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Synthesis of new biologically active compounds containing linked thiazolyl-thiazolidinone heterocycles

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Abstract: A new series of 1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one **5a-j** has been synthesized by the reaction of 2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one **4** with aryl aldehydes. Chemical structures of all the new compounds were established by IR, ^{1}H, ^{13}C NMR, MS and elemental data. The compounds **5a-j** were evaluated for their antibacterial activity against Gram-positive bacteria *viz*. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), *Staphylococcus aureus* (MTCC 96) and Gram-negative bacteria *viz*. *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39), *Chromobacterium violaceum* (MTCC 2656). Amongst them, compounds containing [(4-chlorophenyl)methylidene] moiety **5b**, [(3-nitrophenyl)methylidene] moiety **5d** and [(2-thienyl)methylidene] moiety **5j** showed significant antibacterial activity, almost equal/more than the activity of the standard drug Streptomycin. Further, the compounds **5a-j** were also screened for their antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996). Most of these new compounds showed appreciable activity against test bacteria and fungi and emerged as potential molecules for further development.

Keywords: Synthesis; thiazole; thiazolidin-4-one; antibacterial activity; antifungal activity.

1. Introduction

Heterocyclic compounds represent one of the most active classes of compounds possessing a wide spectrum of biological activities, including antibacterial, antifungal, and other biological activities.[1-6] Further, the treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity. Similarly in recent decades, an increased incidence of fungal infections has

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been observed as a consequence of the growing number of immunocompromised patients and the frequent use of antibacterial and cytotoxic drugs. For many fungal infections, polyenes, such as amphotericin B, represent the standard therapy. Polyenes bind to membrane sterols, leading to membrane permeability, leakage and cell death. However, the clinical use of amphotericin B is limited by a high frequency of renal toxicity, and several adverse effects.[7] Though the various molecules designed and synthesized for the above aim and to reduce the adverse effects, it was demonstrated that thiazoles and its derivatives offer several advantages in terms of decreased toxicity after oral or intravenous[8] administration and are often employed in the treatment of fungal infections, therefore the thiazoles and its derivatives could be considered as possible antimicrobial agents.[9]

Further, the thiazole nucleus appears frequently in the structure of various natural products and biologically active compounds, notably thiamine (vitamin-B), antibiotics such as penicillin, micrococcin[10], troglitazone[11] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)thiazole-4-carboxylic acids.[12] Similarly, there has been a considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities.[13] Thiazolidinone ring also occurs in nature; thus actithiazic acid isolated from *Streptomyces* strains exhibits highly specific *in vitro* activity against *Mycobacterium tuberculosis*[14]. Thiazolidinone derivatives are also known to exhibit diverse bioactivities such as anti-convulsant[15], antidiarrheal[16], anti-platelet activating factor[17], anti-histaminic[18], anti-diabetic[19], cyclooxy genase (COX) inhibitory[20], Ca^{2+}-channel blocker[21], platelet activating factor (PAF) antagonist[22], cardioprotective[23], anti-ischemic[24], anti-cancer[25], tumor necrosis factor-α antagonist[26] and nematicidal activities.[27] The synthesis of heterocycles containing multi-structure in a molecule has received much attention in recent years[28]. However, literature survey revealed that linked heterocycles containing thiazole and thiazolidinone have seldom been reported.

Based on the wide spectum of biological profile of thiazole and thiazolidin-4-one and their increasing importance in pharmaceutical, and biological field, and in continuation of our on going research on biologically active heterocycles,[29,30] it was thought of interest to accommodate thiazole and thiazolidin-4-one moieties in a single molecular frame work to synthesize some new heterocyclic compounds with potential biological activity.

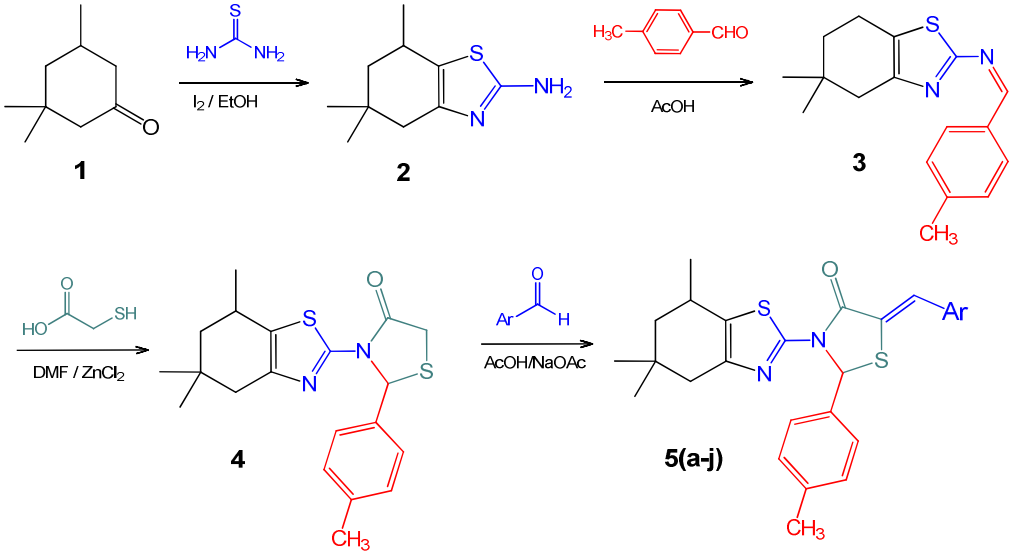
The present investigation deals with the synthesis of some new 1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one **5a-j** in good yields, from 2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one **4**. The antibacterial and antifungal activities of the compounds **5a-j** have also been evaluated.

2. Results and Discussion

Cyclocondensation of compound **1** with thiaourea in the presence of iodine in ethanol at reflux for 6 h, gave 5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine **2** in 62% yield.[31] Further, condensation of compound **2** with p-methylbenzaldehyde in acetic acid at reflux for 3 h, afforded *N*-[(*E*)-1-(4-methylphenyl)methyldene]-*N*-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)amine **3** in 64% yield. The one-pot synthesis of 2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one **4** was carried out by the condensation-cyclization reaction between compound **3** and mercaptoacetic acid in the presence of $ZnCl_2$ in dimethylformamide solvent under reflux for 6 h. Further, compounds **4** on condensation with aromatic aldehydes in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature for gave 1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one **5a-j** in 62-72% yields (**Scheme 1**). The versatility of the reaction is well demonstrated by the fact that a variety of aromatic aldehydes with electron-releasing and electron-withdrawing substituents afforded their corresponding compounds **5a-j** in good yields. The structures of all the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and MS spectral data.

In the IR spectra of compounds **5a–j**, the amide carbonyl (C=O) and conjugated double bond (C=C) absorption bands were observed at 1698 and 1614 cm^{-1} respectively, confirm the condensation involving the methylene group and the aldehyde system. Further, support was obtained from the ^{1}H NMR spectra, the disappearence of the signal corresponding to the CH2-S protons at 3.71 ppm indicated the condensation with carbonyl group. The N–CH–S proton of thiazolidin-4-one ring

appeared at 6.62 ppm, the other aromatic and aliphatic protons appeared at the expected regiod. In the ^{13}C NMR spectra, the prominent signals corresponding to the carbons of thiazolidin-4-one ring in all the compounds observed nearly at 161.0, 141.3 and 71.8 ppm, are proof of further evidence of their structures. In summary, all the synthesized compounds exhibited satisfactory spectral data consistent with their structures.



5: Ar = (**a**) 4-CH_3-C_6H_4; (**b**) 4-Cl-C_6H_4; (**c**) 4-NO_2-C_6H_4; (**d**) 3-NO_2-C_6H_4; (**e**) 4-OH-C_6H_4; (**f**) 2-OH-C_6H_4; (**g**) 4-$(CH_3)_2$N-C_6H_4 ; (**h**) 4-(OH)-3-CH_3O)-C_6H_3; (**i**) 2-furyl; (**j**) 2-thienyl

Scheme 1. Synthetic pathways for compounds **5a-j**

2.1. Antibacterial Activity

All the compounds **6a-j** were assayed for their antibacterial activity against three representative Gram-positive bacteria *viz*. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), *Staphylococcus aureus* (MTCC 96) and Gram-negative bacteria *viz*. *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39), *Chromobacterium violaceum* (MTCC 2656) by disc diffusion method,[32] and the mean inhibition zone data are reported in **Table 1**. All assays included the solvent and reference controls. Streptomycin was used as standard drug.

The investigation of antibacterial screening data reveal that almost all the compounds **5a-j** are active and showing moderate to good antibacterial activity. Amongst them, compounds containing [(4-chlorophenyl)methylidene] moiety **5b**, [(3-nitrophenyl)methylidene] moiety **5d** and [(2-thienyl) methylidene] moiety **5j** showed significant antibacterial activity, almost equal/more than the activity of the standard drug Streptomycin. Further, compounds **5b**, **5d** and **5j** were active against *P. aeruginosa*, compounds **5b**, **5j** were active against *C. violaceum* (**Table 1** and **2**). The remaining compounds showed moderate to good activity.

2.2. Antifungal Activity

The compounds **5a-j** were also screened for their antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996) in dimethyl sulfoxide (DMSO) by disc difusion method.[32] Amphotericin B was used as a standard drug and the mean inhibition zone (MZI) data were measured and compared with controls, the MZI values of the compounds screened are given in **Table 2**.

The antifungal screening data showed appreciable activity of the test compounds. Among the screened compounds, compound **5b** is highly active against *T. rubrum* and *T. mentagrophytes*, compound **5d** is also active against *C. albicans* and compound **5j** is highly active against *C. albicans* and *T. mentagrophytes*, the activity of these compounds are almost equal to the standard. It is

interesting to note that the compounds **5d** and **5j** showed good antifungal activity towards *C. albicans* which is more than the activity of standard drug.

Table 1. Antibacterial Activity of Compounds **5a-j**

Compound	Mean zone inhibition (MZI)[a] in 100 μg/mL					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
6a	19	15	29	15	20	17
6b	29	20	28	17	24	21
6c	16	18	24	12	17	17
6d	31	24	31	16	25	19
6e	15	18	20	12	22	17
6f	25	12	21	10	22	11
6g	18	16	11	14	19	19
6h	20	20	26	16	24	21
6i	22	23	19	12	22	16
6j	27	25	28	20	22	21
Streptomycin	30	20	31	15	25	20

[a]Values are mean (n = 3).

Table 2. Antifungal Activity of Compounds **5a-j**

Compound	Mean zone inhibition (MZI)[a] in 100 μg/mL			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagropytes*
5a	16	18	12	19
5b	24	22	17	23
5c	16	20	18	18
5d	21	25	18	23
5e	14	20	17	20
5f	12	19	13	19
5g	13	13	16	20
5h	20	22	17	12
5i	14	14	18	20
5j	24	24	22	22
Amphotericin B	22	25	20	22

[a]Values are mean (n = 3).

3. Conclusions

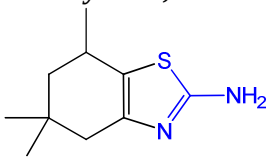
A new series of 1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one **5a-j** has been synthesized and evaluated for their antimicrobial activity against Gram-positive, Gram-negative bacterial and fungi. Most of the compounds showed a moderate degree of antimicrobial activity. Amongst them, compounds containing [(4-chlorophenyl)methylidene] moiety **5b**, [(3-nitrophenyl)methylidene] moiety **5d** and [(2-thienyl) methylidene] moiety **5j** showed significant antibacterial activity, almost equal/more than the activity of the standard drug streptomycin. Further, these compounds showed appreciable activity against the test fungi, and emerged as potential molecules for further development.

4. Experimental

Reagents were of commercial grade and were used as supplied or were prepared according to procedures described in literature. Reactions were monitored by thin-layer chromatography (TLC) on

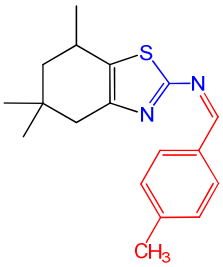
pre-coated silica gel F_{254} plates from Merck, and compounds visualized either by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR, ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, N) determined by means of a Perkin–Elmer 240 CHN elemental analyzer, were within ± 0.4% of theory.

4.1. Synthesis of 5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine (2):



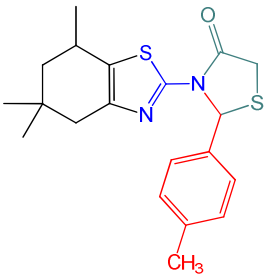
To a solution of compound **1** (1.4g, 0.01 mol) in ethanol (10 mL), thiourea (1.52g, 0.02 mol) and iodine (2.54 g, 0.01 mol) were added and the reaction mixture was heated under reflux for 6 hrs. The reaction mixture was then cooled to 20 ^{o}C and quenched in water (50 mL). The quenched mass was basified with liquor ammonia solution and extracted with ethyl acetate (100 mL). The ethyl acetate extract was then concentrated and the crude residue was purified by column chromatography using chloroform as eluent and silicagel (70-230 mesh) as solid phase. The pure fraction on concentration gave the pure compound **2** in 62% of yield, Pale white solid m.p. 55-57 ^{o}C; IR (KBr): *v* 3480-3275, 2953, 2877, 1562, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 0.94 (s, 6H, CH_3), 1.27-1.29 (d, *J* = 6.7 Hz, 3H, CH_3), 1.30-1.40 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.07 (s, 2H, CH_2), 2.41-2.45 (m, 1H, CH), 4.96 (bs, 2H, NH_2); ^{13}C NMR ($CDCl_3$): *δ* 21.7, 28.5 (2 x CH_3), 31.3, 36.4, 47.0, 47.7, 128.6, 139.4, 156.5; MS: *m/z* (%) 197 (M^{+}+1, 33), 180 (100), 166 (47). *Anal. Calcd*. for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.21; N, 14.27. Found: C, 61.14; H, 8.22; N, 14.20.

4.2. Synthesis of *N*-[(*E*)-1-(4-methyl*phenyl)methyldene]-N-(5,5,7-trimethyl-4,5,6,7-tetrahydro- 1,3-benzothiazol-2-yl)amine (3):



A mixture of compound **3** (1.96 g, 0.01 mol), 4-methylbenzaldehyde (1.2 mL, 0.01 mol) and acetic acid (0.5 mL) was refluxed in toluene for 3 h using a Dean-stark apparatus and the water formed was removed azeiotropically. The progress of the reaction was checked by TLC using toluene: ethyl acetate (4:1) as an eluent. After completion of the reaction, solvent was removed by distillation to give solid, which was filtered, and recrystallized from ethyl alcohol to give pure compound 4 in 64% of yield, Dark yellow solid m.p. 136-138 ^{o}C; IR (KBr): *v* 3052, 2988, 1625, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6): *δ* 0.94 (s, 6H, CH_3), 1.27-1.30 (d, *J* = 6.7 Hz, 3H, CH_3), 1.40-1.45 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.08 (s, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.24-2.30 (m, 1H, CH), 7.00 (d, *J* = 7.2 Hz, 2H, ArH), 7.50 (d, *J* = 7.2 Hz, 2H, ArH), 8.20 (s, 1H, CH=N); ^{13}C NMR (DMSO-d_6): *δ* 19.0, 22.4, 26.4, 26.9 (2 x CH_3), 36.2, 43.8, 47.8, 122.4, 128.3 (2 x CHAr), 129.0 (2 x CHAr), 136.7, 140.6, 141.1, 160.0, 162.5; MS: *m/z* (%) 298 (M^{+}, 71), 195 (23), 180 (100), 104 (63). *Anal. Calcd* for $C_{18}H_{22}N_2S$: C, 72.44; H, 7.43; N, 9.39. Found: C, 72.40; H, 7.39; N, 9.32.

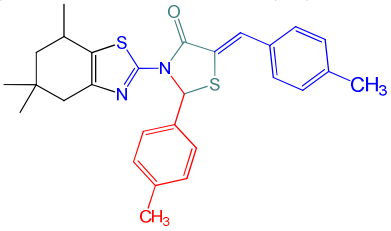
4.3. Synthesis of 2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol- 2-yl)-1,3-thiazolan-4-one (4):



A mixture of compound **3** (2.98g, 0.01 mol), thioglycolic acid (2.5 mL, 0.022 mol) in *N*, *N*-dimethylformamide (20 mL) with a pinch of anhydrous $ZnCl_2$, was refluxed for 6 h, the progress of the reaction was checked by TLC using toluene: ether (3:1) as an eluent. The reaction mixture was cooled to room temperature and then poured into crussed ice. It was set-aside at room temperature overnight. The solid thus separated was filtered, washed several times with water, and purified by column chromatography on silica-gel with hexane-ethyl acetate as eluent to afford pure compound 5 in 62% yield; Brown solid m.p. 147-149 ^{o}C; IR (KBr): *v* 3062, 1698, 1612, 1604, 1475 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.94 (s, 6H, CH_3), 1.27-1.30 (d, *J* = 6.6 Hz, 3H, CH_3), 1.40-1.45 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.20 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.50-2.55 (m, 1H, CH), 3.71 (s, 2H, CH_2-S), 5.90 (s, 1H, CH-S), 7.10-7.20 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6): δ 19.2, 22.7 (2x CH_3), 27.8, 28.1, 34.7, 35.2, 42.3, 45.8, 73.1, 125.1, 126.4 (2 x CHAr), 127.6 (2 x CHAr), 133.4, 134.6, 139.0, 146.8, 173.4; MS: *m/z* (%) 372 (M^+, 100), 281 (46), 331 (17), 180 (28). *Anal. Calcd* for $C_{20}H_{24}N_2OS_2$: C, 64.48; H, 6.49; N, 7.52. Found: C, 62.42; H, 6.43; N, 7.50.

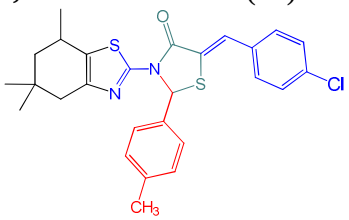
4.4. General procedure for the synthesis of 1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (5a-j): A mixture of compound **4** (3.72g, 0.01 mol), corresposnding aldehyde (0.01 mol) and sodium acetate (0.02 mol) in anhydrous glacial acetic acid (10 mL), was refluxed for 6 h. The reaction mixture was concentrated and then poured into ice cold water, the solid thus separated, was filtered, washed with water, the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to afford pure compounds **5a-j**in 68-74% yields. All the products were characterized by IR, ^{1}H, ^{13}C NMR, MS and elemental analyses.

4.4.1. 2-(4-methylphenyl)-5-[(*Z*)-1-(4-methylphenyl)methylidene]-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (5a):



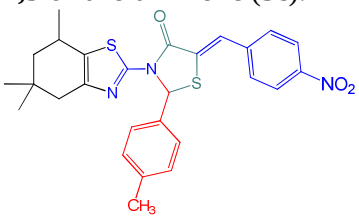
Yield 62%, Yellow solid, m.p. 156-158 ^{o}C; IR (KBr): *v* 3067, 2974, 1698, 1614, 1604, 1477 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ0.94 (s, 6H, CH_3), 1.20-1.25 (d, *J* = 6.7 Hz, 3H, CH_3), 1.52-1.55 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.60-2.65 (m, 1H, CH), 6.62 (s, 1H, CH-S), 7.10-7.30 (m, 6H, ArH), 7.52 (d, *J* = 7.6 Hz, 2H, ArH), 7.70 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 23.2, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 126.3 (2 x CHAr), 127.0, 128.9, 129.0 (2 x CHAr), 129.7, 130.4 (2 x CHAr), 131.6 (2 x CHAr), 133.8, 136.5, 136.9, 138.5, 141.3, 142.0, 161.0; MS: *m/z* (%) 474 (M^+, 72), 383 (17), 330 (100), 182 (82). *Anal. Calcd* for $C_{28}H_{30}N_2OS_2$: C, 70.85; H, 6.37; N, 5.90. Found: C, 70.82; H, 6.32; N, 5.84.

4.4.2. 5-[(*Z*)-1-(4-chlorophenyl)methylidene]-2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (5b):



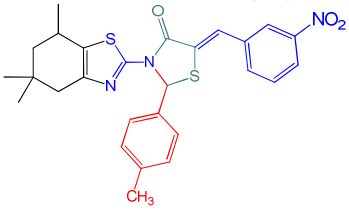
Yield 67%, Yellow solid m.p. 167-169 ^{o}C; IR (KBr): *v* 3062, 2965, 1698, 1617, 1477, 687 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.93 (s, 6H, CH_3), 1.20-1.25 (d, J = 6.7 Hz, 3H, CH_3), 1.52-1.55 (quasi d, J = 4.6 Hz, 2H, CH_2), 2.07 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.62-2.65 (m, 1H, CH), 6.68 (s, 1H, CH-S), 7.20 (d, J = 7.8 Hz, 2H, ArH), 7.55-7.60 (m, 6H, ArH), 7.80 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 126.3 (2 x CHAr), 127.0, 127.6, 128.9 (2 x CHAr), 129.1, 130.3 (2 x CHAr), 132.8 (2 x CHAr), 133.8, 134.3, 136.5, 138.5, 141.3, 142.0, 161.0; MS: *m/z* 495 (M^+). *Anal. Calcd* for $C_{27}H_{27}ClN_2OS_2$: C, 65.50; H, 5.50; N, 5.66. Found: C, 65.44; H, 5.48; N, 5.60.

4.4.3. 2-(4-methylphenyl)-5-[(*Z*)-1-(4-nitrophenyl)methylidene]-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (5c):



Yield 70%, Brown solid m.p. 192-194 ^{o}C; IR (KBr): *v* 3067, 2962, 1699, 1612, 1542, 1477, 1371 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.92 (s, 6H, CH_3), 1.21-1.25 (d, J = 6.7 Hz, 3H, CH_3), 1.54-1.57 (quasi d, J = 4.6 Hz, 2H, CH_2), 2.10 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.61-2.66 (m, 1H, CH), 6.62 (s, 1H, CH-S), 7.10-7.20 (m, 6H, ArH), 7.72 (s, 1H, CH=C), 8.12 (d, J = 8.3 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 125.6, 126.3 (2 x CHAr), 127.0, 128.9 (2 x CHAr), 130.1, 130.9 (2 x CHAr), 133.8 (2 x CHAr), 136.5, 138.5, 141.3, 142.0, 142.8, 146.8, 161.0; MS: *m/z* 505 (M^+). *Anal. Calcd* for $C_{27}H_{27}N_3O_3S_2$: C, 64.14; H, 5.38; N, 8.31. Found: C, 64.11; H, 5.32; N, 8.28.

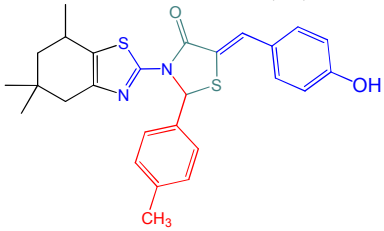
4.4.4. 2-(4-methylphenyl)-5-[(*Z*)-1-(3-nitrophenyl)methylidene]-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (5d):



Yield 66%, Pale brown solid m.p. 183-185 ^{o}C; IR (KBr): *v* 3069, 2972, 1694, 1614, 1541, 1477, 1374 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.96 (s, 6H, CH_3), 1.20-1.25 (d, J = 6.7 Hz, 3H, CH_3), 1.54-1.56 (quasi d, J = 4.6 Hz, 2H, CH_2), 2.10 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.60-2.65 (m, 1H, CH), 6.62 (s, 1H, CH-S), 7.10-7.20 (m, 4H, ArH), 7.80-7.90 (m, 4H, ArH), 8.26 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 121.8, 126.3 (2 x CHAr), 126.7, 127.0 (2 x CHAr), 128.9 , 131.3, 132.1, 133.8, 135.1, 135.8, 136.5, 138.5, 141.3, 142.0, 152.4, 161.0; MS: *m/z*

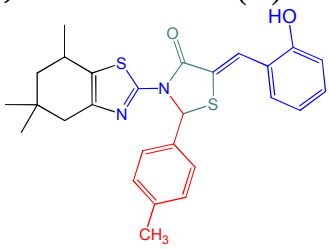
505 (M^+). *Anal. Calcd* for $C_{27}H_{27}N_3O_3S_2$: C, 64.14; H, 5.38; N, 8.31. Found: C, 64.12; H, 5.34; N, 8.26.

4.4.5. 5-[(*Z*)-1-(4-hydroxyphenyl)methylidene]-2-(4-methylphenyl)-3-(5,5,7-trimethyl-4, 5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (**5e**):



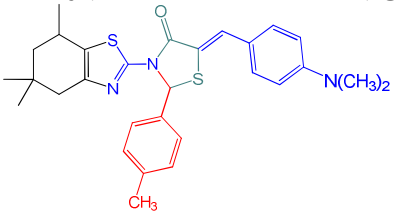
Yield 67%, Pale yellow solid m.p. 163-164 ^oC; IR (KBr): *v* 3342-3210, 3071, 2975, 1695, 1616, 1478 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.94 (s, 6H, CH_3), 1.19-.122 (d, *J* = 6.7 Hz, 3H, CH_3), 1.52-1.55 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.60-2.65 (m, 1H, CH), 5.24 (s, 1H, OH), 6.62 (s, 1H, CH-S), 6.91 (d, *J* = 7.8 Hz, 2H, ArH), 7.10-7.20 (m, 6H, ArH), 7.72 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 115.4, 126.3 (2 x CHAr), 126.9, 127.0, 128.7 (2 x CHAr), 128.9, 132.3 (2 x CHAr), 133.8 (2 x CHAr), 136.5, 138.5, 141.3, 142.0, 157.6, 161.0; MS: *m/z* 476 (M^+). *Anal. Calcd* for $C_{27}H_{28}N_2O_2S_2$: C, 68.04; H, 5.92; N, 5.88. Found: C, 68.00; H, 5.87; N, 5.81.

4.4.6. 5-[(*Z*)-1-(2-hydroxyphenyl)methylidene]-2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5, 6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (**5f**):



Yield 66%, Pink solid m.p. 171-173 ^oC; IR (KBr): *v* 3345-3250, 3077, 2972, 1699, 1612, 1479 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.96 (s, 6H, CH_3), 1.20-1.25 (d, *J* = 6.7 Hz, 3H, CH_3), 1.55-1.60 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.11 (s, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.61-2.64 (m, 1H, CH), 4.60 (s, 1H, OH), 6.62 (s, 1H, CH-S), 7.10-7.20 (m, 8H, ArH), 7.80 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 116.4, 118.7, 122.9, 126.3 (2 x CHAr), 127.0, 128.9 (2 x CHAr), 130.4, 130.9, 131.4, 133.8, 136.5, 138.5, 141.3, 142.0, 156.8, 161.0; MS: *m/z* 476 (M^+). *Anal. Calcd* for $C_{27}H_{28}N_2O_2S_2$: C, 68.04; H, 5.92; N, 5.88. Found: C, 68.02; H, 5.88; N, 5.84.

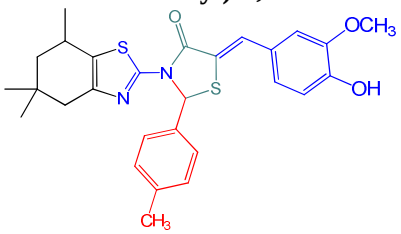
4.4.7. 5-(*Z*)-1-[4-(dimethylamino)phenyl]methylidene-2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (**5g**):



Yield 64%, Pale red solid m.p. 184-186 ^oC; IR (KBr): *v* 3068, 2978, 1698, 1616, 1478 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.91 (s, 6H, CH_3), 1.22-1.25 (d, *J* = 6.7 Hz, 3H, CH_3), 1.52-1.55 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.60-2.65 (m, 1H, CH), 2.98 (s, 6H, N-CH_3), 6.62 (s, 1H, CH-S), 6.70-6.80 (m, 4H, ArH), 7.10-7.20 (m, 4H, ArH), 7.69 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7 (2 x CH_3), 38.4, 42.1, 45.7, 71.8, 114.5, 120.4, 126.3 (2 x CHAr), 127.0, 128.3 (2 x CHAr), 128.9, 132.1 (2 x CHAr), 133.8 (2 x CHAr), 136.5, 138.5, 141.3,

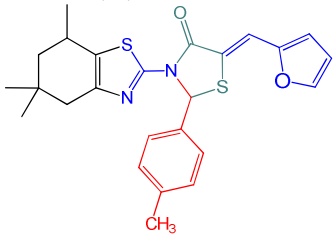
142.0, 151.7, 161.0; MS: *m/z* 504 (M^+ + 1). *Anal. Calcd* for $C_{29}H_{33}N_3OS_2$: C, 69.15; H, 6.60; N, 8.34. Found: C, 69.12; H, 6.58; N, 8.30.

4.4.8. 5-[(*Z*)-1-(4-hydroxy-3-methoxyphenyl)methylidene]-2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (**5h**):



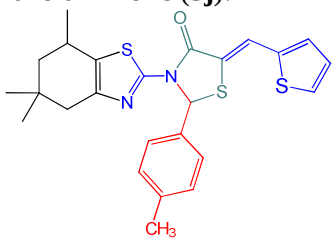
Yield 69%, Orange solid m.p. 155-157 ^oC; IR (KBr): *v* 3340-3250, 3070, 2978, 1698, 1616, 1478, 1270 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.94 (s, 6H, CH_3), 1.19-1.22 (d, *J* = 6.7 Hz, 3H, CH_3), 1.52-1.55 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.60-2.65 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 5.21 (s, 1H, OH), 6.62 (s, 1H, CH-S), 6.70-6.80 (m, 4H, ArH), 7.10-7.20 (m, 4H, ArH), 7.63 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 57.3, 71.8, 114.2, 115.7, 126.3 (2 x CHAr), 127.0, 127.3, 127.6, 128.9 (2 x CHAr), 132.3, 133.8, 136.5, 138.5, 141.3, 142.0, 147.3, 148.1, 161.0; MS: *m/z* 506 (M^+). *Anal. Calcd* for $C_{28}H_{30}N_2O_3S_2$: C, 66.38; H, 5.97; N, 5.53. Found: C, 66.32; H, 5.94; N, 5.49.

4.4.9. 5-[(*Z*)-1-(2-furyl)methylidene]-2-(4-methylphenyl)-3-(5,5,7-trimethyl-4,5,6,7-tetra- hydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (**5i**):



Yield 71%, Black solid m.p. 172-174 ^oC; IR (KBr): *v* 3068, 2978, 1698, 1616, 1478, 1030 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.94 (s, 6H, CH_3), 1.19 -1.22 (d, *J* = 6.7 Hz, 3H, CH_3), 1.52-1.55 (quasi d, *J* = 4.6 Hz, 2H, CH_2), 2.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.60-2.65 (m, 1H, CH), 6.10-6.20 (m, 2H, ArH), 6.62 (s, 1H, CH-S), 7.10-7.20 (m, 5H, ArH), 7.90 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 110.2, 121.4, 126.3 (2 x CHAr), 127.0 , 128.9(2 x CHAr), 133.8, 136.5, 136.9, 138.5, 141.3, 142.0, 146.7, 153.4, 161.0; MS: *m/z* 450 (M^+). *Anal. Calcd* for $C_{25}H_{26}N_2O_2S_2$: C, 66.64; H, 5.82; N, 6.22. Found: C, 66.61; H, 5.80; N, 6.14.

4.4.10. 2-(4-methylphenyl)-5-[(*Z*)-1-(2-thienyl)methylidene]-3-(5,5,7-trimethyl-4,5,6,7-tetra-hydro-1,3-benzothiazol-2-yl)-1,3-thiazolan-4-one (**5j**):



Yield 72%, Black solid m.p. 159-161 ^oC; IR (KBr): *v* 3062, 2946, 1694, 1612, 1479, 957 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.94 (s, 6H, CH_3), 1.19-1.22 (d, *J* = 6.7 Hz, 3H, CH_3), 1.52-1.55 (quasi d, *J* = 4.6 Hz, CH_2), 2.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.60-2.65 (m, 1H, CH), 6.60-6.70 (m, 3H, ArH, CH-S), 7.10-7.20 (m, 5H, ArH), 7.91 (s, 1H, CH=C); ^{13}C NMR (DMSO-d_6): δ 18.5, 22.7, 26.8, 29.1 (2 x CH_3), 36.7, 42.1, 45.7, 71.8, 123.0, 126.3 (2 x CHAr), 127.0, 128.0, 128.9 (2 x CHAr), 129.5, 133.8, 136.5, 138.5, 141.3, 142.0, 142.8, 150.6, 161.0; MS: *m/z* 466 (M^+). *Anal. Calcd* for $C_{25}H_{26}N_2OS_3$: C, 64.34; H, 5.62; N, 6.00. Found: C, 64.30; H, 5.58; N, 5.95.

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