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DRUG SYNTHESIS

SYNTHESIS AND BIOLOGICAL STUDIES OF TRIAZOLO-/THIADIAZOLO-BENZOXAZINES

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Abstract: Diethyl bromomalonate (**2**) with an equimolar amount of 2-aminophenol (**1**) in the presence of sodium fluoride undergoes a cyclization reaction to form 2*H*,4*H*-2-ethoxycarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (**3**). Furthermore, compound 3 undergoes a condensation reaction with hydrazine hydrate in the presence of methanol to yield 2*H*,4*H*-2-hydrazinocarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (**4**), which on further reaction with aryl isothiocyanates gave 2*H*,4*H*-2-[(4'-substituted)-phenylthiosemicarbazino]-carbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (**5**). Compound 5 on treatment with NaOH, conc. H_2SO_4 and diethylmalonate (**6**), afforded 2*H*,4*H*-2-[2'*H*-3'-thioxo-4'-substituted phenyl-1',2',4'-triazole-5-yl]- 3,4-dihydro-3-oxo-1,4benzoxazine (**7**), 2*H*,4*H*-2-[2'-amino-(substituted)-phenyl-1',3',4'-thiadiazol-5-yl]-3,4-dihydro-3-oxo-1,4-benzoxazine (**8**) and 2*H*,4*H*-2-[5'*H*-5'-dihydro-2'-thioxo-3'-phenyl-4',6'-dioxo-1,3-diazine]-aminocarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (**9**), respectively. The synthesized compounds were investigated for their antibacterial activities against Gram positive as well as Gram negative bacteria with ampicillin trihydrate as standard drug. Structures have been elucidated on the basis of spectral and chemical analyses.

Keywords: triazoles, thiadiazoles, 1,4-benzoxazine

2,3-Dihydro-1,4-benzoxazines are an important class of molecules, which are a common heterocyclic scaffold in biologically active and medicinally significant compounds. For example, levofloxacin that exhibits excellent activities against Gram-positive and Gram-negative bacteria, possesses 2,3-dihydro-1,4-benzoxazine moiety. In addition, some benzoxazines are central nervous system depressants, antipsychotic agents, calcium antagonists, and antibacterial agents; moreover, some are potential drugs for neuroprotective, antitumor, antithrombotic, antihypertensive agents, and cardiovascular drugs (1). Due to the importance of 1,4-benzoxazines, several synthetic methods for 2,3-dihydro-1,4-benzoxazines have been reported over the past few decades (1, 2). In addition, 1,2,4-triazole derivatives are of interests due to their bioactivity, including antibacterial (3–5) and antifungal (6, 7) properties. In recent years, attention has been increasingly paid to the synthesis of heterocyclic compounds, which exhibits various biological activities (8–11). Thiadiazole nucleus, which incorporates a toxophoric N-C-S linkage, exhibits a large number of pharmacological activities (12). A number of 1,3,4-thiadiazoles possess antimicrobial properties comparable with sulfonamide drugs (13).

Nowadays, application of ultrasound (sonochemistry) has become an exciting field of research. The chemical effects of ultrasound are diverse and include substantial improvements in both stoichiometric and catalytic chemical reactions. Ultrasonic irradiation accelerates the reactivity million fold and many synthetically useful reactions were successfully accomplished (14, 15). As compared to conventional conditions, viz. strong base and long reaction time, the ultrasonic irradiation procedure is milder and more conventional leading to higher yields in shorter reaction time (16, 17).

Keeping these observations in mind and in continuation of our contribution in the synthesis of heterocyclic compounds (18–22) we report herein the synthesis of the versatile and hitherto unreported thiosemicarbazides and their utility as a building blocks in the synthesis of several new heterocyclic compounds.

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EXPERIMENTAL

All chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India). Melting points of all synthesized compounds were determined in open capillary tubes using Veego VMP-1 melting point apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. IR spectra in KBr pellets were recorded on Perkin-Elmer spectrophotometer in the range of 4000–400 cm^{-1}. ^1H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard (chemical shifts in δ ppm). The mass spectra were taken on a Jeol SX-102/PA-6000 (EI) spectrometer.

2*H*,4*H*-2-ethoxycarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (3)

Method A (ultrasound method)

Diethyl bromomalonate (**2**) (0.01 mole), 2-aminophenol (**1**) (0.01 mole), sodium fluoride (0.02 mole) and dimethylformamide (20 mL) were taken in 100 mL round bottom flask and subjected to sonication for 17 min. After completion of the reaction (monitored by TLC), the mixture was poured on crushed ice. Solid thus obtained was filtered, washed with dil. HCl, water and recrystallized from ethanol to afford **3**. (Yield 78%, m.p. 78–80°C).

Method B (conventional)

An equimolar mixture of compound **1, 2** (0.01 mole), sodium fluoride (0.02 mole) and dimethylformamide (50 mL) were refluxed for about 8–9 h. The product was isolated in a similar manner as in method A. (Yield 61%)

IR (KBr, cm^{-1}): 3384 (NH), 3045 (CH, arom.), 1734 (C=O). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.28 (t, *J* = 7.1 Hz, 3H, CH_3), 4.30 (q, *J* = 7.1 Hz, 2H, CH_2), 4.66 (s, 1H, CH), 6.65–6.88 (m, 4H, ArH), 10.10 (s, 1H, ring NH).

2*H*,4*H*-2-Hydrazino carbonyl -3, 4-dihydro-3-oxo-1, 4-benzoxazine (4)

Method A (ultrasound method)

Compound (**3**) (0.01 mole), hydrazine hydrate (0.02 mole) and dry methanol (20 mL) were taken in 100 mL round bottom flask and subjected to sonication for 10 min. Upon completion of the reaction (monitored by TLC), the mixture was then poured onto crushed ice and solid thus obtained was washed with water and recrystallized from methanol to get **4** (yield 80%, m.p. 218°C).

Method B (conventional)

In a round bottom flask (100 mL) fitted with a reflux condenser, a mixture of **3** (0.01 mole) and hydrazine hydrate (0.02 mole) in dry methanol (70 mL) was heated on a steam bath for 6 h. The reaction mixture was then concentrated, cooled and recrystallized to get the product (yield 68%).

IR (KBr, cm^{-1}): 3410–3230 (NH-NH_2), 3045 (CH, arom.), 1664 (C=O). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 4.25 (s, 2H, NH_2), 4.60 (s, 1H, CH), 5.20 (s, 1H, NH), 6.20–6.80 (m, 4H, ArH), 10.24 (s, 1H, ring NH).

2*H*,4*H*-2-[(4'-substituted)-phenylthiosemicarbazino]-carbonyl-3,4-dihydro-3-oxo-1,4-benzoxazines (5a-d)

Method A (ultrasound method)

Substituted isothiocynate (0.01 mole), **4** (0.01 mole) and ethanol (15 mL) were exposed to ultrasound irradiation for 15 min. Upon completion of the reaction (monitoring by TLC) the mixture was then quenched onto crushed ice. The product that precipitated out was filtered, washed with water and recrystallized from ethanol. The physical data of the compounds are given in Table 1.

Method B (conventional)

The same amounts of above reactants were refluxed on water bath for 6 h. The reaction was monitored by TLC and after completion of the reaction, the content was poured onto crushed ice. The solid obtained was filtered, washed with water and recrystallized from ethanol to yield compounds **5a**–**d**.

5a: IR (KBr, cm^{-1}): 3220 (NH), 1680 (C=O), 1590 (C=N). ^1H NMR (DMSO-d_6, δ, ppm): 4.54 (s, 1H, CH), 6.87–7.38 (m, 9H, ArH), 8.94 (s, 1H, NH), 9.24 (s, 1H, NH), 9.47 (s, 1H, NH), 10.12 (s, 1H, ring NH). Analysis: calcd. for $C_{16}H_{14}N_4O_3S$: C, 56.14; H, 4.09; N, 16.37%; found: C, 56.10; H, 4.07; N, 16.34%.

5b: IR (KBr, cm^{-1}): 3210 (NH), 1660 (C=O), 1570 (C=N).

5c: IR (KBr, cm^{-1}): 3214 (NH), 1665 (C=O), 1548 (C=N).

5d: IR (KBr, cm^{-1}): 3222 (NH), 1685 (C=O), 1580 (C=N). ^1H NMR (DMSO-d_6, δ, ppm): 3.84 (s, 3H, OCH_3), 4.47 (s, 1H, CH), 7.04–7.52 (m, 8H, ArH), 9.10 (s, 1H, NH), 9.37 (s, 1H, NH), 9.54 (s, 1H, NH), 10.20 (s, 1H, ring NH). Analysis:. calcd. for $C_{17}H_{16}N_4O_4S$: C, 54.84; H, 4.30; N, 15.05%; found: C, 54.80; H, 4.27; N, 15.02%.

2*H*,4*H*-2-[2'*H*-3'-thioxo-4'-substituted phenyl-1',2',4'-triazol-5-yl]-3,4-dihydro-3-oxo-1,4-benzoxazines (7a–d)

Method A (ultrasound method)

A mixture of respective **5** (0.005 mole) and 2 M NaOH (10 mL) was subjected for ultrasound irradiation for 24 min. Progress of the reaction was monitored by TLC. After completion of reaction, the contents were poured onto crushed ice and acidified with acetic acid. The products obtained were separated by filtration and recrystallized from DMF/water. The physical data of the compounds are given in Table 1.

Method B (conventional)

A mixture of **5** (0.005 mole) and 2 M NaOH (10 mL) was heated under mild reflux for 5 h. The product was isolated in a similar manner as described above.

7a: IR (KBr, cm^{-1}): 3250 (NH), 1675 (C=O), 1620 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 4.58 (s, 1H, CH), 7.05–7.52 (m, 9H, ArH), 9.48 (s, 1H, triazole-ring NH), 10.25 (s, 1H, ring NH). ^{13}C NMR (DMSO-d_6, δ, ppm): 81.24 (CH), 122–145 (ArC), 151.51 (C=N-NH), 167.73 (C=O), 184.33 (C=S). MS (m/z): 325 (M^+), 248, 190, 149.

7b: IR (KBr, cm^{-1}): 3230 (NH), 1680 (C=O), 1610 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.37 (s, 3H, CH_3), 4.54 (s, 1H, CH), 7.10–7.58 (m, 8H, ArH), 9.56 (s, 1H, triazole-ring NH), 10.22 (s, 1H, ring NH). ^{13}C NMR (DMSO-d_6, δ, ppm): 21.38 (CH_3), 79.81 (CH), 123–145 (ArC), 152.47 (C=N-NH), 166.17 (C=O), 185.55 (C=S). MS (m/z): 339 (M^+), 248, 190, 149.

7c: IR (KBr, cm^{-1}): 3210 (NH), 1660 (C=O), 1600 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 4.55 (s, 1H, CH), 6.89–7.32 (m, 8H, ArH), 9.55 (s, 1H, triazole-ring NH), 10.20 (s, 1H, ring NH).

7d: IR (KBr, cm^{-1}): 3242 (NH), 1685 (C=O), 1625 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 3.87 (s, 3H, OCH_3), 4.48 (s, 1H, CH), 7.05–7.52 (m, 8H, ArH), 9.57 (s, 1H, triazole-ring NH), 10.24 (s, 1H, ring NH). MS (m/z): 355 (M^+), 248, 190, 149, 108.

2*H*,4*H*-2-[2'amino-(substituted) phenyl-1',3',4'-thiadiazol-5-yl]-3,4-dihydro-3-oxo-1,4-benzoxazines (8a–d)

Method A (ultrasound method)

A mixture of **5** and conc. H_2SO_4 (5 mL) was subjected to ultrasound irradiation for 28 min. The reaction mixture was poured onto crushed ice. The solid separated was filtered and washed with water

Table 1. Characterization of compounds **5a–9d**.

Compd.	Ar	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)	
					Ultrasound	Conv.
5a	Phenyl	$C_{16}H_{14}N_4O_3S$	342	147–149	85	62
5b	4-Methylphenyl	$C_{17}H_{16}N_4O_3S$	356	162–163	84	65
5c	4-Chlorophenyl	$C_{16}H_{13}N_4O_3SCl$	376.5	178–180	82	60
5d	4-Methoxyphenyl	$C_{17}H_{16}N_4O_4S$	372	160–162	80	59
7a	Phenyl	$C_{16}H_{12}N_4O_2S$	324	245–247	86	67
7b	4-Methylphenyl	$C_{17}H_{14}N_4O_2S$	338	257–258	84	69
7c	4-Chlorophenyl	$C_{16}H_{11}N_4O_2SCl$	358.5	286–288	80	62
7d	4-Methoxyphenyl	$C_{17}H_{14}N_4O_3S$	354	> 300	78	60
8a	Phenyl	$C_{16}H_{12}N_4O_2S$	324	280–282	76	57
8b	4-Methylphenyl	$C_{17}H_{14}N_4O_2S$	338	263–265	79	69
8c	4-Chlorophenyl	$C_{16}H_{11}N_4O_2SCl$	358.5	288–290	81	58
8d	4-Methoxyphenyl	$C_{17}H_{14}N_4O_3S$	354	245–246	80	63
9a	Phenyl	$C_{19}H_{14}N_4O_5S$	410	> 300	79	60
9b	4-Methylphenyl	$C_{20}H_{16}N_4O_5S$	424	287–289	82	58
9c	4-Chlorophenyl	$C_{19}H_{13}N_4O_5SCl$	444.5	252–254	75	62
9d	4-Methoxyphenyl	$C_{20}H_{16}N_4O_6S$	440	273–275	76	64

to yield **8**. The physical data of the compounds are given in Table 1.

Method B (conventional)

The same amounts of reagents were stirred at room temperature for 2 h and then poured onto crushed ice. The solid obtained was filtered and washed with water to yield **8**.

8a: IR (KBr, cm^{-1}): 3255 (NH), 1670 (C=O), 1408 (C-S-C). ^{1}H NMR (DMSO-d_6 δ, ppm): 4.60 (s, 1H, CH), 7.01–7.46 (m, 9H, ArH), 9.45 (s, 1H, NH), 10.27 (s, 1H, ring NH). ^{13}C NMR (DMSO-d_6, δ, ppm): 82.54 (CH), 121–144 (ArC), 154.54 (C=N), 157.21 (C=N), 167.54 (C=O). MS (m/z): 325 (M^+), 248, 233, 189, 149.

8b: IR (KBr, cm^{-1}): 3248 (NH), 1680 (C=O), 1412 (C-S-C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.37 (s, 3H, CH_3), 4.66 (s, 1H, CH), 6.97–7.52 (m, 8H, ArH), 9.47 (s, 1H, NH), 10.20 (s, 1H, ring NH). ^{13}C NMR, (DMSO-d_6, δ, ppm): 23.69 (CH_3), 81.78 (CH), 122–147 (ArC), 152.57 (C=N), 155.83 (C=N), 166.33 (C=O). MS (m/z): 339 (M^+), 248, 233, 189, 149.

8c: IR (KBr, cm^{-1}): 3210 (NH), 1665 (C=O), 1410 (C-S-C). ^{1}H NMR (DMSO-d_6, δ, ppm): 4.57 (s, 1H, CH), 7.05–7.38 (m, 8H, ArH), 9.45 (s, 1H, NH), 10.27 (s, 1H, ring NH).

8d: IR (KBr, cm^{-1}): 3250 (NH), 1680 (C=O), 1418 (C-S-C). ^{1}H NMR (DMSO-d_6, δ, ppm): 3.84 (s, 3H, OCH_3), 4.55 (s, 1H, CH), 7.01–7.52 (m, 8H, ArH), 9.47 (s, 1H, NH), 10.14 (s, 1H, ring NH). MS (m/z): 355 (M^+), 248, 233, 189, 149.

2*H*,4*H*-2-[5'*H*-5'-dihydro-2'-thioxo-3'-phenyl-4',6'-dioxo-1,3-diazine]-aminocarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazines (9a–d)

Method A (ultrasound method)

Equimolar mixture of **5**, diethylmalonate **6** (0.01 mole), ethanol (25 mL) and pyridine (0.02 mole) in 100 mL round bottom flask was subjected to sonication for 25 min. Upon completion of the reaction (monitored by TLC) the reaction mixture was poured onto crushed ice. The precipitate was filtered and the solid was then crystallized from ethanol. The physical data of the compounds are given in Table 1.

Method B (conventional)

Appropriate **5** (0.01 mole) was dissolved in ethanol (50 mL) and to it was added diethylmalonate **6** (0.01 mole) and pyridine (0.02 mole). The reaction mixture, after refluxing for 8 h, was cooled to room temperature and poured onto crushed ice. The product was isolated in a similar manner as described above.

9a: IR (KBr, cm^{-1}): 3260 (NH), 1690 (C=O), 1593 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.57 (s, 2H, CH_2), 4.62 (s, 1H, CH), 6.88–7.57 (m, 9H, ArH), 9.36 (s, 1H, NH), 10.12 (s, 1H, ring NH). ^{13}C NMR (DMSO-d_6, δ, ppm): 11.74 (CH_2), 78.52 (CH), 122–148 (ArC), 163.21 (C=O), 166.55 (2 × C=O), 171.24 (C=O), 184.27 (C=S). MS (m/z): 411 (M^+), 334, 264, 192, 149.

9b: IR (KBr, cm^{-1}): 3268 (NH), 1690 (C=O), 1590 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.52 (s, 2H, CH_2), 2.38 (s, 2H, CH_3), 4.52 (s, 1H, CH), 6.88–7.51 (m, 8H, ArH), 9.52 (s, 1H, NH), 10.10 (s, 1H, ring NH). ^{13}C NMR (DMSO-d_6, δ, ppm): 12.38 (CH_2), 27.32 (CH_3), 80.35 (CH), 122–145 (ArC), 162.24 (C=O), 165.87 (C=O), 169.56 (2 × C=O), 183.27 (C=S). MS (m/z): 425 (M^+), 334, 264, 192, 149.

9c: IR (KBr, cm^{-1}): 3230 (NH), 1672 (C=O), 1584 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.55 (s, 2H, CH_2), 4.60 (s, 1H, CH), 6.94–7.43 (m, 8H, ArH), 9.36 (s, 1H, NH), 10.12 (s, 1H, ring NH).

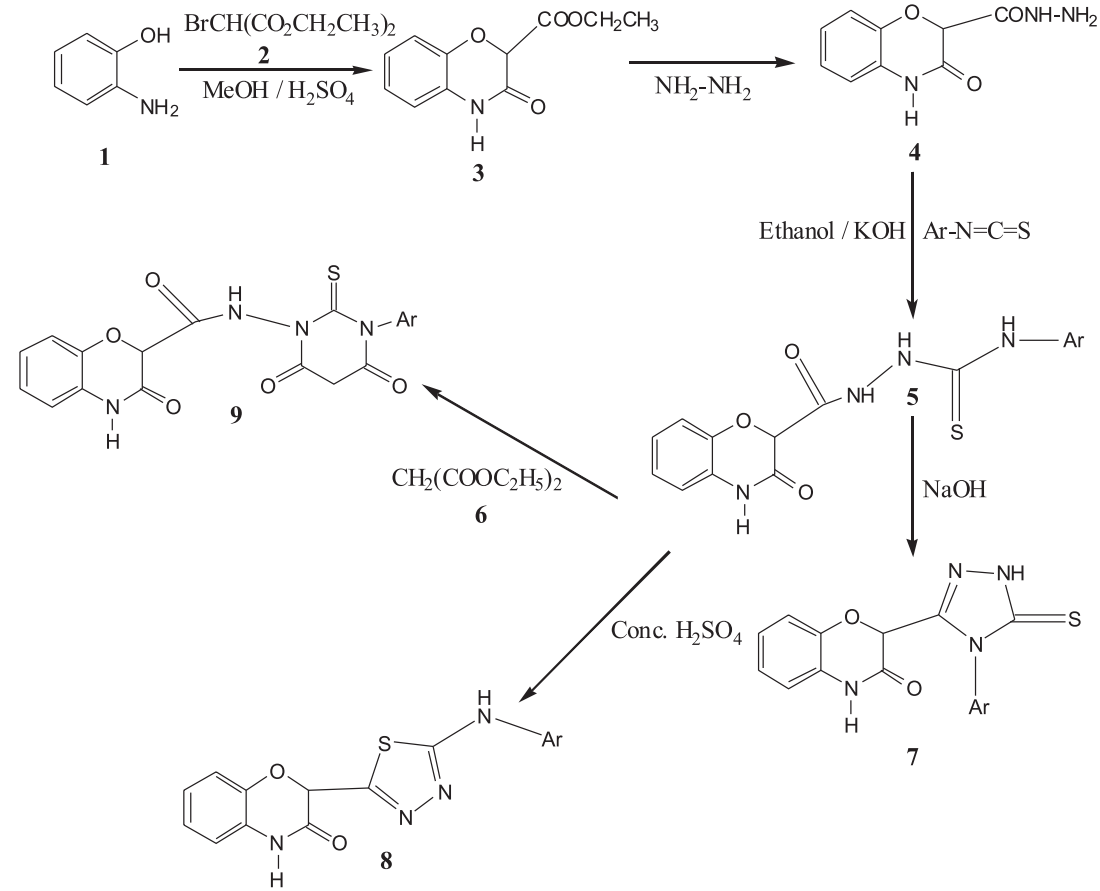
9d: IR (KBr, cm^{-1}): 3270 (NH), 1685 (C=O), 1590 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.45 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.43 (s, 1H, CH), 6.91–7.47 (m, 8H, ArH), 9.38 (s, 1H, NH), 10.15 (s, 1H, ring NH). MS (m/z): 441 (M^+), 334, 264, 192, 149.

Antimicrobial evaluation

Representative compounds were evaluated for their antibacterial activity against Gram-negative bacteria, *E. coli* and *P. aeruginosa* and Gram-positive bacteria, *S. aureus*, and *C. diphtheriae* using disc diffusion method (23, 24). The zone of inhibition was measured in mm and the activity was compared with standard drug – ampicillin trihydrate. The results of antibacterial screening studies are reported in Table 2.

RESULTS AND DISCUSSION

The new series of heterocyclic compounds **7**, **8** and **9** have been synthesized as depicted in Scheme 1. 2-Aminophenol (**1**) with an equimolar amount of diethyl bromomalonate **(2)** in the presence of DMF and sodium fluoride undergoes cyclization to form 2*H*,4*H*-2-ethoxycarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (**3**). Compound **3** was subsequently reacted with hydrazine hydrate in dry methanol to form 2*H*,4*H*-2-hydrazinocarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (**4**), which on further treatment with substituted phenyl isothiocyanates yielded 2*H*,4*H*-2-[(4'-substituted) phenylthiosemicarbazino]-carbonyl-3,4-dihydro-3-oxo-1,4-benzoxazines



Scheme 1. Synthesis of 1,4-benzoxazines

Table 2. *In vitro* antibacterial activity of selected compounds **7, 8** and **9**.

Compd.	Zone of inhibition (in mm)*			
	Gram positive		Gram negative	
	S. aureus	*C. diphtheria*	*E. coli*	*P. aeruginosa*
7a	14	16	15	11
7b	23	21	16	12
7c	18	20	21	19
8a	16	17	10	11
8b	23	21	14	15
8c	19	20	20	18
8d	21	22	14	15
9a	15	13	13	11
9c	21	23	22	20
9d	20	19	14	11
Ampicillin trihydrate	27	25	24	22
DMSO	0	0	0	0

* Concentration selected was 100 µg/mL and DMSO was used as the solvent.

(**5**). The structure assignments of compounds **5** were established by spectroscopic and elemental analysis. In their ^{1}H NMR spectral data the signal of thiosemicarbazide group protons NHCS (9.2–9.5 ppm) and CONH (8.9 ppm) are observed. Also in the IR spectra the absorption of thiosemicarbazide NH (3210–3230 cm^{-1}), C=O (1670–1690) and C=N (1550–1580 cm^{-1}) clearly confirm the formation of **5**. Compounds **5** on treatment with NaOH, conc. H_2SO_4 and diethylmalonate (**6**) undergo cyclization to gave 2*H*,4*H*-2-[2'*H*-3'-thioxo-4'-substituted phenyl-1',2',4'-triazol-5-yl]-3,4-dihydro-3-oxo-1,4-benzoxazines (**7**), 2*H*,4*H*-2-[2'-amino-(substituted) phenyl-1',3',4'-thiadiazol-5-yl]-3,4-dihydro-3-oxo-1,4-benzoxazines (**8**) and 2*H*,4*H*-2-[5'*H*-5'-dihydro-2'-thioxo-3'-phenyl-4',6'-dioxo-1,3-diazine]-aminocarbonyl-3,4-dihydro-3-oxo-1,4-benzoxazines (**9**), respectively, with a good yield. The spectral data are in good agreement with the proposed structures. Thus, the IR spectra of compounds **8** showed NH band in the region of 3350–3400 cm^{-1} and C-S-C absorption bands at 1350–1450 cm^{-1}. Also their ^{1}H NMR spectra supported the formation of **8**. Similarly, the confirmation of compounds **7** and **9** were due to C=S signal shown in the region of 180–185 ppm in ^{13}C NMR spectra supporting the proposed structure (see experimental section).

CONCLUSION

In conclusion, the ultrasound irradiation for synthesis of the title compounds offers reduction in reaction time, operation simplicity, cleaner reaction, easy work up and improved yields. The procedure clearly highlights the advantages of ultrasound. The synthesized compounds **7b**, **8b**, **8d**, and **9d** with a methyl and methoxy substituent, respectively, showed moderate activity against Gram positive and Gram negative organisms, whereas compound **7a**, **8a** and **9a** with no substituent showed very low activity. The highest degree of activity against Gram negative microorganisms, *S. aureus* and *C. diphtheria*, was shown by **7c**, **8c** and **9c** with a chloro substituent. The substituted, chloro derivatives of the title compounds were found to be the lead for antimicrobial agents. The data reported in this article may be helpful guide for the medical chemists who are working in this area.

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