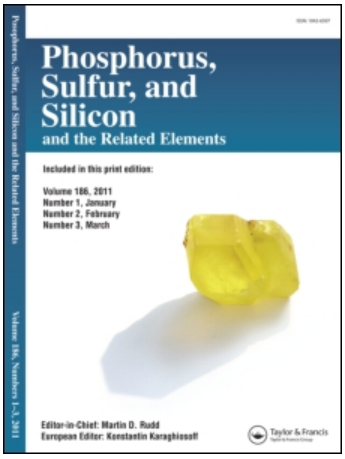

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Solvent-Free Synthesis of Some 1,5-Benzothiazepines and Benzodiazepines and Their Antibacterial Activity

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Solvent-Free Synthesis of Some 1,5-Benzothiazepines and Benzodiazepines and Their Antibacterial Activity

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An efficient and convenient synthesis of 1, 5-benzothiazepines (3a-3f) and 1, 5-benzodiazepines (4a-4f) from chalcones (2a-2f) by the action of o-amino thiophenol and o-phenylenediamine in the presence of inorganic support is reported. These compounds are characterized by elemental analysis and spectral studies viz: IR, ^{1}H NMR, and ^{13}C NMR. Newly synthesized compounds were screened for their antibacterial activity against β-subtilis, E-coli, and S. typhis.

Keywords Antibacterial activity; benzothiazepines and benzodiazepines; o-amino thiophenol; o-phenylenediamine

INTRODUCTION

Benzodiazepines and benzothiazepines are an important class of compounds in the medicinal chemistry. They constitute the basic framework of drugs such as diltiazem[1,2] and thiazesim[3] and are well recognized for their multifaceted pharmacological and medicinal applications. Benzothiazepines have displayed a wide range of biological activities viz. antifungal, antibacterial,[4] antifeedant,[5] analgesic,[6] and anticonvulsant.[7]

Benzodiazepines are used as tranquilizers, anti-inflammatories and anticonvulsants, anticancer,[8] antiasthamatic,[9] antiepileptic drugs, and in the treatment of Alzheimer's disease.[10]

In addition, 1,5-benzothiazepines and benzodiazepines are used as starting materials for the preparation of fused ring compounds such as triazolo[11] and oxadiazolo-benzodiazepines.[12] Despite their importance from a biological and synthetic point-of-view, few methods of

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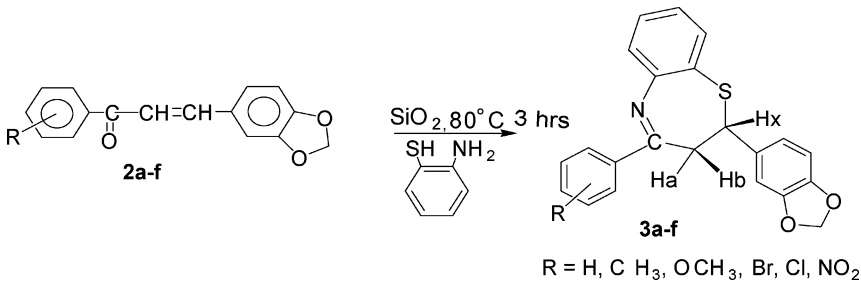


SCHEME 1

synthesis of 1, 5-benzodiazepines are reported in the literature. These includes condensation reactions of o-phenylenediamine with α, β-unsaturated carbonyl compounds,[13] β-haloketones,[14] Yb(Otf),[15] MgO and $POCl_3$,[16] silicagel,[17] amberlyst-15,[18] and acetic acid under microwave conditions.[19] 1,5-Benzodiazepines are also prepared by the reaction of α, β-unsaturated ketones with o-nitroaniline induced by $TiCl_4$-Sm[20] and o-nitro phenyl azide induced by SmI_2.[21] 1,5-Benzothiazepines have generally been synthesized by the reaction of o-amino thiophenol with α, β-unsaturated ketones;[22] 1,5-benzothiazepines have also been synthesized from o-amino thiophenol, ω-bromo acetophenone and aromatic aldehyde.[23] They were also prepared by reacting α, β-unsaturated ketones with bis (2-nitrophenyl) disulfide in the presence of $TiCl_4$/Sm.[24] 1,5-benzothiazepines have also been synthesized by the use of inorganic solid support under solvent free condition.[25] We report herein the synthesis of 1,5-benzodiazepines and benzothiazepines by the reaction of chalcones with o-phenylenediamine or o-amino thiophenol in the presence of an inorganic solid support.

RESULT AND DISCUSSION

Chalcones (2a-f) react with o-amino thiophenol in the presence of silica gel at 80°C for 3 h under solvent free conditions resulting in the formation of 2,3-dihydro-2(1,3-benzodioxol-5-yl) 4-phenyl derivative-1, 5-benzothiazepines(3a-f) in good yield (Scheme 1, Tables I and II). These compounds were screened for their antibacterial activity against β-subtilis, *E-coli*, and *S. typhis* (Table III).

The thiazepine derivatives (3a-f) probably involves the intermediate [5] (Scheme 3) which was formed by 1,2- and 1,4- type addition[26] of o-amino thiophenol with chalcones (2a-2f). The sulfur atom, being more nucleophilic in nature than the nitrogen atom, attacks the β-carbon of chalcones and give intermediate that undergoes dehydration in a non-aqueous medium, easily. The newly synthesized thiazepines derivative

were characterized on the basis of their elemental analysis (Table I) and IR, ^{1}H NMR, ^{13}C NMR (Table II).

The reaction of chalcones with o-phenylenediamine was performed in the presence of an inorganic support alumina at 80°C for 4 h to afford the corresponding 2,4- dihydro-1H,-1,5-benzodiazepines (Scheme 2). The heterocyclic products were characterized based on their elemental analysis (Table I) and IR, ^{1}H NMR, ^{13}C NMR (Table II).

The IR spectrum of 2a showed an absorption band at 1645 cm^{-1} corresponding to the carbonyl group which were absent in the titled compounds 3a and 4a. 2-amino-thiophenol displayed peaks at 3430–2550 cm^{1} corresponding to NH and SH, which were also found to be absent in the IR spectrum of 3a and 4a thus further confirming the ring closure.

The appearance of a sharp absorption band near 1620 cm^{-1} in 3a and 4a confirmed the presence of C=N group. The ^{1}H NMR spectrum of 3a and 4a showed signals at δ 3.06 (t, 1H, J = 12.7 Hz) for H_X, 3.30 (dd, 1H, J = 13.0 Hz, J = 4.6 Hz) for $H_{a,}$ 4.98 (dd, 1H, J = 12.6 Hz, J = 4.6 Hz) for $H_{b,}$ 6.0 (2H, s) for dioxymethylene group, and peaks for aromatic protons appears in the range of δ 7.23–7.8 ppm. The ^{13}C NMR spectrum of 3a and 4a were recorded in DMSO-d_6 as a solvent and showed signals at δ 158.47 (C=N), 59.33 (CH), 55.81 (CH_2) 116–138 ppm (12 Aromatic carbon) and δ 100.2 (OCH_2O). To conclude, the present investigation describes a two-step synthesis of the heterocycles **3** and **4**.

Antibacterial Activity

The compound 3a-3f were screened for their antibacterial activity against pathogenic organisms *B. subtilis*, *E. coli,* and *S. typhi* at concentration of 1000 μg using norfloxacin as standard. Solution was made in acetone and the method employed was cup plate method.[27] The zones of inhibition formed were measured in mm and are shown in Table III.

CONCLUSION

In summary, this work demonstrates an efficient and convenient method for synthesis of 1,5-benzothiazepines and benzodiazepines and results so obtained confirms the superiority of the solvent free conditions over previously reported classical methods.

EXPERIMENTAL

General

Melting points of all the synthesized compounds are uncorrected. The purity of compounds was checked by thin layer chromatography

TABLE I Elemental Analysis of 1, 5-Benzothiazepines and 1, 5-Benzodiazepines

Compounds	Mol. formula	M.p. (°C)	Yield[a] (%)	Elemental analysis calculated (found)			
				C	H	N	S
3a	$C_{22}H_{17}O_2NS$	135	67	73.53 (73.52)	4.73 (4.72)	3.89 (3.86)	8.91 (8.90)
3b	$C_{23}H_{19}O_2NS$	165	60	73.99 (73.98)	5.09 (5.04)	3.75 (3.76)	8.57 (8.56)
3c	$C_{23}H_{19}O_3NS$	150	63	70.95 (70.94)	4.88 (4.83)	3.59 (3.57)	8.22 (8.20)
3d	$C_{22}H_{16}O_2NSBr$	144	62	60.34 (60.33)	3.65 (3.64)	3.20 (3.17)	7.31 (7.30)
3e	$C_{22}H_{16}O_2NSCl$	130	60	67.09 (67.08)	4.06 (4.03)	3.55 (3.54)	8.13 (8.11)
3f	$C_{22}H_{16}O_4N_2S$	140	65	65.34 (65.33)	3.96 (3.93)	6.93 (6.93)	7.92 (7.91)
4a	$C_{22}H_{18}O_2N_2$	160	70	77.19 (77.18)	5.26 (5.24)	8.18 (8.17)	—
4b	$C_{23}H_{20}O_2N_2$	182	76	77.52 (77.50)	5.61 (5.62)	7.86 (7.84)	—
4c	$C_{23}H_{20}O_3N_2$	170	72	74.19 (74.15)	5.37 (5.33)	7.52 (7.51)	—
4d	$C_{22}H_{17}O_2N_2Br$	164	74	62.78 (62.75)	4.04 (4.03)	6.65 (6.64)	—
4e	$C_{22}H_{17}O_2N_2Cl$	158	70	70.11 (70.10)	4.51 (4.52)	7.43 (7.42)	—
4f	$C_{22}H_{17}O_4N_3$	155	60	68.21 (68.20)	4.39 (4.33)	10.85 (10.86)	—

TABLE II Spectroscopic Data of 1, 5-Benzothiazepines and 1, 5-Benzodiazepines

Compounds	IR (KBr)	^{1}H NMR (DMSO-D_6)	^{13}C NMR (DMSO-D_6)
3a	3082 cm^{-1}, 1592 cm^{-1}, 1503 cm^{-1}, 1624 cm^{-1} 1488 cm^{-1}, 1452 cm^{-1}, 1100 cm^{-1}.	δ 3.06(t, 1H, J = 12.7 Hz), 3.30 (dd, 1H, J = 13.0 Hz, J = 4.6 Hz), 4.98 (dd, 1H, J = 12.6 Hz, J = 4.6 Hz) 6.0 (2H, s), δ 7.23–7.30 (m, 8H), 7.32 (1H, dd, J = 7.8 Hz, J = 2.8 Hz), 7.25 (1H, d, J = 2.3 Hz).	δ 100.2 (OCH_2O), 158.47 (C═N), 59.33 (CH), 55.81 (CH_2) 116–138 ppm (12 Aromatic carbons).
3b	3080 cm^{-1}, 2930 cm^{-1}, 1610 cm^{-1}, 1570 cm^{-1}, 1460 cm^{-1}, 1125 cm^{-1}.	δ 3.02 (t, 1H J = 13.0 Hz), 3.25 (dd, 1H, J = 12.7 Hz, J = 4.5 Hz), 4.87 (dd, 1H J = 12.8 Hz J = 4.4 Hz), 2.37 (3H, s), 7.22 (2H, d, J = 7.7 Hz), 7.66 (2H, dd, J = 7.7 Hz, J = 2.4Hz), 7.31 (1H, dd, J = 7.8 Hz, J = 2.8 Hz) 7.24 (1H, d, J = 2.3 Hz), 6.85 (1H, d, J = 7.8 Hz), 7.58 (2H, dd, J = 7.9 Hz J = 2.3 Hz) 7.45 (2H, dd, J = 8.1 J = 2.36 Hz) 5.97 (2H, s)	δ 20.6 (CH_3), 156.5 (C═N), 100.05 (OCH_2O), 58.21 (CH), 56 (CH_2), 120–145 ppm (11Aromatic carbons).
3c	3085 cm^{-1}, 2945 cm^{-1}, 1620 cm^{-1}, 1560 cm^{-1}, 1450 cm^{-1}, 1175 cm^{-1}	δ 3.04 (t, 1H J = 12.8 Hz), 3.24 (dd, 1H, J = 12.9 Hz, J = 4.3 Hz), 4.90 (dd, 1H J = 12.6 Hz J = 4.2 Hz), 3.87 (3H, s), 7.32 (2H, d, J = 7.8 Hz), 7.62 (2H, dd, J = 7.8Hz, J = 2.3Hz), 7.32 (1H, dd, J = 7.6 Hz, J = 2.81 Hz) 7.34 (1H, d, J = 2.32 Hz), 6.95 (1H, d, J = 7.7 Hz), 7.68 (2H, dd, J = 7.8 Hz J = 2.32 Hz) 7.35 (2H, dd, J = 8.12 J = 2.32 Hz) 6.07 (2H, s)	δ 56.6 (OCH_3), 154.5 (C═N), 100 (OCH_2O), 57.21 (CH), 57 (CH_2), 122–149 ppm (11Aromatic carbons).
3d	3060 cm^{-1}, 2970 cm^{-1}, 1640 cm^{-1}, 1590 cm^{-1}, 1477 cm^{-1}	δ 3.11 (t, 1H J = 12.5 Hz), 3.22 (dd, 1H, J = 12.7 Hz, J = 4.5 Hz), 4.92 (dd, 1H J = 12.7 Hz J = 4.4 Hz), 5.98 (2H, s) 7.37 (2H, dd, J = 7.8 Hz, J = 2.12 Hz), 7.70 (2H, dd, J = 7.8 Hz, J = 2.12 Hz), 7.22 (1H, dd, J = 7.82 Hz, J = 2.20 Hz) 6.90 (1H, d, J = 7.8 Hz), 7.22 (1H, d, J = 2.22 Hz), 7.69 (2H, dd, J = 7.7 Hz J = 2.23 Hz) 7.56 (2H, dd, J = 8.0 Hz, J = 2.4 Hz)	δ 155.5 (C═N), 100.01 (OCH_2O), 59.31 (CH), 54.97 (CH_2), 123–145 ppm (11 Aromatic carbons).

(*Continued on next page*)

TABLE II Spectroscopic Data of 1, 5-Benzothiazepines and 1, 5-Benzodiazepines (*Continued*)

Compounds	IR (KBr)	^{1}H NMR (DMSO-D_6)	^{13}C NMR (DMSO-D_6)
3e	3050 cm^{-1}, 2940 cm^{-1}, 1620 cm^{-1}, 1590 cm^{-1}, 1505 cm^{-1}, 1662 cm^{-1}	δ 3.09 (t, 1H J = 12.6 Hz), 3.25 (dd, 1H, J = 12.8 Hz, J = 4.6 Hz), 4.90 (dd, 1H J = 12.8 Hz J = 4.5 Hz), 6.01 (2H, s) 7.27 (2H, dd, J = 7.7 Hz, J = 2.1 Hz), 7.67 (2H, dd, J = 7.7 Hz, J = 2.2 Hz), 7.28 (1H, dd, J = 7.9 Hz, J = 2.23 Hz) 6.87 (1H, d, J = 7.9 Hz), 7.25 (1H, d, J = 2.23 Hz), 7.59 (2H, dd, J = 7.8 Hz J = 2.2 Hz) 7.46 (2H, dd, J = 8.1 Hz, J = 2.3 Hz)	δ 156.5 (C=N), 100.06 (OCH_2O), 59.21 (CH), 55.87 (CH_2), 118–139 ppm (11 Aromatic carbons).
3f	3089 cm^{-1}, 2935 cm^{-1}, 1630 cm^{-1}, 1570 cm^{-1}, 1455 cm^{-1}	δ 3.10 (t, 1H J = 12.6 Hz), 3.24 (dd, 1H, J = 12.82 Hz, J = 4.4 Hz), 4.82 (dd, 1H J = 12.65 Hz J = 4.5 Hz), 5.88 (2H, s) 7.47 (2H, dd, J = 7.7 Hz, J = 2.22 Hz), 7.80 (2H, dd, J = 7.7 Hz, J = 2.22 Hz), 7.32 (1H, dd, J = 7.78 Hz, J = 2.24 Hz) 6.94 (1H, d, J = 7.82 Hz), 7.24 (1H, d, J = 2.24 Hz), 7.67 (2H, dd, J = 7.6 Hz J = 2.23 Hz) 7.54 (2H, dd, J = 8.04 Hz, J = 2.42 Hz)	δ 158.5 (C=N), 99.91 (OCH_2O), 59.31 (CH), 54.67 (CH_2), 115–147 ppm (11 Aromatic carbons).
4a	3310 cm^{-1}, 3080 cm^{-1}, 1620 cm^{-1}, 1590 cm^{-1}, 1505 cm^{-1}, 1470 cm^{-1}, 1100 cm^{-1}.	δ 3.04 (dd, 1H J = 13.5 Hz, J = 9.2 Hz), 3.24 (dd, 1H, J = 13.5 Hz, J = 3.8 Hz), 3.76 (br, s, 1H), 5.19 (dd, 1H J = 9.1 Hz, J = 3.8 Hz) 7.22–7.40 (5H, m) 7.25 (1H, d, J = 2.1 Hz), 6.87 (1H, d, J = 7.9 Hz), 7.28 (1H, dd, J = 7.9 Hz, J = 2.23 Hz) 6.87 (1H, d, J = 7.9 Hz), 7.31 (1H, dd, J = 12.1Hz, J = 2.1 Hz), 7.58 (2H, dd, J = 7.8 Hz J = 2.2 Hz) 7.46 (2H, dd, J = 8.05 Hz, J = 2.3 Hz) 6.0 (2H, s)	δ 158.05 (C=N), 100.02 (OCH_2O), 59.23 (CH), 55.78 (CH_2), 116–139 ppm (12 Aromatic carbons).
4b	3207 cm^{-1}, 3060 cm^{-1}, 1625 cm^{-1}, 1580 cm^{-1}, 1506 cm^{-1}, 1455 cm^{-1}, 1075 cm^{-1}.	δ 3.02 (dd, 1H J = 13.5 Hz, J = 9.3 Hz), 3.26 (dd, 1H, J = 13.5 Hz, J = 3.8 Hz), 2.37 (3H, s) 3.78 (br, s, 1H), 5.23 (dd, 1H J = 9.3 Hz, J = 3.7 Hz) 7.22 (2H, d, J = 7 Hz) 7.66 (2H, d, J = 7 Hz), 7.25 (1H, d, J = 2.3 Hz), 6.86 (1H, dd, J = 7.8 Hz,)7.31(1H, dd, J = 7.8 Hz, J = 2.8 Hz), 7.58 (2H, dd, J = 7.9 1Hz, J = 2.3 Hz), 7.46 (2H, dd, J = 8.1 Hz J = 2.36 Hz) 6.01 (2H, s).	δ 156.05 (C=N), 100.01 (OCH_2O), δ 20.6 (CH_3), 58.23 (CH), 55.25 (CH_2), 1162–142 ppm (11 Aromatic carbons).

(*Continued on next page*)

TABLE II Spectroscopic Data of 1, 5-Benzothiazepines and 1, 5-Benzodiazepines (*Continued*)

4c	3212 cm^{-1}, 3075 cm^{-1}, 1628 cm^{-1}, 1540 cm^{-1}, 1496 cm^{-1}, 1445 cm^{-1}, 1085 cm^{-1}.	δ 3.03 (dd, 1H J = 13.55 Hz, J = 9.34 Hz), 3.36 (dd, 1H, J = 13.55 Hz, J = 3.78 Hz), 3.87 (3H, s), 3.8 (br, s, 1H), 5.33 (dd, 1H J = 9.43 Hz, J = 3.67 Hz) 7.25 (2H, d, J = 7.2 Hz) 7.56 (2H, d, J = 7.2 Hz), 7.23 (1H, d, J = 2.33 Hz), 6.83 (1H, dd, J = 7.87 Hz,) 7.34 (1H, dd, J = 7.84 Hz, J = 2.8 Hz), 7.68 (2H, dd, J = 7.91 Hz, J = 2.13 Hz), 7.56 (2H, dd, J = 8.12 Hz J = 2.46 Hz) 6.11 (2H, s)	δ 56.6 (OCH_3), δ 161.00 (C═N), 100.12 (OCH_2O), 56.49 (CH), 54.69 (CH_2), 120–146 ppm (11 Aromatic carbons).
4d	3231 cm^{-1}, 3050 cm^{-1}, 1635 cm^{-1}, 1565 cm^{-1}, 1510 cm^{-1}, 1453 cm^{-1}, 1065 cm^{-1}.	δ 3.04 (dd, 1H J = 13.45 Hz, J = 9.32 Hz), 3.46 (dd, 1H, J = 13.45 Hz, J = 3.7 Hz), 3.76 (br, s, 1H), 5.33 (dd, 1H J = 9.31 Hz, J = 3.72 Hz) 7.24 (2H, d, J = 7.1 Hz) 7.61 (2H, d, J = 7.1 Hz), 7.22 (1H, d, J = 2.31 Hz), 6.80 (1H, dd, J = 7.81 Hz,) 7.34 (1H, dd, J = 7.81 Hz, J = 2.7 Hz), 7.55 (2H, dd, J = 7.92 Hz, J = 2.13 Hz), 7.42 (2H, dd, J = 8.02 Hz J = 2.31 Hz) 6.00 (2H, s)	δ 157.02 (C═N), 98.98 (OCH_2O), 58.77 (CH), 54.74 (CH_2), 117–147 ppm (11 Aromatic carbons).
4e	3237 cm^{-1}, 3040 cm^{-1}, 1627 cm^{-1}, 1538 cm^{-1}, 1516 cm^{-1}, 1445 cm^{-1}, 1055 cm^{-1}.	δ 3.00 (dd, 1H J = 13.52 Hz, J = 9.32Hz), 3.24 (dd, 1H, J = 13.52 Hz, J = 3.81 Hz), 3.8 (br, s, 1H), 5.33 (dd, 1H J = 9.23 Hz, J = 3.77 Hz) 7.32 (2H, d, J = 7.2 Hz) 7.60 (2H, d, J = 7.2 Hz), 7.22 (1H, d, J = 2.2 Hz), 6.82 (1H, dd, J = 7.81 Hz,) 7.30 (1H, dd, J = 7.82 Hz, J = 2.82 Hz), 7.62 (2H, dd, J = 7.90 Hz, J = 2.3 Hz), 7.42 (2H, dd, J = 8.11 Hz J = 2.26 Hz) 6.04 (2H, s)	δ 155.65 (C═N), 102.26 (OCH_2O), 58.69 (CH), 56.25 (CH_2), 117–140 ppm (11 Aromatic carbons).
4f	3227 cm^{-1}, 3030 cm^{-1}, 1595 cm^{-1}, 1540 cm^{-1}, 1506 cm^{-1}, 1455 cm^{-1}, 1074 cm^{-1}.	δ 3.07 (dd, 1H J = 13.45 Hz, J = 9.2 Hz), 3.20 (dd, 1H, J = 13.45 Hz, J = 3.78 Hz), 3.8 (br, s, 1H), 5.23 (dd, 1H J = 9.23 Hz, J = 3.67 Hz) 7.24 (2H, d, J = 7.2 Hz) 7.60 (2H, d, J = 7.2 Hz), 7.30 (1H, d, J = 2.32 Hz), 6.80 (1H, dd, J = 7.78 Hz,) 7.30 (1H, dd, J = 7.78 Hz, J = 2.82 Hz), 7.62 (2H, dd, J = 7.90 Hz, J = 2.23 Hz), 7.48 (2H, dd, J = 8.08 Hz J = 2.32 Hz) 6.01 (2H, s)	δ 157.34 (C═N), 101.52 (OCH_2O), 60.53 (CH), 54.75 (CH_2), 119–146 ppm (11 Aromatic carbons).

TABLE III Antibacterial Activities of the Compounds 3a-3f

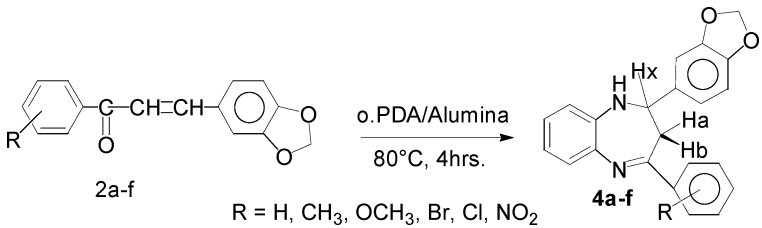
	Antibacterial activity (zone of inhibition in mm)		
Compounds	*B. subtilis*	*E. coli*	*S. typhis*
3a	12	15	17
3b	12	14	13
3c	14	13	10
3d	15	14	17
3e	17	11	13
3f	13	12	14
Norfloxacin	26	28	26

$<$ 11 mm = Inactive; 12–16 mm = weakly active; and 17–21 = moderately active.

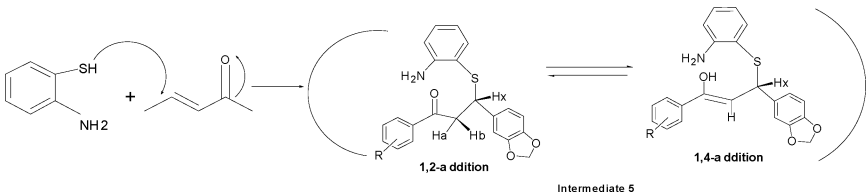
using silica gel 'G' as adsorbent. The infrared spectra were recorded on Nicolet-Megna FT-IR 550 Spectrometer by using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Model DRX-300 at 300.13 and 75.48 MHz spectrometer using TMS as internal standard.

(1) Preparation of 2, 3-Dihydro-2(1, 3-benzodipxol-5-yl) 4-Phenyl derivative-1, 5-Benzothiazepines (3a-f)—General Procedure

A concentrated solution of chalcones (2a-f) (0.05 mol) in diethyl ether (30 ml) were mixed with Silica gel (4 g), followed by addition of o-aminothiophenol. The reaction mixture was stirred at 80°C for 3 h under a nitrogen atmosphere. Silica gel was separated by filtration after eluting the product with ethyl acetate. Solvent was removed by evaporation under reduced pressure. The crude product was crystallized from methanol. Analytical and spectroscopic data of the synthesized compounds are given in Tables I and II.



SCHEME 2



SCHEME 3

(2) Preparation of 2, 3-Dihydro-2(1, 3-benzodipxol-5-yl) 4-Phenyl Derivative-1,5-Benzodiazepines (4a-f) —General Procedure

A concentrated solution of chalcones (2a-f) (0.05 mol) in diethyl ether (40 ml) were mixed with Alumina (2 g), followed by addition of o-phenylenediamine. The reaction mixture was stirred at 80°C for 4 h under nitrogen atmosphere. Alumina was separated by filtration after eluting the product with ethyl acetate. Solvent was removed by evaporation under reduced pressure. The crude product was crystallized from methanol. Analytical data & Spectroscopic data of the synthesized compounds are given in Tables I and II.

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