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Synthesis and biological activity of novel 3-(4-methylthio benzene sulfonyl)-2,4-dimethyl/2,4-diphenyl/4-methyl-2-phenyl/2-ethoxy-4-methyl/ 2, 4-diethoxy–1,5-benzothiazepines

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Abstract: An efficient synthesis of novel 2,3,4-trisubstituted 1,5-benzothiazepines **5a-e** incorporating sulfonyl group is described. Compounds **5a-e** were synthesized by the reaction of 3-(4-methylthio benzene sulfonyl)-2,4-dimethyl/2,4-diphenyl/4-methyl-2-phenyl/2-ethoxy-4-methyl/2,4-diethoxy propane-1,3-dione **4a-e** with 2-aminobenzenethiol in acidic condition. Formation of compounds **4a-e** were achieved by the reaction of 4-methylthio benzene sulfonyl chloride (**2**) with 2,4-dimethyl/2,4-diphenyl/4-methyl-2-phenyl/2-ethoxy-4-methyl /2,4-diethoxy propane-1,3-dione **3a-e**. The structure of the compounds has been established by elemental, IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analyses. The *in vitro* antibacterial and antifungal activities of the synthesized substituted 1,5-benzothiazepines were investigated against two bacterial strains, viz. *Staphylococcus aureus* and *Klebsiella pneumonie* and two fungal strains, viz. *Aspergillus niger* and *Candida albicans*. The compound 5c was found to more active against all tested microorganisms.

Keywords: Propane-1,3-dione; Substituted benzothiazepine; Sulfonyl compound; Biological activity.

Introduction

Heterocyclic compounds are having profound impact on our modern world coupled with its future. Indeed, the coverage of heterocyclic compounds is vast and constitute important domain for the society viz. energy, environment, biology, medicine, agribusiness and materials. Benzothiazepines have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals [1]. The superiority of *diltiazem* over other conventional vasodilators has resulted in to discovery of other useful compounds in recent years.

The utility of 1,5-benzothiazepines and its derivatives as medicament is well explored. A literature survey reveals the enhanced bioactivity of annulated benzothiazepines, such as antimicrobial [2-8], antipsychotropic [9-11], antihypertensive [12-15], cardiovascular [16-18], antiasthma [19], anticancer [20,21], platelate aggregation inhibitor and Ca antagonist [22-25]. The research on the compounds containing sulfonyl group have been a focus of attention for a long time due to their diversified biological activities. Sulfones occupy a unique position in the drug industry with their antimalarial [26], bactericidal [27-29] and antitubercular activity [30-32]. The sulfone *Depsone* (sulfone) is well known antileprotic drug [33].

The introductions of an alkyl substituent at the desired position in heterocycles are often key intermediate in the synthesis of pharmaceutical drugs. Relatively large number of 1,5- benzothiazepine derivatives having various substituents at position-

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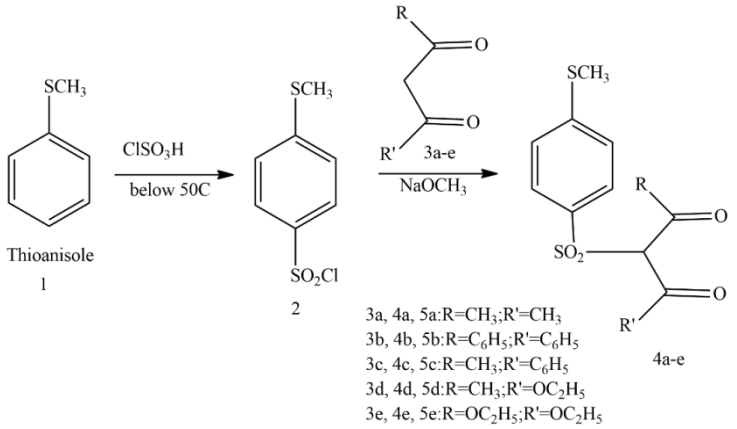
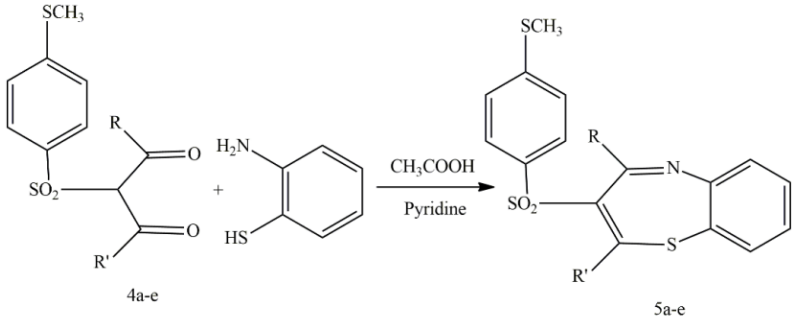
2,3,4,5 have been reported in the literature [34-36]. To the best of our knowledge, there is no report on the synthesis of 2,3,4 trisubstituted 1,5-benzothiazepine, incorporating 4-methylthio benzene sulfonyl unit. Hence for the above mentioned reason and in a continuous to our research for better and improved drugs, we investigated the synthesis of novel 2,3,4-trisubstituted 1,5-benzothiazepines **5a-e** with the assumption that the incorporation of bioactive heterocyclic moiety in to a single framework may result in to the production of novel heterocycles with enhanced bioactivity.

Results and discussion

Thioanisole **1** was first sulphonated with $ClSO_3H$ (chlorosulphonic acid) to afford the 4-methylthio benzene sulfonyl chloride **2** which was condensed with 2,4-dimethyl/2,4-diphenyl/4-methyl-2-phenyl /2-ethoxy-4-methyl/2,4-diethoxy propane-1,3-dione **3a-e** in the presence of sodium methoxide to yield **4a-e** [37-38] (Scheme **1**). The condensation of **4a-e** with 2-aminobenzenethiol and acetic acid (5N) in presence of pyridine afforded **5a-e** (Scheme **2**).



Scheme 1. Synthesis of substituted propane-1,3-diones



Scheme 2. Synthesis of substituted 1,5-benzothiazepines

In this context, suitability of different normality (1N to 13N) of acetic acid examined. A higher yield of 1,5-benzothiazepines **5a-e** was achieved when we used 5N acetic acid. It appears that the reaction is initiated by nucleophilic attack of sulphydryl electrons rather than by lone pair of electron of amino group, at enolic carbon of propane-1,3-dione and than dehydrative cyclisation results in 1,5-benzothiazepines.

In their IR spectra a characteristic C=N band was assigned around 1600 cm^{-1} referring to the presence of a C=N double bond in the seven membered heterocycle and compounds **5a-e** also did not reveal the presence of carbonyl functional group as a strong and sharp absorption band in the region 1700-1725 cm^{-1}, confirmed the formation of benzothiazepine nucleus. The 1H NMR spectra of the compounds **5a-e** did not reveal the presence of methane proton as singlet in the region δ 7.10-7.16 were absent, which confirmed the formation of benzothiazepine nucleus. A sharp singlet at δ 2.15 was attributed to six protons of two methyl groups present on the position-2 and 4 in 1,5-benzothiazepine ring **5a**. A sharp singlet at δ 1.56 was attributed to three protons of one methyl group attached to the position-4 in benzothiazepine ring **5c.** A quartet was observed at δ 4.23 (J = 7.0 Hz) of methylene protons (2H) in the ethoxy (-O-CH_2-CH_3) and a triplet at δ 1.63 (J =7.0 Hz) showed the presence of three protons of the methyl part of ethoxy (-O-CH_2-

CH_3) group **5d-e**. The ^{13}C NMR and Mass data for the compounds **5a-e** are presented as spectral data and these data are in good agreement with their structure.

Antimicrobial and anthelmintic activities of novel compounds (5a-e):

The novel compounds **5a-e** have been screened for antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumonie* and antifungal activity against *Aspergillus niger* and *Candida albicans* by the cup plate method [39,40]. Crofloxin and Ciclopiroxolamine were used as standards for comparison of antibacterial and antifungal activities, respectively. The anthelmintic activity was carried out on earthworms *Pherituma posthuma*, by a technique as described by Bagavant *et al* [41] with modification. Piperazine citrate was used as standard drug. The results indicate that compounds **5a-e** were active against all the four organisms (Table **1** and Table **2**).

Table 1: Antimicrobial activities of compounds (5a-e)

Compounds	Antibacterial activity				Antifungal activity			
	S.aureus		*K.pneumoniae*		*A.niger*		*C.albicans*	
	IZ[a]	AI[b]	IZ[a]	AI[b]	IZ[a]	AI[b]	IZ[a]	AI[b]
5a	13	0.54	15	0.58	16	0.73	14	0.58
5b	17	0.71	19	0.73	10	0.45	18	0.75
5c	18	0.75	25	0.96	17	0.77	23	0.96
5d	11	0.46	16	0.62	15	0.68	13	0.54
5e	20	0.83	18	0.69	17	0.77	15	0.63
Standard	24	-	26	-	22	-	24	-

[a]IZ = Inhibition zone (mm), [b](AI) =Activity Index

[b](AI) = Inhibition zone of test compounds/inhibition zone of standard.

Table 2: Anthelmintic activities of novel compounds (5a-e)

compounds	Anthelmintic activity (in min)	
	Paralysis	**Death**
5a	93	99
5b	82	112
5c	86	114
5d	88	110
5e	97	117
Standard	100	125

Experimental

All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Nicolet-Megna FT-IR 550 spectrophotometer in KBr pellets. The ^1H NMR and ^{13}C NMR spectra were run on a DRX-300 instrument at 300.13 and 75 MHz, respectively, in $CDCl_3$ using TMS as an internal standard. The Mass spectra were obtained on an LCMS instrument. TLC checked the purity of the newly synthesized compounds. Satisfactory C, H, N analyses were obtained for all the compounds.

Preparation of Substituted 1,5-Benzothiazepines (5a-e):

A mixture of substituted propane-1,3-dione (4a-e, 0.05m mol), 2-Aminobenzenethiol (0.05m mol), acetic acid (3ml, 5N) and pyridine (5ml) was heated at reflux for 5-6 hours. Then solvent was evaporated under reduced pressure. The mixture was cooled and poured on to crushed ice with vigorous stirring. The pale yellow precipitate (5b, 5d and 5e) and faint brown precipitate (5a and 5c) formed was filtered and dried.

The benzothiazepines (5a-e) obtained were purified by column chromatography (benzene: $CHCl_3$, 50:50, 25:75, 15:85, 5:95) and crystallized from methanol. Purity of the compounds were checked by TLC using ($CHCl_3$: CH_3OH, 9:1) as mobile phase.

3-(4-methylthio benzene sulfonyl)-2,4-dimethyl-1,5-benzothiazepine (5a):

Isolated as faint brown needles; Yield: 82%; M.p.143 ˚C; Anal. Calcd. for $C_{18}H_{17}NO_2S_3$: C, 57.60; H, 4.53; N, 3.73. Found: C, 57.21; H, 4.08;N, 3.12. IR (KBr, cm^{-1}): 3045, 2905, 1595, 1415, 1335, 1290, 1125, 690. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.51(3H, s, S-CH_3), 7.55-7.80 (8H, m, Ar-H), 2.15 (6H, s, CH_3). ^{13}C-NMR ($CDCl_3$, δ, ppm): 14.81 (S-CH_3), 144.00-117.12 (Ar-C), 96.42 (SO_2-C), 141.22 (C-S), 165.50 (C=N). LCMS: 374 (M^+H^+).

3-(4-methylthio benzene sulfonyl)-2,4-diphenyl-1,5-benzothiazepine (5b):

Isolated as pale yellow needles; Yield: 76%; M.p.135 ˚C; Anal.Calcd.for $C_{28}H_{21}NO_2S_3$: C, 67.33; H, 4.20; N, 2.80. Found: C, 66.91; H, 3.78; N, 2.44. IR (KBr, cm^{-1}): 3035, 1530, 1420, 1350, 1295, 1140, 695. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.51 (3H, s, S-CH_3), 6.80-7.94 (18H, m, Ar-H). ^{13}C-NMR ($CDCl_3$, δ, ppm): 14.81 (S-CH_3), 144.42-127.00 (Ar-C), 95.12 (SO_2-C), 152.24 (C-S), 164.61 (C=N). LCMS: 498 (M^+H^+).

3-(4-methylthio benzene sulfonyl)-4-methyl-2-phenyl-1,5-benzothiazepine (5c):

Isolated as faint brown plates; Yield: 62%; M.p.103 ˚C; Anal.Calcd.for $C_{23}H_{19}NO_2S_3$: C, 63.15; H, 4.34; N, 3.20. Found: C, 62.81; H, 4.03; N, 2.83. IR (KBr, cm^{-1}): 3010, 2895, 1625, 1415, 1335, 1290, 1150, 705. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.42 (3H, s, S-CH_3), 6.73-7.98 (13H, m, Ar-H), 1.58 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$, δ, ppm): 14.81 (S-CH_3), 144.00-127.82 (Ar-C), 95.24 (SO_2-C), 152.21 (C-S), 164.60 (C=N). LCMS: 438 (M^+H^+).

3-(4-methylthio benzene sulfonyl)-2-ethoxy-4-methyl-1,5-benzothiazepine (5d):

Isolated as pale yellow plates; Yield: 72%; M.p.84 ˚C; Anal. Calcd. for $C_{19}H_{19}NO_3S_3$: C, 56.29; H, 4.69; N, 3.45. Found: C, 55.89; H, 4.33; N, 3.04. IR (KBr, cm^{-1}): 3060, 2885, 1585, 1445, 1340, 1330, 1280, 1125, 1015, 715.^{1}H-NMR ($CDCl_3$, δ, ppm): 2.41 (3H, s, S-CH_3), 6.97-7.94 (8H, m, Ar-H), 1.63 (3H, t, OCH_2-CH_3, *J* =7.0 Hz), 4.23(2H, q, OCH_2CH_3, *J* = 7.0 Hz), 1.68 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$, δ, ppm): 14.81 (S-CH_3), 144.00-117.82 (Ar-C), 69.74 (SO_2-C), 168.36 (C-S), 164.62 (C=N). LCMS: 406 (M^+H^+).

3-(4-methylthio benzene sulfonyl)-2,4-diethoxy-1,5-benzothiazepine (5e):

Isolated as pale yellow needles; Yield: 68%; M.p.124 ˚C; Anal. Calcd. for $C_{20}H_{21}NO_4S_3$: C, 55.17; H, 4.82; N, 3.21. Found: C, 54.84; H, 4.38; N, 2.55. IR (KBr, cm^{-1}): 3050, 2905, 1600, 1415, 1310, 1290, 1270, 1155, 1010, 695. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.48 (3H, s, S-CH_3), 6.94-7.76 (8H, m, Ar-H), 1.63 (6H, t, OCH_2-CH_3, *J* =7.0Hz), 4.23 (4H, q, OCH_2CH_3, *J* =7.0Hz). ^{13}C-NMR ($CDCl_3$, δ, ppm): 14.21 (S-CH_3), 144.00-117.32 (Ar-C), 15.42-14.80 (OCH_2CH_3), 68.72-64.0 (OCH_2CH_3), 68.34 (SO_2-C), 167.38 (C-S), 164.72 (C=N). LCMS: 436 (M^+H^+).

Conclusion

Compound (5a-e), have been successfully synthesized and characterized. A higher yield of compound (5a-e) was achieved when we used 5N acetic acid. Elemental analysis, C, H, N and spectral (IR, 1H NMR, 13C NMR and LCMS) results were good agreement with predicted formulae. The antimicrobial and anthelmintic activities results indicate that compounds 5a-e were active against organisms.

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