369 are new types of compounds. Compound 367d was further characterized by X-ray diffraction analysis.

At room temperature, reaction of chloroacetyl chloride (366a) with 365a,b, followed by the addition of triethyl amine, gave the expected product 367a,b. All of these compounds were in the form of white crystal. The chemical shifts of the three protons on the seven membered ring and the corresponding coupling constants are different.

When the 2-position has a methyl group, the NMR signal of proton 4-H is shifted upfield significantly such that it is between the signals of 3-H and 3'-H. When 365a and 366a are reacted at room temperature, product 367a is obtained in 80% yield. However, the product of the reaction between 365b and 366b, which is also white crystals, gives an IR spectrum very different from that of 367a. In addition to the typical β-lactam carbonyl absorption at 1700 cm⁻¹, another band at 1640 cm⁻¹ is also observed. The mass spectrum
shows that four chlorine atoms are present in the molecule. It was therefore concluded that this is a product resulting from one molecule of 365_B reacting with two molecules of 366_A. The NMR spectrum of this compound does not show an AMX signal attributable to the three protons on the seven membered ring but instead gives a signal corresponding to a 2H doublet with a coupling constant of 7 Hz at δ 1.46. Other signals are: δ 3.98 (s, 3H), 4.85 (m, 1H), 4.20 (s, 1H), and 6.04 (d, 1H, J = 7.1 Hz). Combining the NMR data with MS fragment analysis, it is reasonable to conclude that the seven-membered ring at 365_B fragments during the reaction to give a product with structure 369_Ba. This shows that compounds 366_A and 366_B have different reactivity.

This reaction gives very different results at different temperatures. When carried out at room temperature, compounds 365_A and 366_B produced 367_Ab as the major product. When carried out at reflux temperature, a compound bearing the structural features of 369_Ab is obtained as the major product. The NMR spectrum of this 369_Ab shows two doublets at δ 6.44 and 6.96 (J = 16 Hz), suggesting that the two protons of the −CH=CH− double bond in 369_Ab are trans to each other, while in the case of 369_Bb, these two protons are cis to each other.

When the reaction of 365_A and 366_A was carried out at reflux temperature, a low melting-point crystalline solid was obtained in addition to a small amount of the expected 367_Aa. The IR spectrum of this compound showed absorption at 1676 cm⁻¹; while the band at 1750 cm⁻¹, which is the typical carbonyl absorption for a β-lactam, is not present. Mass spectrometry shows that this compound has a molecular ion peak with the same m/z value as 367_Aa, but that the fragmentation pattern is different. This suggests that this newly obtained compound is a structural isomer of 367_Aa. The NMR spectrum of this compound did not show signals for the three protons of the AMX system but showed two doublets at δ 3.50 and 3.95 with a coupling constant of J = 13.5 Hz, and two doublets at δ 6.53 and 6.88 ppm with a coupling constant of J = 15.7 Hz. This indicates that this compound should have the structure of 368_Aa, with the two protons on the C=C double bond in a trans relation. When 365_A and 366_A were heated under reflux, the low melting-point compound 368_Ba was obtained along with a small amount of the expected compound 369_Ba. The IR spectrum of 368_Ba showed an absorption at 1680 cm⁻¹. Its mass spectrum shows an M⁺ ion with m/z 359, but with a different fragmentation pattern from that of 367_Ba. The NMR spectrum of compound 368_Ba showed two groups of signals: δ 1.46 (d, 3H, J = 4.8), 3.77 (s, 3H), 4.02 (dd, 2H, J = 13), 4.52 (m, 1H), 5.99 (d, 1H, J = 6.4); 1.48 (d, 3H, J = 4.8), 3.82 (s, 3H), 4.12 (s, 2H), 4.71 (m, 1H), 6.19 (d, 1H, J = 7.1), and 6.85–7.51 (m, 1H) for aromatic protons. The chemical shifts for the major signals of these two compounds are quite similar, with about 0.2 ppm differences. This may indicate that 368_Ba is a mixture of a pair of stereoisomers.

As with the case of 368_Ba, the NMR spectrum of the reaction product of 365_B with 366_A showed two groups of NMR signals, one of which is described as: δ 1.48 (d, 3H, J = 6.9), 3.80 (s, 3H), 4.54 (m, 1H), 5.99 (d, 1H, J = 7.3), 6.27 (s, 1H); while the other is as follows: δ 1.55 (d, 3H, J = 6.4), 3.82 (s, 3H), 4.79 (m, 1H), 6.24 (s, 1H), 6.27 (d, 1H, J = 7.3). Signals for aromatic protons appear at δ 6.87–7.48 (m, 1H). This suggests that these two compounds may be diastereomers of 368_Ba. Based on these observations, there is a propose reaction mechanism.

If the reaction proceeds as proposed, there should be an intermediate 371, and a rearrangement should occur with the presence of a nucleophile in the reaction system. When trace amount of water was added to the above reaction system,

<table>
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<tr>
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<td>Cl</td>
<td>C₆H₅</td>
<td>Ph</td>
<td>4</td>
</tr>
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<tr>
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<td>Ph</td>
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</tr>
<tr>
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<td>Cl</td>
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</tr>
<tr>
<td>(h)</td>
<td>H</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>10</td>
</tr>
</tbody>
</table>

*(a) Yields of crude product based on bis (o-nitrophenyl)disulfides*
a different result was obtained. The product with structure 370 was isolated, indicating the possible existence of intermediate 371 [79] (Scheme 62).

5.4. Synthesis of Dihydro1,5-benzothiazepines via Reactions of α,β-Unsaturated Ketones with o-Aminothiophenol. Dihydrobenzothiazepines, 1,5-benzothiazepines 372 (prepared from o-aminothiophenol and α,β-unsaturated ketones in excellent yields) were reacted with various acyl chlorides, including phthalimidoacetyl chloride (prepared from phthalic anhydride and glycine), chloroacetyl chloride, dichloroacetyl chloride, and phenoxyacetyl chloride, in the presence of Et$_3$N in anhydrous benzene, to give 2a,4-disubstituted 2-phthalimido,2-chloro-,2,2-dichloro-, or 2-phenoxy-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-ones 373–376 through parallel solution-phase synthesis. (Yield of some representative examples: 373a: 79%, 374i: 67%, 374k: 60%; 375b: 86%, 375d: 73%).

This could be rationalized as follows. A zwitterionic intermediate 377 could be formed from two pathways: (i) Triethylamine abstracts an α-hydrogen next to the carbonyl group in the positively charged N-acylated benzothiazepine intermediate which in turn yields the less sterically hindered zwitterionic intermediate 377. (ii) The heterocyclic nitrogen atom of the benzothiazepine scaffold 1 forms an N–C bond with the carbonyl group of a ketene, the latter generated from acyl chloride and triethylamine. The N–C interaction should occur from the less hindered side of the ketene over the small group H for phthalimidoketene, chloroketene, and phenoxyketene.

The zwitterionic intermediate 377 then undergoes conrotatory ring closure to form a β-lactam ring to afford azeto[2,1-d][1,5]benzothiazepin-1-ones 373–376.

Because ring closure in the downward direction of the N–C bond in the thiazepine ring (path a) would require ring contraction of the thiazepine ring, this path is not energetically favorable. Although the conrotatory ring closure could occur...
in the upward direction of the N–C bond (path b) to provide
products with cis R1, R2, and R3 substituents, this process is
forbidden because R2 and R3 substituents occupy in the steric
hindered 1,3-quasi-axial positions of the thiazepin ring.

The conrotatory ring closure can occur only with the
sense shown (downward, path c), in which the thiazepine
framework rotates downwards to yield a boat-like product
via β-lactam ring formation. If the conrotatory ring closure,
in which the whole thiazepin ring rotates upwards (path d),
occurs upwards, a β-lactam ring would form from the inside
of the thiazepin ring. This is an unfavorable process because
the lope of the orbital in the thiazepine locates in the inside of
the boat bottom; it cannot overlap with the lope of the orbital
in the enolate part.

This boat-like product formed then undergoes conformati-
onal transfer to produce finally the predominant chair-like
products [80] (Scheme 63).

5.5. Reduction of Oxygen-Bridged 1,5-Benzothiazepines.
The 2,3,4,5-tetrahydro-1,5-benzothiazepine derivatives 39a
(Scheme 6) and b upon reduction with LiAlH4 (3M) yielded
378a and b (39 and 45% yield, resp.). Although the reduction
of both double bonds to give 379a and b is expected, only the
C=N double bond was reduced and the oxygen bridge was
opened as well to give 378a and b. In an attempt to achieve a
fully reduced 2,3,4,5-tetrahydro-1,5-benzothiazepine deriv-
ative, a higher amount of LiAlH4 was used for the reduction
of 39b as an example, and the reaction mixture was refluxed
for 30 minutes after stirring overnight at room temperature.
Thereby, a new reduction benzothiazepine product 380 was
isolated (65% yield) [9] (Scheme 64).

5.6. Ring-Opening Reaction of 3-(1H-1,2,4-Triazol-1-yl)-1,5-
benzothiazepine with Phenylonitrile Oxide. Benzohydrox-
iminoyl chloride when added while stirring to a solution
of 1,5-benzothiazepine containing 1,2,4-triazole moiety
dissolved in methylene chloride while drop wise adding
of triethylamine gave the ring-opened product (Z)-2-
((Z)-1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl)allylidene)-
aminophenyl-N-hydroxybenzimidothioate 381 (27.3%
yield) and not the expected 1,5-thiazepine 382 [10]
(Scheme 65).

5.7. Reaction of 2,3-Dihydro[1,5]benzothiazepines with Ben-
zychromoximinoyl Chloride. When selected benzohydroximi-
noyl chloride derivatives were added to a stirred solution
of the 1,5-benzothiazepine 45a–d in methylene chloride,
Et3N dissolved in dichloromethane, and the reaction mixture
stirred at room temperature for 4 days, the oxadiazolothiazepine 383a–l were obtained in moderate yield (31–48%) [11] (Scheme 66).

5.8. Reaction of 1,5-Benzothiazepines with Chloroacetyl Chloride and Phenoxy-acetyl Chloride in Presence of Et$_3$N. The 1,5-benzothiazepines 49a–e when reacted with chloroacetyl chloride or phenoxyacetyl chloride, in the presence of triethylamine in anhydrous benzene, gave 2-chloro- or 2-phenoxy-2a-(2-phenyl-1,2,3-triazole-4-yl)-4-aryl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5] benzothiazepin-1-ones 384a–j in 59–36% yield through parallel solution-phase synthesis [12] (Scheme 67).

5.9. 1,3-Dipolar Cycloadditions of (E)-2-(7-Phenoxyquinolin-6-yl)-4-substituted Phenyl-2,3-dihydrobenzo[1,5]thiazepine with Benzhydroximinoyl Chlorides or Hydrazonoyl Chlorides in the Presence of Et$_3$N. The benzothiazepine derivatives 57a–c underwent 1,3-dipolar cycloadditions with benzhydroximinoyl chlorides or hydrazonoyl chlorides in the presence of Et$_3$N to afford the formation of cycloadducts 385a–l and 386a–i, respectively.

A conceivable intramolecular 1,3-dipolar cycloaddition mechanism is proposed. The conformation of the central 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepine ring adopts a boat-like conformation. In the presence of Et$_3$N, the nitrile oxide generated in situ, C=N double bond in the benzothiazepine ring forms a cyclic transition state, the σ-bonds of C=N and C=O were formed simultaneously to obtain the 1,2,4-oxadiazole ring, the central thiazepine ring of the cycloadduct also adopts a boat-like conformation. The plausible mechanism of compounds 386a–l was proposed analogously [14] (Scheme 68).
Parallel solution-phase synthesis of 2a,3,4,5-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones in the presence of NEt₃

<table>
<thead>
<tr>
<th>(a)</th>
<th>(b)</th>
<th>(c)</th>
<th>(d)</th>
<th>(e)</th>
<th>(f)</th>
<th>(g)</th>
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</tr>
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Stereostructure of 2,2a,4-trisubstituted 2a,3,4,5-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones.

Scheme 63: Continued.
5.10. 1,3-Dipolar Cycloaddition of Nitrile Oxide and Triethylamine, with the Hexa Hydropyrido-[3,4-c][1,5]benzothiazepines. The 1,3-dipolar cycloaddition of nitrile oxide, generated in situ from benzohydroximinoyl chloride and Et₃N, with 2-methyl-11-aryl-4-[(E)-arylmethylidene]-1,2,3,4,11,11-a hexahydropyrido[3,4-c][1,5]benzothiazepines 103a-j afforded novel 6-methyl-1-phenyl-8-aryl-4-[(E)-arylmethylidene]-4,5,6,7a,8-hexahydropyrido[3,4-c]-[1,5]benzothiazepines 387a-j. This reaction completed in 20–30 min affording the benzothiazepine 387 almost quantitatively. The triethylamine hydrochloride formed during the reaction can be filtered, neutralized and reused. Hence the only waste generated in this reaction is hydrochloric acid and the atom economy of the reaction is very high, that is, 94%. Therefore, this study presented a highly atom economic protocol for the stereoselective synthesis of a series of new 1,2,4]oxadiazolo[5, 4-d]pyrido[3, 4-c][1, 5]benzothiazepines via nitrile oxide cycloaddition [27] (Scheme 69).

5.11. Reduction of Dihydrobenzothiazepine with Either NaBH₄ or with o-ATP or DAPDS and with H₂ Using Pt. Sodium borohydride reduction of the dihydrobenzothiazepine 156b provided the tetrahydrobenzothiazepine 388. Compound 388 is also formed by the reduction of 156b with o-ATP (Adenosine-5’-triphosphate) (catalytic amount) in ethanol containing an acid. However, it is well known that o-ATP is contaminated with a little amount of di o-aminophenyl disulphide (DAPDS) (VI) due to its aerial oxidation. Hence, the involvement of DAPDS in the reduction of 156b could not be ruled out. Keeping this in view, 156b was also treated with DAPDS as well as o-ATP in refluxing EtOH in the presence of an acid (HCl or HBr). In all of these cases
Scheme 64: Reduction of oxygen-bridged 1,5-benzothiazepines.

Scheme 65: Ring-opening reaction of 3-(1H-1,2,4-triazol-1-yl)-1,5-benzothiazepine with phenylnitrite oxide.

388 was obtained in good yields (75%). Because reduction is catalyzed by both o-ATP as well as DAPDS it may be suggested that in the reduction of 156b with o-ATP/H⁺ in EtOH, the effective catalyst is o-ATP. The nucleophilic addition of o-ATP to the initially formed carbocation 389 may result in the formation of 390, which may cleave to 388 and 1,2-benzothioquinone imine 391. The addition of EtOH to 391 may give rise to another intermediate 392, which may in turn regenerate o-ATP with a concomitant elimination of the corresponding carbonyl compound. Compound 391 may re-enter the reductive cycle, which may continue until 156b is completely reduced to 388. However, when DAPDS is used in place of o-ATP, it may first undergo acid-catalyzed dis-proportionation to give 391 and o-ATP, which may catalyze the reduction as previously described.

It is worth mentioning that the present reductive one-step conversion of 156b into 388 by using o-ATP or DAPDS in acidic EtOH is quite significant as it constitutes a convenient access to tetrahydrobenzothiazepine derivatives 388. Also this procedure is cheaper than the reduction of 156 to 388 by using NaBH₄ as a reducing agent.

The reduction of 157a with H₂ using Pt resulted in the formation of tetrahydrobenzothiazepine derivative 388. The reduction product 388 obtained by this method was found identical to the product that was obtained by the reduction of 156 with either NaBH₄, o-ATP, or DPDS in EtOH containing...
5.12. Extrusion of Sulfur Atom of the Benzothiazepine. The benzothiazepine structures 182 seemed to be quite unstable and, under basic conditions or on heating, can be transformed into quinoline rings 394 by elimination of the sulfur atom. Therefore, upon heating the benzothiazepine 182a to 120°C, an efficient extrusion of sulfur atom for the benzothiazepine with the aromatic substituent was observed and gave 3-fluoro-2-(4-fluorophenyl)-4-(perfluorobutyl)quinoline 394a in 80% yield [44–47] (Scheme 71).

5.13. Reactions of 2-Carboxy-2,3-dihydro-1,5-benzothiazepines with $K_2CO_3$ and Chloroacetyl Chloride under Microwave Irradiation. The substituted-1,5-benzothiazepine 202a was adsorbed on activated potassium carbonate with the help of methanol. The solvent was removed under reduce pressure using a rotatory evaporator. To this, chloroacetyl chloride was added and mixed thoroughly and resulting reaction mixture was irradiated in the microwave oven. After completion of the reaction (monitored by TLC), the reaction

\[
\begin{align*}
\text{Scheme 66: Reaction of 2,3-dihydro[1,5]benzothiazepines with benzohydroximinoyl chloride.} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 67} \\
\end{align*}
\]

<table>
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<tr>
<th>R1</th>
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\[
\begin{align*}
\text{Scheme 68: Reaction of 2,3-dihydro[1,5]benzothiazepines with benzohydroximinoyl chloride.} \\
\end{align*}
\]

an acid. This was further confirmed by TLC, m.p., and mixed m.p.s of these compounds. The formation of 388 was further confirmed by the conversion into the corresponding acetyl derivatives 393 using Ac₂O and pyridine [37] (Scheme 70).
mixture was cooled (r.t.), added to ice water and the supernatant aqueous layer decanted and filtered to yield desired azeto[2,1-d][1,5]benzothiazepine 395a. Yield = 78%; time = 4 min. All other azeto-[2,1-d][1,5]benzothiazepine 395b–m were similarly prepared under solvent-free conditions using K$_2$CO$_3$ under microwaves [53] (Scheme 72).

5.14. Hydrolysis of Sodium Salts of 1,5-Benzothiazepine-2-carboxylic Acid. The sodium salts of 1,5-benzothiazepine-2-carboxylic acid 396a–b were obtained by hydrolysis of 238a–b in water solution [59] (Scheme 73).

6. Infrared, Ultraviolet, $^{1}$H, $^{13}$C NMR, and $^{19}$F (Selected Examples)

6.1. Infrared. Fourier transfer infrared (KBr) of 2-(2-phenoxyquinolin-3-yl)-4-phenyl-2,3-dihydrobenzo[1,5]thiazepine 57a (Scheme 74) and 5-(2-phenoxyquinolin-3-yl)-1,3a-diphenyl-4,5-dihydro-3aH-benzo[1,2,4]oxadiazolo[4,5-d][1,5]thiazepine 385a contained absorption bands for C=N, and C–O–C around 1596 and 1244 cm$^{-1}$ regions, respectively [14]. The spectrum of (E)-2-(2-(4-(phenylthio)phenyl)-2,3-dihydrobenzo[1,5]thiazepin-4-yl) phenol 70a showed bands for OH, C=C, C=N and C–S–C at 3430, 1622, 1460, and 673 cm$^{-1}$ [3]. The appearance of a sharp absorption band near 1620 cm$^{-1}$ confirmed the presence of C=N group in the spectrum of (S,E)-2-(benzo[d][1,3]dioxol-5-yl)-4-phenyl-2,3-dihydrobenzo[1,5]thiazepine 94a [25].

2-chloro-7-methoxy-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepin-2-one 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26]. The IR spectrum (KBr) of 2-(2-chlorophenyl)-8-ethoxy-4-(thiophen-2-yl)-2,3,4,5 tetrahydrobenzo[1,5]thiazepine 241l cleared the presence of NH (br, 3146) and C=O (1690–1650) cm$^{-1}$ [60]. IR spectrum (KBr) of 2-(4-methyl-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d]benzo[1,5]thiazepine-4-carboxylic acid 99a revealed in its IR spectrum two carbonyl bands at 1680 and 1725 cm$^{-1}$, beside a broad band for OH group around 3288 cm$^{-1}$ and another band at 748 cm$^{-1}$ which could be due to C–Cl oscillating frequencies [26].
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The structures of all azeto[2,1-\d][1,5]benzothiazepines 99a–f, as well as the product 101, have been elucidated.

4-methyl-2-phenoxy-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-d][1,5]benzothiazepine 387a realized one carbyl absorption band around 1771 and 1763 cm\(^{-1}\), respectively [80].

6.2. Ultraviolet. The ultraviolet spectra of several 1,5-thiazepine derivatives were characterized by electronic bands in 317–251 nm region, for example, 39a: UV (MeOH), \(\lambda_{\text{max}}(\varepsilon)\): 511 (56925), 323 (20780), 286 (21080), and 252 (24600), 281 (26800), 380 (3500), and 486 (1500) [55].

Synthesis of [1,5] benzothiazepines 103 and 387

<table>
<thead>
<tr>
<th>Ar 103 or 387</th>
<th>103</th>
<th>MW method</th>
<th>Conventional method</th>
<th>387</th>
<th>Yield (%)</th>
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<tr>
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<td>80</td>
<td>10</td>
<td>30</td>
<td>(a) 94</td>
</tr>
<tr>
<td>(b) 4-Cl-Ph</td>
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<td>79</td>
<td>10</td>
<td>28</td>
<td>(b) 96</td>
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<tr>
<td>(c) 4-Me-Ph</td>
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<td>75</td>
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<tr>
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<td>70</td>
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<tr>
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<tr>
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<td>75</td>
<td>10</td>
<td>25</td>
<td>(j) 97</td>
</tr>
</tbody>
</table>

(a) Yield after recrystallisation. (b) Yield after column purification.

Scheme 69: 1,3-Dipolar cycloaddition of nitrile oxide and triethylamine, with the hexahydropyrido-[3,4-c][1,5]benzothiazepines.

6.3. \(^1\)H NMR. Proton NMR spectrum (DMSO-\(d_6\), 400 MHz) \(\delta\) ppm: of (Z)-2-(4-fluorophenyl)-4-(2-(methylsulfonyl)phenyl)-3-(o-tolylsulfonyl)-2,3-dihydrobenzo[1,5]thiazepine 387a displayed signals at \(\delta\): 2.50 (s, 3H, Ar–CH), 3.27 (s, 3H, SO\(_2\)CH), 3.44–3.71 (two nondiagonistic doublets, 2H, 2 methine protons), and 6.82–8.13 (m, 19H, Ar–H) [8].

The PMR spectrum [300.13 MHz] [DMSO-\(d_6\)] of (S, E)-2-(benzo[\(d\)][1,3]dioxol-5-yl)-4-phenyl-2,3-dihydrobenzo[1,5]thiazepine 94a showed signals at \(\delta\): 3.06 (t, 1H, \(J = 12.7\) Hz) for H\(_{\text{ax}}\), 3.30 (dd, 1H, \(J = 13.0\) Hz, \(J = 4.6\) Hz) for H\(_{\text{ax}}\), 4.98 (dd, 1H, \(J = 12.6\) Hz, \(J = 4.6\) Hz) for H\(_{\text{ax}}\), and 6.0 (2H, s) for dioxyimethylene group, and peaks for aromatic protons appeared in the range of \(\delta\): 7.23–7.8 ppm [25].

The structures of all azeto[2,1-d][1,5]benzothiazepines 99a–f, as well as the product 101, have been elucidated.
Scheme 70: Reduction of dihydro-1,5-benzothiazepine with either NaBH₄ or with o-ATP or DAPDS, as well as with H₂ using Pt.
Scheme 71: Extrusion of sulfur atom of 1,5-benzothiazepine.

Scheme 72: Reactions of 2-carboxy-2,3-dihydro-1,5-benzothiazepines with K$_2$CO$_3$ and chloroacetyl chloride under microwave irradiation.

Scheme 73: Hydrolysis of sodium salts of 1,5-benzothiazepine-2-carboxylic acid.

by spectroscopic studies. Theoretically, compound 99a–f exhibiting two chiral centers could exist in two diastereomeric forms; however, the $^1$H NMR spectra and chromatographic studies of the isolated compounds indicated the formation of only one diastereomer. For example, the PMR spectrum (CDCl$_3$, 300.15 MHz) of 2-chloro-7-methoxy-1-oxo-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[1,2-\textit{d}][1,5]thiaz-epine-4-carboxylic acid
99a displayed signals at δ: 3.75 (s, 3H, OCH₃), 3.08 (dd, 1H, H₁), Jₐ₋ₐ = 15.28, Jₐ₋ₓ = 9.15 Hz), 3.62 (dd, 1H, H₂, Jₐ₋ₐ = 15.28, Jₐ₋ₓ = 8.12 Hz), 4.02 (dd, 1H, H₃, Jₐ₋ₐ = 9.15 Hz, Jₐ₋ₓ = 8.12 Hz), 5.12 (s, 1H, Cl–CH), 6.58–7.79 (m, 8H, Ar–H), 7.18–7.47 (14H, m, ArH), and 7.78 (2H, s, ArH). The spectrum (CDCl₃, 300.15 MHz) of 2-chloro-3-ethoxy-4-(thiophen-2-yl)-2,5-dihydrobenzo[1,3]thiazepin-7(6H)-one revealed signals at δ = 3.62 (2H, dd, Jₓ₁ = 4.82 Hz, Jₓ₂ = 1.98 Hz), 5.47 (2H, dd, Jₓ₁ = 11.4 Hz, Jₓ₂ = 5.1 Hz, Hₓ₂), 6.84 (2H, s, ArH), 7.19–7.35 (8H, m, ArH), 7.40–7.47 (8H, m, ArH), 7.55–7.65 (10H, m, ArH), 7.78 (2H, s, ArH), and 7.91 (4H, d, J = 8.1 Hz, ArH), respectively [30].

The relative stereo configurations of 2a,d were identified based on the same reaction mechanism and NOESY spectra in which C₂–H shows a long-distance coupling with C₅–Ha for products 373a, 374i, and 376a. The observation indicated that these two hydrogen atoms should be cis. On the basis of coupling constants (J) and the Karplus equation, C₂–He and C₅–H have an angle near 90° (J < 2 Hz) and C₅–Ha and C₆–H an angle near 180° (J around 10 Hz). This indicates that C₂–H and C₅–H are trans for products 373a, 373b, and 376a. Thus, R¹ is trans to phthalimido, chloro, or phenoxy group in the products 373a, 374i, and 376a. R¹ is also trans to R² for all products,
which is known from starting materials. Consequently, R²
and phthalimido, chloro, or phenoxy group in the products
373a, 374i, and 376a are cis. Namely, the cycloaddition is a
stereospecific reaction. The ¹H NMR spectra of cycloadducts
373–376 indicate that only one pair of diastereomers were
present in each of the cycloaddition reactions [80].

6.4. ¹³C NMR. ¹³C NMR (CDCl₃, 400 MHz) δ, 100.6 MHz
of trans-2-(4‴-chlorophenyl)-4-(2‴-hydroxyphenyl)-2,3,4,5-
tetrahydro-1,5-benzothiazepine 380 revealed signals at 118.1
(C-3′), 120.3 (C-5′), 122.5 (C-6), 125.3 (C-8), 125.5 (C-10),
126.4 (C-9a), 128.7 (C-2‴/6‴), 128.8 (C-6′), 129.2
(C-3‴/5‴), 129.7 and 129.8 (C-7 and C-40), 133.2 (C-
4″), 134.2 (C-9), 144.0 (C-1‴), 146.4 (C-5a), and 159.6
(C-2″) ppm [9]. The spectrum (CDCl₃, 400 MHz) δ, 100.6 MHz of 2-phenyl-4-(2‴-hydroxyphenyl)-4,5-dihydro-
1,5-benzothiazepine 378a showed signals at 61.2 (C-4),
117.6 (C-6), 118.6 (C-3′), 120.3 (C-8), 120.4 (C-1‴), 122.6
(C-4′), 123.1 (C-9a), 123.8 (C-3), 126.0 (C-5′), 126.3 (C-
6′), 1275 (C-4″), 128.4 (C-3‴/5‴), 129.1 (C-2‴/6‴), 130.4
(C-9), 130.6 (C-7), 131.4 (C-2), 135.6 (C-1‴), 141.1 (C-5a),
and 155.8 (C-2″) ppm [9]. In the ¹³C NMR spectrum of
378a (Scheme 76), there is only one peak in the aliphatic
region at δ = 61.2 ppm (CH) [9]. Also, the spectrum of 2-(4‴-chlorophenyl)-4-(2‴-hydroxyphenyl)-4,5-dihydro-
1,5-benzothiazepine 378b (CDCl₃, δ, 400 MHz) displayed the
following: 61.5 (C-4), 117.6 (C-6), 118.3 (C-3′), 120.2 (C-4′),
122.6 (C-1‴), 123.4 (C-3 and C-9a), 126.1 (C-5′),
126.3 (C-6′), 134.4 (C-4″), 129.1 (C-3‴/5‴), 130.2 (C-9), 130.4
The benzo derivatives of azepines, like benzothiazepines, constitute a class of compounds with specific applications. The X-ray diffraction study showed that in the molecule of compound 20, the seven-membered heterocycle has a distorted boat conformation, with the deviation from the plane of the atoms C3, C6, and C7 by 0.599(5), 1.214(7), and 1.226(7) Å, respectively. This conformation, in turn, leads to a lack of conjugation of the C5=O double bond with the aromatic ring, which is confirmed by the values of bond lengths [C(2)−C(5) 1.2742(16) Å, N(3)−C(5) 1.4136(15) Å] and torsion angle C4=N(5)C(6)C(7) 52.64(16)° (Scheme 78).

The location of the substituents at the C(2)−C(3) corresponds to staggered conformation the hydrogen atoms are almost antiperiplanar to each other (torsion angle H(2A)C(2)C(3)H(1A) is 167°). In the crystal, the molecules are packed along b axis due to sufficiently strong CH····O interaction between C(2)−H(2A) group and the oxygen atom of the nitro group (2.36 Å), as well as due to a shortcontact between the electron pair of the sulfur atom and the π-density of benzothiazepine ring (the shortest S···O contact is 3.48 Å) [6].

7.1. Crystal Structures of a Pair of N-Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine and N-Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine.

The benzo derivatives of azepines, like benzothiazepines, constitute a class of compounds with specific applications.
Colorless crystals of N-formyl-2,3,4,5-tetrahydro-2,4-di-phenyl-1,5-benzothiazepine (FDPBT) and of N-chloroacet-yl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine (CTMBT) were chosen for the single crystal X-ray data collection. The Enraf-NoniusCAD4 diffractometer with graphite monochromated CuKα radiation employing ω - 2θ scan mode was used for data collection. The perspective views of the molecules using ORTEP III are shown for FDPBT and for CTMBT. The interatomic distances spanned by bonds in the two benzothiazepines are in good agreement with each other. The two structural entities in CTMBT duplicate each other in relation to atomic intimacies, as seen from the bond distances and bond angles. In general, N-formyl-2,3,4,5-tetrahydro-2,4-diphenyl-1,5-benzothiazepine (FDPBT), C_{25}H_{19}NO_5, FW = 345.44, monoclinic, P2_1 = c, α = 112.268(1)°, β = 90.0297(1)°, γ = 18.3815(1)°, β = 104.77(1)°, V = 1801.8(3)Å^3, Z = 4, D_{calc} = 1.270 Mg/m^3, μ = 3.504 mm^{-1}, F000 = 1192, CuKα = 1.5418 Å, final RI and wR2 are 0.0610 and 0.1609, respectively. The septilateral ring of the benzothiazepine in the two structures adheres to an identical boat conformation. The prow and stern angles are nearly the same for both the medium-sized rings [81] (Schemes 79, 80, and 81).

8. Applications (Selected Patents)

Several patents have been reported for 2-azetidinone derivatives (included in combination with several tetrahydro-1,5-benzothiazepine derivatives or pharmaceutically acceptable salts, solvates, solvates of such salts, and prodrugs thereof
for the treatment of hyperlipidaemic conditions). These 2-azetidinones possess cholesterol absorption inhibitory activity and accordingly of value in the treatment of disease states associated with hyperlipidaemic conditions, possess ileal bile acid transport (IBAT) inhibitory activity as well of value in the treatment of disease states associated with hyperlipidaemic conditions. They are therefore useful in methods of treatment of a warm-blooded animal, such as man [82–86]. Some other 1,5-benziazepine derivatives and their related intermediates were patented for their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions and associated conditions such as atherosclerosis [87]. The process for preparing diltiazem and novel intermediates for use in that process, has been patented. Diltiazem is: (2S-cis)-3-(acyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one. Diltiazem is a calcium channel blocker with coronary vasodilating, antihypertensive, and psychotropic activity. Vasodilating action is the highest selling chiral cardiac prescription drug, which was synthesized by resolution methods [88]. Substituted piperazines of azepines, oxazepines, and 1,5-thiazepines have been reported as antipsychotic and are of use as antagonists of dopamine $D_2$ receptor and as agents for the treatment of psychosis and bipolar disorders [89].
Some thiazolo-1,5-thiazepines and analogs and derivatives were patented as anti-integrase inhibitors. These compounds are useful as treatments for HIV disease [90]. Recently, some molecularly diverse coumarins clubbed with benzothiazepines, and its aza-analogs-benzodiazepines by molecular hybridization were screened for their M. tuberculosis activity against H(37)Rv strains using microplate alamar blue assay (MABA). Three compounds, in-between, were found significantly active in primary anti-tuberculosis (TB) assay at MIC < 6.25 µM. IC (50) values of two of these benzothiazepine products in level-2 screening were observed as >10 µg/mL and 3.63 µg/mL, respectively [81].

9. Conclusion and Future Look

The presented paper comprises the recent ten-year survey for most published articles about benzo[1,5]thiazepines and their related derivatives; synthesis, chemical, physical, and biological properties. The common strategy for the construction of the 1,5-benzothiazepine moiety is the reaction of 1,3-diarylp-2-enones with o-aminothiophenol and 1,3-difunctional three-carbon building blocks. Among them, α,β-unsaturated carbonyl compounds such as enones and yrones are suited best for Michael addition reaction of 1,3-diarylprop-2-enones with construction of the 1,5-benzothiazepine moiety is the use of ultrasound irradiation in organic transformation has been used to improve reaction efficiency. The 1,5-benzothiazepine framework has been identified as a pluripotent pharmacophore with derivatives encompassing CNS-acting agents, anti-HIV, anti-Tuberculosis (TB) and antitumor agents, angiotensin converting enzyme inhibitors, antimicrobial and antifungal compounds, calmodulin antagonists, bradykinin receptor agonists, and Ca²⁺ blockers.

Additions, dihydro 1,5-benzothiazepines have become increasingly interesting since many derivatives exhibit antifungal, antibacterial, antifeedant, anti-inflammatory, analgesic, and anticonvulsant activity. Likewise, the related 1,5-benzothiazepines display a comparable spectrum of biological activity. Moreover, benzothiazepines possess highly interesting pharmaceutical properties and a diversity-oriented synthesis approach using the advantages of multicomponent reactions.

It is hoped in the future to find a milder, selective, nonhazardous, and inexpensive solvents and there is necessity to develop a more effective synthetic procedure for the synthesis of 1,5-benzothiazepines. Also, it is hoped to discover other new active benzo[1,5]thiazepines and other related derivatives for solving the most nowadays serious human diabetic as well as Alzheimer's disease problems that cause health troubles for millions of people around the world.

Abbreviations

TPP: Tetraphenylporphyrin
NMM: N-Methylmorpholine
DIAD: Diisopropyl azodicarboxylate
HATU: Peptide coupling reagent: 2-((H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium
DBU: 1,8-Diaza bicyclo[5.4.0]undec-7-ene
EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Edc: Ethylene dichloride
PTC: p-Toluenesulphonyl chloride
DCM: Dichloromethane
TBAB: Tetrabutylammonium bromide
TFA: Trifluoroacetic acid
TEBA-Cl: Triethylbenzylammonium chloride
CAN: Ceric ammonium nitrate
La Y Zeolite: Lanthanum-containing Y zeolite
DAPDS: Di o-aminophenyl disulphide
o-ATP: Adenosine 5'-triphosphate
TTFD: Tetraisopropylthiuram disulphide
m-COPA: meta-Chloroperbenzoic acid
HMDS: Hexamethyl disilazane
DCC: 1,3-Dicyclohexylcarbodiimide or N,N-dicyclohexylcarbodiimide
SmI₂: Samarium diiodide (Kagan Reagent)
DMD: Dimethyldioxirane
RCM: Ring-closing metathesis
MCR: Multicomponent reaction
Oxone: Potassium peroxymonosulfate
IBAT: Ileal bile acid transport.

References

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