Review

Fused 1,5-Benzothiazepines from *o*-Aminothiophenol and its Derivatives as Versatile Synthons[1]

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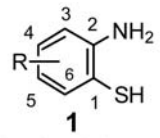
Abstract

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

Keywords: *o*-aminothiophenol, chalcones, cyclocondensation, green synthesis, 1,3-dipolar cycloadditions.

1. Introduction



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R = (**a**) H, (**b**) 4-Cl, (**c**) 4-MeO, (**d**) 4-CF_3, (**e**) 5-Me, (**f**) 5-MeO, (**g**) 5-F, (**h**) 5-EtO, (**i**) 5-CF_3, (**j**) 3-Br, (**k**) 3-CF_3, (**l**) 3,4-Me_2

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

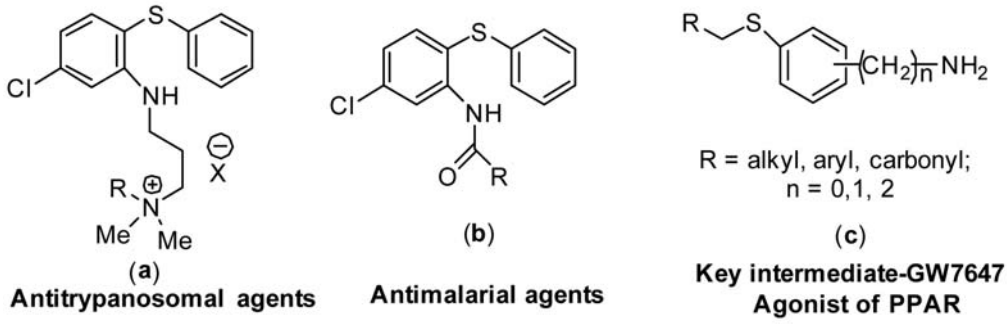


Figure 1. Examples of *o*-aminothiophenol derivatives with interesting biological properties.

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

very little has been reviewed[5] on the versatility of *o*-aminothiophenols and its derivatives as fundamental synthetic building blocks in heterocyclic synthesis. In spite of the fact that there appeared voluminous literature on the synthesis,[6] toxicity,[7] occupational health hazards,[8] industrial[9] and environmental pollution[10] of *o*-aminothiophenol and its derivatives, in recent times a detailed account on the reactions with carbonyl group and other functionalities is not reported till now. This necessitated us to review and highlight the current reactions in the field of 1,5-benzothiazepines. Consequently, this review attempts to present the work encompassing synthetic versatility of *o*-aminothiophenol and its derivatives **1** as building blocks for the preparation of a wide range of 1,5-benzothiazepines.

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

The present review summarizes the methods for preparing benzothiazepines and related annulated thiazepines. The preparative methods include ring closure reactions, aromatizations and ring transformations. Several reviews have focused on the synthesis,[11–13] reactions,[14] medicinal chemistry, [15] biological properties[16,17] of 1,5-benzothiazepines as they are privileged scaffolds in drug discovery. The presence of benzothiazepines moiety in natural products and pharmaceuticals determines their potential use as antipsychotic agents, for example quetiapine (trade name, seroquel)[18] (Figure 2a), the angina relieving calcium channel blocker diltiazem[19] (Figure 2b), the inhibitor of the lipoprotein disorders GW 577[20] (Figure 2c), the hypertensive agent clentiazem[21] (Figure 2d) and the GABA blocker thiazesim[22] (Figure 2e). Recently, a family of 1,5-benzothiazepine derivatives has been reported as potent and selective bradykinin receptor antagonists as JMV 1645[23] (Figure 2f). The present review is divided into 7 sections based on the type of reaction or nature of benzothiazepine formed or employed.

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

One of the most widely employed methods for the preparation of 1,5-benzothiazepines involves the reaction of *o*-aminothiophenol (*o*-ATP, **1**) with α,β-unsaturated esters, α,β-unsaturated ketones or chalcones[24] both under acidic and basic conditions. Although in all reactions between a dinucleophile (*o*-aminothiophenol) with a dielectrophile

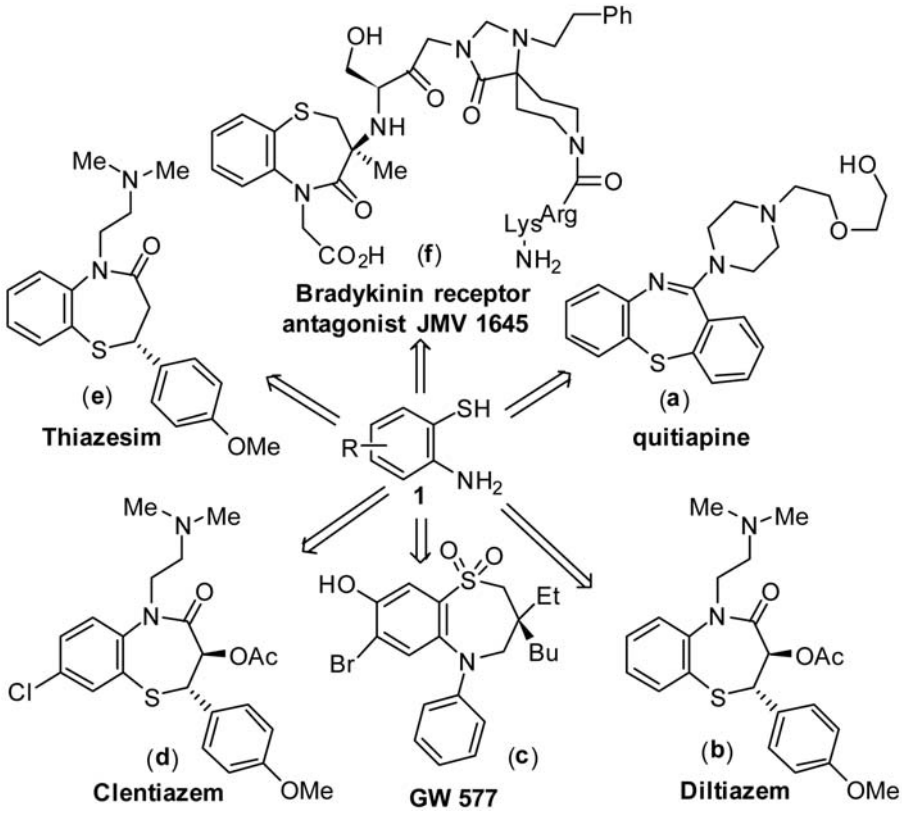


Figure 2. Examples of 1,5-benzothiazepine derivatives with interesting biological properties.

of the type discussed in scheme, two compounds can be formed;[25] since only benzothiazepines were isolated it was assumed that the reaction starts by the 1,4-Michael addition of the SH on the –C=C– double bond followed by the condensation of the NH_2 on the carbonyl group.

2. 1. 1,5-Benzothiazepines Based on Bielectrophiles

2. 2. Baylis–Hillman Derivatives

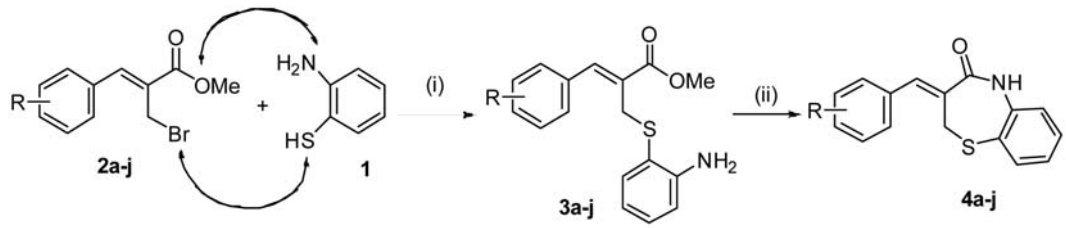
The Baylis–Hillmann adducts are utilized very well as building blocks for the synthesis of natural products and biologically active molecules.[26] Murugan *et al.*[27] reported the synthesis of dihydro-benzothiazepin-4-ones using Baylis–Hillman chemistry. A variety of (2*Z*)-2-(bromomethyl)-3-arylprop-2-enaoates (**2a**–**j**) prepared from the corresponding Baylis–Hillman adduct were treated with *o*-aminothiophenol (**1**) in the presence of potassium *t*-butoxide in THF at r.t. giving *S*-alkylated acrylates **3a**–**j** in good yields. The crude intermediates **3a**–**j** were treated with *p*-toluenesulfonic acid in xylene under reflux conditions to give the (*Z*)-3-arylidene-2,3-dihydrobenzo[*b*][1,4]thiazepin-4-(5*H*)-ones (**4a**–**j**) in 65–71% yield. The formation of seven-membered benzothiazepinone can be rationalized by selectively tethering the sulfur atom of the *o*-aminothiophenol (**1**) with allylic carbon, which is attached to the bromine atom of the compound **2**, at one end and at the other end by tethering the nitrogen atom of the *o*-aminothiophenol with carbonyl carbon present in the bromo derivative of the Baylis–Hillman adducts **2**[28] as shown in Scheme 1.

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

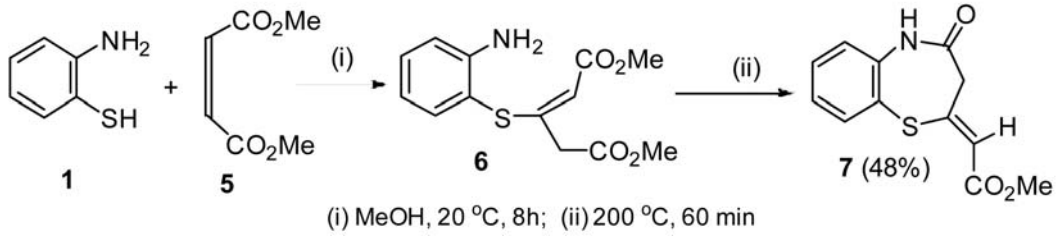
o-Aminothiophenol (**1**) reacts with dimethyl allen-1,3-dicarboxylate (**5**) to give first the Michael adduct **6**. The cyclization reaction of thioenol ether **6** at 200 °C gave the 1,5-benzothiazepinone **7** in 48% yield.[29] A consideration of Baldwin's rules[30] and vector analysis suggests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

2. 4. β-Propiolactone / β-Butyrolactone as a Precursor

4,5-Differently substituted / *o*-aminothiophenols (**1**) are conveniently converted into 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**8a**–**l**) by a reaction with β-propiolactone or β-butyrolactone in anhydrous pyridine followed by the treatment with Ac_2O. The lower reactivity of β-butyrolactone results in the poorer yields of benzothiazepines **8a**–**l** (30–80%).[31] The yields of 1,5-benzothiazepine derivatives depend also upon both the nature and position of the substituent. The electron withdrawing substituents were also found to decrease the yield to some extent, which could be attributed to the retarded formation of the amino acid intermediate due to the decreased nucleophilicity of the sulfur atom. The presence of an electron releasing group at 5-position affects the reactivity of **1** in agreement with previous observa-



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



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

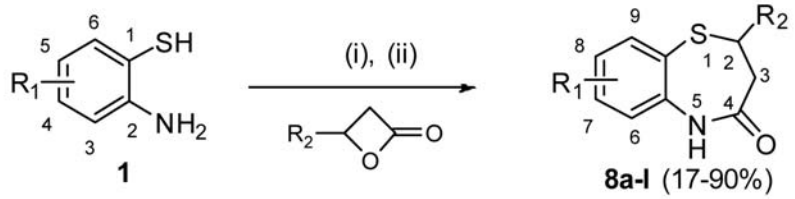
tions on similar reactions.[32] When 4-methoxy-2-aminobenzenethiol was used, the lowest yields of the corresponding benzothiazepinones **8c**,**8k** were obtained (Scheme 3).

2. 5. π Acceptors as Reactants

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

2. 6. Thiazepinopyridazine Derivatives

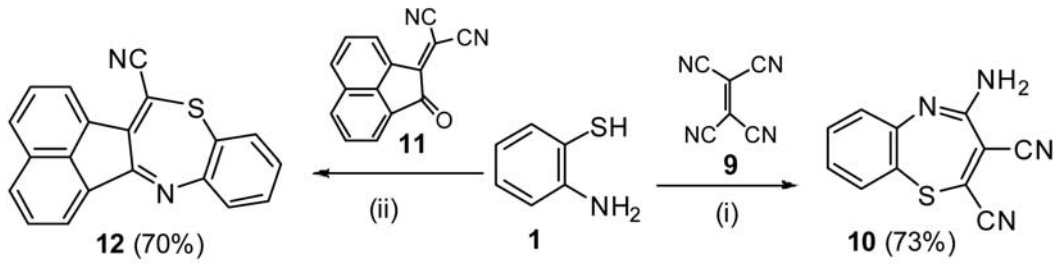
The reaction of 4-benzoyl-5,6-diphenylpyridazine-3-(2*H*)-one (**13**) with $POCl_3$ at 100 °C gave the chlorinated product 4-benzoyl-3-chloro-5,6-diphenylpyridazine (**14**). The condensation of chloro derivative **14** with *o*-aminothiophenol (**1**) in ethanol gave thiazepinopyridazine derivative **15** in 85% yield[35] (Scheme 5).



(i) pyridine, 70 °C, 5 h; (ii) Ac_2O, 60 °C, 30 min

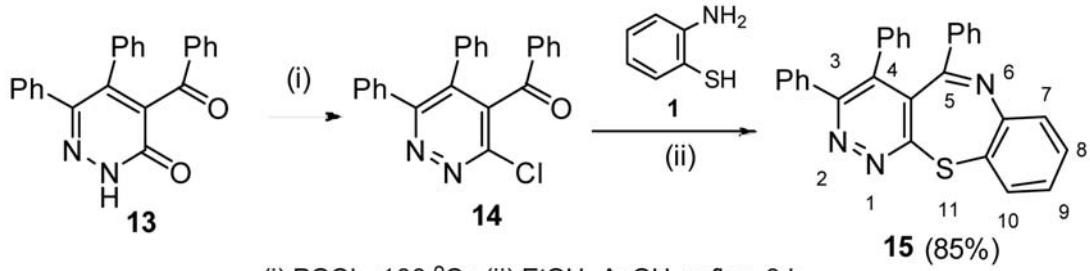
(**a**) R_1 = H, R_2 = H (90%); (**b**) R_1 = 7-Cl, R_2 = H (76%); (**c**) R_1 = 7-MeO, R_2 = H (20%);
(**d**) R_1= 7-CF_3 R_2 = H (57%); (**e**) R_1 = 8-Cl, R_2 = H (76%); (**f**) R_1 = 8-Br, R_2 = H (52%);
(**g**) R_1 = 8-Me, R_2 = H (59%); (**h**) R_1 = 8-MeO, R_2 = H (52%); (**i**) R_1 = H, R_2 = Me (80%);
(**j**) R_1 = 7-Cl, R_2 = Me (68%); (**k**) R_1 = 7-MeO, R_2 = Me (17%); (**l**) R_1= 7-CF_3 R_2 = Me (46%)

Scheme 3. Synthesis of 2,3-dihydro-1,5-benzothiazepin-4-ones **8a–l**.



(i) EtOAc, r.t, 12 h; (ii) MeCN, reflux, 5 h

Scheme 4. Synthesis of benzothiazepine derivatives **10**,**12**.



(i) $POCl_3$, 100 °C ; (ii) EtOH, AcOH, reflux, 3 h

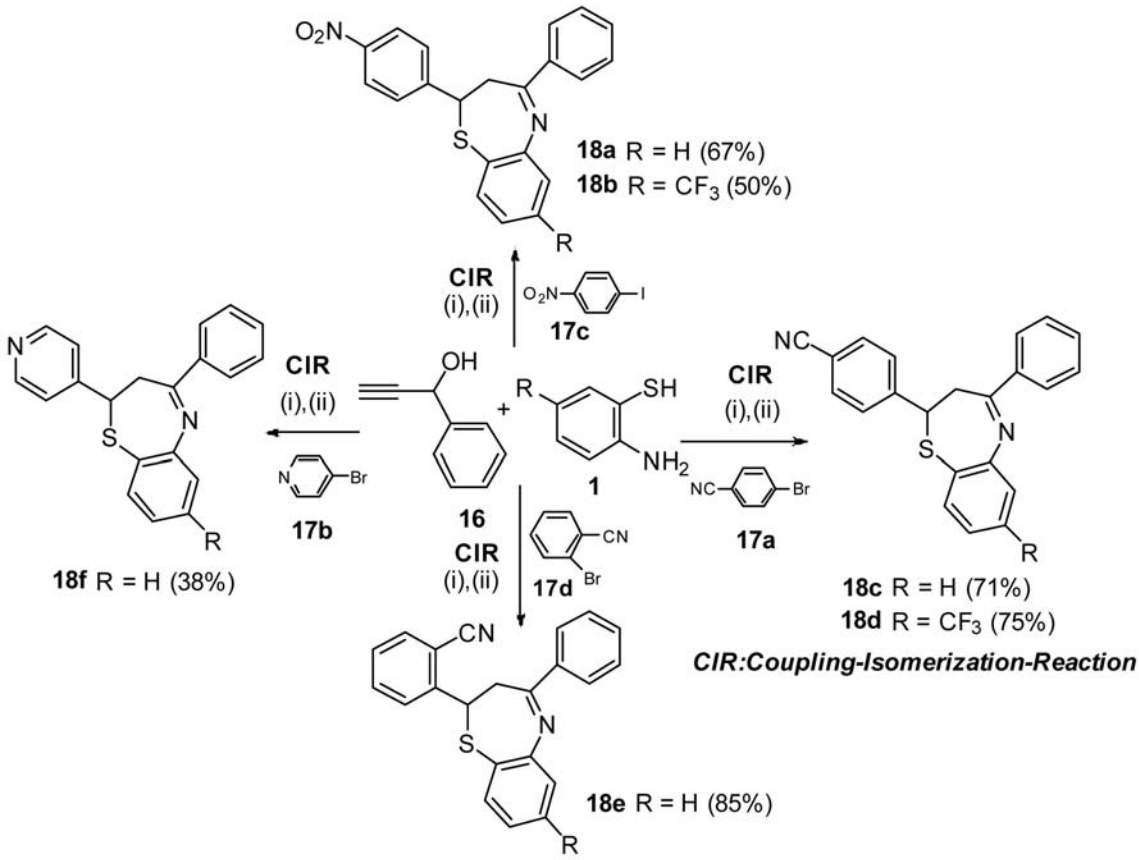
Scheme 5. Synthesis of thiazepinopyridazine derivative **15**.

2. 7. Sonogashira Coupling-isomerization Reaction

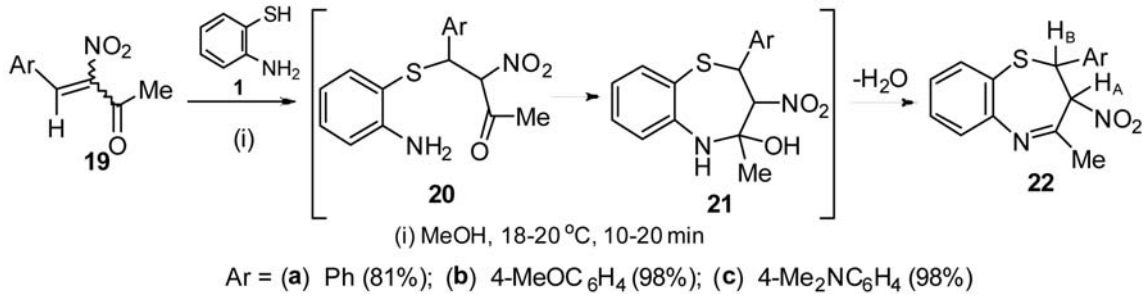
The reaction of 1-phenylpropynol (**16**) and electron poor (hetero) aryl halides **17a–d** under reaction conditions of the Sonogashira coupling in a boiling mixture of THF and Et_3N gave the *in situ* generated enone as Michael acceptor. The subsequent addition of 5-trifluoromethyl / *o*-aminothiophenol (**1**) as a suitable 1,4-dinucleophile component and acetic acid to the reaction mass, gave the beige to yellow 2,3-dihydro[*b*]1,4]thiazepines,[36] **18a–f** in 38–85% yield (Scheme 6).

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

Reaction of 4-aryl-3-nitrobut-3-en-2-ones[37] (**19**) with *o*-aminothiophenol (**1**) occurred at 18–20 °C in methanol to give crystalline 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines (**22a–c**) in 81–98% yield.[38] The process may follow nucleophilic addition pattern with a subsequent heterocyclization of *S*-adducts **20**,**21** (Scheme 7).



Scheme 6. Synthesis of 2,3-dihydro[*b*]1,4-thiazepines **18 a–f**.



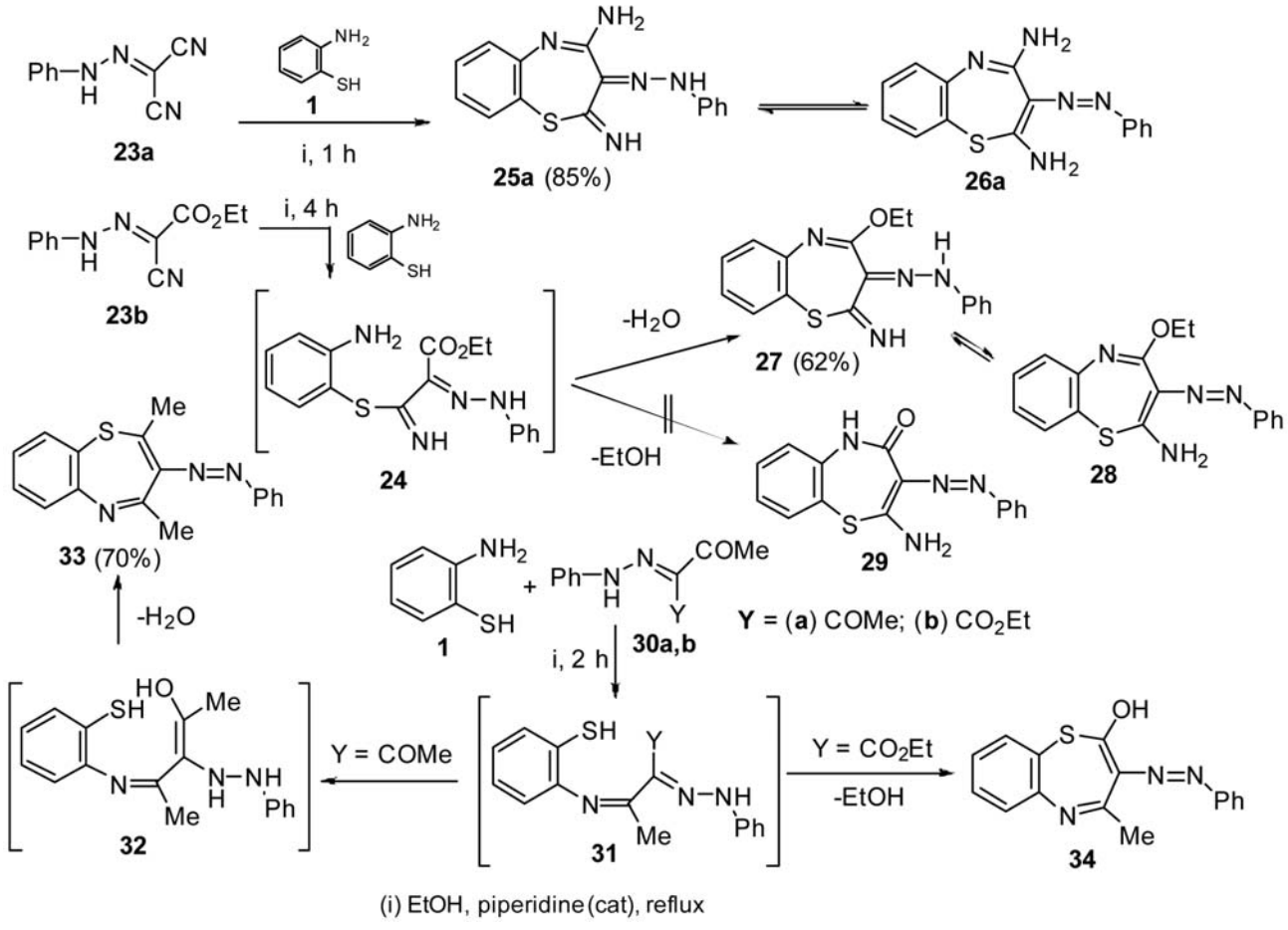
Scheme 7. Synthesis of 2-aryl-4-methyl-3-nitro-1,5-benzothiazepines **22a–c**.

2. 9. Phenylazo-benzothiazepines

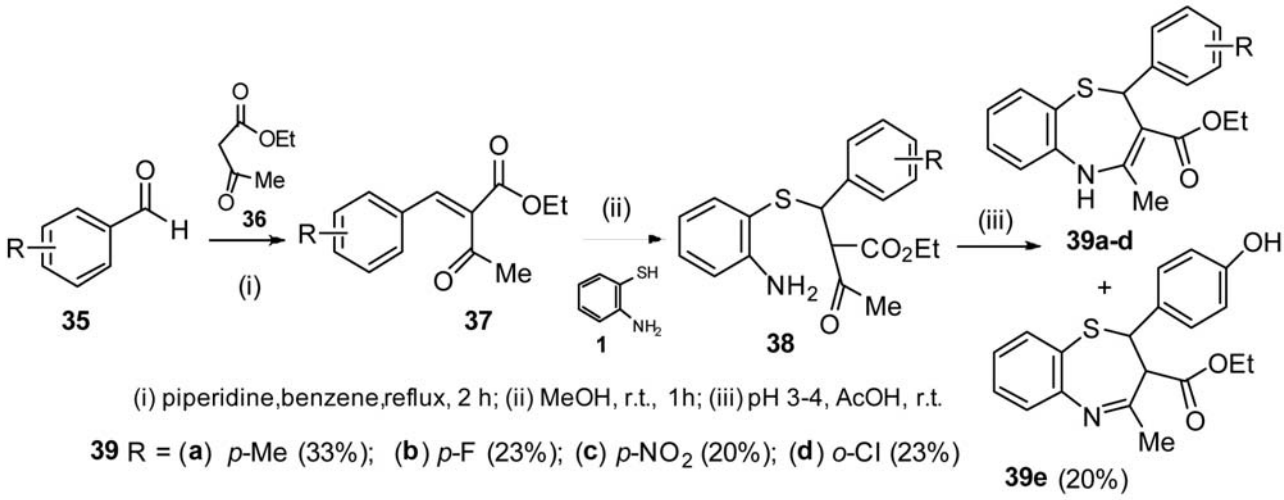
Abd ElLatif *et al.*[39] have reported the synthesis of polysubstituted-1,5-benzothiazepine using as the key intermediates hydrazono derivatives **23** and **30**. Phenylhydrazono-malononitrile (**23a**) and phenylhydrazono ethyl cyanoacetate (**23b**) reacted with *o*-aminothiophenol (**1**) in the presence of piperidine in ethanol under reflux conditions to give 2-amino-3-phenylazo-1,5-benzothiazepine derivatives **26** and **28** in 62–85% yield. The 4-amino-2-imino-3-phenyl-hydrazo-1,5-benzothiazepine (**25a**) seems to be formed *via* a nucleophilic addition of the –SH function of **1** to the –CN function of **23a** (Y = CN) to yield the intermediate similar to **24** (Scheme 8). Further cyclization through a similar addition of the NH_2 to the second –CN function finally yielded **25a** which could isomerise to 2,4-diamino-3-phenylazo-1,5-benzothiazepine (**26a**) in 85% yield. In the case of **23b** (Y = CO_2Et), it seems that the reaction proceeds *via* elimination of water from the intermediate **24** resulting in the formation of 4-ethoxy-2-imino-3-phenylhydrazo-1,5-benzothiazepine (**27**) which might be present as 2-amino-4-ethoxy-3-phenylazo-1,5-benzothiazepine (**28**). The formation of compound **29** was ruled out based on spectral and elemental analytical data. However, the phenylhydrazonoacetylacetone (**30a**) underwent condensation with *o*-aminothiophenol (**1**) in the presence of piperidine in ethanol very easily to yield the key intermediate **31** (Y = COMe), which in turn loses another molecule of water from the intermediate **32** to yield 2,4-dimethyl-3-phenylazo-1,5-benzothiazepine (**33**) in 70% yield. On the other hand, phenyl hydrazonoethylacetoacetate (**30b**) (Y = CO_2Et) condensed with **1** to yield the corresponding 2-hydroxy-4-methoxy-3-phenylazo-1,5-benzothiazepine (**34**) *via* loss of ethanol directly from the intermediate **31** (Y = CO_2Et) (Scheme 8).

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

The Knoevenagel condensation of aromatic aldehydes **35** with ethyl acetoacetate (**36**) in dry benzene catalysed by piperidine under reflux conditions gave 3-benzylidene ethyl acetoacetate (**37**). The Michael addition of *o*-aminothiophenol (**1**) to the compound **37** yielded the corresponding ethyl acetoacetate derivative **38**. The intramo-



Scheme 8. Synthesis of 3-phenylazo-1,5-benzothiazepine derivatives **25**–**34**.

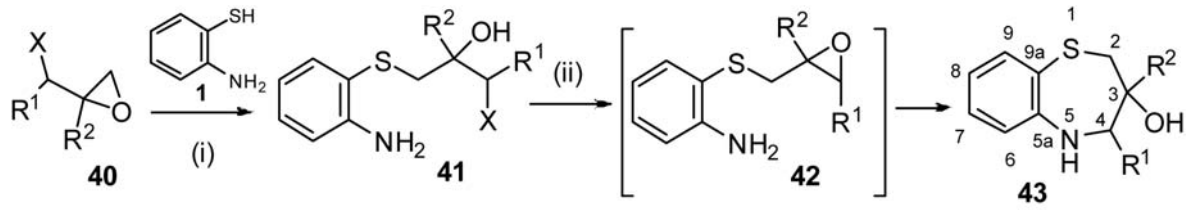


Scheme 9. Synthesis of 2-aryl-3-ethoxycarbonyl-1,5-benzothiazepines **39a**–**e**.

lecular cyclization of **38** followed by a dehydration at pH 3–4 in acetic acid / methanol provided 2,3/2,5-dihydro-4-methyl-2-aryl-3-ethoxycarbonyl-1,5-benzothiazepines (**39a**–**e**) in 20–33% yield.[40] The synthesized compounds were tested for their antimicrobial activities by standard disc diffusion method. The assayed collection included the following microorganisms: *C. albicans* (ATCC 10231), *S. aureus* (ATCC 25923), *S. epidermidis* (ATCC 26069) and *E. coli* (ATCC 44753) using disk diffusion methods. Fluconazole was used as a standard drug against fungi and vancomycin against bacteria. In the disc diffusion method, sterile paper discs (φ 6 mm) impregnated with compounds dissolved in DMSO at conc. of 12.5, 50, 100, 200 μg / disc were used. Preliminary study of the assay revealed[41] that substituent on the phenyl rings had a large effect on the antimicrobial activity; compound **39e** exhibited the greatest antimicrobial activity (Scheme 9).

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

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



Substrate					Product		
40	**Config**	**R^1**	**R^2**	**X**	**43**	**Config**	**% Y**
a	-	H	H	Cl	**a**	–	90
b	-	H	H	Br	**a**	–	87
c	-	H	Me	Br	**b**	–	72
d	*syn*	Me	H	Br	**c**	*cis*	87
e	*syn*	Pr	H	Br	**d**	*cis*	78
f	*anti*	Pr	H	Br	**e**	*trans*	59
g	*anti*	Ph	H	Br	**f**	*trans*	51

Scheme 10. Synthesis of 3-hydroxytetrahydro-1,5-benzothiazepines **43a**–**f**.

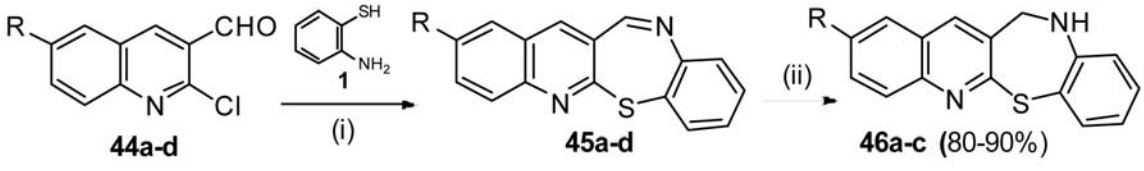
introduced at the position 3 (R^2) and 4 (R^1) by properly choosing starting 2-(1-haloalkyl)oxiranes **40**. The stereochemistry at C-4 and C-3 was confirmed by NOESY spectroscopy and analysis of the vicinal coupling constants.[43] It is noteworthy that the reaction proceeded in a stereospecific manner (*i.e.*, *syn* **40** gave *cis* **43** and *anti* **40** gave *trans* **43**). These results suggest the reaction proceeded *via* the oxirane interemediate **42** (Scheme 10).

2. 12. Quinobenzothiazepines

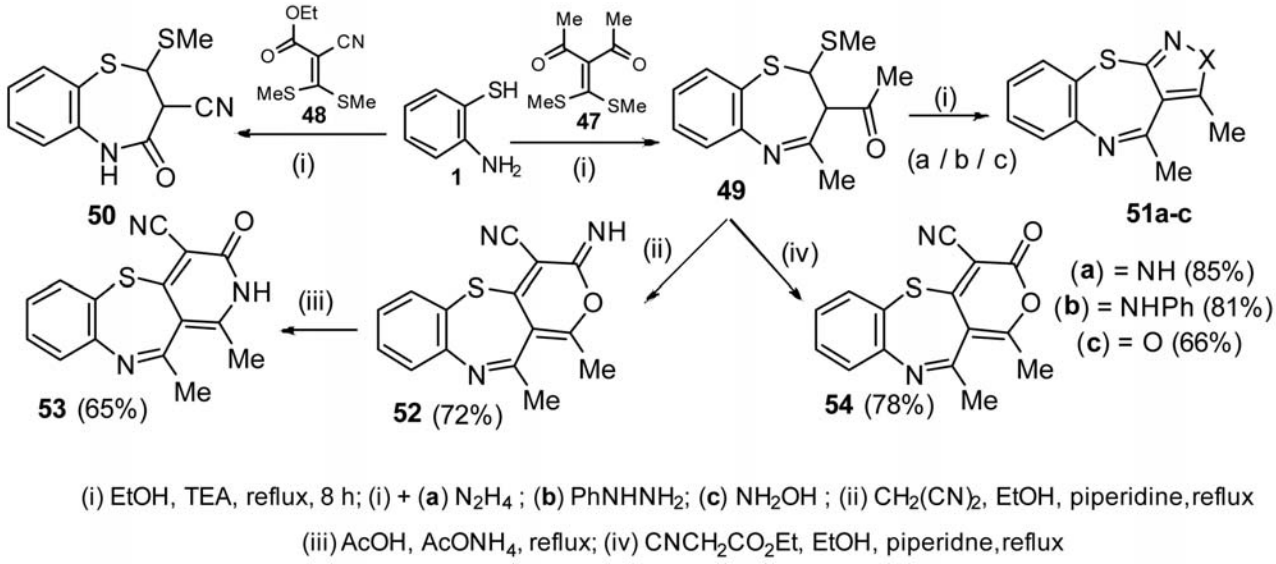
One-pot synthesis of quino[2,3-*b*][1,5]benzothiazepines was described[44] by the condensation of 2-chloroquinoline-3-carboxaldehydes **44a–d** with *o*-aminothiophenol (**1**) in DMF and in the presence of dry potassium carbonate at r.t. in 40–81% yield. The intermediary imines could not be isolated[45] and the reduction of benzothiazepines **45a–c** with lithium aluminum hydride in ether gave the corresponding 11,12-dihydro derivatives **46a–c** in 80–90% yield.[44] The tetracyclic derivative **45** could derive from the base promoted formation of a Schiff base. The probable driving force for the reaction which leads to **45** is the base catalysed displacement of the chlorine in **44** by the sulfur atom of **1**, although the initial formation of an imine cannot be ruled out (Scheme 11).

2. 13. α-Oxoketene / α-Cyanoketene Thioacetals as Synthons

The reaction of α-oxo / cyanoketene *S*,*S*-acetals[46] **47**,**48** with *o*-aminothiophenol (**1**) in the presence of ethanol and triethylamine as a catalyst under reflux conditions gave 1,5-benzothiazepine derivatives **49**,**50**. The reaction of benzothiazepine **49** with hydrazine, phenylhydrazine or hydroxylamine in ethanol gave the corresponding azolobenzothiazepines **51a–c** in 66–85% yield.[47] Reaction of compound **49** with malononitrile afforded pyrano[4,3-*b*]benzothiazepines **52**, which underwent cyclization into pyrido[4,3-*b*][1,5]benzothiazepine **53**. Also reaction of compound **49** with ethyl cyanoacetate afforded pyrano[4,3-*b*][1,5]benzothiazepin-3-one **54**. The reaction pathway was assumed to proceed *via* a nucleophilic addition of an active methylene at the ethylenic bond of the thiazepine ring with an elimination of the MeSH molecule followed by the enolization and cyclization to the desired pyrano-benzothiazepine derivatives (Scheme 12).



Scheme 11. Synthesis of quino2,3-*b*1,5benzothiazepine derivatives **45**,**46a–c**.



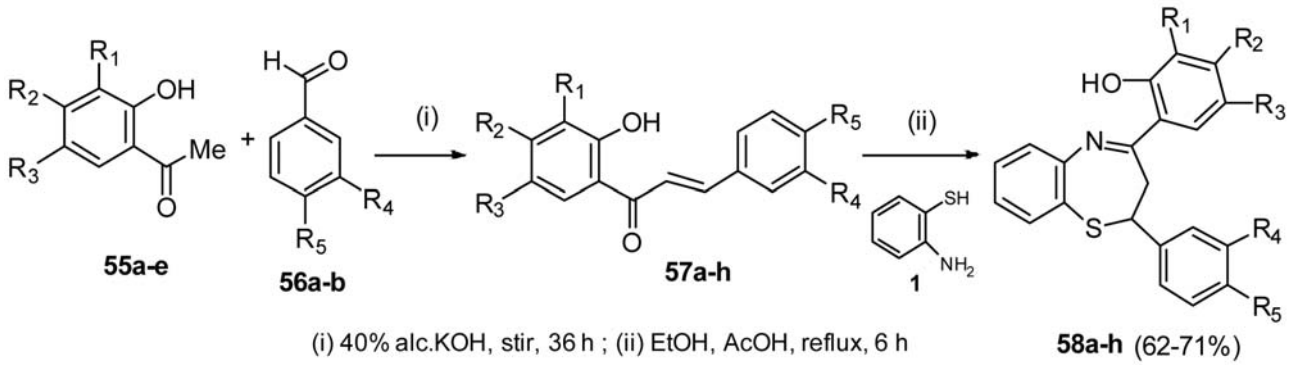
Scheme 12. Synthesis of azolo / pyrano / pyridobenzothiazepines **51a–c**,**52**–**54**.

3. Preparation of 1,5-Benzothiazepines from Chalcones

Chalcones are the principal precursors for the biosynthesis of flavonoids and isoflavonoids. A three carbon α,β-unsaturated carbonyl system constitutes chalcones. Chalcones are the condensation products of aromatic aldehydes with acetophenones in the presence of a catalyst. These compounds are of high interest,[48] due to their use as intermediates[49] in the synthesis of a series of heterocyclic compounds, such as benzothiazepines,[50] the pyrazolines[51] and flavones.[52] Although there are several methods available for the synthesis of chalcones the most important of them is by Claisen–Schmidt condensation performed in an acidic or basic medium under homogeneous conditions.[53] The various types of benzothiazepines synthesized by employing chalcones are illustrated in Schemes 13–15 and are summarized[56–59] in Table 1 (Schemes 16–19).

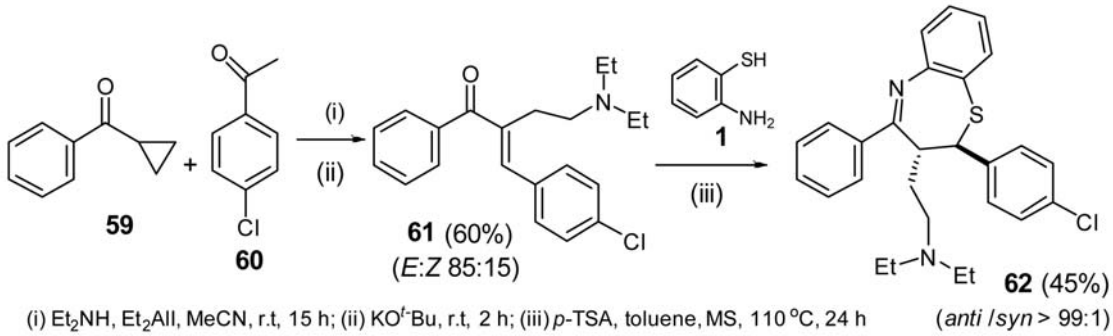
3. 1. 2,4-Diaryl-1,5-benzothiazepines

The Claisen–Schmidt condensation of various substituted acetophenones **55** with aromatic aldehydes in the presence of ethanol and KOH gave (*E*)-1-(5-substituted-2-hydroxyphenyl)-3-(4-substituted phenyl)prop-2-en-1-ones (chalcones) (**57a–h**). The chalcones on reaction with *o*-aminothiophenol (**1**) under reflux conditions in ethanol in the presence of glacial AcOH gave 1,5-benzothiazepine derivatives **58a–h** in 58–71% yield[54] (Scheme 13). All the synthesized compounds were screened for their *in vitro* antimicrobial activity against Gram-positive organisms *P. aeruginosa* and *S. aureus* and Gram-negative organism *E. coli* using Gentamicin and Cefixime as a reference standard by paper disc diffusion method. All the tested compounds were evaluated at 50–100 μg/mL concentration. The microbial data revealed that **58e** has shown better activity for Gram positive bacteria *S. aureus* ATCC 259223 (13–17 mm) (Scheme 13).



58	R_1	R_2	R_3	R_4	R_5	% Y
a	H	H	H	H	F	70
b	H	H	Me	H	F	63
c	H	H	Cl	H	F	66
d	Cl	H	Cl	H	F	71
e	H	Me	Cl	H	F	69
f	H	H	H	MeO-	MeO-	70
g	H	H	Me	MeO-	MeO-	58
h	H	H	Cl	MeO-	MeO-	62

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



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

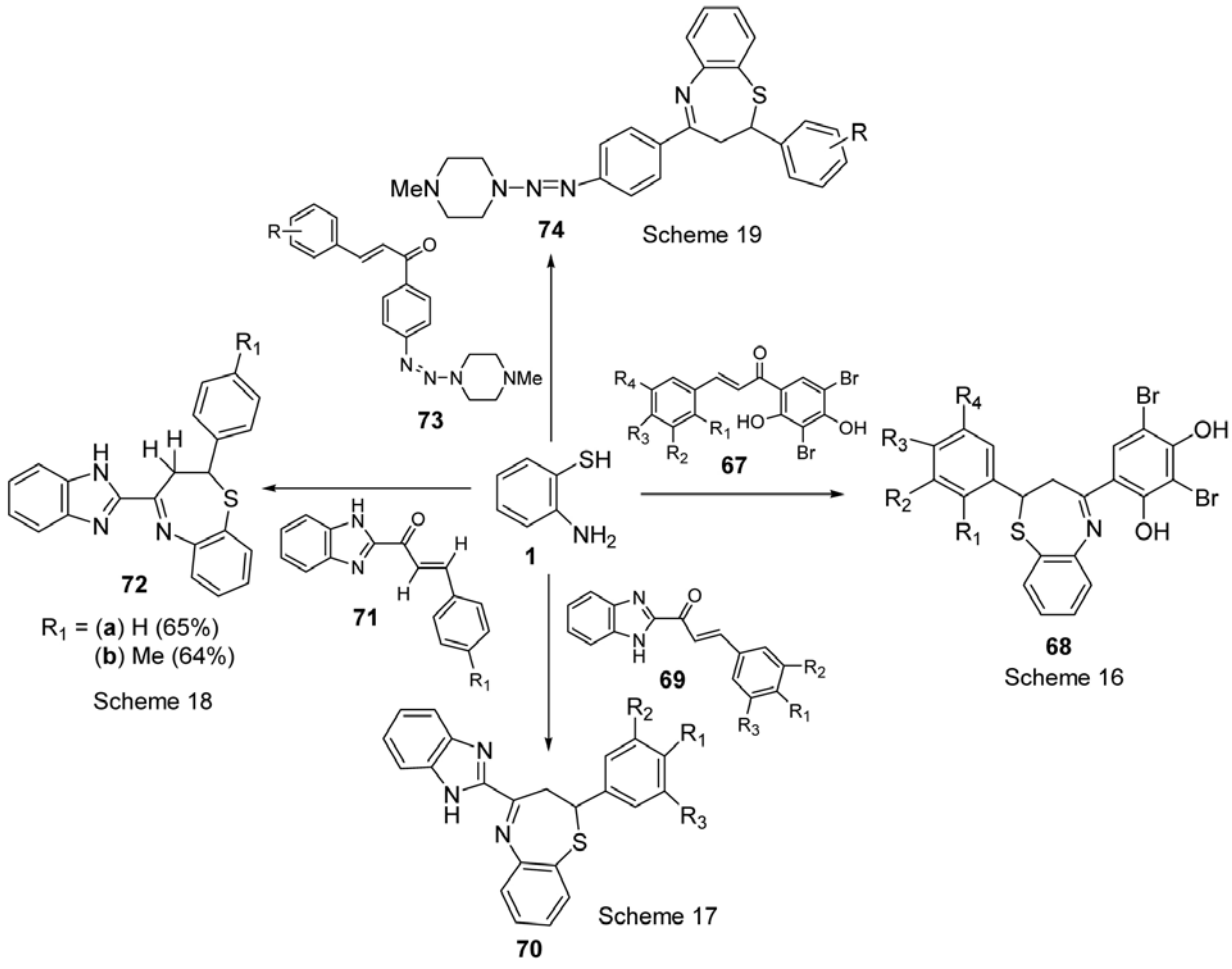
3. 2. α-Substituted α,β-Enone as a Reactant

The reaction of cyclopropyl phenyl ketone (**59**), 4-chlorobenzaldehyde (**60**) and diethylamine in the presence of diethylaluminium iodide as the Lewis acid followed by Hofmann elimination of the formed intermediate pyrrolidinium salt with KO*t*-Bu gave the α-substituted-α,β-enone in 60% yield with *E/Z* ratio of 85:15.[55] The reaction of α,β-enone **61** with *o*-aminothiophenol (**1**) in toluene in the presence of *p*-TSA gave the 1,5-benzothiazepine scaffold **62** in 45% yield. LC/MS analysis and NMR experiments indicated the formation of only one diastereoisomer, which was determined by NOESY experiments to be *anti* (Scheme 14).

3. 3. *cis*-(±)-1,5-Benzothiazepines

Rao *et al*.[56] have reported the synthesis of 1,5-benzothiazepines by cyclocondensation reaction of *o*-aminot-

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



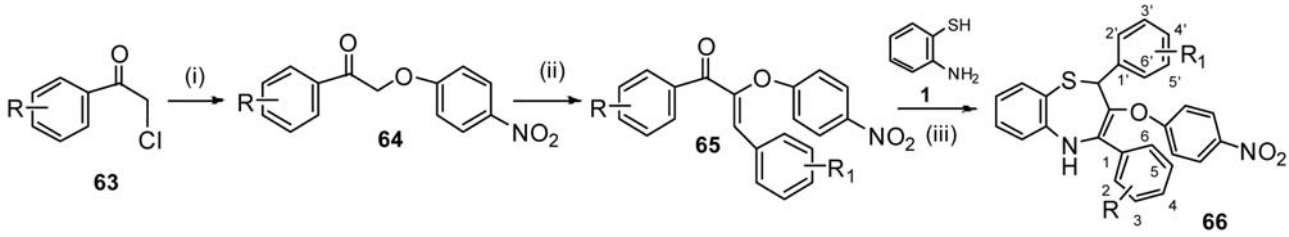
Ref

Scheme 16: 2,3-Diaryl-1,5-Benzothiazepines: (i) DMF, Al_2O_3 (basic), MWI, 90 °C, 7 min (57)
68 (a) R_1= R_2 = R_3 = R_4 = H (78%); **(b)** R_1 = Cl, R_2 = R_3 = R_4 = H (82%); **(c)** R_1= R_3 = Cl, R_2 = R_4 = H (84%);
(d) R_1= F,R_2 = R_3 = R_4 = H (83%); **(e)** R_1= R_2 = R_4 = H, R_3 = F (86%); **(f)** R_1= R_2 = R_4 = H, R_3 = Cl (80%);
(g) R_1= R_2 = R_4 = H, R_3 = MeO (89%); **(h)** R_1 = R_2 = R_4 = H, R_3 = MeO (81%); **(i)** R_1 = R_2 = R_4 = H, R_3 = Br (89%)

Scheme 17: Microwave mediated synthesis: (i) Benzene, AcOH(cat), MWI, 6 min (58)
69 (a) R_1= R_2 = R_3 = H ; **(b)** R_1 = MeO,R_2 = R_3 = H ; **(c)** R_1= R_2 = MeO, R_3 = H;
(d) R_1 = R_2 = R_3 = MeO ; **(e)** R_1 = Cl, R_2 = R_3 = H ; **(f)** R_1 = Me_2N R_2 = R_3 = H

Scheme 18: Benzoimidazolyl-benzothiazepines: (i) MeOH, AcOH (cat), reflux, 4 h (59)

Scheme 19: Piperazinyl-diazenyl-1,5-benzothiazepines: (i) DMF, AcOH, reflux, 9 h (60)
74 R = **(a)** H (67%); **(b)** MeO (61%); **(c)** 4-MeO (58%); **(d)** 3-Br (66%); **(e)** 2-Cl (61%); **(f)** Me2N (58%);
(g) 3-NO_2 (65%); **(h)** 2-OH (66%); **(i)** 3-OH-4-MeO (63%); **(j)** 3,4-$(MeO)_2$ (69%)



(i) EtOH, 4-$NO_2C_6H_4OH$, Na_2CO_3, reflux, 6 h ; (ii) Arylaldehydes, NH_4OAc, EtOH, reflux, 12 h; (iii) toluene, piperidine, reflux, 2 h

66 (**a**) R = R_1 = H (50%); (**b**) R = H, R_1 = 2'-Cl (56%); (**c**) R = H, R_1 = 4'-MeO (54%); (**d**) R = 4-Me, R_1 = H (53%); (**e**) R = 4-Cl, R_1 = H (60%); (**f**) R = 4-Br, R_1 = H (57%)

Scheme 15. Synthesis of cis-(±)-2,4-diaryl-3-(4-nitrophenoxy)-1,5-benzothiazepines **66a–f**.

hiophenol (**1**) with Michael acceptors. The Friedel–Crafts acylation of benzene / substituted benzene with chloroacetyl chloride in the presence of aluminium chloride gave the phenacyl chloride **63** which underwent etherification with 4-nitrophenol in the presence of sodium carbonate in ethanol medium to give nitroether derivative **64**. α-(4-Nitrophenoxy)chalcones **65** were obtained by a condensation reaction of **64** with arylaldehydes in the presence of NH_4OAc in EtOH. The cyclocondensation of chalcones **65** with *o*-aminothiophenol (**1**) in the presence of piperidine and dry toluene under reflux conditions gave the *cis*-(**±**)-2-aryl-3-(4-nitrophenoxy)-4-phenyl-1,5-benzothiazepines (**66**) in 50–70% yield (Scheme 15).

4. Green Synthesis

Green chemistry with its twelve principles would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the number of the stages of the synthetic routes and minimize waste as far as practically possible. In this way, organic synthesis will be part of the effort for sustainable development.[61,62] Green chemistry is also interested for research and alternative innovations on many practical aspects of organic synthesis.[63,64] The various types of benzothiazepines synthesized by employing the green principles are illustrated in Schemes 20–24 and summarized in Table 2 (Schemes 25–30).

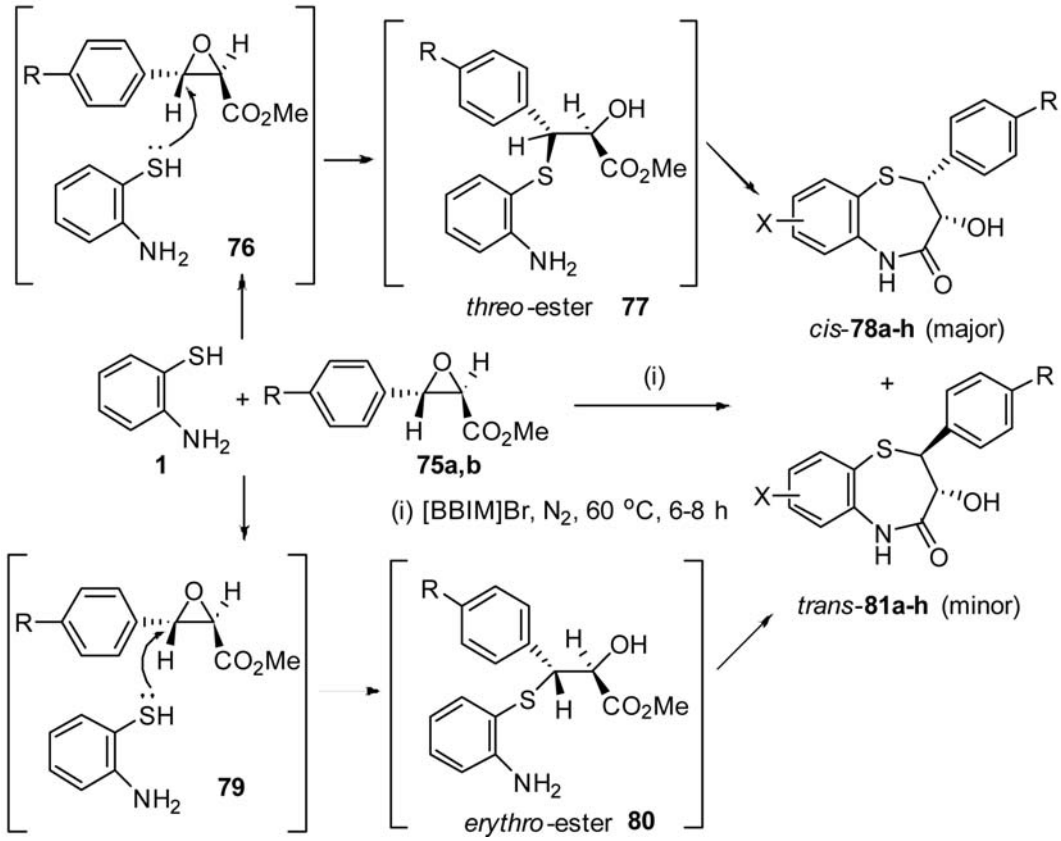
4. 1. Ionic Liquid Mediated Regioselective Synthesis

The reaction between *o*-aminothiophenol (**1**) and methyl-(±)-*trans*-3-(4-methoxy / benzyloxyphenyl)glycidate (**75a**,**b**) under N_2 atmosphere at 60 °C in the presence of ionic liquid 1-butyl-3-methylimidazolium bromide ([BMIM]Br) gave (+)/(±)-*cis*-2-(4-methoxy/benzyloxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4[5*H*]-ones (**78a**–**h**) as major products.[65] The corresponding *trans* stereoisomer **81a**–**h** were obtained as minor products in each case (Scheme 20). The stereochemistry (*i.e.* *cis* and *trans*) of compounds **78a**–**h** and **81a**–**h** was determined from the ^{1}H NMR vicinal coupling constant data.

In the ionic liquid, the oxirane opens stereoselectively, followed by a subsequent cyclization resulting in the formation of products. The stereoselectivity and overall yield with glycidate **75b** is better than with glycidate **75a** because of the better electron donating ability of **75b** (due to benzyloxy substitutent), thereby resulting in increased carbocationic character of the benzylic carbon in the transition state. This observation is in agreement with an earlier report.[66] The total yields of compounds **78** and **81** and the *cis*/*trans* ratio were dependent on the electron withdrawing effect of the substituents attached to *o*-aminothiophenols **1**. The total yields of compounds **78** and **81** follow the order 7-CF_3 > 9-Cl > 8-Cl > 7-Cl > H and 7-CF_3 > 8-Cl > H when the reaction was carried out with the corresponding substituted *o*-aminothiophenol (**1**) and glycidates **75a** and **75b**, respectively.

4. 2. Microwave Irradiation

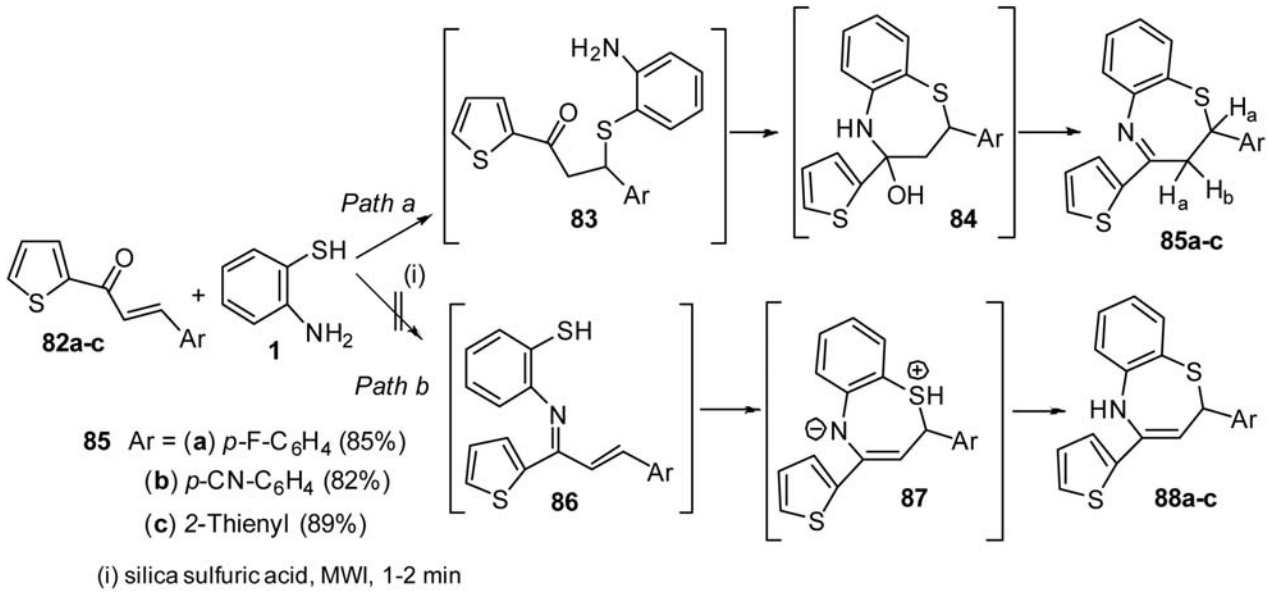
The reaction of chalcones **82a**–**c** with *o*-aminothiophenol (**1**) in the presence of silica-sulfuric acid without solvent under microwave irradiation for 1–2 min at 105–110 °C (2450 MHz, 800 W modified Amana domestic microwave oven) afforded 2-aryl-2,3-dihydro-4-(thiophen-2-yl)-1,5-benzothiazepine derivatives (**85a**–**c**) in 82–89% yield.[69] The reaction may involve two pathways: (a) conjugate addition of the sulfhydryl to the α,β-unsaturated carbonyl group of **82a**–**c** leading to the intermediate formation of the thia-Michael adduct **83**, which upon a subsequent intramolecular nucleophilic attack by the NH_2 group on the carbonyl carbon followed by the dehydration forms the 2,3-dihydro-1,5-benzothiazepine **85a**–**c** (*path a*) or (b) condensation of the amino group of **1** with carbonyl group of **82a**–**c** leading to the intermediate formation of aza-diene **86**, which upon a subsequent intramolecular conjugate addition by the sulfhydryl group forms the isomeric 2,5-dihydro-1,5-benzothiazepines **88a**–**c** (*path b*).[70] The reaction products **85a**–**c** that are assumed to be formed *via* path *a* were identified by their



78	X	R	%Y	*Cis / Trans*
a	H	MeO	72	76/24
b	7-Cl	MeO	80	82/18
c	8-Cl	MeO	82	84/16
d	9-Cl	MeO	84	86/14

78	X	R	%Y	*Cis / Trans*
e	7-CF_3	MeO	86	90/10
f	H	BzO	76	82/18
g	8-Cl	BzO	82	86/14
h	7-CF_3	BzO	88	90/14

Scheme 20. Ionic liquid mediated regioselective synthesis of 1,5-benzothiazepines **78**,**81a**–**h**.



Scheme 21. Synthesis of 4-thiophenyl-1,5-benzothiazepines **85a**–**c**.

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

4. 3. Solid Phase Synthesis Approach

The reaction of Wang bromide resin **89** and ketone **90** in the presence of Cs_2CO_3 and NaI in DMF at 50 °C for 5 h gave the corresponding anchored ketone **91** in a quantitative yield. In the next step the formation of chalcone **92** was readily achieved by adding an excess of the desired ketone **91** to the anchored aldehyde (or *vice versa*) in THF / MeOH and using freshly prepared NaOMe as a base at r.t. The resin supported chalcone **92** was reacted with *o*-aminothiophenol in ethanol or THF in the presence of a few drops of AcOH at 60 °C for 5 h giving the resin bound 1,5-benzothiazepine derivatives. TFA cleavage in DCM at r.t. for 1 h gave the 1,5-benzothiazepine **93** in a total yield of 60–80 % (Scheme 22).[69]

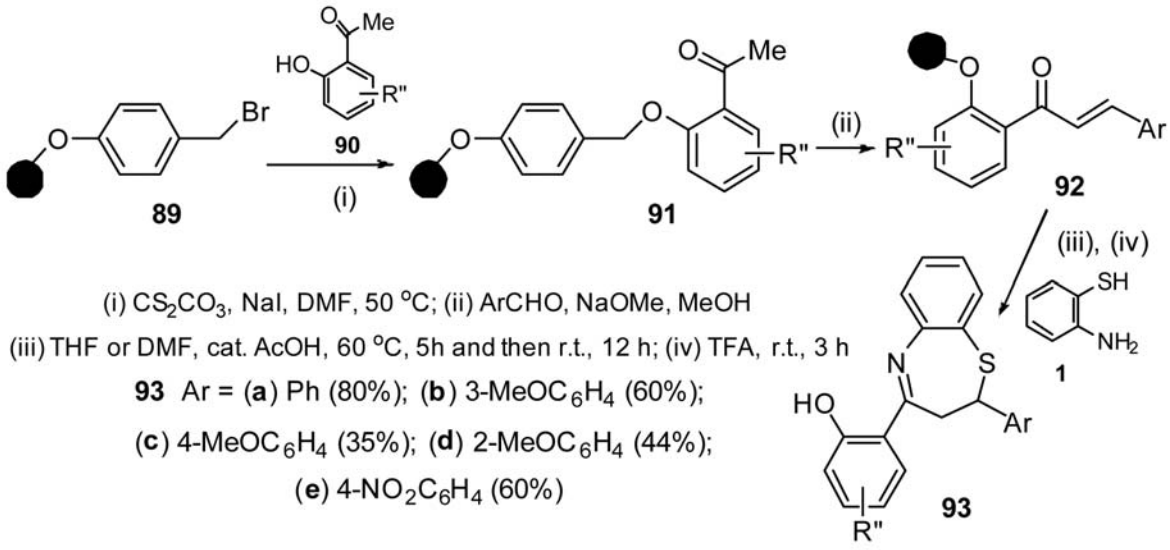
The synthesis of 1,5-benzothiazepines using tetrabutylammonium tribromide [TBATB] as a phase transfer catalyst (PTC) in water,[76] sodium dodecylsulfate (SDS) in water,[77] Al_2O_3 nano particles as inorganic solid support,[79] microwave irradiation in the presence of 2-methoxyethanol,[80] DMF[81] as examples of alternative and environmentally benign reaction conditions are summarized in Schemes 23–27 (Table 2).[70–74]

5. Mannich Base Derivatives

Mannich bases were at first used to improve water solubility of compounds currently in use, but later they were used to enhance the activity of some compounds with dialkylamino methyl groups.[75] The Mannich reaction plays a key role in synthesis giving easy access to nitrogen containing compounds. Their functionalization towards various possible activities is still under investigation. Since numerous heterocyclic aromatic tricyclics, including pyrrolobenzodiazepines[76] and pyrrolobenzoxazepines[77] bearing a basic side chain have been found to possess psychotropic activity, Kumar and Kaur *et al.*[78,79] aimed at the synthesis of 3-(dimethylamino)methyl derivatives of 1,5-benzothiazepines in order to assess if any biological property could be ascribed to this series of compounds.

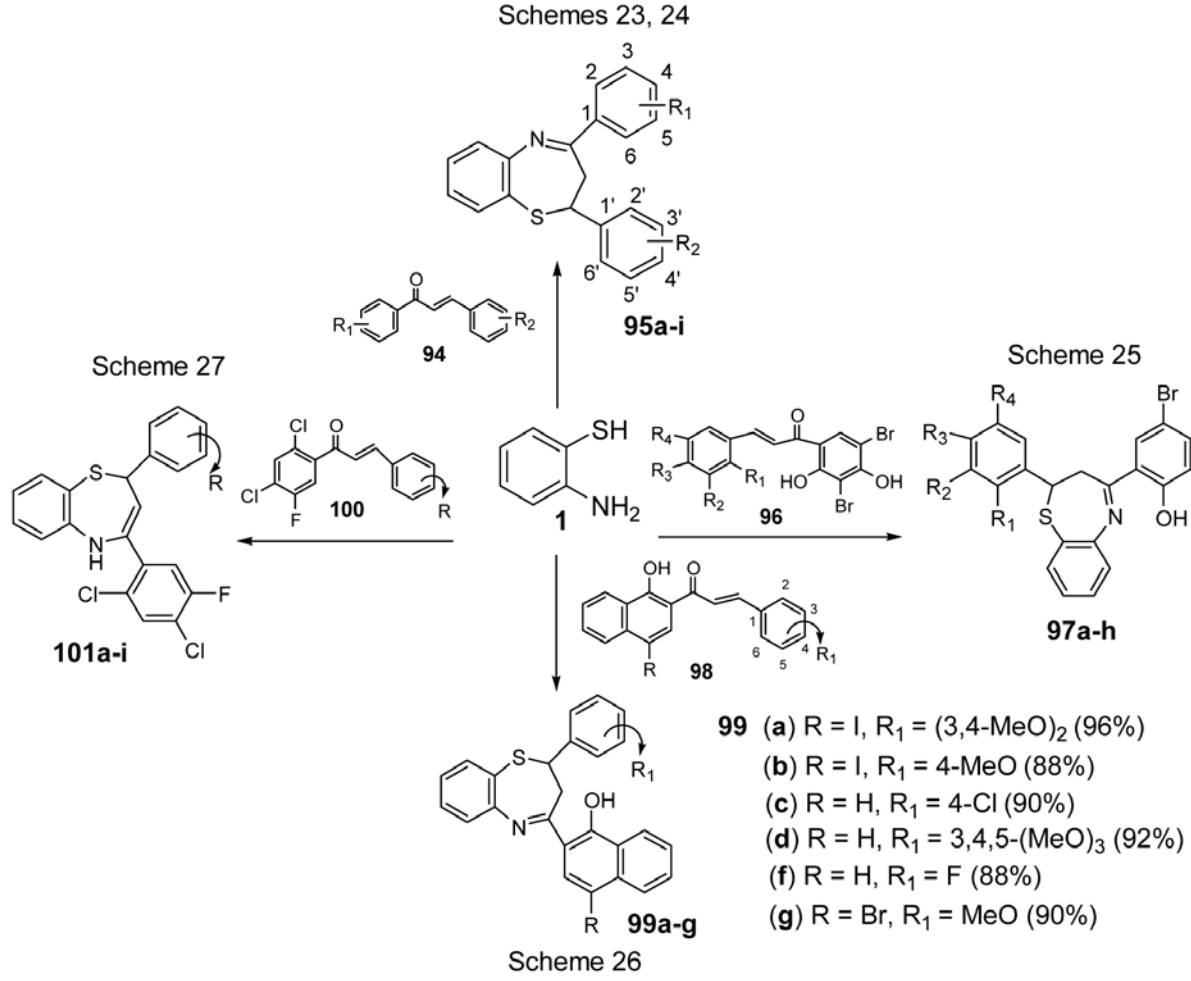
5. 1. Benzthiazepine Derivatives as Anticonvulsant Agents

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



Scheme 22. Solid phase synthesis of 1,5-benzothiazepines **93a–e**.

Table 2. Examples of 1,5-benzthiazepine derivatives by green synthesis



Schme 23: Water, tetrabutylammonium tribromide (TBATB), 80 °C, 5–8 h — Ref
95 (a) $R_1 = R_2 = H$ (87%); **(b)** R_1 = 4-MeO, R_2 =H (84%); **(c)** R_1 = H, R_2 = 4'-MeO (90%); (70)
(d) R_1 = H, R_2 =3'-NO_2 (94%); **(e)** R_1 = 4-OH, R_2 = H (80%); **(f)** R_1 = H, R_2 = 4'-Cl (88%);
(g) R_1 = 2-OH, R_2 = H (84%); **(h)** R_1 = 4-Cl, R_2 = 4'-MeO (87%); **(i)** R_1 = 2-OH, R_2 = 4'-OH (80%)

Scheme 24: Water, sodium dodecylsulfate (SDS), 110 °C, 8–16 h (71)
95 (a) $R_1 = R_2 = H$ (65%); **(b)** R_1 = H, R_2 = 4'-Cl (72%); **(c)** R_1 = 4-Cl, R_2 = H (76%); **(d)** R_1 = 4-Cl, R_2 = 4'-MeO (74%);
(e) R_1 = 4-Me, R_2 = 4'-MeO (61%); **(f)** R_1 = 4-NO2, R_2 = 4'-MeO (66%); **(g)** R_1 = H, R2 = 4'-MeS (65%);
(h) R_1 = 4-MeS, R_2 = 4'-Me (71%); **(i)** R_1 = 4-CF3, R_2 = 4'-MeS (73%); **(j)** R_1 = 4-CF3, R_2 = 4'-SO_2Me (75%)

Scheme 25: Al_2O_3 (basic), microwave irradiation, 5–7 min (72)
97 (a) $R_1 = R_2 = R_3 = R_4 = H$ (78%); **(b)** R_1 = Cl, $R_2 = R_3 = R_4 = H$ (82%); **(c)** R_1 = F, $R_2 = R_3 = R_4 = H$ (83%)
(d) $R_1 = R_2$ = H, R_3 = F, R4 = H (86%); **(e)** $R_1 = R_2$ = H, R_3 = Cl, R_4 = H (80%); **(f)** $R_1 = R_2$ = H, R_3 = Me, R_4 = H (81%)
(g) R_1 = Cl, R_2 = H, R_3 = Cl, R_4 = H (84%); **(h)** $R_1 = R_2$ = H, R_3 = MeO, R_4 = H (89%)

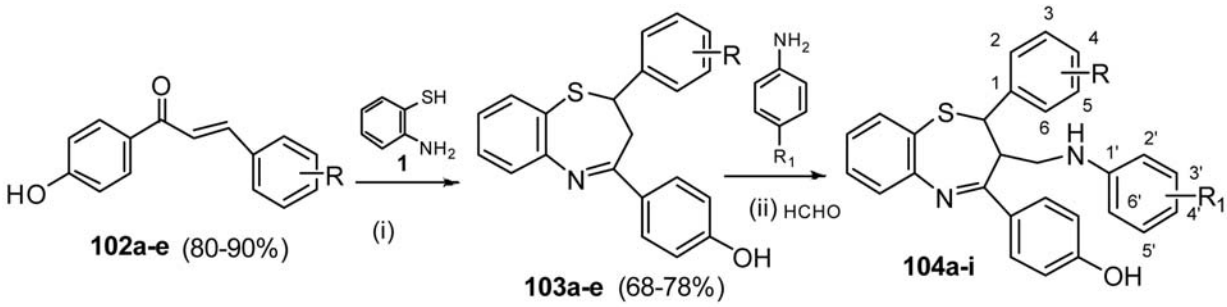
Scheme 26: 2-Methoxy ethanol, piperidine, microwave irradiation, 4-5 min (73)
101 R = **(a)** H (82%); **(b)** 2-NO2 (80%); **(c)** 3-NO2 (82%); **(d)** 2-Cl (85%); **(e)** 4-Cl (90%);
(f) 4-Me2N (79%); **(g)** 4-MeO, 3-OH (75%); **(h)** 3,4,5-(MeO) 3 (85%); **(i)** 4-MeO (89%)

Scheme 27: Microwave irradiation, DMF, AcOH (cat), 2–3 min (73)

at the third position of benzothiazepine ring) have shown most potent activity of 90% against MES test which is more potent than the standard drug phenytoin sodium (Scheme 28).

5. 2. Benzothiazepinylpyridine Derivatives

2-Acetylpyridine was reacted with various substituted aromatic aldehydes to yield 2-(substituted benzylidenechalconyl)pyridines (**105a–c**), which on cyclisation with *o*-ami-



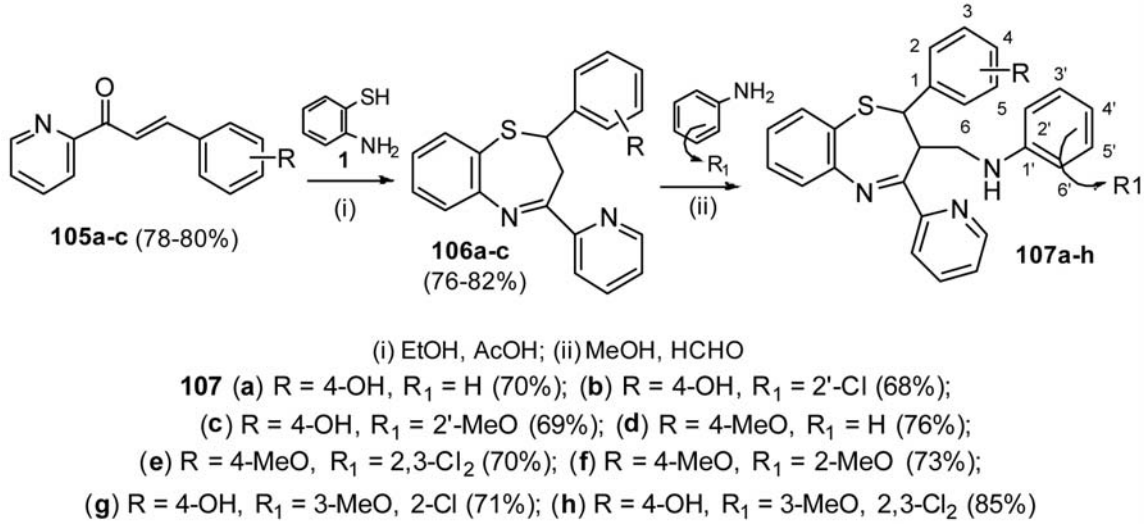
Scheme 28. Synthesis of 2,4-diaryl-3-(4-substituted phenylaminomethylene)-1,5-enzothiazepines **104a–i.**

nothiophenol (**1**) in the presence of glacial AcOH gave 2-[(2-substituted phenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]pyridines (**106a–c**) in 76–82% yield.[79] Compounds **106a–c** further undergo Mannich reaction with various substituted anilines in methanol to afford 2-[2-(substituted phenyl)-3-(substituted phenylamino)methyl-2,3-dihydro-1,5-benzothiazepin-4-yl]pyridines (**107a–h**) in 68–85% yield (Scheme 29). All the synthesized compounds **106a–c** and **107a–h** were tested for their anticonvulsant activity. Anticonvulsant activity was determined by supramaximal electroshock seizure pattern tests (SMES). This activity was performed by following the method of Toman *et al.*[80] in albino rats. The effect of unknown compounds was compared with the standard drug phenytoin sodium and the LD_{50} was determined in albino rats weighing 100–120 g of either sex by the method of Smith.[81] The results show that compounds having 2,3-dichlorophenyl moiety at the 3rd position of benzothiazepine ring (*i.e.* compounds **107e** and **107h**) exhibited more potent anticonvulsant activity than the reference drug.

Some more examples of this category of 1,5-benzothiazepine derivatives synthesized using the methodology discussed in reaction Schemes 28 and 29 are summarized in the Table 3 (Schemes 30–33).[82–84]

6. 1,3-Dipolar Cycloaddition Reactions

The field of 1,3-dipolar cycloaddition chemistry developed dramatically during the past twenty-five years turning out to be a general method for the synthesis of five membered heterocyclic rings containing the pyrrolidine structural unit.[85,86] Recently, a lot of new compounds containing various heterocyclic rings, such as oxadiazole, imidazole and triazole annelated to the 1,5-benzothiazepine ring were synthesized by numerous research groups.[14] It is well documented that the pharmacological activity could be increased when an additional heterocyclic ring is fused to the heptatomic nucleus.[87] Taking this into con-



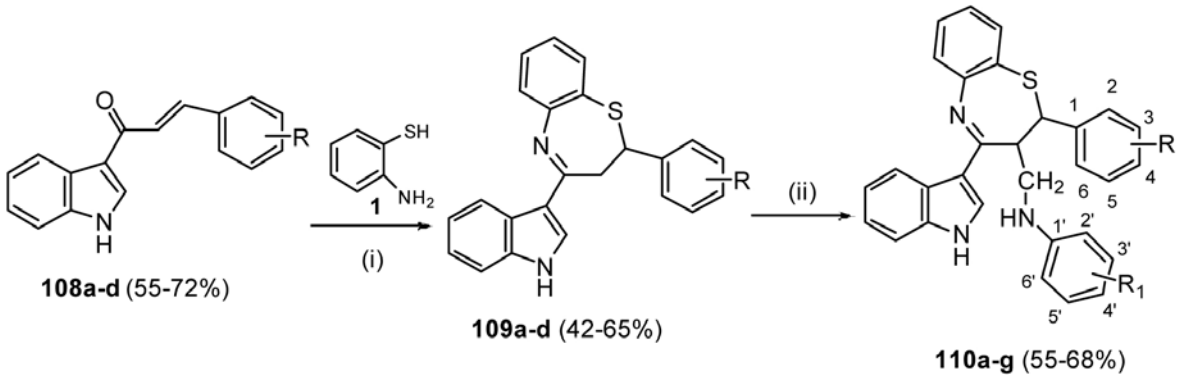
Scheme 29. Synthesis of 1,5-benzothiazepinyl pyridine derivatives **107a–h**.

Table 3. Examples of 1,5-benzthiazepine derivatives by Mannich reaction

Scheme 30: Benzothiazepinyl indoles 110a–g: (i) AcOH, reflux, 4 h; (ii) MeOH, HCHO, Ar'NH_2, reflux, 6 h.

Ref

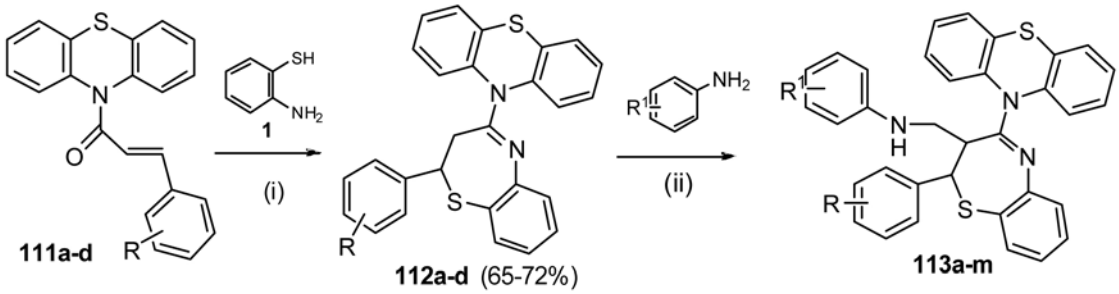
(82)



110 (**a**) R = H, R_1 = H (60%); (**b**) R = H, R_1 = 2'-Cl (55%); (**c**) R = 4-MeO, R_1 = H (68%);
(**d**) R = 4-MeO, R_1 = 2'-Cl (58%); (**e**) R = 4-Me_2N, R_1 = H (65%);
(**f**) R = 4-Me_2N, R_1 = 3'-Cl (60%); (**g**) R = 3-MeO-4-OH, R_1 = 3'-Cl (65%)

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

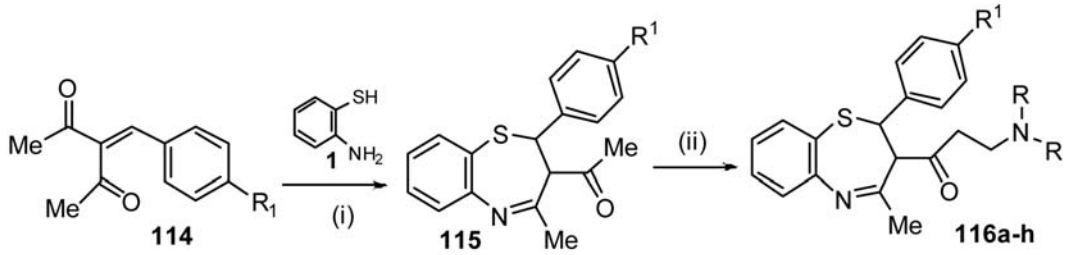
(83)



113 (**a**) R = R^1 = H (73%); (**b**) R = H, R^1 = 2'-Cl (68%); (**c**) R = H, R^1 = 3'Cl (68%);
(**d**) R = H, R^1 = 2'MeO (65%); (**e**) R = 4-MeO, R^1 = H (72%); (**f**) R = 4-MeO, R^1 = 2'Cl (70%);
(**g**) R = 4-MeO, R^1 = 3'Cl (74%); (**h**) R = 4-MeO, R^1 = 2'MeO (70%); (**i**) R = 4-Me_2N, R^1 = H (74%);
(**j**) R = 4-Me_2N, R^1 = 2'Cl (67%); (**k**) R = 4-Me_2N, R^1 = 3'Cl (65%);
(**l**) R = 4-OH,3-MeO, R^1 = 2'H (60%); (**m**) R = 4-OH,3-MeO, R^1 = 2'Cl (68%)

Scheme 32: 4-Methyl-1,5-benzothiazepinyl derivatives 116a–h: (i) AcOH, reflux, 4 h; (ii) MeOH, HCHO, RNH_2, reflux, 6 h.

(84)

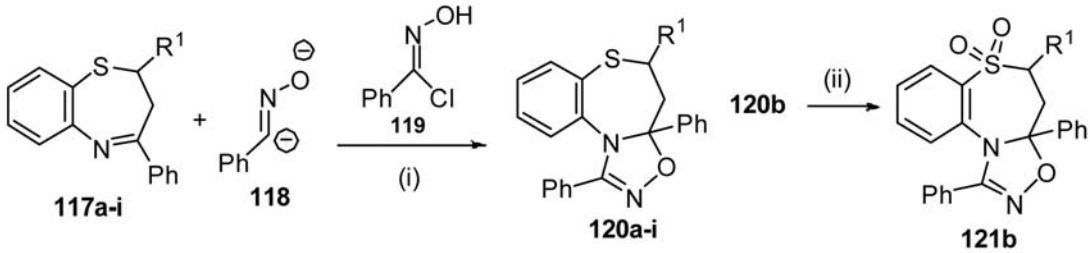


116 (**a**) R^1 = H, R = Me (37%); (**b**) R^1 = 4-Cl, R = Me (35%); (**c**) R^1 = 2-Cl, R = Me (49%);
(**d**) R = 2-NO_2, R_1 = Me (51%); (**e**) R^1 = H, R = Et (36%); (**f**) R^1 = 4-Cl, R = Et (38%);
(**g**) R^1 = 2-Cl, R = Et (37%); (**h**) R = 2-NO_2, R_1 = Et (35%)

sideration, the synthesis of 1,5-benzothiazepine derivatives containing quinoline, 1,2,4-oxadiazoline or 1,2,4-triazole moieties *via* 1,3-dipolar cycloaddition reaction was reported recently by various research groups.[89,93–103]

6. 1. Oxadiazolo-benzothiazepines

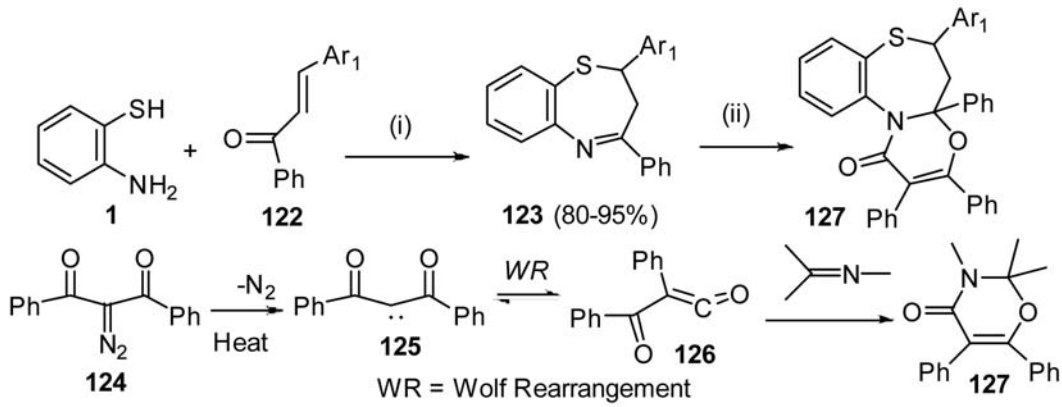
The 1,5-benzothiazepine derivatives **117a–i** were synthesized according to the previously reported methodology.[88] The reaction between 1,5-benzothiazepine derivatives **117a–i** and benzonitrile oxide **118** generated *in situ* from benzohydroximinoyl chloride (**119**) and Et_3N in DCM leads to 3a,4-dihydro-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepines (**120a–i**) in 37–68% yield.[89] The oxadiazole ring is fused at the "*d*" edge of the heptatomic nucleus and the cycloaddition reaction has been found to be regiospecific and affords a single regioisomer according to the FMO approach. The stereochemistry of the synthesized compounds was unambiguously determined by NOE measurements in combination with the analysis of proton coupling constants and previous studies.[88] The 5-substituent occupies a quasi-equatorial position in the predominant confirmation and the substituent at C-3a occupies a nearly axial position. The anticonvulsant properties of these derivatives **120a–i** were evaluated in DBA/2 mice, which were genetically susceptible to sound-induced seizures.[90] DBA/2 mice were exposed to auditory stimulation following intraperitonial administration of drugs at the concentration of 0.1 mL / 10 g body weight of mouse. Auditory stimulation (12–16 kHz, 109 dB) was applied for 60 s or until tonic extension occurred. The results were compared with the activity shown by clinically useful anticonvulsant 1,5-benzothiazepines such as clobazam and desmethylclobazam, ED_{50} values were calculated by the method of probits analysis.[91] The 5-(4-bromophenyl)-1,3-diphenyl derivative **120b**, the most active compound of the series, is over 20 times more active than the parent benzothiazepine **117b** and shows an activity comparable to clobazam and is better than desmethylclobazam (Scheme 33).



(i) MDC, Et_3N, r.t., 24 h; (ii) AcOH, H_2O_2, reflux, 5 h

120 (**a**) $R_1 = C_6H_5$ (40%); (**b**) $R_1 = 4\text{-}BrC_6H_4$ (45%); (**c**) $R_1 = 4\text{-}ClC_6H_4$ (80%); (**d**) $R_1 = 4\text{-}CNC_6H_4$ (52%); (**e**) $R_1 = 4\text{-}FC_6H_4$ (37%); (**f**) $R_1 = 4\text{-}MeOC_6H_4$ (48%); (**g**) $R_1 = 4\text{-}MeC_6H_4$ (50%); (**h**) $R_1 = 4\text{-}NO_2C_6H_4$(68%); (**i**) $R_1 = 4\text{-}CF_3C_6H_4$ (39%)

Scheme 33. Synthesis of oxadiazolo-benzothiazepines **120a–i**,**121**.



(i) MeOH, piperidine, reflux, 30 min; (ii) $PhCOC(N_2)COPh$, xylene, 100 °C, 15 min

127 (**a**) Ar_1 = Ph (93%); (**b**) Ar_1= *o*-ClC_6H_4 (92%); (**c**) Ar_1= *m*-ClC_6H_4(88%); (**d**) Ar_1= *p*-ClC_6H_4 (88%); (**e**) Ar_1= *o*-BrC_6H_4 (89%); (**f**) Ar_1= *m*-BrC_6H_4 (87%); (**g**) Ar_1= *p*-BrC_6H_4 (91%); (**h**) Ar_1= *o*-$MeOC_6H_4$ (44%)

Scheme 34. Synthesis of 1,5-benzothiazepine derivatives **127a–h** by cycloaddition reactions.

6. 2. Cycloaddition Reactions

The conjugated system of Ar–N=C–Ar of 1,5-benzothiazepine is non-planar and the –C=N– bond in this system is more rigid than that in other systems. Roma *et al*. reported[92] the cycloaddition reaction of the –C=N– bond of 1,5-benzothiazepines **123** with α-carbonyl ketene and the seven membered heterocyclic tricyclic systems **127** were obtained. The reaction of α,β-unsaturated ketones **122** and *o*-aminothiophenol (**1**) in methanol in the presence of piperidine gave the 2,3-dihydro-1,5-benzothiazepines **123** in 80–95% yield. The reaction of 1,5-benzothiazepines **123** with 2-diazo-1,3-diphenyl-1,3-propanedione (**124**) in xylene at 100 °C afforded (4a,6-diaryl-2,3-diphenyl)-4a,5,6,12-tetrahydro-1*H*-1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-ones (**127**) in high yields[93] (Scheme 34). All seven membered rings in these heterocyclic compounds take the slightly distorted boat-like conformation and *cis*-fused 1,3-oxazinone rings take the half-chair confirmation.

7. Fluoro Benzothiazepines

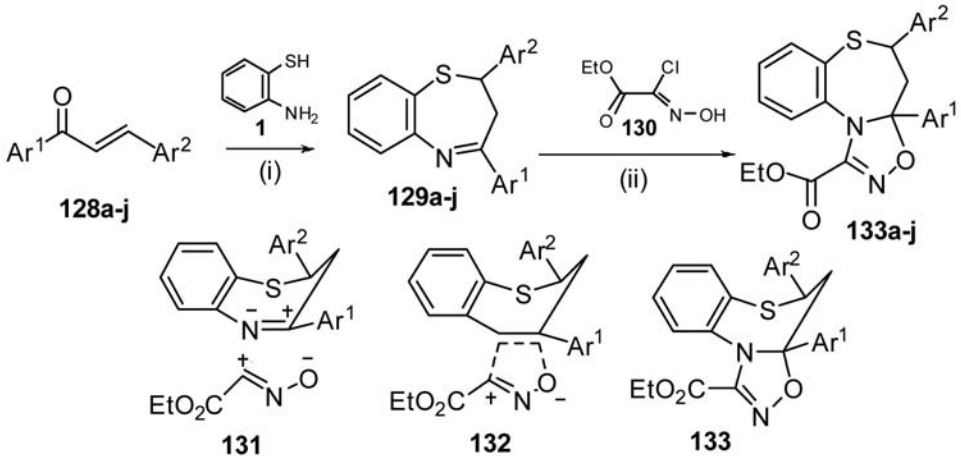
The chemistry of heterocyclic compounds with incorporated fluorine atoms is a rather promising area of

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

Scheme 35: Hexahydro-oxadiazolo-pyrido-benzothiazepines 133a–j: (i) MeOH, AcOH, piperidine, reflux, 30 min, r.t., 12 h; (ii) Et_3N, DCM, r.t., 48 h.

Ref

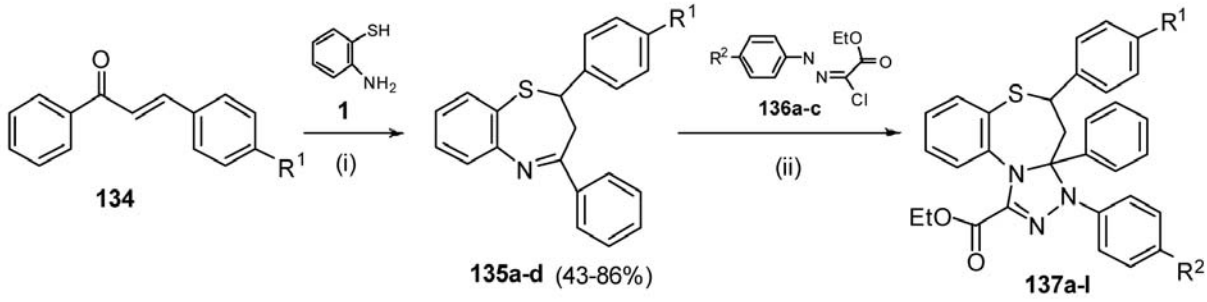
(94)



133 (**a**) $Ar^1 = Ar^2$ = Ph (34%); (**b**) Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4(35%); (**c**) Ar^1 = Ph, Ar^2 = *p*-$MeOC_6H_4$(35%); (**d**) Ar^1 = Ph, Ar^2 = *p*-$NO_2C_6H_4$(33%); (**e**) Ar^1 = *p*-ClC_6H_4, Ar^2 = *p*-$NO_2C_6H_4$ (33%); (**f**) Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph (31%); (**g**) Ar^1 = *p*-ClC_6H_4, Ar^2 = *p*-$MeOC_6H_4$ (23%); (**h**) Ar^1 = *p*-ClC_6H_4, Ar^2 = *p*-$NO_2C_6H_4$ (25%); (**i**) Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = *p*-$MeOC_6H_4$(36%); (**j**) Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = *p*-ClC_6H_4 (32%)

Scheme 36: Triazolo-benzothiazepines 137a–l: (i) MeOH, AcOH (cat), reflux 4 h, r.t., 12 h; (ii) DCM, Et_3N, r.t., 72 h.

(95)



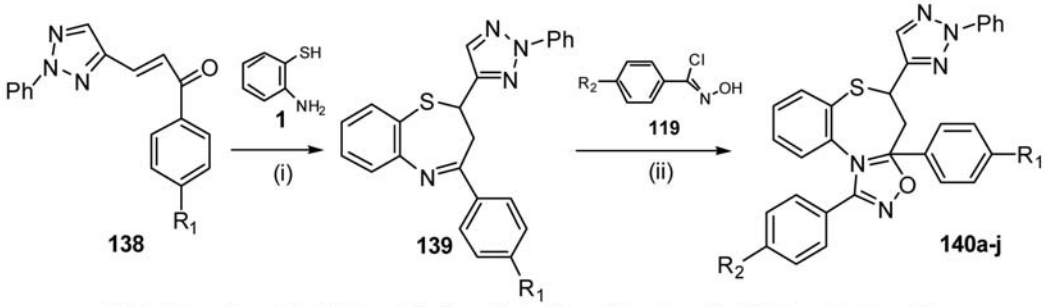
137 (**a**) $R_1 = R_2$ = H (25%); (**b**) R_1= H, R_2 = Cl (31%); (**c**) R_1= H, R_2 = Me (30%); (**d**) R_1= Cl, R_2 = H (26%); (**e**) $R_1 = R_2$ = Cl (32%); (**f**) R_1= Cl, R_2 = Me (29%); (**g**) R_1= MeO, R_2 = H (21%); (**h**) R_1= MeO, R_2 = Cl (27%); (**i**) R_1= MeO, R_2 = Me (33%); (**j**) R_1= NO_2, R_2 = H (22%); (**k**) R_1= NO_2, R_2 = Cl (31%); (**l**) R_1= NO_2, R_2 = Me (28%)

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

Scheme 37: Oxadiazolo-1,5-benzothiazepine-containing 2-phenyl-1,2,3-triazole 140a–h: (i) EtOH, AcOH (cat), reflux 6 h, r.t., 12h; (ii) DCM, Et_3N, r.t., 72 h.

Ref

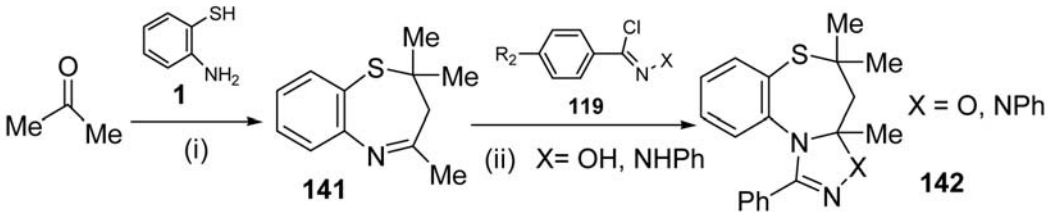
(96)



140 (**a**) $R_1 = R_2 = H$; (**b**) $R_1 = Cl$, $R_2 = H$; (**c**) $R_1 = Me$, $R_2 = H$; (**d**) $R_1 = Br$, $R_2 = H$; (**e**) $R_1 = MeO$, $R_2 = H$; (**f**) $R_1 = H$, $R_2 = MeO$; (**g**) $R_1 = Cl$, $R_2 = MeO$; (**h**) $R_1 = Me$, $R_2 = MeO$

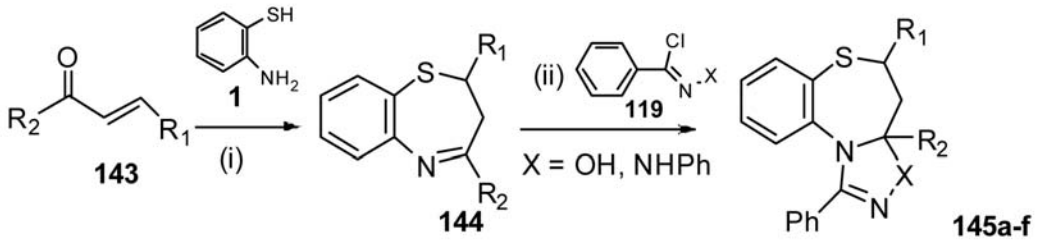
Scheme 38: Tricyclic 1,5-Benzothiazepines 142: (i) MeOH, AcOH (cat), reflux 8 h; (ii) DCM, Et_3N, r.t., 24 h.

(97)



Scheme 39: Tetrahydro-1,2,4-triazolo/oxadiazolo-benzothiazepine 145a–f: (i) EtOH, AcOH (cat), reflux 6 h; (ii) DCM, Et_3N, r.t., 48 h.

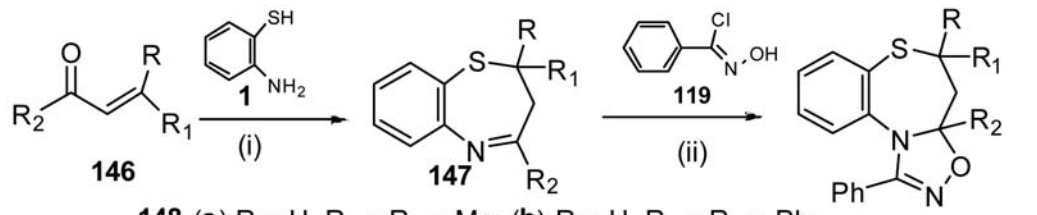
(98)



145 (**a**) $R_1 = R_2 = Ph$; (**b**) $R_1 = 2\text{-}ClC_6H_4$, $R_2 = Ph$; (**c**) $R_1 = 3\text{-}ClC_6H_4$, $R_2 = Ph$; (**d**) $R_1 = 4\text{-}ClC_6H_4$, $R_2 = Ph$; (**e**) $R_1 = R_2 = 2\text{-}MeC_6H_4$; (**f**) $R_1 = 2\text{-}BrC_6H_4$, $R_2 = Ph$

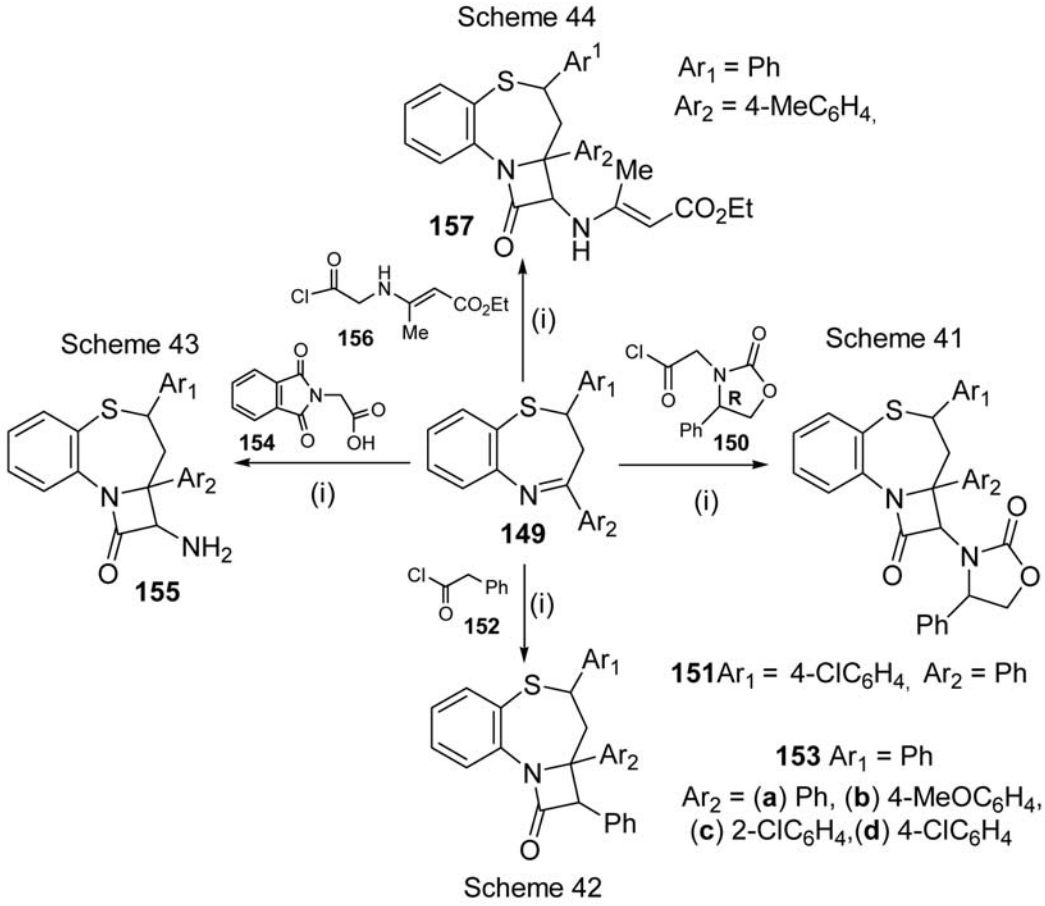
Scheme 40: Oxadiazolo-1,5-benzothiazepine 148a–d: (i) MeOH, AcOH (cat), reflux 12 h; (ii) DCM, Et_3N, r.t., 4 days.

(99)



148 (**a**) R = H, $R_1 = R_2 = Me$; (**b**) R = H, $R_1 = R_2 = Ph$; (**c**) $R = R_1 = R_2 = Me$; (**d**) R = Me, $R_1 = R_2 = Ph$

Table 6. Examples of 1,5-benzthiazepine derivatives prepared by cycloaddition reaction



Ref

(100)

Schme 41: (*N*-protected amino)-β-lactam-1,5-benzothiazepine derivatives 151: (i) DCM, Et_3N, 72 h, r.t. (101)

Scheme 42: α-Phenyl-β-lactam derivatives of 1,5-benzothiazepines 153a–d: (i) Benzene, Et_3N, 48 h, r.t. (102)

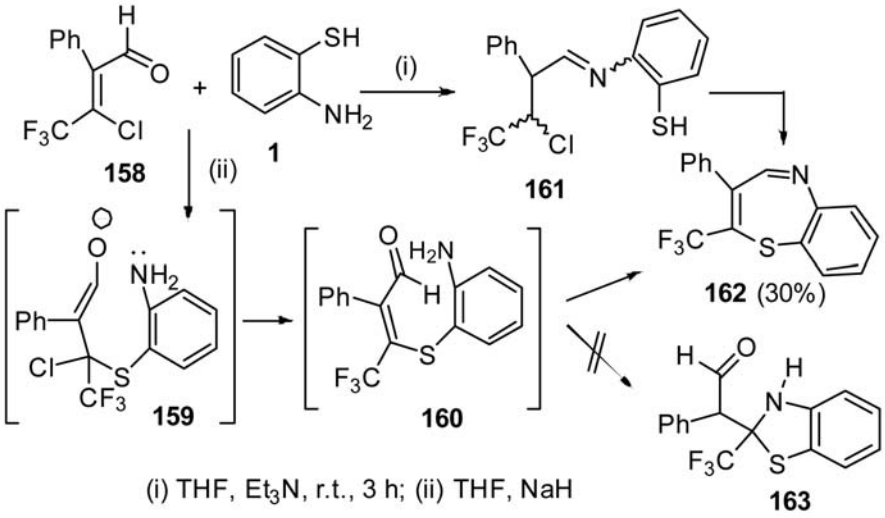
Scheme 43: α-amino-β-lactam derivatives of 1,5-benzothiazepines 155 a–l: (i) DCM, Et_3N, 72 h, r.t. (103)
155 (a) Ar_1= Ar_2 = Ph ; **(b)** Ar_1= Ph, Ar_2 = 4-MeC_6H_4; (c) Ar_1= Ph, Ar_2 = 4-EtC_6H_4;
(d) Ar_1= 4-ClC_6H_4, Ar_2 = Ph; (e) Ar1= 4-ClC_6H_4, Ar_2 = 4-MeC_6H_4;
(h) Ar_1= 2-ClC_6H_4, Ar_2 = 4-MeC_6H_4; (i) Ar_1= 2-ClC_6H_4, Ar_2 = 4-EtC_6H_4;
(j) Ar_1= 4-$MeOC_6H_4$, Ar_2 = Ph; (k) Ar_1 = 4-$MeOC_6H_4$, Ar_2 = 4-MeC_6H_4

Scheme 44: α-(*N*-protected amino)-β-lactam-1,5-benzothiazepines 157: (i) DCM, Et_3N, 72 h, r.t.

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

7. 1. Trifluorobenzothiazepines

β-Trifluoromethyl-β-chloroacroleins **158** on the reaction with *o*-aminothiophenol (**1**) in the presence of triethylamine and in THF at. r.t. for 3 h gave benzothiazepine **162** in 30% yield. In a basic medium, such as in the presence of sodium hydride, the tetrahedral intermediate **159** is probably formed.[108] The competition between the rate of intramolecular cyclization of the tetrahedral intermediate (**159→163**) and the elimination of the chloride anion (**159→160**) depends on the nucleophilicity of the amino group. Owing to the poor nucleophilicity of the amino group of **159**, the elimination of the chloride anion occurs, resulting in the formation of **162**



Scheme 45. Synthesis of trifluoro-1,5-benzothiazepine **162**.

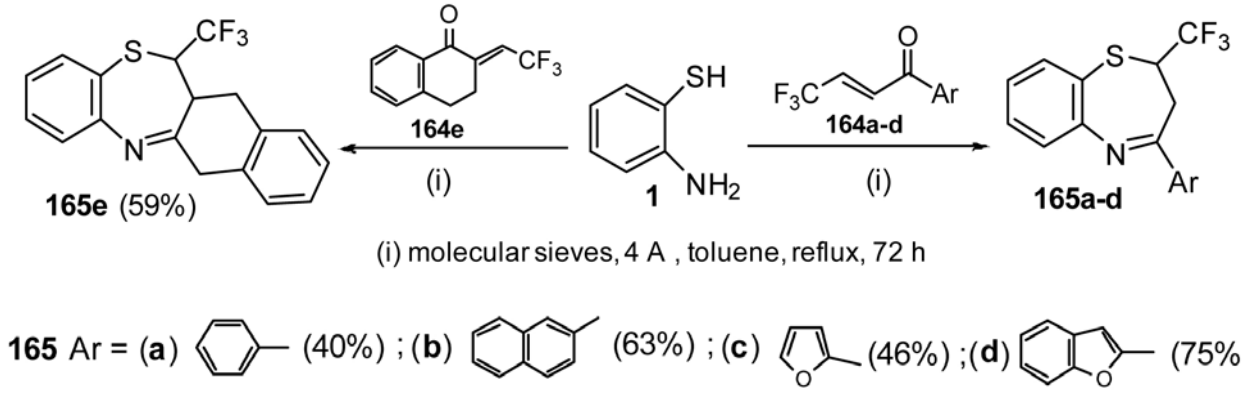
(**159**→**160**→**162**, yield 30%). The benzothiazepine **162** was also obtained by cyclization of the iminothiol **161** (Scheme 45).

7. 2. Trifluoromethylated Enones as Reactants

The reaction between β-trifluoromethylated enones **164a**–**e** and *o*-aminothiophenol (**1**) in toluene in the presence of molecular sieves under reflux conditions, gave the fluorinated 1,5-benzothiazepines **165a**–**e** in good yields.[104] The two steps required for the formation of the thiazepine ring are equilibrium between Michael / retro-Michael reaction and ketone / imine formation. Consequently, if **164** is electrophilic enough to react with **1**, these equilibrium should be simply displaced by favoring the formation of the imine. With this logic and reaction conditions the other 1,5-benzothiazepines were obtained with excellent yields (Scheme 46).

7. 3. Fluorinated Benzothiazepine Fused β-Lactam Derivatives

The reaction of 3/4/5-differently substituted *o*-aminothiophenols **1** and 3-(substituted benzoyl)-2-propionic acid **166** in the presence of Montmorillonite KSF under microwave irradiation gave 2-carboxy-2,3-dihydro-1,5-benzothiazepines **167a**–**i** in 70–82% yield. The reaction of 1,5-benzothiazepines **167** with chloroacetyl chloride in the presence of K_2CO_3 under microwave irradiation in the absence of any solvent gave the β-lactam derivatives, namely azeto[2,1-*d*][1,5] benzothiazepine derivatives **168a**–**i** in 75–85% yield.[110] Structures of all β-lactam fused benzothiazepine derivatives have been elucidated by elemental analyses and spectral data. The synthesized compounds were screened for antifungal activity against three pathogenic fungi, namely *Rhizoctonia solani* (causing root rot of okra), *Fusarium oxysporum* (causing wilt of mustard) and *Collectrotrichum caposici* (causing leaf spot and fruit rot of chili) using pot trial method.[111] In the pot trial experiments it was found that compounds having



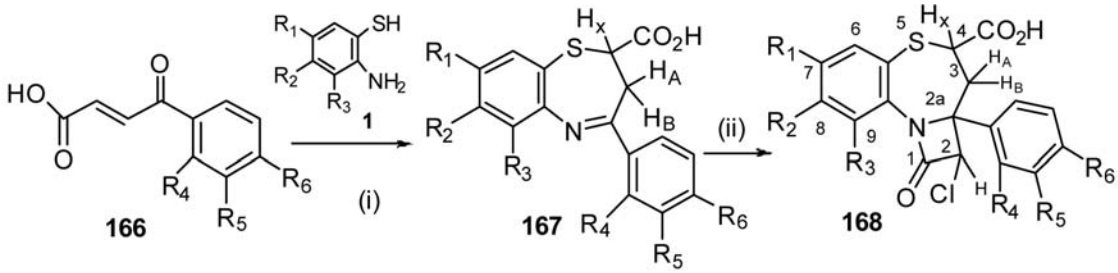
Scheme 46. Synthesis of aryl / heteroaryl trifluorobenzothiazepines **165a**–**d**.

alkoxy (OR) and trifluromethyl (CF_3) groups showed maximum germination (76–80%) indicating that it is the most effective in controlling the growth of the pathogen. "Baynate" and "Thiran", recommended as standard fungicides as seed dressers to control this disease are also having –N–C–S– linkage similar to the synthesized compounds (Scheme 47).

8. Miscellaneous 1,5-Benzothiazepines

8.1. Aryl-phenylindeno-benzothiazepines

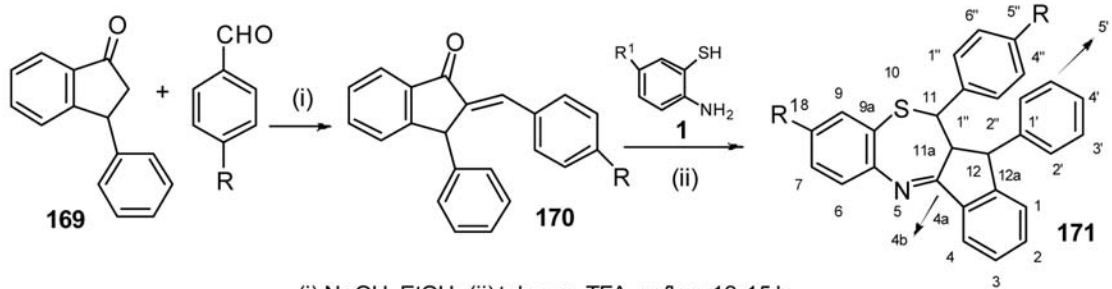
The condensation of 3-phenylindan-1-one (**169**) and the appropriate *p*-substituted benzaldehydes in NaOH / ethanol gave 2-(*E*)-benzylidene / *p*-substituted benzylidene-3-phenylindan-1-ones (**170**) in excellent yields.[112] Condensation of equimolar quantities of 2-(*E*)-benzylidene / *p*-substituted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



(i) Montmorrillonite KSF, Microwave irradiation (MWI); (ii) $ClCH_2COCl$, K_2CO_3, MWI

168	R_1	R_2	R_3	R_4	R_5	R_6	%Y
a	Me	H	H	H	H	F	78
b	F	H	H	H	H	F	80
c	MeO	H	H	H	H	F	83
d	EtO	H	H	Me	H	F	85
e	H	CF_3	H	H	Cl	H	75
f	H	H	Br	H	CF_3	H	80
g	CF_3	H	H	H	H	OH	84
h	H	H	CF_3	Me	H	F	85
i	H	Me	Me	H	CF_3	H	82

Scheme 47. Fluorinated benzothiazepine fused β-lactam derivatives **168a–i**.



(i) NaOH, EtOH; (ii) toluene, TFA, reflux, 12-15 h

171 (**a**) R = R^1 = H (70%); (**b**) R = H, R^1 = Me (72%); (**c**) R = R^1 = MeO (74%); (**d**) R = R^1 = Cl (78%); (**e**) R = Me, R^1 = MeO (78%); (**f**) R = Me, R^1 = Cl (82%); (**g**) R = MeO, R^1 = H (75%); (**h**) R = MeO, R^1 = Me (79%); (**i**) R = Cl, R^1 = H (81%); (**j**) R = Cl, R^1 = Me (82%); (**k**) R = Cl, R^1 = MeO (83%); (**l**) R = R^1 = Cl (82%)

Scheme 48. Synthesis of aryl-phenylindeno-benzothiazepines **171a–l**.

determined as described in the literature.[114] Penicillin and streptomycin were used as reference compounds and MIC were determined in terms of μmol / mL. The antimicrobial data indicated that compounds **171d–f, 171i–l** exhibited very promising antibacterial activity (Scheme 48).

8. 2. Acyl Benzothiazepines

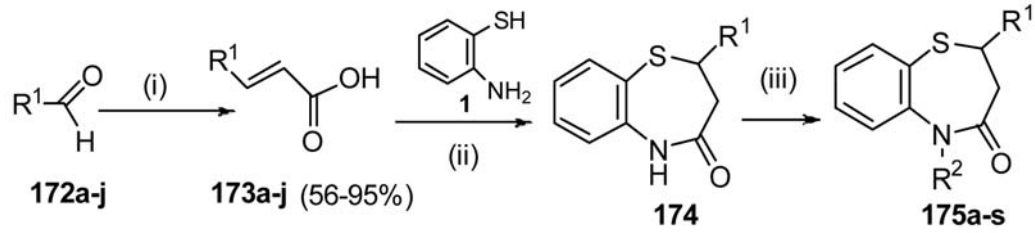
The Knoevenagel condensation of various aromatic aldehydes **172a–j** with propanedioic acid in the presence of pyridine and piperidine under reflux conditions gave the 3-substituted acrylic acids **173a–j** in 56–95% yield. The cyclization of the resulting acids **173a–j** with *o*-aminothiophenol (**1**) without any solvent at 180 °C for 6 h gave the key intermediates of 2,3-dihydro-1,5-benzothiazepine-4(5*H*)-one **174** analogs in moderate yields after recrystallization. The electrophilic substitution of alkyl or acyl halides in the presence of NaH at –10 °C for 30 min gave the *N*-alkyl, aromatic alkyl or acylbenzothiazepine analogs **175a–s** in 15–95% yield.[115] It is worth noting that the unfavorable attack of C-3 position could be avoided under this reaction conditions and as a result high yields of 80–95% were obtained[116] (Scheme 49).

8. 3. *trans*-7-Aryl-benzopyrano -benzothiazepines

Reaction of 4-chromanone **176** with various aromatic aldehydes **177a–i** in the presence of AcOH and HCl at 0 °C gave the *trans*-3-arylidenyl derivatives of chroman-4-ones in 80–96% yield. The absence of *cis*-3-arylindinyl compounds was ascertained by HPLC. The reaction of arylidenes **178a–i** and *o*-aminothiophenol (**1**) in 1:1 (v/v) solution of ethanol / toluene in the presence of a strong acid, such as TFA with conc. HCl for 2 h gave *trans*-7-aryl-6*H*-6a,7-dihydro[1]benzo-pyrano[3,4-*c*][1,5]benzothiazepines[117] (**181a–i**) in 87–97% yield. These reactions did not require the usual work up since the products **181a–i** precipitated from the reaction medium in pure state upon standing. The mechanism involves reaction of **178** with **1** by a Michael type addition to give the adduct **179**, which then undergoes an intramolecular nucleophilic addition of the amino group to the carbonyl moiety to give intermediate **180**. This intermediate then undergoes dehydration to give **181**. The structures of **181a–i** were confirmed by ^{1}H NMR, ^{13}C NMR spectroscopy and in the case of **181a** and **181g** by X-ray crystallography (Scheme 50).

8. 4. Benzopyrano-benzothiazepinones

3-Formylchromones **182**[118] reacted with *o*-aminothiophenol (**1**) in the presence of *p*-toluenesulfonic acid in benzene under reflux conditions for 30 min giving 5a,11-dihydro[1]benzopyrano[2,3-*b*][1,5]benzothiazepin-13-ones (**184a–c**) in 70–81% yield. Prolonged heating of the reaction mixture led to the dihydro products **184** being formed in admixture with the corresponding dehydrogenated compounds **185** reflecting the ease with which the more conjugated product is formed from the dihydro com-

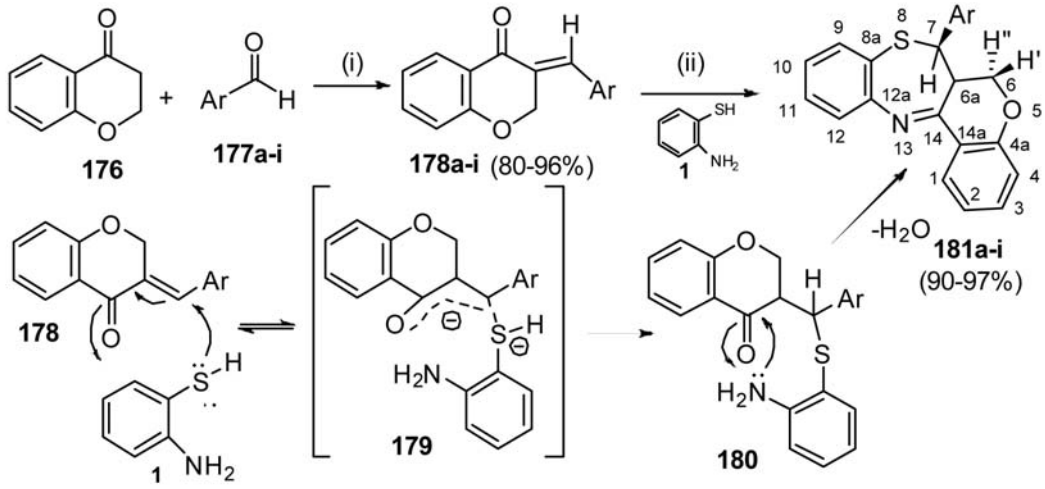


(i) $CH_2(CO_2H)_2$, pyridine, piperidine, 2 h, reflux; (ii) 4 A MS, 180 °C 6 h;
(iii) R^2X, X = Cl, Br, I / NaH, DMF, -10 °C, 30 min

175	R^1	R^2	% Y
a	2-thienyl	Et	65
b	2-thienyl	^{i}Pr	50
c	2-thienyl	^{n}Bu	62
d	2-thienyl	Bn	15
e	2-furyl	Bn	75
f	H	Bn	78
g	Me	Bn	79
h	3-pyridyl	Bn	60
i	Ph	Bn	89

175	R^1	R^2	% Y
j	Ph	2-NO_2-Bn	75
k	Ph	2-F-Bn	87
l	Ph	2-Cl-Bn	95
m	Ph	2-Br-Bn	62
n	Ph	2-Me-Bn	85
o	Ph	4-MeO-Bn	60
p	$PhCH_2$	2-NO_2-Bn	95
q	4-F-Ph	2-NO_2-Bn	91
r	4-Cl-Ph	2-NO_2-Bn	88
s	4-Br-Ph	2-NO_2-Bn	93

Scheme 49. Synthesis of acylbenzothiazepines **175a–s**.



(i) AcOH, HCl, 0 °C, 24 h; (ii) EtOH, toluene (1:1), conc. HCl, TFA, reflux, 2 h

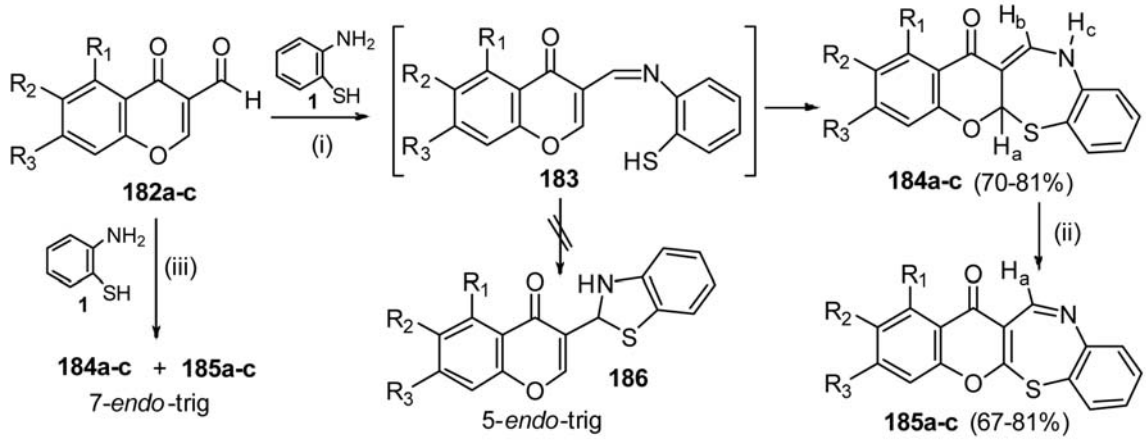
181 Ar = (**a**) Ph (97%); (**b**) 4-$MeOC_6H_4$ (92%); (**c**) 4-MeC_6H_4 (90%); (**d**) 2-thienyl (94%); (**e**) 4-ClC_6H_4 (87%); (**f**) 4-BrC_6H_4 (92%); (**g**) 2,5-$(MeO)_2C_6H_3$ (90%); (**h**) 2,3,4-$(MeO)_3C_6H_2$ (94%); (**i**) 3,4,5-$(MeO)_3C_6H_2$ (94%)

Scheme 50. Synthesis of *trans*-7-aryl-benzopyrano-benzothiazepines **181a–i**.

pounds **184a–c**.[119] The cyclization stage proceeds *via* an intramolecular 1,4-nucleophilic addition process which leads to the 7-membered **184** rather than the alternative 5-membered ring **186**. This conclusion is in agreement with the Baldwin prediction[30] that the 7-*endo-trig* process is favored whereas the 5-*endo-trig* is not. The dehydrogenation reaction of dihydro derivatives **184a–c** with chloroanil in xylene under reflux conditions gave the [1]benzopyrano[2,3-*b*][1,5] benzothiazepine-13-ones **185a–c** in high yields (Scheme 51).

8. 5. 4-Fluorophenyl-6-phenyl[1]benzopyrano [3,4-c][1,5]benzothiazepines

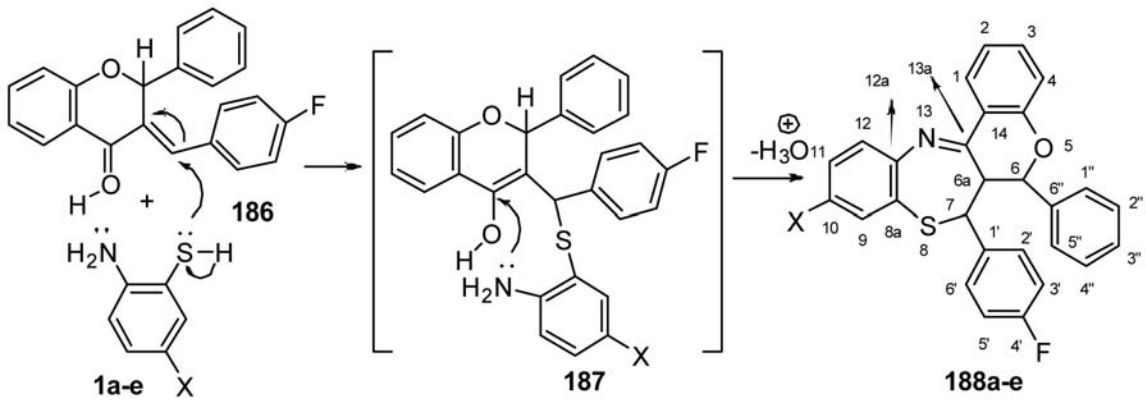
The condensation of 3-(4-fluorobenzylidene)-flavanone (**186**) (flavindogenide)[120] with 5-substi-tuted *o*-aminothiophenols **1a–e** in toluene in the presence of catalytic amount of TFA under reflux conditions gave a series of 10-substituted-6a,7-dihydro-6*H*-7-(4-fluorophenyl)-6-phenyl[1]benzopyrano[3,4-*c*][1,5] benzothiazepines **188a–e** in 58–68% yield.[121] The protonation of



(i) benzene, *p*-TsOH, reflux, 30 min; (ii) xylene, chloroanil, reflux, 15 h; (iii) benzene, *p*-TsOH, reflux, 30 h

184 / **185** (**a**) $R_1 = R_2 = R_3 = H$; (**b**) R_1 = Me, $R_2 = H$, R_3 = Me ; (**c**) $R_1 = H$, R_2 = Me, $R_3 = H$

Scheme 51. Synthesis of benzopyrano-benzothiazepinones **184**,**185a–c**.



Scheme 52. Synthesis of 4-fluorophenyl-6-phenyl1benzopyrano3,4-*c*1,5benzothiazepines **188a**–**e**.

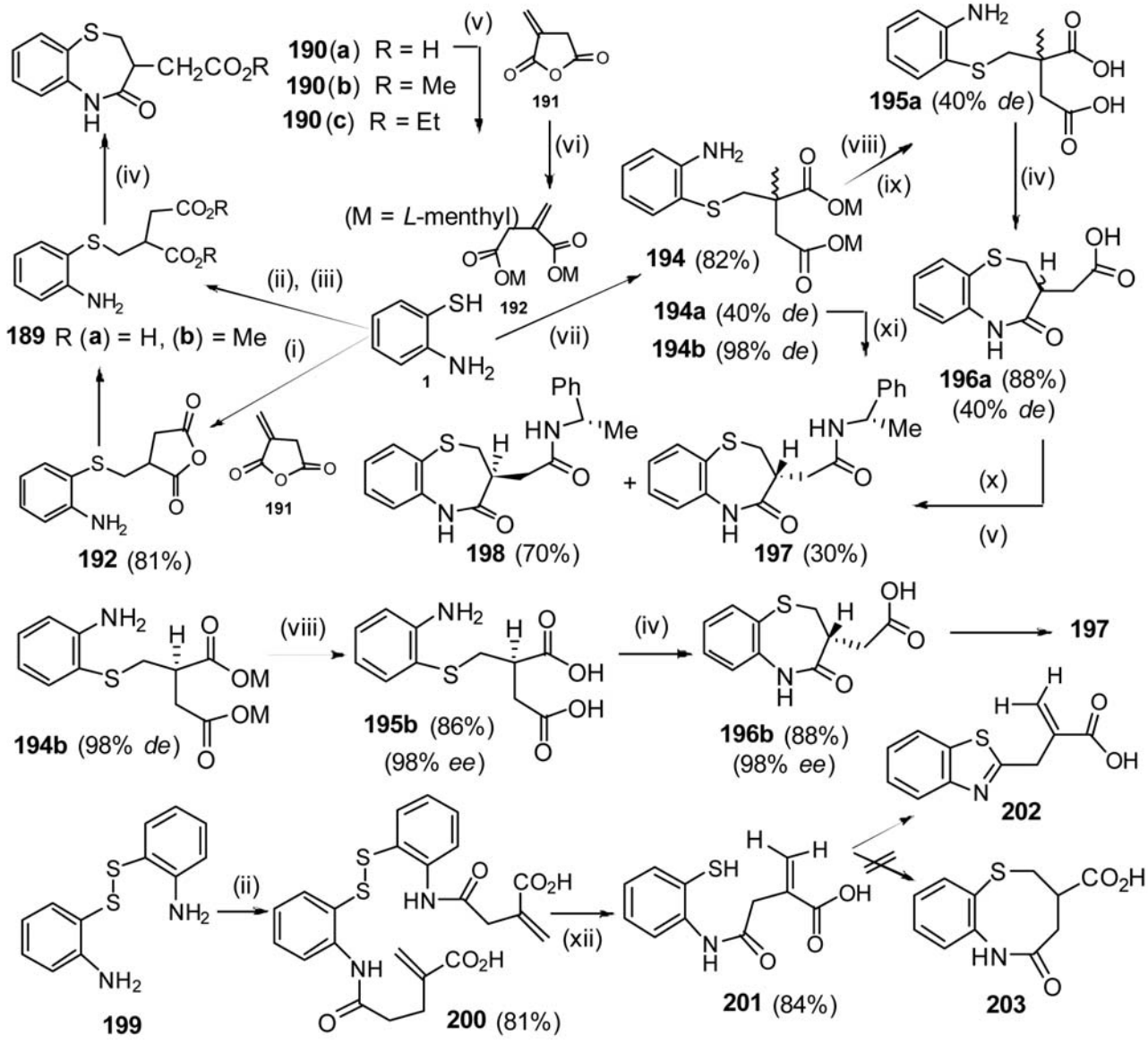
the carbonyl carbon in flavindogenide causes a drift of electrons from α,β-unsaturated carbon to the carbonyl carbon. As a result, vinyl carbon becomes poorer in electron density and is prone to a nucleophilic attack by sulfhydryl electrons. This results in the formation of an intermediate, which immediately further reacts with the amino group. The dehydrative cyclization accompanied by the elimination of a protonated water molecule results in the formation of –C=N– bond. All synthesized compounds were screened for their antimicrobial activity against the bacteria *E. coli* and *Alteromonas tetraodonis* (GFC) at the conc. of 100 μg / disc using the filter paper disc method[122] with bacitracin as the reference standard. The compounds **188a**,**b**,**f** showed higher relative activity (activity index = 1.14–1.28) against *E. coli,* whereas against GFC the compound **188f** was found to be of higher relative activity (activity index = 1.28) (Scheme 52).

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

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

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

The reaction of *o*-aminothiophenol disulfide (**199**) with 2.2 equiv. of itaconic anhydride (**191**) in THF at r.t. afforded the dicarboxylic acid **200** in 81% yield. The triphenyl phosphine induced reductive cleavage of the S–S bond in the diacid **200** formed the unisolable interme-



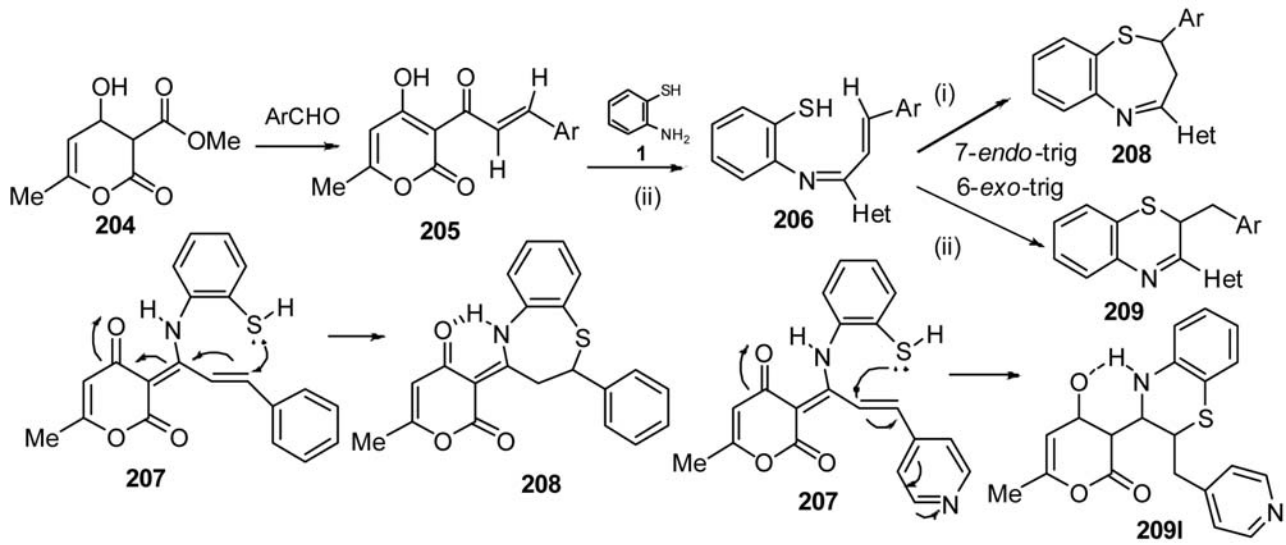
(i) THF, r.t., 12 h ; (ii) itaconic acid, THF, r.t., 36 h; (iii) dimethyl itaconate, THF, r.t, 24 h;
(iv) EDCI, DMAP (cat), THF, r.t.,4 h; (v) MeOH/EtOH, H^+, H_2SO_4, 50 °C, 2 h;
(vi) *L*-menthol *p*-TSA, toluene, reflux, 36 h; (vii) anhyd AcOH, r.t, 36 h; (viii) AcOH, HCl (3:1) reflux, 12 h;
(ix) 10 % aq.$NaHCO_3$, AcOH; (x) (R) -(+) 1-phenylethylamine,EDCI, THF, DMAP, 10 /11 3.7);
(xi) Three recrystallizations from petroleum ether; (xii) TPP, 1,4-dioxane, water, (4:1), HCl, r.t., 2 h

Scheme 53. Synthesis of enantiomerically pure 1,5-benzothiazepines **197**,**198**.

diary acid **201**, which by an *in situ* intramolecular dehydrative cyclization furnished the 2-benzothiazo-2-yl methyl acrylic acid (**202**) in 84% yield. The expected benzothiazocine **203** was not obtained, indicating the reluctance for the intramolecular Michael type addition of thiol in **201** to form the eight membered heterocycle (Scheme 53).

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

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



Method **A** = (i) piperidine(cat), EtOH, reflux, 15 min; **B** = (ii) piperidine (cat), EtOH, reflux, 2 h, AcOH, reflux, 2 h

1208/209	Ar	Method	% Y
1a	C_6H_5	A	85
1b	4-ClC_6H_4	A	83
1c	4-MeC_6H_4	A	84
1d	4-OHC_6H_4	A	79
1e	2-OHC_6H_4	A	82
1f	4-$MeOC_6H_4$	A	85
1g	4-$Me_2NC_6H_4$	A	86
1h	2-$NO_2C_6H_4$	A	76
1i	3-$NO_2C_6H_4$	A/B	75
1j	4-$NO_2C_6H_4$	A	78
1k	2-thienyl	A/B	81
5h	2-$NO_2C_6H_4$	B	83
5j	4-$NO_2C_6H_4$	B	81
5l	4-pyridyl	A/B	79

Scheme 54. Synthesis of 1,5-benzothiazepines and 1,4-benzothiazines **208**,**209**.

205 reacted with *o*-aminothiophenol (**1**) in EtOH / AcOH to afford dihydro-1,5-benzothiazepines **208** and/or dihydro-1,4-benzothiazines **209** in 76–86% yield.[125] Both kinds of molecules can be formed from the same kind of intermediate by a 7-*endo-trig* and 6-*exo-trig* mechanism. This is a formal representation and does imply whether the N–C or S–C bond is formed first. The formation of the seven membered ring in the case of a phenyl substituent and that of the six membered ring in the case of pyridine as an example of an electron withdrawing substituent that include *o*-nitro and *p*-nitrophenyl groups, is illustrated in **207**. In the case of pyridine, the protonation of the pyridine nitrogen should catalytically even increase its electron withdrawing properties. Thus, based on the structures of aldehydes or reaction conditions, the products **208**,**209** are formed (Scheme 54).

7. Conclusions

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

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Povzetek

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