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Microwave-assisted synthesis of some new bis-1,3-benzoxazines and their antimicrobial activity

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Abstract: A series of bis-1, 3-benzoxazines (**3a-f**) were synthesized from reduced product of propane-1, 3-diamine Schiff bases in the presence of formalin under conventional heating and microwave irradiation. The structures of newly synthesized diamines and bis-1, 3-benzoxazines were established on the basis of spectroscopic data. Further, all the synthesized compounds were screened for antimicrobial activity. Some of the compounds showed very good activity compared to standard drugs against all pathogenic bacteria and fungi.

Keywords: Bis-schiff bases, bis-1, 3-propane diamines, microwave irradiation, antimicrobial activity.

1. Introduction

3, 4-Dihydro-2H-1,3-benzoxazines are bicyclic heterocycles that are of significant interest in the polymeric and pharmacological field. Benzoxazines are important class of benzfused heterocycles with wide spectrum of biological activity such as antimicrobial[1,2], analgesics[3], antibacterial[4], neuoprotective[5], D_2 receptor antagonistic activity[6], antimycobacterial[7], antiviral[8], antifungal activity[9] these type of compounds have been important subject of researchers. In addition, N-substituted 3,4-dihydro-2H-1,3-benzoxazines are potential intermediates for the preparation of phenol formaldehyde resins[10]. Hence the synthesis of these compounds including attracted great interest. Several methods have been reported for the preparation of these compounds in literature for example,an important method was developed by using mannich-type condensations of phenol, with primary amines and two equivalent of formaldehyde[11]. Condensation of *o*-aminomethyl phenol with an aldehyde or ketones provided another route[12]. Reactions of primary amines with oxygen-containing dihalocompounds established a way to prepare 3,4-dissymmetric-substituted 3,4-dihydro-1,3-benzoxazines[13]. Recently, rhodium-catalyzed reactions of 2-(alkenyloxy)benzylamines have been developed as a way to generate 3,4-dihydro-1,3-benzoxazines an allylic cleavage followed by regioselective carbonylation at the internal carbon atom[14]. However, some drawback existed in previous methods. Moreover, the presence of some functional groups in the benzoxazine is incompatible with the use of this direct synthetic methodology. This is the case of the phenolic group that is desirable to prepare new polymeric materials with well-defined properties. This fact and the aim to prepare the bis-1,3-benzoxazine and its antimicrobial studies lead us to explore the utility of alternative synthetic routes.

The microwave induced enhancement of organic reactions is currently a focus of attention for chemists due to the decreased reaction time, improved yields and easier work up as compared to conventional methods[15]. In microwave synthesis, to avoid accidents low boiling, toxic and poisonous solvents are often avoided. The use of microwave for the synthesis of organic compounds has proved to

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be efficient, safe and environmentally benign techniques with shorter reaction time[16]. In view of above findings, the synthesis of new biologically active bis-1,3-benzoxazine derivatives under conventional and non conventional(microwave irradiation) methods, are reported herein.

2. Experimental

2.1. Chemical Materials and Apparatus

Melting points were determined in an open capillary tube and are uncorrected. The chemicals and solvents used were of laboratory grade and were purified. Purity of compounds and completion of the reaction was monitored by thin layer chromatography using hexane/ethyl acetate (7:3) as the mobile phase on precoated sheetes of silica gel-G (Merck, Germany) using iodine vapour for detection. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 with an Avance spectrometer (Bruker, Germany) at 400-MHz frequency using TMS as an internal standard. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.Synthos-3000, Anton Paar reaction system was used for microwave synthesis.

*2.2. General Procedure for N^1,N^3-dibenzylpropane-1,3-diamines (**2a-f**)*

Sodium borohydride (0.04 mol) was added to a solution of bis-Schiff bases **1a-f** (0.01 mol) in MeOH (10 mL) and the mixture was stirred for 30 min. at room temperature. The solid separated, on pouring the reaction mixture into ice-cold water, was filtered and recrystallized from petroleum ether to get **2a-f**.

*2.3. Physical and Spectral Data for **2a-f***

2,2'-((propane-1,3-diylbis(azanediyl))bis(methylene))diphenol) ***(2a)*****:** White solid, IR (KBr) 3450 cm^{-1}(-OH), 3305 cm^{-1} (-NH), 2924 cm^{-1} (-CH of –CH_2); ^{1}H NMR (DMSO d_6) δ: 1.60 (m, 2H, CH_2), 2.52 (t, *J*=4.2 Hz, 4H, 2-NCH_2), 3.75 (s, 4H, 2-CH_2), 4.32 (s, 2H, 2-NH), 6.80 (dd, *J*=7.1 and 2.1 Hz 2H), 6.85 (dd, *J*=7.1and 2.1 Hz, 2H), 6.87 (dd, *J*=7.3 and 2.1 Hz, 2H), 7.35(dd, *J*=7.3 and 2.1Hz, 2H), 10.22 (s, 2H, 2Ar-OH); Anal Calcd for $C_{17}H_{22}N_2O_2$ (286): C 71.32; H 7.69; N 9.79. Found C 71.25; H 7.50; N 9.85.

2,2'-((propane-1,3-diylbis(azanediyl))bis(methylene))bis(4-bromophenol) ***(2b)****:* Pale yellow solid, IR (KBr) 3470 cm^{-1} (-OH), 3325 cm^{-1} (-NH), 2940 cm^{-1} (-CH of –CH_2); ^{1}H NMR (DMSO d_6) δ: 1.68 (m, 2H, CH_2), 2.60 (t, *J*=4.2 Hz ,4H, 2-NCH_2), 3.79 (s, 4H, 2-CH_2), 4.40 (s, 2H, 2-NH), 6.70 (dd, *J*=7.3 and 2.3 Hz, 2H), 7.20 (d, *J*=7.3 Hz, 2H), 7.30 (d, *J*=2.3 Hz, 2H), 11.10 (s, 2H, 2Ar-OH); Anal Calcd for $C_{17}H_{20}Br_2N_2O_2$ (442): C 46.15; H 4.52; N 6.33. Found C 46.00; H 4.75; N 6.15.

6,6'-((propane-1,3-diylbis(azanediyl))bis(methylene))bis(2,4-dibromophenol) ***(2c)***: Yellow solid, IR (KBr) 3480 cm^{-1} (-OH), 3340 cm^{-1} (-NH), 2960 cm^{-1} (-CH of –CH_2); ^{1}H NMR (DMSO d_6) δ: 1.75 (m, 2H, CH_2), 2.69 (t, *J*=5.8 Hz 4H, 2-NCH_2), 3.80 (s, 4H, 2-CH_2), 4.48 (s, 2H, 2-NH), 6.95 (d, *J*=2.5 Hz, 2H), 7.65 (d, *J*=2.5 Hz, 2H), 11.15 (s, 2H,2Ar-OH); Anal Calcd for $C_{17}H_{18}Br_4N_2O_2$ (598): C 34.11; H 3.01; N 4.68. Found C 34.01; H 3.00; N 4.10.

2,2'-((propane-1,3-diylbis(azanediyl))bis(methylene))bis(4-chlorophenol) ***(2d)***: White solid, IR (KBr) 3472 cm^{-1} (-OH), 3330 cm^{-1} (-NH),2945 cm^{-1} (-CH of –CH_2); ^{1}H NMR (DMSO d_6) δ: 1.69 (m, 2H, CH_2), 2.59 (t, *J*=4.6 Hz, 4H, 2-NCH_2), 3.81 (s, 4H, 2-CH_2), 4.43 (s, 2H, 2-NH), 6.75 (dd, *J*=7.4 and 2.5Hz, 2H), 7.20 (d, *J*=7.4 Hz, 2H), 7.30 (d, *J*=2.5 Hz, 2H), 11.10 (s, 2H, 2 Ar-OH); Anal Calcd for $C_{17}H_{20}Cl_2N_2O_2$ (354.9): C 57.48; H 4.79; N 7.88. Found C 57.65; H 4.85; N 7.90

6,6'-((propane-1,3-diylbis(azanediyl))bis(methylene))bis(2,4-diiodophenol) ***(2e)****:* Orange solid, IR (KBr) 3482 cm^{-1} (-OH), 3345 cm^{-1} (-NH),2965 cm^{-1} (-CH of –CH_2); ^{1}H NMR (DMSO d_6) δ: 1.76 (m, 2H, CH_2), 2.70 (t, *J*=5.9 Hz, 4H, 2-NCH_2) 3.82 (s, 4H, 2-CH_2), 4.50 (s, 2H, 2-NH), 7.15 (d, *J*=2.6 Hz, 2H), 7.70 (d, *J*=2.6 Hz, 2H), 11.20 (s,2H, 2Ar-OH); Anal Calcd for $C_{17}H_{18}I_4N_2O_2$ (790): C 25.82; H 2.22; N 3.54. Found C 25.70; H 2.30; N 3.45.

*2f ,2'-((propane-1,3-diylbis(azanediyl))bis(methylene))bis(4-methylphenol) (**2f**)*: White solid, IR (KBr) 3470 cm^{-1} (-OH), 3325 cm^{-1} (-NH), 2940 cm^{-1} (-CH of $–CH_2$); ^{1}H NMR (DMSO d_6) δ: 1.68 (m, 2H, CH_2), 2.30 (s, 6H, 2-CH_3) 2.55 (t, *J*=4.2 Hz, 4H, 2-NCH_2), 3.79 (s, 4H, 2-CH_2), 4.40 (s, 2H, 2-NH), 6.60 (dd, *J*=7.1 and 2.0 Hz, 2H), 7.20(d, *J*=7.1 Hz, 2H), 7.30 (d, *J*=2.0 Hz 2H), 11.00 (s, 2H, 2 Ar-OH); Anal Calcd for $C_{19}H_{26}N_2O_2$ (314): C 72.61; H 8.28; N 8.91. Found C 72.50; H 8.40; N 8.70.

*2.3 General Procedure for the 1,3-benzoxazines (**3a-f**)*

2.3.1. Conventional Method

A mixture of 2,2ˋ [propane-1,3-diylbis(iminomethanediyl)]bis(substituted phenol) **2** (0.005 mol) and formalin (35%,w/v, 0.010 mol), in 30 mL absolute ethanol was refluxed for 3-4 hrs. The solid separated, on pouring the reaction mixture into ice-cold water, was filtered and recrystallized from ethanol to get **3a-f**.

2.3.2. Microwave Method

A homogenous mixture of 2,2ˋ [propane-1,3-diylbis(iminomethanediyl)]bis(substituted phenol) **2** (0.005 mol) and formalin (35%,w/v, 0.010 mol), was taken in a glass vial equipped with cap and then subjected to microwave irradiation at 100W for 5-10 min. progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured in cold water. The solid that formed was filtered, dried and recrystalized from ethanol to afford the pure bis-1, 3-benzoxazines **3a-f**.

*2.3.3. Physical and Spectral Data for **3a-f***

*1,3-bis(2H-benzo[e][1,3]oxazin-3(4H)-yl)propane (**3a**)*: White solid, IR (KBr) 3070cm^{-1} (-CH of $–CH_2$), 1148cm^{-1}(-C-O); ^{1}H NMR (DMSO d_6) δ: 1.50 (m, 2H, CH_2), 2.39(t, *J*=4.1Hz, 4H, 2-NCH_2), 4.58 (s, 4H, rings, 2-NCH_2), 5.50 (s, 4H, rings 2-OCH_2), 6.75 (dd, *J*=7.0 and 2.1 Hz, 2H) 6.80 (dd, *J*=7.0 and 2.1 Hz, 2H), 6.85 (dd, *J*=7.3&2.0Hz,2H), 7.30(dd, *J*=7.2&2.1Hz 2H); Anal Calcd for $C_{19}H_{22}N_2O_2$ (310): C 73.54; H 7.69; N 9.03. Found C 73.50; H 7.85; N 9.75.

*1,3-bis(6-bromo-2H-benzo[e][1,3]oxazin-3(4H)-yl)propane (**3b**)*: White solid, IR (KBr) 3075cm^{-1}(-CH of $–CH_2$), 1155cm^{-1}(-C-O); ^{1}H NMR (DMSO d_6) δ: 1.52 (m, 2H, CH_2), 2.42 (t, *J*=4.3 Hz, 4H, 2-NCH_2), 4.60 (s, 4H, rings 2-NCH_2), 5.55 (s, 4H, rings 2-OCH_2), 6.65(dd, *J*=7.2 and 2.2 Hz, 2H), 7.15 (d, *J*=7.2 Hz, 2H), 7.30 (d, *J*=2.2 Hz, 2H); Anal Calcd for $C_{19}H_{20}Br_2N_2O_2$ (468): C 48.71; H 4.27; N 5.98. Found C 48.85; H 4.35; N 6.00

*1,3-bis(6,8-dibromo-2H-benzo[e][1,3]oxazin-3(4H)-yl)propane (**3c**)*: Brown solid, IR (KBr) 3085cm^{-1} (-CH of $–CH_2$), 1164cm^{-1}(-C-O); ^{1}H NMR (DMSO d_6) δ: 1.58 (m, 2H, CH_2), 2.50 (t, *J*=5.6 Hz, 4H, 2-NCH_2), 4.67 (s, 4H, rings 2-NCH_2), 5.60 (s, 4H, rings 2-OCH_2), 6.90 (d, *J*=2.4 Hz, 2H), 7.55 (d, *J*=2.4 Hz, 2H); Anal Calcd for $C_{19}H_{18}Br_4N_2O_2$ (626): C 36.42; H 2.87; N 4.47. Found C 36.50; H 2.95; N 4.35.

*1,3-bis(6-chloro-2H-benzo[e][1,3]oxazin-3(4H)-yl)propane (**3d**)*: White solid, IR (KBr) 3078cm^{-1}(-CH of $–CH_2$), 1156cm^{-1}(-C-O); ^{1}H NMR (DMSO d_6) δ: 1.54 (m, 2H, CH_2), 2.45 (t, 4H, *J*=4.5Hz, 2-NCH_2), 4.61 (s, 4H, rings 2-NCH_2), 5.57 (s, 4H, rings 2-OCH_2), 6.70 (dd, *J*=7.3 and 2.3 Hz, 2H), 7.20 (d, *J*=7.3Hz, 2H), 7.30 (d, *J*=2.3 Hz, 2H); Anal Calcd for $C_{19}H_{20}Cl_2N_2O_2$ (378.9): C 60.17; H 5.32; N 7.39 Found C 60.50; H 5.35; N 7.40

*1,3-bis(6,8-diiodo-2H-benzo[e][1,3]oxazin-3(4H)-yl)propane (**3e**)*: Yellow solid, IR (KBr) 3083cm^{-1} (-CH of $–CH_2$), 1160cm^{-1}(-C-O);^{1}H NMR (DMSO d_6) δ: 1.50 (m, 2H, CH_2), 2.45 (t,4H, 2-NCH_2, J=5.7Hz), 4.52 (s, 4H, rings 2-NCH_2), 5.49 (s, 4H, rings 2-OCH_2), 7.10(d, *J*=2.4Hz 2H), 7.50 (d, *J*=2.4 Hz, 2H); Anal Calcd for $C_{19}H_{18}I_4N_2O_2$ (814): C 28.00; H 2.21; N 3.43. Found C 28.05; H 2.15; N 3.40.

*1,3-bis(6-methyl-2H-benzo[e][1,3]oxazin-3(4H)-yl)propane (**3f**)*: White solid, IR (KBr) 3070cm^{-1}(-CH of $–CH_2$), 1148cm^{-1}(-C-O); ^{1}H NMR (DMSO d_6 δ: 1.48 (m, 2H, CH_2), 2.10 (s, 6H,2-ArCH_3), 2.38 (t,

J=4.0 Hz, 4H, 2-NCH_2), 4.55 (s, 4H, rings 2-NCH_2), 5.50 (s, 4H, rings 2-OCH_2), 6.55 (dd, *J*=6.50 and 2.0 Hz, 2H), 7.00 (d, *J*=6.50 Hz, 2H), 7.20 (d, *J*=2.0 Hz 2H); Anal Calcd for $C_{21}H_{26}N_2O_2$ (338): C 74.55; H 7.69; N 8.28. Found C 74.50; H 7.65; N 8.30

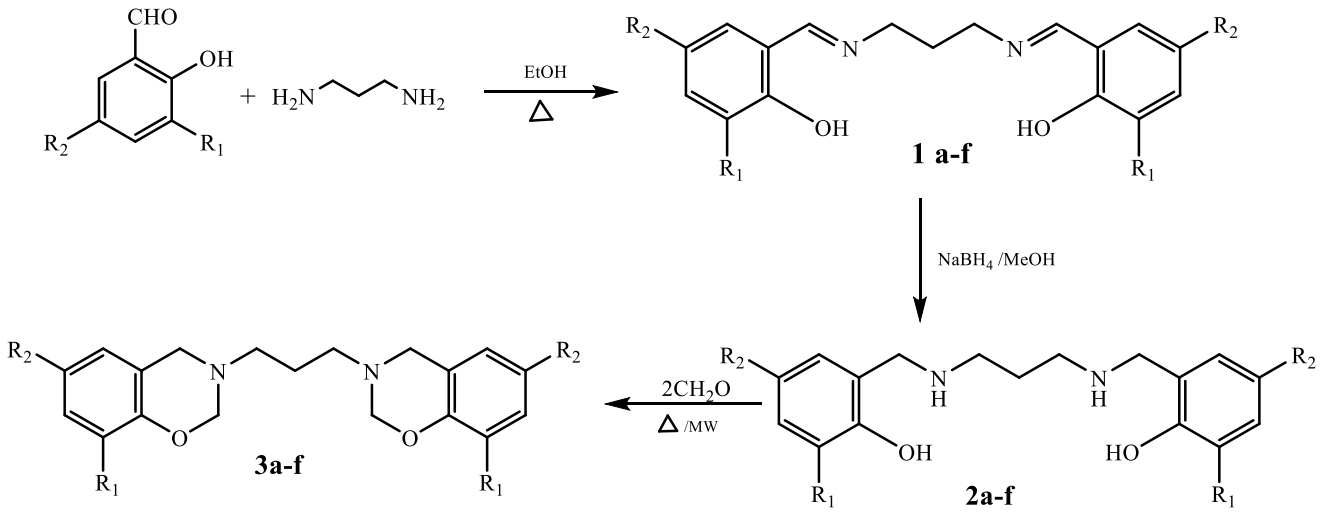
2.4. Antimicrobial Activity

Newly synthesized compounds (**3a-f**) were screened for antimicrobial activity against Gram-positive bacteria *Staphylococcus aureus* (MTCC-96), the Gram-negative bacteria *Escherichia coli* (MTCC-443) in the nutrient agar media, and fungi *Aspergillus niger* (MTCC-281) and *Aspergillus flavus* (MTCC-1323) in sabouraud dextrose medium at 200, 100, 50, 25, and 12.5µg/mL concentrations by using borth dilution method[18-20]. The minimum inhibitory concentrations (MIC's) values were determined by comparison to ofloxacin and ketoconazole as the reference drugs for bacterial and fungal activity respectively, as shown in table-**2**. Standard antibiotics ofloxacin and ketoconazole were used as reference drugs at 50, 25, 12.5µg/mL concentrations. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of the compound that inhibits the visible growth of microorganism on the plate.

3. Results and Discussion

3.1. Chemistry

In this article, we report the synthesis of new biologically active bis-1,3-benzoxazines derivatives **3a-f** under conventional and non-conventional (microwave irradiation) methods. The synthesis of new derivatives of bis-1,3-benzoxazine (**3a-f**) was performed as outlined in scheme 1.



Scheme 1. Synthesis of bis-1, 3-benzoxazines

Our syntheses are based on three step reactions. In our previous study, we reported microwave induced synthesis of bis-Schiff bases of propane-1, 3-diamine.[17] In the present study, following this procedure, at first we reacted different salicyl aldehydes with 1,3-propandiamine to give bis Schiff bases **1a-f** which were used for further reactions without characterization. At the second step bis-Schiff bases **1a-f** were reduced with $NaBH_4$ to give

N[1],*N*[3]-dibenzylpropane-1,3-diamines **2a-f.** Cyclization of *N*[1],*N*[3]-dibenzylpropane-1,3-diamines **2a-f** with formaldehyde gave benzoxazines **3a-f**.

It was found that the synthesis of bis-1,3-benzoxazines **3a-f** by conventional methods took a longer time and gave lower yields when compared to the microwave irradiation technique in which the reaction proceeded smoothly with excellent yields, within a 5-10 minutes (Table 1)

Table1. Comparison for the yields of the synthesized compounds **3a-f**

Compounds	M.P. ºC	Conventional method		MWI	
		t/h	Yield,%	t/min	Yield, %
3a	115	3.0	65	08	85
3b	145	3.5	60	10	80
3c	165	4.0	60	10	80
3d	155	3.0	62	10	85
3e	148	4.0	61	06	87
3f	170	3.0	60	10	84

IR spectra of the dibenzylpropane-1,3-diamines **2a-f** showed the absorption bands at 3450 and 3300 cm^{-1} due to OH and NH groups respectively. The ^{1}H NMR spectrum of **2a-f** showed singlet in between δ 3.70-4.00 is due to benzylic CH_2 protons which is directly attached to aromatic ring whereas a broad singlet in between δ 4.32-5.00 is due to NH protons respectively confirming a reductions. The compounds **2a-f** underwent smooth ring closure in presence of formaldehyde, involving internal Mannich reaction to give bis-1, 3-benzoxazines **3a-f**. The IR spectrum of **3a-f** showed the absence of bands due to OH and NH group which were observed in its precursor. Its ^{1}H NMR spectrum displayed two distinct singlet at δ 4.10 and δ 5.08 due to newly formed 1,3-oxazine ring, methylene protons (CH_2 and NCH_2O) respectively confirming cyclization.

3.2. Antimicrobial Activity

The investigation of antibacterial and antifungal screening data revealed that all tested compounds **3a-f** showed good to moderate inhibition at 12.5-200μg/mL in DMSO. The compounds **3c**, **3d**, **3e**, showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active -Br(**3c**), –Cl(**3d**), -I(**3e**), groups attached to phenyl group at 2,3 and 4th position in bis-benzoxazines. When the substitution of these groups is replaced by hydrogen or another group, a sharp decrease in activity against most of strains was observed. Compound **3a**, **3b**, **3f**, exhibited moderate activity compared to that of standard ofloxacin against all the bacterial strain. Further the result showed that Gram-negative exhibited better activity than Gram-positive organism.

Table 2. Antibacterial and Antifungal activity of title compounds **3a-3f**

Entry	MIC* (minimum inhibitory concentration			
	S. aureus	*E.coli*	*A.niger*	*A.flavus*
3a	100	50	200	200
3b	200	200	100	50
3c	25	25	25	25
3d	25	12.5	12.5	12.5
3e	12.5	12.5	12.5	12.5
3f	200	200	50	150
Ofloxacin	25	12.5	NT	NT
Ketoconazole	NT	NT	12.5	25

* MIC(minimum inhibitory concentration) as given μg/mL. NT: Not tested.

Compounds **3d**, **3e**, **3f**, showed comparatively good activity against all the fungal strains, while compound **3a**, **3b** showed moderate activity against the fungal strains. The structures of these compounds contain biologically active, chloro, iodo, bromo and hydroxyl substituted groups.

4. Conclusion

A new series of bis-1,3-benzoxazines **3a-f** were synthesized under conventional and microwave irradiation conditions. In microwave irradiation method, the reactions were completed in shorter times with better yields compared to the conventional method. All the new compounds were screened for their antimicrobial activities. It was observed that compounds **3c**, **3d**, **3e** exhibited broad spectrum of antibacterial and antifungal activity against all the tested strains compared to the standard drugs at their respective concentrations.

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Supporting Information

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