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Synthesis of Novel Substituted 1,5-Benzothiazepines Containing 1,4-Benzodioxane Sulfonyl Moiety

Sandhya Chhakra, A. Mukherjee, H.L. Singh and Suresh Singh Chauhan✉

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ABSTRACT

An efficient synthesis of novel 2,3,4-trisubstituted 1,5-benzothiazepines **(4a-e)** incorporating the sulfonyl group is described. Compound **(4a-e)** was synthesized by the reaction of 3-(1,4-dioxane-6-sulfonyl)-2,4-dimethyl/4-methyl-2-phenyl/2,4-diphenyl/2-ethoxy-4-methyl/2,4-diethoxy propane-1,3-dione **(3a-e)** with 2-aminobenzenethiol with ZnO nanoparticles/pyridine. Formation of compound **(3a-e)** was achieved by the reaction of 1,4-dioxane-6-sulfonyl chloride **(1)** with 2,4-dimethyl/4-methyl-2-phenyl/2,4-diphenyl/2-ethoxy-4-methyl/2,4-diethoxy propane-1,3-dione **(2a-e).** The benzothiazepines (**4a-e**) obtained were purified by column chromatography (benzene: $CHCl_3$, 40:60, 30:70, 20:80, 10:90) and crystallized from methanol. The purity of the compounds was checked by TLC using ($CHCl_3$: CH_3OH, 9:1) as the mobile phase. The structure of the compounds has been established by elemental, IR, ^1H NMR, ^{13}C NMR and Mass spectral analyses. Frontier molecular orbitals of the title compounds have been studied in the ground state speculatively. The reactivity of a molecule using diverse descriptors such as softness, electrophilicity, electronegativity, HOMO-LUMO energy gap is calculated additionally discussed.

KEYWORDS

Propane-1,3-dione, ZnO nanoparticles, Substituted benzothiazepine, 1,4-Benzodioxane, Sulfonyl compound, Spectral studies.

INTRODUCTION

Benzothiazepines are having the significant effect on our cutting-edge world as a result of its multidimensional uses in the field of medications and pharmaceuticals [1]. The revelation of 1,5-benzothiazepine turns out to be most exciting inferable from the finding that a few individuals from this class were protected as psychopharmacological and cardiovascular specialists. The predominance of diltiazem over other ordinary vasodilators has resulted into discovery of other useful compounds in recent years. A literature survey reveals the enhanced bioactivity of annulated benzothiazepines, such as antipsychotropic [2,3], antimicrobial [4], antibacterial [5], antihypertensive [6], anti-HIV [7] cardiovascular [8], antiasthma [9], anticancer [10], anticonvulsant [11], antimalarial [12], anti-inflammatory [13], platelate aggregation inhibitor and Ca antagonist [14].

The compounds containing dioxane rings are of enthusiasm for the presentation of an assortment of substituents into a common

Author affiliations:

Chemistry Research Lab ABB GF 07, Department of Chemistry, Mody University of Science and Technology, Lakshmangarh-332311, India

✉To whom correspondence to be addressed:

E-mail: sureshsingh2288@gmail.com

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skeleton, novel transformations and can provide new and general routes to a variety of organic molecules. 1,4-Benzodioxane ring were characterized and evaluated for various biological activity such as antimicrobial [15] and antioxidant activity [16], antihepatotoxic [17], α-adrenergic blocking agent [18] and anti-inflammatory [19].

Other than this gathering compound additionally contain sulphonyl group which has been a focus of attention for a long time due to their diversified biological activities [20]. Sulfones occupy a unique position in the drug industry with their antimalarial [21], bactericidal [22,23] and antitubercular activity [24,25]. The sulfone depsone (sulfone) is a well known antileprotic drug [26].

Generally, 1,5-benzothiazepines are synthesized by the condensation of *o*-aminothiophenol with α,β-unsaturated carbonyl compounds [27,28], 2-(bromomethyl)aziridines [29], acetylenic ketones [30], α-oxoketene-S,S-acetal [31], chalcone analog dehydroacetic acid [27], aromatic aldehyde and 1,3-dicarbonyl with aluminium nitrate [32], α,β-unsaturated dicarbonyl [33], acetylenic ketones [30], α,β,γ,δ-unsaturated ketones [34]. A variety of reagents and solvents such as ceric ammonium nitrate [35], trifluoroacetic acid [36], dimethylformamide with acetic acid [37] or piperidine [38] have been utilized for the condensation reaction.

Nonetheless, every one of these methods has impediments, such as extreme reaction conditions, low yields and also several side-reactions. Herein, a modified method for the preparation of 1,5-benzothiazepine derivatives with β-diketones and β-ketoesters is reported with high yields. It was found that a mixture of ZnO nanoparticles/pyridine was capable of producing high yields of 1,5-benzothiazepines (**4a-e**), by condensation of 2-amino thiophenol with β-diketones and β-ketoesters (**3a-e**) under mild conditions.

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 ^{1}H NMR and ^{13}C NMR spectra were run on a BRUKER AVANCE II 400 NMR spectrometer at 400.13 and 100.61 MHz, respectively in $CDCl_3$ using TMS as an internal standard. The Mass spectra were obtained on the Q-TOF MICROMASS instrument. TLC checked the purity of the newly synthesized compounds. Satisfactory C, H, N analyses were obtained for all the compounds. Hypothetical calculations have been performed utilizing the Gaussian 03 software. The Becke's three-parameter hybrid utilitarian using the B3LYP correlation utilitarian with 6.31G+ (d,p) basis set.

Preparation of substituted β-diketone/β-ketoester (3a-e): Placed β-diketone/β-ketoester (**2a-e**) (0.01 M) and sodium methoxide (0.01 M) in a dry round-bottomed flask fitted with a guard tube and stirred for 2 h on a magnetic stirrer at 60-70 °C, until a creamy mass was obtained. The sulphonyl chloride derivative (**1**) (0.01 M) was then added in small portion and dry ethanol (5 mL) was added as the solvent to effect proper stirring of the reaction mixture. The reaction mixture was refluxed at a temperature of 95-105 °C for about 27 to 32 h. The completion of the reaction was monitored through TLC. After the reaction was completed the reaction mass was cooled and ethanol was removed under reduced pressure. The reaction mixture was extracted using chloroform and then washed with water. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4. The chloroform was distilled off and purification of the compound was done by column chromatography using silica gel as absorbent and $CHCl_3$:MeOH (9:1) as the mobile phase. The product was recrystallized from methanol. The purity of β-diketones and β-ketoesters was checked through TLC using ($CHCl_3$: benzene, 8:2) upper layer as the mobile phase.

Preparation of substituted 1,5-benzothiazepines (4a-e): A mixture of substituted propane-1,3-dione (**3a-e**, 0.05 mmol), 2-aminobenzenethiol (0.05 mmol), ZnO nanoparticles (0.5 g) and pyridine (5 mL) were heated at 80-90 °C for 4-6 h. The solvent was evaporated under reduced pressure. The mixture was cooled and poured on crushed ice along with vigorous stirring with the removal of ZnO nanoparticles. The pale yellow precipitate (**4b** and **4e**) and faint brown precipitate (**4a**, **4c** and **4d**) formed was filtered and dried. The benzothiazepines (**4a-e**) obtained, were purified by column chromatography and crystallized from methanol. The purity of the compounds was checked by TLC using ($CHCl_3$:CH_3OH, 8:2) as the mobile phase.

Spectral data

2-(1,4-Benzodioxane-6-sulphonyl)-1,3-dimethyl propane-1,3-dione (3a): Isolated as light creamy compound; m.p.: 85 °C; Yield: 80 %; Anal. calcd. (%) for $C_{13}H_{14}O_6S$: C, 52.34; H, 4.69. Found (%): C, 52.30; H, 4.53. IR (KBr, ν_{max}, cm^{-1}): 3030, 2919, 1714, 1456-1621, 1259-1165, 2850. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.61 (4H, s, O-CH_2-CH_2-O), 6.54-6.65 (3H, m, Ar-H), 1.26 (6H, s, CH_3), 5.50 (1H, s, CH). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 77.39 (O-C), 118.35-138.15 (Ar-C), 110.12 (SO_2-C), 143.90 (C-S), 206.01 (C=O). MS: 298 (M^+H^+).

2-(1,4-Benzodioxane-6-sulphonyl)-1-methyl-3-phenyl propane-1,3-dione (3b): Isolated as light orange compound; m.p.: 80 °C; Yield: 75 %; Anal. calcd. (%) for $C_{18}H_{16}O_6S$: C, 60.00; H, 4.44. Found (%): C, 59.87; H, 4.32. IR (KBr, ν_{max}, cm^{-1}): 3030, 2919, 1710, 1456-1621, 1259-1170, 2850. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.34 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 7.10-8.05 (8H, m, Ar-H), 1.37 (3H, s, CH_3), 4.75 (H, s, CH). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm):76.75 (O-C), 120.72-139.12 (Ar-C), 105.18 (SO_2-C), 143.22 (C-S), 207.15 (C=O).MS:360 (M^+H^+).

2-(1,4-Benzodioxanes-6-sulphonyl)-1,3-diphenyl propane-1,3-dione (3c): Isolated as light pink crystal; m.p.: 85 °C; Yield: 78 %; Anal. calcd. (%) for $C_{23}H_{18}O_6S$: C, 65.40; H, 4.26. Found (%): C, 65.31; H, 4.20. IR (KBr, ν_{max}, cm^{-1}): 3025, 2920, 1710, 1457-1620, 1260-1169. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.33 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 7.97-8.07 (13H, m, Ar-H), 6.85 (H, s, CH). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 77.07 (O-C), 122.72-138.28 (Ar-C), 110.12 (SO_2-C), 143.90 (C-S), 206.05 (C=O).MS:422 (M^+H^+).

2-(1,4-Benzodioxane-6-sulphonyl)-3-ethoxy-1-methyl propane-1,3-dione (3d): Isolated as dark brown needal crystal; m.p.: 75 °C; Yield: 76 %; Anal. calcd. (%) for $C_{14}H_{16}O_7S$: C, 51.21; H, 4.87. Found (%): C, 51.15; H, 4.78. IR (KBr, ν_{max}, cm^{-1}): 3029, 2919, 1710, 1456-1621, 1255-1172, 2851, 1216. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.32 (4H, s, O-CH_2-CH_2-

O, *J* = 2.7 Hz), 7.16-7.40 (3H, m, Ar-H), 1.26 (3H, s, CH_3), 3.05-3.23 (2H, q, O-CH_2), 1.04-1.08 (3H, t, O-CH_2-CH_3), 4.75 (H, s, CH). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 76.14 (O-C), 119.80-138.87 (Ar-C), 108.12 (SO_2-C), 143.22 (C-S), 205.18 (C=O) MS: 328 (M^+H^+).

2-(1,4-Benzodioxane-6-sulphonyl)-1,3-diethoxy propane-1,3-dione (3e): Isolated as light creamy crystal; m.p.: 80 °C; Yield: 70 %; Anal. calcd. (%) for $C_{15}H_{18}O_8S$: C, 50.27; H, 5.02. Found (%): C, 50.19; H, 4.92. IR (KBr, ν_{max}, cm^{-1}): 3030, 2922, 1708, 1621-1456, 1259-1170, 2851, 1216. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.32 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 7.16-8.01 (3H, m, Ar-H), 1.25-1.28 (3H, t, O-CH_2-CH_3), 3.05-3.23 (2H, q, O-CH_2), 4.75 (H, s, CH). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 76.75 (O-C), 118.85-138.08 (Ar-C), 110.42 (SO_2-C), 143.02 (C-S), 207.05 (C=O).MS:358 (M^+H^+).

3-(1,4-Benzodioxane-6-sulphonyl)-2,4-dimethyl-1,5-benzothiazepine (4a): Isolated as pale yellow needles; m.p.: 140 °C; Yield: 80 %; Anal. calcd. (%) for $C_{19}H_{17}NO_4S_2$: C, 58.91; H, 4.39; N, 3.61. Found (%): C, 58.80; H, 4.30; N, 3.55. IR (KBr, ν_{max}, cm^{-1}): 3030, 2919, 1612-1583, 1621-1456, 1214-1170, 2850, 671. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.41 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 6.40-7.32 (7H, m, Ar-H, *J* = 8.04 Hz), 2.50 (6H, s, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm):76.75 (O-C), 122.72-129.51 (Ar-C), 110.12 (SO_2-C), 143.90 (C-S), 156.50 (C=N). MS: 387 (M^+H^+).

3-(1,4-Benzodioxane-6-sulphonyl)-4-methyl-2-phenyl-1,5-benzothiazepine (4b): Isolated as pale yellow compound; m.p.: 149 °C; Yield: 75 %; Anal. calcd. (%) for $C_{24}H_{19}NO_4S_2$: C, 64.14; H, 4.23; N, 3.11. Found (%): C, 64.10; H, 4.19; N, 3.08. IR (KBr, ν_{max}, cm^{-1}): 3030, 2919, 1611-1582, 1455-1620, 1215-1168, 2851, 670. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.41 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 6.40-7.80 (12H, m, Ar-H, *J* = 8.04 Hz), 1.26 (3H, s, CH_3).^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 76.74 (O-C), 120.18-139.08 (Ar-C), 107.18 (SO_2-C), 143.22 (C-S), 161.05 (C=N). MS: 449 (M^+H^+).

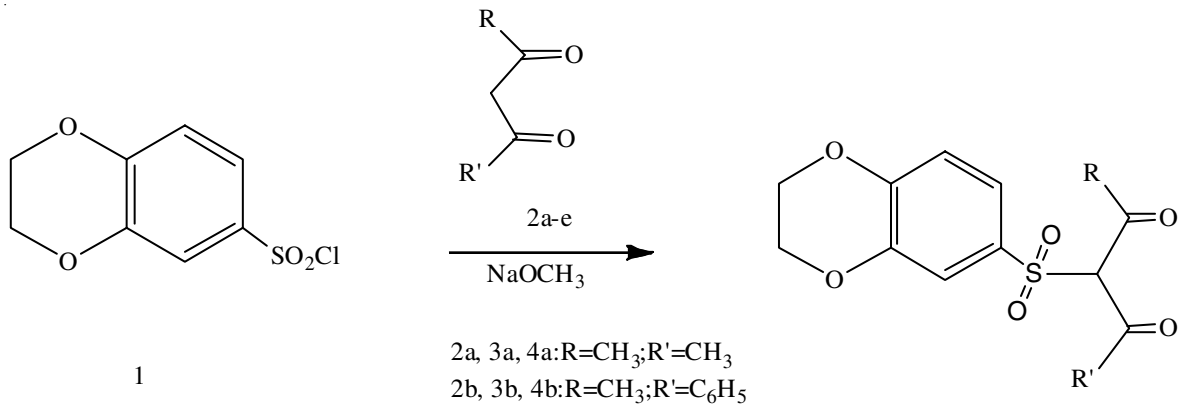
3-(1,4-Benzodioxane-6-sulphonyl)-2,4-diphenyl-1,5-benzothiazepine (4c): Isolated as faint brown crystals; m.p.: 155 °C; Yield: 78 %; Anal. calcd. (%) for $C_{29}H_{21}NO_4S_2$: C, 68.10; H, 4.10; N, 2.73. Found (%): C, 68.05; H, 4.01; N, 2.70. IR (KBr, ν_{max}, cm^{-1}): 3030, 2919, 1611-1582, 1620-1455, 1215-1170, 670. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.41 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 6.55-8.00 (17H, m, Ar-H).^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 77.25 (O-C), 122.12-138.32 (Ar-C), 113.05 (SO_2-C), 143.18 (C-S), 163.30 (C=N). MS: 511 (M^+H^+).

3-(1,4-Benzodioxane-6-sulphonyl)-2-ethoxy-4-methyl-1,5-benzothiazepine (4d): Isolated as faint brown crystals; m.p.: 145 °C; Yield: 73 %; Anal. calcd. (%) for $C_{20}H_{19}NO_5S_2$: C, 57.55; H, 4.55; N, 3.35. Found (%): C, 57.51; H, 4.53; N, 3.30. IR (KBr, ν_{max}, cm^{-1}): 3030, 2919, 1611-1582, 1620-1455, 2850, 1216-1170, 670. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.34 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 7.12-8.02 (7H, m, Ar-H, *J* = 8.03), 1.04-1.08 (3H, t, O-CH_2-CH_3), 3.05-3.23 (2H, q, O-CH_2), 1.26 (3H, s, CH_3).^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 76.10 (O-C), 120.50-139.42 (Ar-C), 109.14 (SO_2-C), 143.05 (C-S), 159.10 (C=N). MS: 417 (M^+H^+).

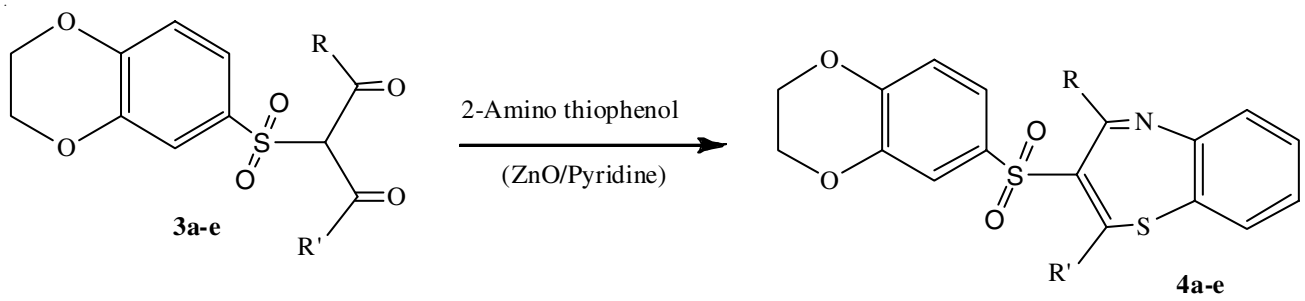
3-(1,4-Benzodioxane-6-sulphonyl)-2,4-diethoxy-1,5-benzothiazepine (4e): Isolated as faint yellow needles; m.p.: 150 °C; Yield: 70 %; Anal. calcd. (%) for $C_{21}H_{21}NO_6S_2$: C, 56.37; H, 4.69; N, 3.13. Found (%): C, 56.28; H, 4.60; N, 3.02. IR (KBr, ν_{max}, cm^{-1}): 3030, 2919, 1611-1582, 1621-1454, 2850, 1215-1169, 670. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.28 (4H, s, O-CH_2-CH_2-O, *J* = 2.7 Hz), 6.56-7.17 (7H, m, Ar-H, *J* = 8.03), 1.04-1.08 (3H, t, O-CH_2-CH_3), 3.05-3.23 (2H, q, O-CH_2).^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 77.06 (O-C), 122.73-129.50 (Ar-C), 110.13 (SO_2-C), 143.90 (C-S), 156.47 (C=N). MS: 447 (M^+H^+).

RESULTS AND DISCUSSION

1,4-Benzodioxane-6-sulphonyl chloride refluxed with β-diketone/β-ketoester in the presence of sodium methoxide to yield (**3a-e**). Assist response of (**3a-e**) with 2-amino thiophenol in the presence of pyridine and ZnO nanoparticles afforded (**4a-e**). It appears that the reaction is initiated by nucleophilic attack of sulphydryl electrons rather than by a lone pair of electron of an amino group, at the enolic carbon of β-diketone/β-ketoester and then dehydrative cyclization results in 1,5-benzothiazepines (**Schemes I** and **II**).



Scheme-I: Synthesis of substituted propane-1,3-diones



Scheme-II: Synthesis of substituted 1,5-benzothiazepines

In their IR spectra 1720-1705 cm^{-1} as a strong and sharp absorption band shows the presence of keto of novel 2-(1,4-benzodioxane-6-sulphonyl)-1,3-dialkyl-1,3-dione (**3a-e**), which is absent in compounds (**4a-e**) and C=N band was assigned around 1600 cm^{-1} referring to the presence of a C=N double bond whereas peaks at 700-670 cm^{-1} assigned for C-S-C band in the seven-membered heterocycles, confirmed the formation of benzothiazepine nucleus (**4a-e**).

The ^{1}H NMR spectra of the compound (**4a-e**) did not reveal the presence of methane proton as a 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 (**4a**). A sharp singlet at δ 1.56 was attributed to three protons of one methyl group attached to the position-4 in benzothiazepine ring (**4c**). 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 (**4d-e**). The ^{13}C NMR and mass data for the compound (**4a-e**) are presented in the experimental section and these data are in good agreement with their structure.

Molecular geometries: The geometric parameters of substituted benzothiazepine derived of diketone were optimized with the B3LYP method at 6-31G+(d,p) level. The chemical structure of compounds **4a-e** are shown in **Scheme-I** and the final optimized molecular structures of these compounds **4a-d** in accordance with the atom numbering scheme were shown in Fig. 1. The optimized energy for benzothiazepines varies

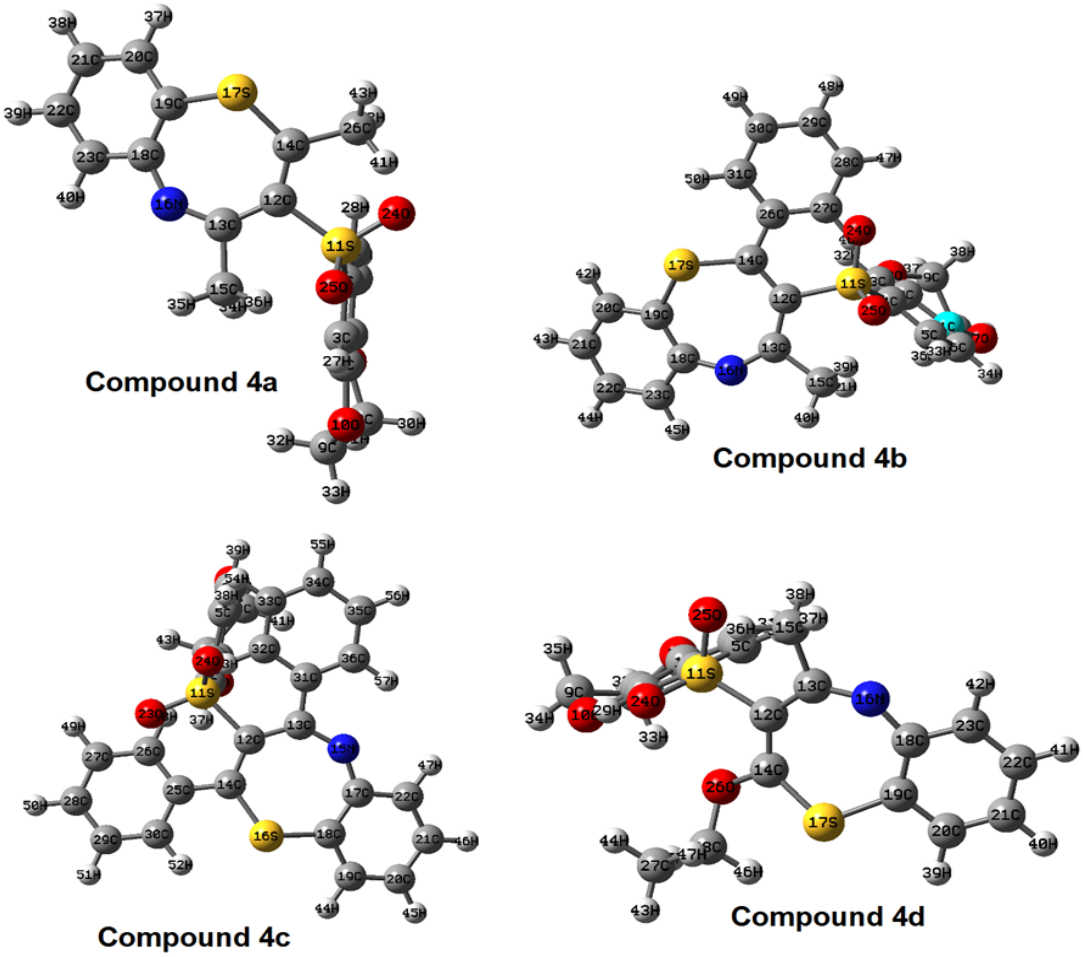


Fig. 1. Optimized structures of benzothiazepines

between 229.602 kcal/mol and 251.864 kcal/mol, which show that these benzothiazepines were stable. Based on these, some structural parameters such as bond lengths, bond angles and dihedral angles have been calculated and are listed in Table-1. The optimized bond lengths of C-C in the aromatic benzene ring are fall in the range from 1.338 to 1.365 Å. The influence of the substituent on the aromatic ring seems to be interesting. The calculated C-S (~1.805) distances are shorter (or equal), whereas the C-N (~1.268 Å) slightly longer than the experimental values. Dipole moment reflects the molecular charge distribution and is given as a vector in three dimensions. Therefore, it can be used as a descriptor to depict the charge movement across the molecule. The direction of the dipole moment vector in a molecule depends on the centers of positive and negative charges.

Frontier molecular orbitals: HOMO, which can be thought the peripheral orbital containing electrons, tends to give these electrons, for example, an electron donor. Then again, LUMO can be thought the deepest orbital containing free places to accept electrons. HOMO-LUMO helps to characterize the

TABLE-1
OPTIMIZED GEOMETRIC PARAMETERS OF COMPOUNDS **4a-e**

Bond length (Å)		Bond angles (°)		Dihedral angles (°)	
Compound **4a**					
$C_{12}S_{11}$	1.780	$C_{12}S_{11}C_4$	109.471	$C_{12}S_{11}C_4C_3$	-120.075
$C_{13}C_{12}$	1.373	$C_{13}C_{12}S_{11}$	115.511	$C_{13}C_{12}S_{11}C_4$	60.146
$C_{14}C_{12}$	1.351	$C_{14}C_{12}S_{11}$	115.499	$C_{14}C_{12}S_{11}C_4$	-120.146
$C_{15}C_{13}$	1.540	$C_{15}C_{13}C_{12}$	114.089	$C_{15}C_{13}C_{12}S_{11}$	11.156
$N_{16}C_{13}$	1.320	$N_{16}C_{13}C_{12}$	131.837	$N_{16}C_{13}C_{12}S_{11}$	-167.822
$S_{17}C_{14}$	1.758	$S_{17}C_{14}C_{12}$	124.759	$S_{17}C_{14}C_{12}S_{11}$	-170.895
$C_{18}N_{16}$	1.313	$C_{18}N_{16}C_{13}$	137.466	$C_{18}N_{16}C_{13}C_{12}$	3.480
$C_{19}C_{18}$	1.365	$C_{19}C_{18}N_{16}$	128.165	$C_{19}C_{18}N_{16}C_{13}$	-19.005
$C_{20}C_{19}$	1.359	$C_{20}C_{19}C_{18}$	119.871	$C_{20}C_{19}C_{18}N_{16}$	176.901
Compound **4b**					
$C_{12}S_{11}$	1.779	$C_{12}S_{11}C_4$	109.430	$C_{12}S_{11}C_4C_3$	59.884
$C_{13}C_{12}$	1.372	$C_{13}C_{12}S_{11}$	115.490	$C_{13}C_{12}S_{11}C_4$	60.045
$C_{14}C_{12}$	1.351	$C_{14}C_{12}S_{11}$	115.514	$C_{14}C_{12}S_{11}C_4$	-120.239
$C_{15}C_{13}$	1.539	$C_{15}C_{13}C_{12}$	114.083	$C_{15}C_{13}C_{12}S_{11}$	11.226
$N_{16}C_{13}$	1.319	$N_{16}C_{13}C_{12}$	131.836	$N_{16}C_{13}C_{12}S_{11}$	-167.743
$S_{17}C_{14}$	1.757	$S_{17}C_{14}C_{12}$	124.755	$S_{17}C_{14}C_{12}S_{11}$	-171.009
$C_{18}N_{16}$	1.313	$C_{18}N_{16}C_{13}$	137.446	$C_{18}N_{16}C_{13}C_{12}$	3.561
$C_{19}C_{18}$	1.365	$C_{19}C_{18}N_{16}$	128.163	$C_{19}C_{18}N_{16}C_{13}$	-19.106
$C_{20}C_{19}$	1.359	$C_{20}C_{19}C_{18}$	119.869	$C_{20}C_{19}C_{18}N_{16}$	176.886
Compound **4c**					
$C_{12}S_{11}$	1.779	$C_{12}S_{11}C_4$	109.430	$C_{12}S_{11}C_4C_3$	59.908
$C_{13}C_{12}$	1.372	$C_{13}C_{12}S_{11}$	115.519	$C_{13}C_{12}S_{11}C_4$	60.309
$C_{14}C_{12}$	1.351	$C_{14}C_{12}S_{11}$	115.509	$C_{14}C_{12}S_{11}C_4$	-119.972
$N_{15}C_{13}$	1.319	$N_{15}C_{13}C_{12}$	131.818	$N_{15}C_{13}C_{12}S_{11}$	-167.525
$S_{16}C_{14}$	1.757	$S_{16}C_{14}C_{12}$	124.748	$S_{16}C_{14}C_{12}S_{11}$	-171.036
$C_{17}N_{15}$	1.313	$C_{17}N_{15}C_{13}$	137.449	$C_{17}N_{15}C_{13}C_{12}$	3.391
$C_{18}C_{17}$	1.365	$C_{18}C_{17}N_{15}$	128.153	$C_{18}C_{17}N_{15}C_{13}$	-19.135
$C_{25}C_{14}$	1.355	$C_{25}C_{14}C_{12}$	117.636	$C_{25}C_{14}C_{12}S_{11}$	7.938
$C_{31}C_{13}$	1.355	$C_{31}C_{13}C_{12}$	114.112	$C_{31}C_{13}C_{12}S_{11}$	11.445
Compound **4d**					
$C_{12}S_{11}$	1.78	$C_{12}S_{11}C_4$	109.471	$C_{12}S_{11}C_4C_3$	119.926
$C_{13}C_{12}$	1.373	$C_{13}C_{12}S_{11}$	115.512	$C_{13}C_{12}S_{11}C_4$	120.145
$C_{14}C_{12}$	1.351	$C_{14}C_{12}S_{11}$	115.500	$C_{14}C_{12}S_{11}C_4$	-60.145
$C_{15}C_{13}$	1.540	$C_{15}C_{13}C_{12}$	114.089	$C_{15}C_{13}C_{12}S_{11}$	11.152
$N_{16}C_{13}$	1.320	$N_{16}C_{13}C_{12}$	131.837	$N_{16}C_{13}C_{12}S_{11}$	-167.826
$S_{17}C_{14}$	1.758	$S_{17}C_{14}C_{12}$	124.756	$S_{17}C_{14}C_{12}S_{11}$	-170.871
$C_{18}N_{16}$	1.313	$C_{18}N_{16}C_{12}$	137.466	$C_{18}N_{16}C_{13}C_{12}$	3.469
$C_{19}C_{18}$	1.365	$C_{19}C_{18}N_{16}$	128.165	$C_{19}C_{18}N_{16}C_{13}$	-19.002
$O_{20}C_{14}$	1.430	$O_{20}C_{14}C_{12}$	117.624	$O_{20}C_{14}C_{12}S_{11}$	8.069
Compound **4e**					
$C_{12}S_{11}$	1.7780	$C_{12}S_{11}C_4$	109.469	$C_{12}S_{11}C_4C_3$	-120.087
$C_{13}C_{12}$	1.373	$C_{13}C_{12}S_{11}$	115.509	$C_{13}C_{12}S_{11}C_4$	0.147
$C_{14}C_{12}$	1.351	$C_{14}C_{12}S_{11}$	115.503	$C_{14}C_{12}S_{11}C_4$	179.856
$C_{15}C_{13}$	1.430	$C_{15}C_{13}C_{12}$	114.085	$C_{15}C_{13}C_{12}S_{11}$	11.172
$N_{16}C_{13}$	1.320	$N_{16}C_{13}C_{12}$	131.833	$N_{16}C_{13}C_{12}S_{11}$	-167.768
$S_{17}C_{14}$	1.758	$S_{17}C_{14}C_{12}$	124.752	$S_{17}C_{14}C_{12}S_{11}$	-170.899
$C_{18}N_{16}$	1.313	$C_{18}N_{16}C_{13}$	137.459	$C_{18}N_{16}C_{13}C_{12}$	3.454
$C_{19}C_{18}$	1.365	$C_{19}C_{18}N_{16}$	128.162	$C_{19}C_{18}N_{16}C_{13}$	-19.030
$C_{20}C_{19}$	1.430	$C_{20}C_{19}C_{18}$	117.624	$C_{20}C_{19}C_{18}N_{16}$	8.042

TABLE-2
COMPUTED MOLECULAR DESCRIPTIONS OF BENZOTHIAZEPINES (**4a-e**)

Parameters	Compounds				
	4a	**4b**	**4c**	**4d**	**4e**
Total energy (kcal/mol)	231.149	244.307	251.864	229.602	233.643
HOMO (eV)	-7.015	-7.162	-7.117	-6.955	-7.477
LUMO (eV)	-2.661	-3.731	-3.671	-2.724	-2.736
Energy gap (eV)	4.354	3.431	3.446	4.231	4.741
Electronegativity (χ): $\chi = (E_{HOMO} + E_{LUMO})/2$	-4.838	-5.446	5.394	4.689	5.106
Chemical potential (μ, eV): ($\mu = E_{LUMO} + E_{HOMO}/2$)	-2.177	-1.7155	-1.723	-2.1155	-2.3705
Chemical hardness (η, eV)	2.177	1.7155	1.723	2.1155	2.3705
Global softness ($S = 1/\eta$)	0.459	0.583	0.580	0.472	0.422
Electrophilicity index ($w = \mu^2/2\eta$)	1.0885	0.8577	0.8615	1.0577	1.1537
Dipole moment (Debye)	17.1741	18.5847	19.3818	18.0783	18.2978

reactivity and kinetic stability of the molecules (Fig. 2). A molecule with a little energy gap is more enraptured and is known as a soft molecule. As of late, the energy gap amongst HOMO and LUMO has been utilized to demonstrate the bioactivity from intramolecular charge exchange, since it is a measure of electron conductivity. The HOMO and LUMO of benzothiazepine (**4a-e**) are shown in Fig. 2 and given in Table-2. The energy of the HOMO is identified with the ionization potential and describes the defenselessness of the molecule towards assault of electrophiles. The energy of LUMO is identified with the electron liking and portrays the helplessness of the molecule towards assault of nucleophiles. Those electronegativity and hardness are clearly used widely on make forecasts with respect to synthetic conduct.

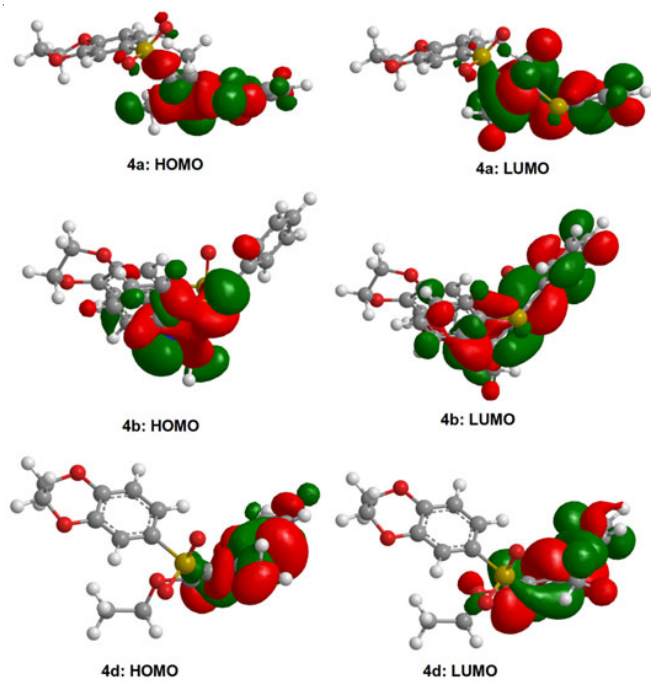


Fig. 2. HOMO-LUMO's of benzothiazepines (**4a**, **4b** and **4d**)

Besides, those compound hardness of a system under beneath impenetrability with charge exchange, while global softness will be relative of the polarizability of the structure. Another electrophilicity index (ω) portrays the electron tolerating capacity of the frameworks. High values of the electrophilicity record increment the electron tolerating capacities of the molecules. In this manner, the electron tolerating capacities of **4a-e** mixes are arranged in the accompanying order: **4e** > **4a** > **4d** > **4c** > **4b**. The HOMO energies, LUMO energies, hardness (η), ionization vitality (IE), Electronegativity (χ), add up to vitality and dipole minute have been processed and are given in Table-2.

Conclusion

Compounds (**3a-e**) and (**4a-e**), have been successfully synthesized and characterized. A higher yield of compound (**4a-e**) was achieved when we used ZnO nanoparticles as a catalyst. Elemental analysis, C, H, N and spectral (IR, ^{1}H NMR, ^{13}C NMR and LCMS) results were good agreement with predicted formulae. The theoretically calculated values of bond lengths, bond angles and dihedral angles of the structure of the minimum energy were investigated. The movement of π-electron cloud from donor to acceptor *i.e.*, intramolecular charge transfer can make the molecules more polarized and the energy gap must be responsible for the reactivity of molecules. The values of electronegativity, chemical hardness, softness and electrophilicity index have been calculated. According to the stability of the molecule to softness, this means that the molecule with least energy gap and means that it is a more reactive molecule.

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