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Research Article

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Synthesis and antibacterial evaluation of bis-[1,5]-benzothiazepines

Ramchandra N. Deshmukh[a], Ramesh V. Dengle[a]* and Gajanan Rashinkar[b]

[a]Department of Chemistry, Vivekanand College, Kolhapur, MS, India
[b]Department of Chemistry, Shivaji University, Kolhapur, MS, India

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ABSTRACT

A series of bis-[1,5]-benzothiazepines (3a-e) were synthesized by base catalyzed reaction of bis-chalcones (1a-e) with two equivalent of 2-aminothiophenol (2). All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The synthesized compounds were evaluated for their in vitro antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Escherchia coli, Pseudomonas aeruginosa and showed significant antibacterial activity.

Keywords: Chalcone, Bis-chalcone, 2-aminothiophenol, bis-[1,5]-benzothiazepines, antibacterial.

INTRODUCTION

1,5-Benzothiazepine is an important seven membered heterocyclic ring system with N and S as heteroatoms. 1,5-Benzothiazepine is a versatile scaffold that features in a number of clinically used drugs due to their potential to provide an active pharmacophore for de novo exploration [1]. Derivatives of 1,5-benzothiazepines are of particular interest for lead discovery because they have been found active against different families of targets, as compound bearing this structural unit possess a broad spectrum of biological activities such as antifeedent [2], antihypertensive [3], antimicrobial [4], coronary vasodilatory [5], antidepressant [6], antiarrythmic [7], calcium channel blocker [8], CNS β-stimulant [9], antifungal [10], anticancer [11], anti-HIV [12], antimalerial [13]. A general way to construct the ring skeleton of 1,5-benzothiazepine is via, the reaction of 2-aminothiophenol with chalcones, β-haloketones [14,15]. Literature survey reveals that most of the 1,5-benzothiazepine ring systems were synthesized by the reaction between 2-aminothiophenol and chalcones having only one α, β-unsaturated site. A very little attention was given on the synthesis of 1,5-benzothiazepines using bis-chalcones [16]. We have synthesized bis-[1,5]-benzothiazepines using bis-chalcones as precursors. In order to know the effect of two 1,5-benzothiazepine nuclei on biological activity it was considered to synthesize new chemical entities incorporating two 1,5-benzothiazepine nuclei in a single molecular framework and to get them evaluated for their biological activity.

EXPERIMENTAL SECTION

General remarks

Melting points were determined in an open capillary and are uncorrected. Purity of the compounds was checked by TLC. IR spectra were recorded on Perkin-Elmer FTIR spectrometer using KBr pellets. ^{1}H NMR, ^{13}C NMR spectra were recorded on Bruker Varian 300 MHz instrument using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were recorded on EI-MS DIP-300 spectrometer. All other chemicals were purchased from local chemical suppliers and were used without further purification.

General procedure for the synthesis of bis-[1,5]-benzothiazepines (3a-e)

To a mixture of bis-chalcone (0.01 mole) and 2-aminothiophenol (0.02 mole) in methanol was added 2-3 drops of piperidine and it was refluxed for 6-8 hours. It was acidified with glacial acetic acid and further refluxed for two hours and cooled. The reaction mixture was left overnight at room temperature. The solid thus obtained was washed

with water and was filtered. In a few cases it was necessary to pour the reaction mixture in water and the solid thus obtained was filtered and crystallized from methanol.

Spectral data of synthesized compounds (3a-e):

2,4-bis(*E*)-2-(4-chlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol (3a): Yellow solid. mp 140-142 ^{o}C, IR (ν_{max}, cm^{-1}): 3449 (Ar-OH), 1611, 1566 (C=N), 751, 714 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.10 (2H, dd, CH_2 , J=12.24 Hz, 11.94 Hz), 3.47 (2H, dd, CH_2, J= 8.49 Hz, 5.13 Hz), 4.93 (1H, dd, CH, J= 4.95 Hz, 4.92 Hz), 5.15 (1H, dd, CH, J= 4.17 Hz, 4.89 Hz), 6.54-8.39 (19H, m, ArH), 15.02 (1H, s, Ar-OH) ; ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 39.71, 39.99 (CH_2), 59.43, 59.63 (CH), 76.37, 76.99, 77.42, 115.18, 118.16, 118.65, 124.25, 125.18, 125.65, 126.80, 126.96, 127.56, 128.06, 128.49, 128.90, 129.95, 130.19, 130.83, 131.56, 132.42, 133.49, 134.03, 134.97, 135.26, 136.77, 141.39, 148.39, 148.57, 165.33, 172.98; MS (Scanning mode ES^{+}) m/z : 637 (M+1): Anal. calcd for $C_{36}H_{26}Cl_2N_2OS_2$: C, 67.81; H, 4.11; N, 4.39; Found: C, 67.84; H, 4.13; N, 4.43.

2,4-bis(E)-2,3-dihydro-2-(4-methoxyphenyl)benzo[b][1,4]thiazepine-4-yl)phenol (3b); Yellow solid. mp 176-178 ^{o}C; IR (ν_{max}, cm^{-1}): 3448 (Ar-OH), 1599, 1510 (C=N), 1250, 1212 (-OCH_3), 756, 629 (C-S). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.12 (2H, dd, CH_2 , J=11.7, 11.7 Hz), 3.49 (2H, dd, CH_2, J= 4.8, 4.8 Hz), 3.78 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.18 (2H, dd, 2CH, J=4.8, 4.5 Hz), 6.83-8.35 (19H, m, ArH); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 29.70, 37.32, 39.02 (CH_2), 55.31, 55.41 (CH), 60.06, 114.19, 118.97, 125.07, 125.68, 126.83, 127.45, 127.70, 129.06, 129.96, 130.20, 130.46, 133.75, 135.27, 135.35, 135.35, 144.18, 148.07, 159.43, 161.66, 167.06, 173.29: MS (Scanning mode ES^{+}) m/z: 629 (M+1); Anal. calcd for $C_{38}H_{32}N_2O_3S_2$: C, 72.58; H, 5.13; N, 4.46; Found: C, 72.61; H, 5.17; N, 4.49.

2,4-bis(E)-2-(4-flurophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol (3c): Yellow solid; mp 142-144^{o}C; IR (ν_{max}, cm^{-1}): 3070 (-OH), 1597, 1506 (C=N), 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.04 (2H, dd, CH_2 , J=11.52, 3.36 Hz), 3.75 (2H, dd, CH_2, J=5.19, 4.11 Hz), 5.02 (1H, dd, CH, J= 7.77, 7.80 Hz), 5.13 (1H, dd, CH, J= 7.77, 5.43 Hz), 6.58-7.16 (19H, m, ArH), 15.10 (1H, s, Ar-OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 39.70 , 39.98 (CH_2) , 40.25 , 40.53 , 59.46 (CH), 76.58, 77.00, 77.43, 111.39, 115.58, 115.86, 117.83, 118.62, 125.29, 126.29, 126.78, 127.80, 129.88, 130.16, 130.76, 131.76, 135.24, 136.93; MS (Scanning mode ES^{+}) m/z: 605 (M+1). Anal. calcd for $C_{36}H_{26}F_2N_2OS_2$: C, 71.50; H, 4.33; N, 4.63. Found: C, 71.54; H, 4.36; N, 4.67.

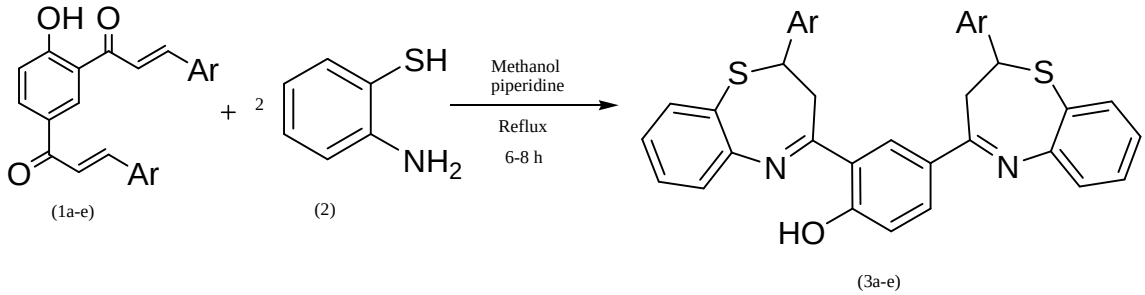
2,4-bis(E)-2,3-dihydro-2-(thiophen-2-yl)benzo[b][1,4]thiazepin-4-yl)phenol (3d): Yellow solid, mp: 164-166 ^{o}C; IR (ν_{max}, cm^{-1}): 3362 (Ar-OH), 1606, 1558 (C=N), 688, 662 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.09 (2H, dd, CH_2, J=11.1, 11.4 Hz), 3.57 (2H, dd, CH_2, J=14.8, 7.2 Hz), 5.32 (1H, dd, CH, J= 3, 6.3 Hz), 5.48 (1H, dd, CH, J= 6.3, 5.7 Hz), 6.60-8.16 (17H, m, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 37.58, 38.54, 55.46, 55.55, 115.2, 117.9, 118.6, 118.6, 118.7, 124.1, 124.2, 124.5, 124.8, 125.3, 125.4, 126.8, 126.9, 128.4, 128.7, 129.8, 130.4, 131.6,132.1, 135.7, 136.8, 146.4, 148.1, 148.6, 167.6,172.9; MS (Scanning mode ES^{+}) m/z: 580 (M^{+}); Anal. calcd for $C_{32}H_{24}N_2OS_4$; Required: C, 66.17; H, 4.17; N 4.81. Found: C, 66.20; H, 4.21; N, 4.84.

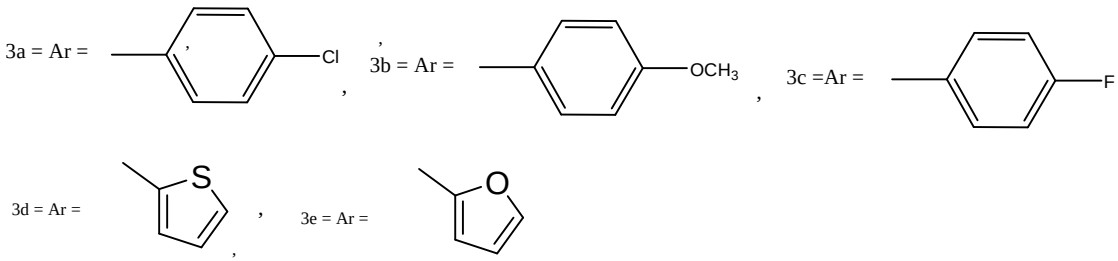
2,4-bis(E)-2-(furan-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepine-4-yl)phenol (3e): Yellow solid, mp: 170-172 ^{o}C; IR (ν_{max}, cm^{-1}): 3362 (Ar-OH), 1606, 1558 (C=N), 688, 662 (C-S); ^{1}H NMR (300 MHz; $CDCl_3$) δ ppm: 3.09 (2H, dd, CH_2, J=12.3, 11.7 Hz), 3.59 (2H, dd, CH_2, J=9.3, 13.2 Hz), 4.14 (1H, dd, CH, J=6.9, 7.2 Hz), 5.44 (1H, dd, CH, J=4.8, 4.5 Hz), 6.60-7.68 (17H, m, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 37.20, 37.34, 54.36, 54.45, 116.2, 116.9, 118.3, 118.9, 124.2, 124.7, 124.9, 125.1, 125.3, 126.1, 126.5, 128.2, 128.6, 130.2, 130.5, 131.4, 132.7, 135.4, 136.8, 146.1, 146.9, 147.6, 165.6, 171.9; MS (Scanning mode ES^{+}) m/z: 548 (M^{+}); Anal. calcd for $C_{32}H_{24}N_2O_3S_2$: Required: C, 70.05; H, 4.41; N, 5.51. Found: C, 70.09; H, 4.45; N, 5.54.

RESULTS AND DISCUSSSION

We describe herein the synthesis of bis-[1,5]-benzothiazepines (3a-e) from bis–chalcones (1a-e). For the synthesis of target compound, the starting compound 2,4-diacyl phenol was prepared by the Friedal-Crafts acylation reaction of 2-hydroxyacetophenone with acetyl chloride in presence of anhydrous $AlCl_3$ in CS_2. Bis-chalcones (1a-e) were prepared by reacting 2,4-diacyl phenol and variously substituted aromatic aldehydes in the presence of base by conventional Claisen-Schmidt condensation [17]. A series of bis-(1,5)-benzothiazepines (3a-e) were synthesized by reaction of bis-chalcones (1a-e) with two equivalent of 2-aminothiophenol (2) in methanol in presence of piperidine catalyst in good yield. All the synthesized compounds were characterized by comparing FTIR, ^{1}H NMR, ^{13}C NMR spectral data with the reported 1,5-benzothiazepines [18-19]. The IR spectrum of compound (3a-e) exhibited sharp band in the region 3070-3362 cm^{-1} for –OH stretching of phenolic ring, band at 1510-1611 cm^{-1} for C=N stretching and band at 662-756 for C-S stretching. The ^{1}H NMR spectrum of the same compounds (3a-e) displayed two doublet of doublet peaks in the region δ 3.04-3.12 and δ 3.47-3.59 for two methylene protons and two doublet of doublet peaks at δ 4.14-5.32 and δ 5.13-5.48 for two methine protons. The phenolic –OH displayed singlet peak in

the region δ 15.02-15.10. The aromatic protons of the compound appear as multiplates at δ 6.54-8.39. The ^{13}C NMR spectrum of the compounds (3a-e) displayed the peaks in the region δ 37.20-39.99 and δ 49.46-59.43 for aliphatic –CH_2 and –CH carbon respectively.





Scheme 1. Synthesis of bis-[1,5]-benzothiazepines

Table 1. Physical data of bis-[1,5]-benzothiazepines

Sr. No	Product	Molecular formula	Molecular weight g	Melting point °C	Yield %
1	3a	$C_{36}H_{26}Cl_2N_2OS_2$	637	140-142	72
2	3b	$C_{38}H_{32}N_2O_3S_2$	628	176-178	74
3	3c	$C_{36}H_{26}F_2N_2OS_2$	604	142-144	66
4	3d	$C_{32}H_{24}N_2OS_4$	580	170-172	70
5	3e	$C_{32}H_{24}N_2O_3S_2$	548	164-166	64

Antibacterial activity

All the synthesized compounds were screened *in vitro* for their antimicrobial activity against Gram-positive bacteria viz. *Staphylococcus aureus, Bacillus subtilis* and Gram-negative bacteria viz. *Escherichia coli*, *Pseudomonas aeruginosa* using ciprofloxacin as standard antibacterial. The antibacterial activity was determined by the cup plate method on agar nutrient media at the concentration of 100 µg per disk using DMSO as solvent. The results of the antibacterial activity are presented in table 2. An examination of antibacterial activity data revealed that the compounds 3a, 3b and 3e having 4-Cl, 4-OCH_3 and furan substituents respectively have showed significant activities against both gram-positive and gram-negative bacteria.

Table 2: Antibacterial activity of compounds 3a-e

Compound	Zone of inhibition (in mm)			
	S. aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***
3a	26	25	27	26
3b	27	26	29	28
3c	18	17	19	18
3d	17	16	17	16
3e	22	24	24	23
Ciprofloxacin	32	34	35	34
DMSO	---	---	---	---

CONCLUSION

In summary, we have synthesized bis-[1,5]-benzothiazepines from easily accessible bis-chalcone precursors. The structures of all the compounds were characterized on the basis of analytical and spectral data. The synthesized compounds were evaluated for their *in vitro* antibacterial activity against gram-positive and gram-negative bacteria and showed significant antibacterial activity. We believe that continuous research on the reported compounds offers scope for extension of variety of other substrates to form products with diverse biological activity.

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