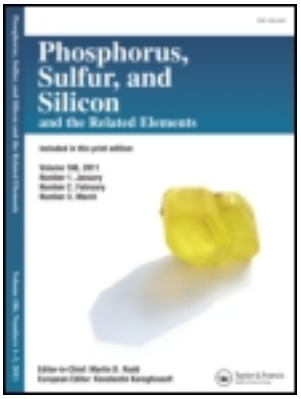


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

An Efficient Synthesis and Antimicrobial Studies of Bioactive 4H-1,4-Benzothiazine and Their Sulfone Derivatives

Naveen Gautam [a], Yogesh Dixit [a], Rahul Dixit [a], Sudesh Kumar Gupta [a] & Dinesh Chand Gautam [a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, 302004, India
Accepted author version posted online: 01 Nov 2012.

To cite this article: Naveen Gautam, Yogesh Dixit, Rahul Dixit, Sudesh Kumar Gupta & Dinesh Chand Gautam (2013) An Efficient Synthesis and Antimicrobial Studies of Bioactive 4H-1,4-Benzothiazine and Their Sulfone Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:8, 1127-1136, DOI: 10.1080/10426507.2012.740703

To link to this article: http://dx.doi.org/10.1080/10426507.2012.740703

Phosphorus, Sulfur, and Silicon, 188:1127–1136, 2013

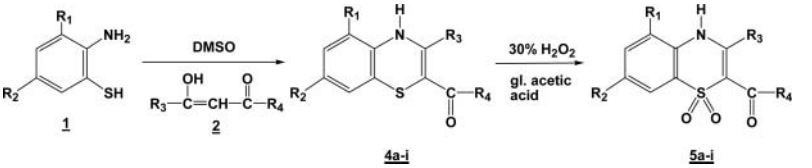
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.740703

Taylor & Francis
Taylor & Francis Group

AN EFFICIENT SYNTHESIS AND ANTIMICROBIAL STUDIES OF BIOACTIVE 4H-1,4-BENZOTHIAZINE AND THEIR SULFONE DERIVATIVES

Naveen Gautam, Yogesh Dixit, Rahul Dixit, Sudesh Kumar Gupta, and Dinesh Chand Gautam
Department of Chemistry, University of Rajasthan, Jaipur 302004, India

GRAPHICAL ABSTRACT



Abstract *4H-1,4-benzothiazines were prepared by condensation followed by oxidative cyclization of substituted 2-aminobenzenethiols with β-diketones in dimethylsulfoxide. On refluxing with 30% hydrogen peroxide in glacial acetic acid, 4H-1,4-benzothiazines yielded 4H-1,4-benzothiazine-1,1-dioxides. Structural evaluation has been done by spectral and elemental analysis. All the synthesized compounds were evaluated for their antibacterial and antifungal activity and all these have shown moderate to high activity against the test microbes.*

Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements *for the following free supplemental files:* Additional text, figures and tables.

Keywords 4H-1,4-benzothiazine; heterocycles; sulfones and antimicrobial activity

INTRODUCTION

4H-1,4-benzothiazine and their analogs constitute an important class of bioactive heterocycles. Literature studies have shown their various chemotherapeutic importances.[1–7] Many of their derivatives are in clinical use[8] as antipsycotics, analgesics, diuretics, antitussives and antihistamics, central nervous system depressants, antiinflammatories, anticancer, tranquilizers, and antibiotic agents.

Received 26 July 2012; accepted 14 October 2012.
Authors are thankful to the Department of Chemistry and the Department of Botany, University of Rajasthan, Jaipur (India) for providing laboratory facilities. Authors are also thankful to Central Drug Research Institute, Lucknow (India) for providing IR, NMR, and Mass spectra. UGC Research Award Scheme, New Delhi is duly acknowledged for financial support.

Address correspondence to Dr. Naveen Gautam, Department of Chemistry, University of Rajasthan, 692, Mahaveer Nagar, Tonk Road, Jaipur- 302018, India. E-mail: ngautam70@yahoo.co.in

4H-1,4-benzothiazines structurally resemble 10H-phenothiazines in having a fold along nitrogen sulfur axis. The molecular configurations of these compounds are between planar and tetragonal folded symmetry. In the later configuration, the nitrogen and sulfur atoms are in SP^3 hybridization state, and the plane containing benzene rings are folded along the axis passing through nitrogen and sulfur. Their nitrogen–sulfur axis is responsible for a number of pharmacological activities. Their pharmacological applications have stimulated our interest to extend synthetic, structural, and antimicrobial studies of 4H-1,4-benzothiazine in search of better medicinal agents.

The oxidation of sulfide linkage in benzothiazine leads to formation of the sulfones. It was considered worthwhile to undertake structural investigation to understand the oxidation behavior of benzothiazine and to study the change in spectral feature caused by conversion of sulfide linkage into sulfones.

Kerby-Bauer[9,10] procedure has been used for the study of antimicrobial activity of newly synthesized 4H-1,4-benzothiazine and their sulfone derivatives.

RESULTS AND DISCUSSION

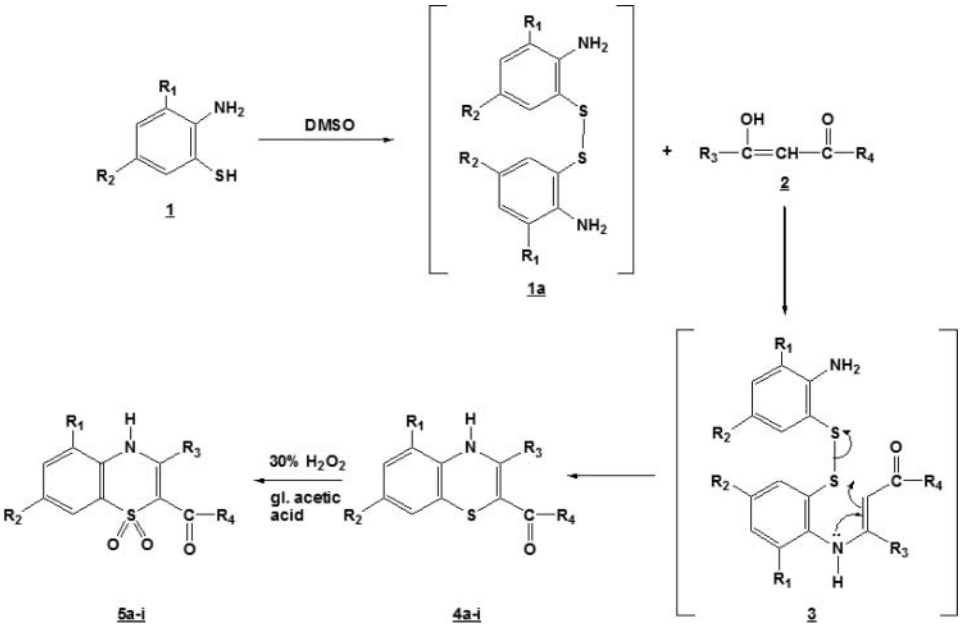
Substituted 4H-1,4-benzothiazines have been synthesized by condensation and oxidative cyclization of 2-amino-3-fluoro/2-amino-3-isopropyl/2-amino-5-isopropyl benzenethiol **1** with β-diketones **2** in dimethyl sulfoxide (DMSO). The reaction is believed to proceed through the formation of an intermediate enaminoketone[11,12] **3**. Under the above experimental conditions, 2-amino-3-fluoro/2-amino-3-isopropyl/2-amino-5-isopropyl benzenethiol **1** is readily oxidized to bis-(2-aminophenyl) disulfide **1a** which cyclizes to 4H-1,4-benzothiazines **4a–i** by scission of sulfur–sulfur bond due to the high reactivity of the α-position of enaminoketones system **3** toward nucleophilic attack. The synthesized substituted 4H-1,4-benzothiazines were converted into corresponding sulfones **5a–i** by oxidation under reflux conditions with 30% hydrogen peroxide in glacial acetic acid[13–18] (Scheme 1).

The physical and analytical data of the synthesized compounds are given in Tables 1 and 2.

IR Spectra (Table 3)

All the 4H-1,4-benzothiazines **4a–i** exhibit a single sharp peak in the region 3410–3250 cm^{-1} due to N-H stretching vibrations. The sharp bands observed in the region 1730–1670 cm^{-1} are attributed to C=O stretching vibrations of carbonyl group. All the 4H-1,4-benzothiazines showed a peak in the region 1060–1005 cm^{-1} due to C-S-C deformation vibrations. Compounds **4c** and **4g** showed two peaks in the regions 1270–1250 cm^{-1} and 1080–1060 cm^{-1} due to asymmetric and symmetric vibrations of OCH_3 groups. Compounds **4a–g** exhibit two bands in the region 1470–1440 cm^{-1} and 1355–1330 cm^{-1} due to CH-deformation vibrations of CH_3 group. Compounds **4f–h** showed a peak in the region 1390–1360 cm^{-1} due to isopropyl deformation vibrations. Compound **4a** exhibits a single sharp peak in the region 695 cm^{-1} due to C-Br stretching vibrations. Compounds **4d** and **4f** exhibit a peak in the region 1340–1330 cm^{-1} and 1130–1120 cm^{-1} due to asymmetric and symmetric vibrations of CF_3 group.

Further, in compounds **4a–e** and **4i**, bands due to C-F stretching vibrations appeared in the region 1275–1260 cm^{-1}.



Scheme 1

The vibrational frequency corresponding to each substituent is shifted to higher frequency in all the synthesized 4H-1,4-benzothiazine sulfones **5a–i**. Sulfone derivatives **5a–i** exhibit a sharp intense peak in the region 1370–1350 cm^{-1} in chloroform which can be assigned to the asymmetric stretching (ν_3) mode of sulfonyl group, while in solid state, this absorption band splits into three bands and appears in the region 1375–1360 cm^{-1}, 1325–1285 cm^{-1}, and 1290–1260 cm^{-1}. The asymmetric stretching vibrations in the sulfones are strongly affected on passing from the solution to the crystalline state. The symmetric stretching vibrations (ν_1) give rise to high intensity doublet in potassium bromide disc in the region 1185–1145 cm^{-1}, whereas in solution it appears at 1180–1140 cm^{-1}. Hence, these frequencies are slightly affected due to the state of aggregation. The bands appeared in the region 585–550 cm^{-1} can be attributed to bending vibration (ν_2).[17]

^{1}H NMR and ^{13}C NMR Spectra (Tables 4 and 5)

All the synthesized 4H-1,4-benzothiazines and their sulfones (**4a–i** and **5a–i**) exhibit a singlet at δ 9.06–7.92 ppm due to the NH-proton. Aromatic protons show multiplets in the region δ 8.10–6.98 ppm. A single sharp peak observed in the region δ 2.55–2.28 ppm in compounds **4a–g** and **5a–g** can be assigned to CH_3 group present at C_3. Two singlets are observed at δ 3.82–3.81 ppm and δ 3.85 ppm in compound **4c, 5c** due to two OCH_3 groups present at ortho- and para-positions in benzoyl side chain at C_2. Compounds **4g** and **5g** exhibit a singlet at δ 3.82 and 3.85 ppm, respectively, due to OCH_3 proton at ortho-position in the benzoyl side chain at C_2. The multiplets observed in the region δ 2.26–2.21 ppm are attributed to C-H proton of isopropyl group in compounds **4f–h** and **5f–h**. Compounds **4f–h** and **5f–h** also show a doublet at δ 1.48–1.40 ppm due to CH_3 proton of isopropyl group.

Table 1 Characterization data of 4H-1,4-benzothiazines **4a–i**

Comp. No.	R_1	R_2	R_3	R_4	mp (range) °C	Yield%	Molecular formula	% found (calcd.)		
								C	H	N
4a	F	H	CH_3	$C_6H_4Br(p)$	102–104	57	$C_{16}H_{11}NSOFBr$	52.59 (52.74)	3.01 (3.02)	3.82 (3.84)
4b	F	H	CH_3	$C_6H_4F(p)$	121–123	51	$C_{16}H_{11}NSOF_2$	63.21 (63.36)	3.61 (3.63)	4.60 (4.62)
4c	F	H	CH_3	$C_6H_3(OCH_3)_2(o,p)$	99–101	60	$C_{18}H_{16}NSO_3F$	62.52 (62.52)	4.61 (4.63)	4.04 (4.05)
4d	F	H	CH_3	CF_3	160–162	53	$C_{11}H_7NOSF_4$	47.60 (47.65)	2.51 (2.52)	5.03 (5.05)
4e	F	H	CH_3	C_6H_5	90–92	54	$C_{16}H_{12}NOSF$	67.28 (67.36)	4.20 (4.21)	4.90 (4.91)
4f	$CH(CH_3)_2$	H	CH_3	CF_3	145–146	68	$C_{14}H_{14}NSOF_3$	55.75 (55.81)	4.63 (4.65)	4.64 (4.65)
4g	$CH(CH_3)_2$	H	CH_3	$C_6H_4OCH_3(o)$	180–182	66	$C_{20}H_{21}NSO_2$	70.68 (70.79)	6.18 (6.19)	4.11 (4.12)
4h	H	$CH(CH_3)_2$	C_6H_5	C_6H_5	215–217	70	$C_{24}H_{21}NSO$	77.55 (77.62)	5.64 (5.66)	3.76 (3.72)
4i	F	H	C_6H_5	C_6H_5	85–86	52	$C_{21}H_{14}NSOF$	72.60 (72.62)	4.02 (4.03)	4.01 (4.03)

Table 2 Characterization data of 4H-1,4-benzothiazine-1,1-dioxides (sulfones) **5a–i**

Comp. No.	R_1	R_2	R_3	R_4	mp (range) °C	Yield%	Molecular formula	% found (calcd.) C	H	N
5a	F	H	CH_3	C_6H_4Br(p)	260–262	70	$C_{16}H_{11}NSO_3FBr$	48.35 (48.48)	2.76 (2.77)	3.51 (3.53)
5b	F	H	CH_3	C_6H_4 F(p)	280–282	68	$C_{16}H_{11}NSO_3F_2$	57.21 (57.31)	3.26 (3.28)	4.15 (4.17)
5c	F	H	CH_3	C_6H_3 $(OCH_3)_2$(o,p)	288–289	62	$C_{18}H_{16}NSO_5F$	57.09 (57.29)	4.22 (4.24)	3.70 (3.71)
d	F	H	CH_3	CF_3	222–224	65	$C_{11}H_7NSO_3F_4$	42.03 (42.71)	2.28 (2.26)	4.48 (4.53)
5e	F	H	CH_3	C_6H_5	264–265	71	$C_{16}H_{12}NSO_3F$	60.45 (60.56)	3.76 (3.78)	4.39 (4.41)
5f	CH $(CH_3)_2$	H	CH_3	CF_3	325–327	75	$C_{14}H_{14}NSO_3F_3$	50.35 (50.45)	4.19 (4.20)	4.18 (4.20)
5g	CH $(CH_3)_2$	H	CH_3	$C_6H_4OCH_3$(o)	322–324	76	$C_{20}H_{21}NSO_4$	64.51 (64.69)	5.64 (5.66)	3.76 (3.77)
5h	H	$CH(CH_3)_2$	C_6H_5	C_6H_5	315–316	58	$C_{24}H_{21}NSO_3$	71.58 (71.46)	5.19 (5.21)	3.44 (3.47)
5i	F	H	C_6H_5	C_6H_5	235–237	61	$C_{21}H_{14}NSO_3F$	66.21 (66.49)	3.67 (3.69)	3.68 (3.69)

Table 3 Infrared spectral data of 4H-1,4-benzothiazines **4a–i** and their sulfones **5a–i***

Comp. No.	R_1	R_2	R_3	R_4	>N−H Str.	>C=O Str.	C−O−C Str.	C-Br Str.	Ar (C-F) Str.	C−S−C Deformation
4a	F	H	CH_3	$C_6H_4Br(p)$	3355	1715	—	695	1265	1030
5a					(3465)	(1740)		(700)	(1270)	(1040)
4b	F	H	CH_3	$C_6H_4F(p)$	3360	1720	—	—	1260	1025
5b					(3420)	(1750)			(1265)	(1030)
4c	F	H	CH_3	C_6H_3 $(OCH_3)_2(o,p)$	3345	1715	1270,1080	—	1265	1060
5c					(3430)	(1718)	(1275,1085)		(1268)	(1070)
4d	F	H	CH_3	CF_3	3410	1730	—	—	1275	1040
5d					(3510)	(1755)			(1280)	(1050)
4e	F	H	CH_3	C_6H_5	3300	1700	—	—	1270	1010
5e					(3440)	(1715)			(1275)	(1025)
4f	$CH(CH_3)_2$	H	CH_3	CF_3	3290	1695	—	—	—	1015
5f					(3385)	(1705)				(1025)
4g	$CH(CH_3)_2$	H	CH_3	$C_6H_4OCH_3$ (o)	3260	1670	1250,1060	—	—	1005
5g					(3380)	(1690)	(1254,1064)			(1030)
4h	H	$CH(CH_3)_2$	C_6H_5	C_6H_5	3250	1690	—	—	—	1020
5h					(3330)	(1710)				(1035)
4i	F	H	C_6H_5	C_6H_5	3350	1710	—	—	1270	1015
5i					(3449)	(1730)			(1274)	(1020)

*Spectral data of sulfones are given in ().

Table 4 ^{1}H NMR and ^{13}C NMR spectral data of 4H-1,4-benzothiazines **4a–i**

Comp. No.	^{1}H NMR (DMSO-d_6, 300 MHz), δ ppm	^{13}C NMR ($CDCl_3$, 300 MHz), δ ppm
4a	8.50 (s, >NH), 7.72–7.01 (m, J = 8.58 Hz, Ar-H), 2.34 (s, -CH_3 proton at C_3)	113.1 (C-2), 138.2 (C-3), 148.8 (C-5), 112.7 (C-6), 120.9 (C-7), 126.1 (C-8), 187.7 (C of CO at C_2), 128.2–136.5 (C of C_6H_4Br at C_2), 16.9 (CH_3 at C_3)
4b	8.61 (s, >NH), 7.60–6.98 (m, J = 8.61 Hz, Ar-H), 2.40 (s, -CH_3 proton at C_3)	113.6 (C-2), 138.4 (C-3), 148.5 (C-5), 113.2 (C-6), 120.2 (C-7), 125.9 (C-8), 187.3 (C of CO at C_2), 116.4–165.5 (C of C_6H_4F at C_2), 16.2 (CH_3 at C_3)
4c	8.71 (s, >NH), 7.80–7.25 (m, J = 8.60 Hz, Ar-H), 2.38 (s, -CH_3 proton at C_3), 3.81 (s, OCH_3 protons at ortho-position in benzoyal side chain at C_2), 3.85 (s, OCH_3 protons at para-position in benzoyal side chain at C_2)	113.3 (C-2), 138.9 (C-3), 150.4 (C-5), 113.8 (C-6), 120.4 (C-7), 125.8 (C-8), 186.8 (C of CO at C_2), 58.4 (C of OCH_3 of $-COC_6H_3(OCH_3)_2$ (o,p) at C_2), 15.8 (CH_3 at C_3)
4d	9.01 (s, >NH), 7.25–6.98 (m, J = 8.57 Hz, Ar-H), 2.52 (s, -CH_3 protons at C_3)	114.2 (C-2), 135.8 (C-3), 148.4 (C-5), 112.6 (C-6), 121.2 (C-7), 124.9 (C-8), 188.8 (C of CO at C_2), 129.2 (CF_3 at C_2), 16.8 (CH_3 at C_3)
4e	8.25 (s, >NH), 8.02–7.10 (m, J = 8.55 Hz, Ar-H), 2.28 (s, -CH_3 protons at C_3)	113.2 (C-2), 139.4 (C-3), 150.5 (C-5), 112.4 (C-6), 121.4 (C-7), 125.9 (C-8), 188.6 (C of CO at C_2), 128.4–135.9 (C of C_6H_5 at C_2), 17.0 (CH_3 at C_3)
4f	8.89 (s, >NH), 7.80–7.60 (m, J = 8.53 Hz, Ar-H), 2.52 (s, -CH_3 protons at C_3), 2.22 (m, J = 5.2 Hz, C-H proton of isopropyl group), 1.40 (d, J = 4.1 Hz, CH_3 protons of isopropyl group)	116.9 (C-2), 136.1 (C-3), 136.0 (C-5), 124.4 (C-6), 118.9 (C-7), 128.6 (C-8), 195.8 (C of CO at C_2), 129.2 (CF_3 at C_2), 16.8 (CH_3 at C_3), 23.2 (CH of isopropyl group at C_5), 25.3 (CH_3 of isopropyl group at C_5)
4g	8.20 (s, >NH), 7.75–7.20 (m, J = 8.55 Hz, Ar-H), 2.30 (s, -CH_3 proton at C_3), 3.82 (s, OCH_3 protons of $COC_6H_4(OCH_3)$ group at C_2), 2.21 (m, J = 6.3 Hz, C-H proton of isopropyl group), 1.45 (d, J = 4.4 Hz, CH_3 protons of isopropyl group)	114.2 (C-2), 139.2 (C-3), 135.8 (C-5), 124.5 (C-6), 117.9 (C-7), 128.1 (C-8), 188.5 (C of CO at C_2), 115.2–162.3 (C of C_6H_5 at C_2), 55.2 (C of OCH_3 of $-COC_6H_4(OCH_3)$ (o) at C_2) 16.9 (CH_3 at C_3), 22.9 (CH of isopropyl group at C_5), 25.2 (CH_3 of isopropyl group at C_5)
4h	8.10 (s, >NH), 7.80–7.75 (m, J = 8.51 Hz, Ar-H), 2.25 (m, J = 5.3 Hz, C-H proton of isopropyl group), 1.42 (d, J = 4.5 Hz, CH_3 protons of isopropyl group)	110.2 (C-2), 142.4 (C-3), 116.2 (C-5), 123.2 (C-6), 138.5 (C-7), 128.1 (C-8), 188.2 (C of CO at C_2), 126.9–137.2 (C of C_6H_5 at C_2), 126.4–135.5 (C of C_6H_5 at C_3), 32.2 (CH of isopropyl group at C_7), 25.2 (CH_3 of isopropyl group at C_7)
4i	7.92 (s, >NH), 7.80–7.17 (m, J = 8.60 Hz,Ar-H)	108.6 (C-2), 142.1 (C-3), 148.8 (C-5), 113.6 (C-6), 121.0 (C-7), 125.9 (C-8), 187.4 (C of CO at C_2), 126.7–136.9 (C of C_6H_5 at C_2), 126.9–134.2 (C of C_6H_5 at C_3)

Figure S1 (Supplemental Materials are available online) contains the ^{13}C NMR spectrum of **4a** as a representative example.

^{13}C NMR spectra of the synthesized 4H-1,4-benzothiazines **4a–i** and their sulfones **5a–i** are given in Tables 4 and 5, respectively.

Table 5 ^{1}H NMR and ^{13}C NMR spectral data of 4H-1,4-benzothiazine sulfones **5a–i**

Comp. No.	^{1}H NMR (DMSO-d_6, 300 MHz), δ ppm	^{13}C NMR ($CDCl_3$, 300 MHz), δ ppm
5a	8.55 (s, >NH), 7.75–7.05 (m, J = 8.60 Hz, Ar-H), 2.40 (s, -CH_3 proton at C_3)	103.2 (C-2), 147.5 (C-3), 149.7 (C-5), 119.6 (C-6), 122.8 (C-7), 121.2 (C-8), 187.5 (C of CO at C_2), 128.5–136.2 (C of C_6H_4Br at C_2), 16.5 (CH_3 at C_3)
5b	8.65 (s, >NH), 7.64–7.00 (m, J = 8.65 Hz, Ar-H), 2.45 (s, -CH_3 proton at C_3)	104.2 (C-2), 146.4 (C-3), 150.2 (C-5), 120.1 (C-6), 123.1 (C-7), 120.7 (C-8), 187.8 (C of CO at C_2), 116.6–165.8 (C of C_6H_4F at C_2), 15.8 (CH_3 at C_3)
5c	8.76 (s, >NH), 7.84–7.30 (m, J = 8.64 Hz, Ar-H), 2.47 (s, -CH_3 proton at C_3), 3.82 (s, OCH_3 protons at ortho-position in benzoyal side chain at C_2), 3.85 (s, OCH_3 protons at para-position in benzoyal side chain at C_2)	105.2 (C-2), 150.9 (C-3), 151.6 (C-5), 121.3 (C-6), 124.6 (C-7), 122.6 (C-8), 186.2 (C of CO at C_2), 58.2 (C of OCH_3 of –COC_6H_3 $(OCH_3)_2$ (o,p) at C_2), 15.5 (CH_3 at C_3)
5d	9.06 (s, >NH), 7.32–6.99 (m, J = 8.60 Hz, Ar-H), 2.55 (s, -CH_3 protons at C_3)	102.4 (C-2), 151.4 (C-3), 150.2 (C-5), 118.9 (C-6), 125.3 (C-7), 121.6 (C-8), 188.4 (C of CO at C_2), 128.8 (CF_3 at C_2), 16.3 (CH_3 at C_3)
5e	8.30 (s, >NH), 8.10–7.12 (m, J = 8.58 Hz, Ar-H), 2.32 (s, -CH_3 protons at C_3)	102.8 (C-2), 145.1 (C-3), 153.4 (C-5), 119.4 (C-6), 122.5 (C-7), 120.5 (C-8), 188.2 (C of CO at C_2), 128.6–135.4 (C of C_6H_5 at C_2), 16.7 (CH_3 at C_3)
5f	8.94 (s, >NH), 7.86–7.65 (m, J = 8.55 Hz, Ar-H), 2.54 (s, -CH_3 protons at C_3), 2.25 (m, J = 5.5 Hz, C-H proton of isopropyl group), 1.44(d, J = 4.2 Hz, CH_3 protons of isopropyl group)	103.9 (C-2), 146.8 (C-3), 137.6 (C-5), 131.6 (C-6), 120.6 (C-7), 125.8 (C-8), 195.1 (C of CO at C_2), 128.5 (CF_3 at C_2), 16.4 (CH_3 at C_3), 23.5 (CH of isopropyl group at C_5), 25.3 (CH_3 of isopropyl group at C_5)
5g	8.26 (s, >NH), 7.80–7.22 (m, J = 8.58 Hz, Ar-H), 2.32 (s, -CH_3 proton at C_3), 3.85 (s, OCH_3 protons of COC_6H_4 (OCH_3) group at C_2), 2.24 (m, J = 6.5 Hz, C-H proton of isopropyl group), 1.48 (d, J = 4.6 Hz, CH_3 protons of isopropyl group)	105.4 (C-2), 144.6 (C-3), 136.9 (C-5), 133.6 (C-6), 119.7 (C-7), 124.5 (C-8), 188.9 (C of CO at C_2), 115.2–162.3 (C of C_6H_5 at C_2), 55.2 (C of OCH_3 of –COC_6H_4 (OCH_3) (o) at C_2) 16.2 (CH_3 at C_3), 23.4 (CH of isopropyl group at C_5), 25.2 (CH_3 of isopropyl group at C_5)
5h	8.14 (s, >NH), 7.83–7.79 (m, J = 8.55 Hz, Ar-H), 2.26 (m, J = 5.5 Hz, C-H proton of isopropyl group), 1.45 (d, J = 4.7 Hz, CH_3 protons of isopropyl group)	100.4 (C-2), 156.4 (C-3), 118.6 (C-5), 132.21(C-6), 140.4 (C-7), 123.9 (C-8), 188.6 (C of CO at C_2), 126.9–137.2 (C of C_6H_5 at C_2), 127.1–134.9 (C of C_6H_5 at C_3), 32.5 (CH of isopropyl group at C_7), 25.4 (CH_3 of isopropyl group at C_7)
5i	7.95 (s, >NH), 7.85–7.20 (m, J = 8.64 Hz,Ar-H)	96.6 (C-2), 155.2 (C-3), 151.3 (C-5), 130.5 (C-6), 123.0 (C-7), 122.8 (C-8), 187.1 (C of CO at C_2), 126.3–136.5 (C of C_6H_5 at C_2), 126.4–134.6 (C of C_6H_5 at C_3)

Antimicrobial Activity

Synthesized compounds were tested for their antifungal activity against *Aspergillus niger* and *Aspergillus flavus* while antibacterial activity was tested against *Staphylococcus aureus* and *Peudomonas fluoroscence*. The activity of these compounds was tested by Kerby-Bauer procedure[9,10] (filter paper disc method). This method allows for the rapid

determination of the efficiency of a drug by measuring the diameter of the zone of inhibition that results from diffusion of the agent into the medium surrounding the disc.

The antifungal and antibacterial activities were determined by measuring the inhibition zone around the disc. The antimicrobial activity of 4H-1,4-benzothiazine and their sulfone derivatives was measured in terms of activity index.

From the antimicrobial activity data (Table S1 Supplemental Materials are available online), it may be concluded that synthesized compound showed good and moderate activity against the microbes.

CONCLUSIONS

The structures proposed for the synthesized compounds were well supported by elemental analysis and spectroscopic data. All these synthesized 4H-1,4-benzothiazines and their sulfone derivatives are novel and showed good and moderate antifungal and antibacterial activities against the respective *S. aureus, P. fluoroscence* (bacteria) and *A. niger, A. flavus* (fungi). Hence, these compounds can be use as an antifungal and antibacterial drugs after that study and analysis of their biomedical aspects. Further biomedical researches are required.

EXPERIMENTAL

All the melting points are uncorrected. The purity of synthesized compound has been checked by thin layer chromatography. IR spectra were recorded in KBr on SHIMADZU 8400S FTIR spectrophotometer. The NMR spectra (^{1}H NMR and ^{13}C NMR) have been recorded at 300 MHz on JEOL AL 300 FT NMR using TMS as internal standard in $CDCl_3$/DMSO-d_6. Mass spectra were recorded on JEOL SX 102/DA 600 using Argon/Xenon as FAB (Fast Atom Bombarding) gas.

Synthesis of Substituted 4H-1,4-benzothiazines 4a–i

To a stirred suspension of β-diketone (**2**; 0.01 mol) in dimethyl sulfoxide (5 mL) was added 2-amino-3-fluoro/2-amino-3-isopropyl/2-amino-5-isopropyl benzenethiol (**1**; 0.01 mol) and the resulting mixture was refluxed for 4 h. The reaction mixture was concentrated and cooled down to room temperature and filtered. The product obtained was washed with petroleum ether and crystallized from methanol.

Synthesis of Sulfone Derivatives of 4H-1,4-benzothiazines 5a–i

To a solution of substituted 4H-1,4-benzothiazine (**4**; 0.01 mol) in 20 mL of glacial acetic acid, 5 mL of 30% hydrogen peroxide was added and refluxed for 15 min. Heating was stopped and portion of 30% hydrogen peroxide (5 mL) was added. The reaction mixture was again refluxed for 3–4 h. The contents were poured in a beaker containing crushed ice. The yellowish residue obtained was filtered and washed with water and recrystallized with ethanol.

REFERENCES

1. Gupta, R. R. (Ed.): *Phenothiazines and 1,4-Benzothiazines-Chemical and Biomedical Aspects*; Elsevier: Amsterdam, **1988,** pp. 160-210.
2. Gupta, R. R.; Kumar, R.; Gautam, R. K. *J. Fluorine Chem.* **1985,** 28(4), 381-385.
3. Gupta, V.; Gupta, R. R. *J. Prakt. Chem.* **1991,** 333(1), 153-156.
4. Gupta, R. R.; Rathore, R. S.; Jain, M.; Saraswat, V. *Pharmazie* **1992,** 47(12), 945-946.
5. Gupta, R. R.; Jain, M.; Rathore, R. S.; Gupta, A. *J. Fluorine Chem.* **1993,** 62(2–3), 191-200.
6. Mukherji, S. K.; Jain, M.; Gupta, A.; Saraswat, V.; Gupta, R. R. *Ind. J. Chem.* **1994,** 33B(10), 990-991.
7. Niewiadomy, A.; Matysiak, J.; Karpińska, M. M. *Arch. Pharm.* **2011,** 344(4), 224-230.
8. Sharma, P. K.; Fogla, A.; Rathore, B. S.; Kumar, M. *Res. Chem. Intermed.* **2011,** 37, 1103-1111.
9. Gould, J. C.; Browie, J. H. *Edinb. Med. J.* **1950,** 59, 178-184.
10. Pawar, Y.; Sonawane, A.; Nagle, P.; Mahulikar, P.; More, D. *Int. J. Curr. Pharm. Res.* **2011,** 3(3), 47-51.
11. Gupta, R. R.; Kumar, R. J. *Fluorine Chem.* **1986,** 31(1), 19-24.
12. Gautam, N.; Gautam, D. C.; Gupta, R. R. *Heterocycl. Commun.* **1997,** 3(5), 401-404.
13. Gautam, N.; Gupta, R.; Gautam, D. C.; Gupta, R. R. *Heterocycl. Commun.* **2000,** 6(4), 369-374.
14. Gautam, N.; Gautam, D. C. *Int. J. Chem. Sci.* **2004,** 2(1), 84-87.
15. Gautam, N.; Hans, D.; Gautam, D. C. *Orient. J. Chem.* **2005,** 21(2), 299-302.
16. Gautam N.; Gautam, D. C. *Orient. J. Chem.* **2006,** 22(2), 457-460.
17. Gautam, V.; Sharma, M.; Panwar, M.; Gautam, N.; Kumar, A.; Sharma, I. K.; Gautam, D. C. *Phosphorus, Sulfur Silicon Relat. Elem.* **2009,** 184(11), 3090-3109.
18. Gupta, S.; Ajmera, N.; Meena, P.; Gautam, N.; Kumar, A.; Gautam, D. C. *Jordan J. Chem.* **2009,** 4(3), 209-221.