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Utilization of ultrasonic irradiation as green and effective one-pot protocol to prepare a novel series of bis-2-amino-1,3,4-oxa(thia)diazoles and bis-tetrazoles

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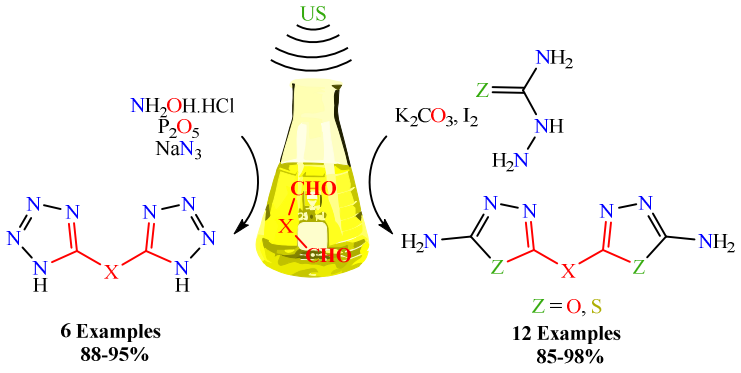
Abstract

In an effective and straightforward conversion, bis-semicarbazones and bis-thiosemicarbazones are transformed into a diversity of novel substituted bis-2-amino-1,3,4-oxadiazoles and bis-2-amino-1,3,4-thiadiazoles, respectively under ultrasonic irradiation. Bis-tetrazoles are obtained from the dialdehydes by sequential reaction with hydroxylamine hydrochloride, phosphorus pentoxide and sodium azide without isolation of the intermediates oximes and nitriles. All the reactions proceed cleanly and smoothly under mild conditions, with short reaction times and broad functional groups possibility. No side reactions were observed.



Keywords: Ultrasound, one-pot reaction, bis-heterocycles, dialdehydes

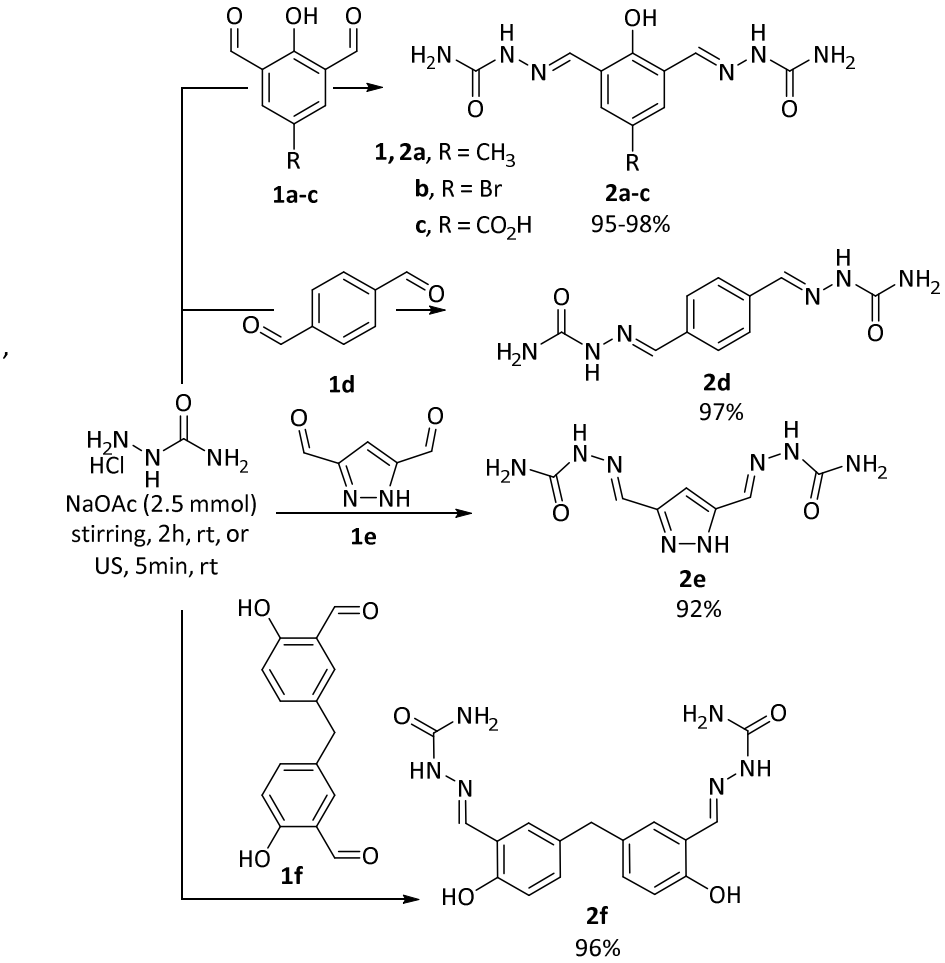
Introduction

Semicarbazides and thiosemicarbazides constitute advantageous precursors for the preparation of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles, respectively. These five-membered rings are an important class of heterocyclic systems which have worthy applications in medicinal, materials, and synthetic chemistry.[1,2] 1,3,4-Oxadiazole derivatives are of particular concern for medicinal chemistry due to plentiful of these derivatives acquire strong anticonvulsant, anticancer and antibacterial activities.[3] They are also applied in material science for the production of optical brighteners and organic light-emitting diodes (OLEDs).[4-6] Furthermore, the 1,3,4-oxadiazole scaffolds are used as sensors for several anions or cations.[7] Also, bis-oxadiazoles are attractive systems having many biological activities[8] and can be used as scintillators because of their luminescent properties.[9] 1,3,4-Thiadiazoles are another important category of heterocyclic compounds which are known for many important pharmacological activities like antimitotic, hypolipidemic, anti-inflammatory, hypoglycaemic, analgesic, anticonvulsive and antimicrobial activities.[10] Tetrazoles are also an important class of nitrogen containing heterocycles with a broad range of medicinal applications such as the synthesis of antihistaminic family drugs (Pranlukast and Pemiroplast) and sartan drugs (Losartan and Candesartan).[11,12] Moreover, tetrazoles are widely used in information recording systems,[13] high density energy materials,[14] and explosives.[15] Many research papers have dealt with the synthesis of 5-substituted 1*H*-tetrazoles,[16-21] 1,3,4-oxadiazoles[22-25] and 1,3,4-thiadiazoles[26-28] under the influence of diverse catalysts and various solvent conditions. Almost all of these methods suffer from habitual obstacles such as expensive reagents, low yield, strong Lewis acids used, long reaction time, water sensitivity and harsh reaction conditions. Thus, there is still some space to develop and improve novel, efficient, mild, and simple synthetic protocols to diminish these drawbacks and would be of considerable relevance to both medicinal and synthetic chemists.

Recently, sonochemical synthesis of several classes of organic compounds has received great interest.[29,30] This is because the ultrasound technique with acoustic cavitation creates highly localized temperatures and pressures that cannot be obtained by other methods. Acoustic cavitation comprises the formation, expansion, and immediately collapse of bubbles in the solution. This process liberates the intensified stored energy in collapsing bubbles in a short time. The released energy can elevate both temperature and pressure up to ~5000 K, and ~1000 bar, respectively, when the applied frequencies range from 20 to 40 kHz.[31] Therefore, the ultrasound-assisted process can be appropriate for reactions which are inaccessible by conventional methods. The cavitation phenomena can influence a reaction both physically and chemically.[32] The physical influence is generation of intensive local convection in the liquid that promotes the mass transfer merits of the system. The chemical influence encompasses the creation of extremely reactive radicals inside the bubble. The radicals created inside the cavitation bubble get discharged into the medium with the shatter of the bubble where they can activate and expedite the chemical reactions; this is the so-called sonochemical effect.[33] To the best of our knowledge, there are no literature examples of the synthesis of bis-1,3,4-oxadiazoles, bis-1,3,4-thiadiazoles and bis-tetrazoles under ultrasound irradiation. Hence, based on the above-mentioned and in continuation with our concern in the development of environment-friendly, mild, and operationally simple protocols for the synthesis of bis-heterocyclic compounds,[34-37] we report hither a rapid ultrasound accelerated synthesis of these compounds.

Results and Discussion

The key intermediate bis-semicarbazones **2a-f** were synthesized form semicarbazide hydrochloride by its condensation reaction with substituted dialdehydes **1a-f** in ethanol-water mixture at room temperature in good yields (Scheme 1). According to our previous results for the preparation of bis-thiosemicarbazone derivatives,[36] ultrasound irradiation can be used to improve the yields and shorten the reaction times in comparison to conventional method. Under ultrasound irradiation (40 kHz), the desired bis-semicarbazone derivatives **2a-f** were obtained within 5 min in quantitative yields (Scheme 1) and were used in the next step without any extra purification. The newly synthesized compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR, mass spectral and elemental analyses. In the ^{1}H NMR spectrum of the bis-semicarbazone **2a**, the CH signal of the azomethine group appeared at 8.11 ppm as a singlet. Two characteristic singlets appeared at δ = 6.43 and 10.30 ppm corresponding to NH_2 and NH groups, respectively. In the ^{13}C NMR spectra of the reaction products, the signal corresponding to the carbon of the aldehydic group (HC=O) disappeared and a new signal, which belong to the azomethine carbon atom (CH=N) of the products was observed.



Scheme 1. Synthesis of bis-semicarbazones (**2a-f**).

The oxidative cyclization of the obtained bis-semicarbazone derivatives **2a-f** with iodine was investigated aiming to obtain the hitherto unreported bis-1,3,4-oxadiazoles **3a-f**. We started our endeavours with bis-semicarbazone **2a**, potassium carbonate and molecular iodine as model substrates to search for appropriate reaction conditions for the synthesis of bis-2-amino-1,3,4-oxadiazole **3a** (Table 1). First, we evaluated the

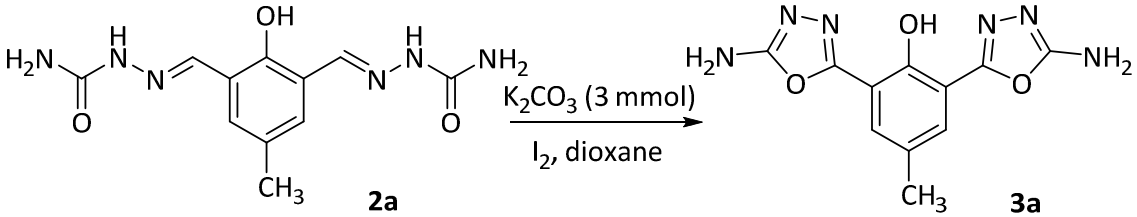
reaction by stirring the substrates in 1,4-dioxane at room temperature under conditions similar to those previously reported (conventional conditions).[38] It was found that the reaction afforded the bis-2-amino-1,3,4-oxadiazole **3a** (confirmed by NMR analysis) with a yield of 66% in 1 h (Table 1, entry 1). Increases in both temperature and time slightly ameliorated the yield of the desired product (**3a**) (Table 1, entries 2, 3). In order to further improve the yield and to decrease the reaction time, we attempted the same reaction under ultrasound irradiation at room temperature and the results are shown in Table 1 (entries 4, 5). From these results, it was observed that the ultrasound irradiation improved the product yield to a maximum of 88% of the bis-2-amino-1,3,4-oxadiazole **3a** within 10 minutes (Table 1, entry 5).

In spite of this satisfactory result, we have evaluated other conditions for optimizing an effective method for this synthetic reaction. By varying the amount of oxidant in the above reaction, it was found that the reaction yield increased with the increase in the amount of iodine from 2.0 to 2.3 equivalents and became steady thereafter (Table 1, entries 7, 12, 13), establishing 2.3 equivalents of iodine as optimal for this protocol. In the next experiment, in order to determine the efficiency of ultrasound heating in the model reaction, a control run was undertaken using thermal heating under the same reaction conditions. It was found that when the temperature during ultrasound irradiation was modulated, 60 ^{o}C was the optimum temperature (Table 1, entry 7). Moreover, on reducing the irradiation time to 5 min, the yield of the required product was decreased and some starting material remained unreacted (Table 1, entry 6). The influence of irradiation frequency on the reaction efficiency was also studied (Table 1, entries 7-11). Several ranges of irradiation frequencies (20-60 kHz) were studied on the model reaction. On screening, it was found that, when the irradiation frequency was 20 kHz (Table 1, entry 8), a low yield was obtained in 10 min. However, the reaction could not improve well in the irradiation frequency of 60 kHz (Table 1, entry 11). In the frequency of 40 kHz, the yield of **3a** was better than that with 30 kHz within 10 min (96%, Table 1, entry 7). By increasing the irradiation frequency from 40 to 50 kHz (Table 1, entries 7, 10), there was no significant improvement in the reaction yield (95%, entry 10).

Eventually, the optimal conditions for the model reaction were identified as ultrasound irradiation of 40 kHz frequency at 60 ^{o}C for 10 min using 2.3 equiv of iodine and 1.0 mmol of bis-semicarbazone derivatives **2a-f** (Table 1, entry 7). After corroborating the feasibility of the model system, the scope of this synthesis was evaluated by using a range of bis-semicarbazone derivatives **2b-f** (Scheme 2, method 1). It was found that sonication is superior to the conventional method as it generates in almost all cases nearly quantitative yields of the desired products without the need for tedious purification steps.

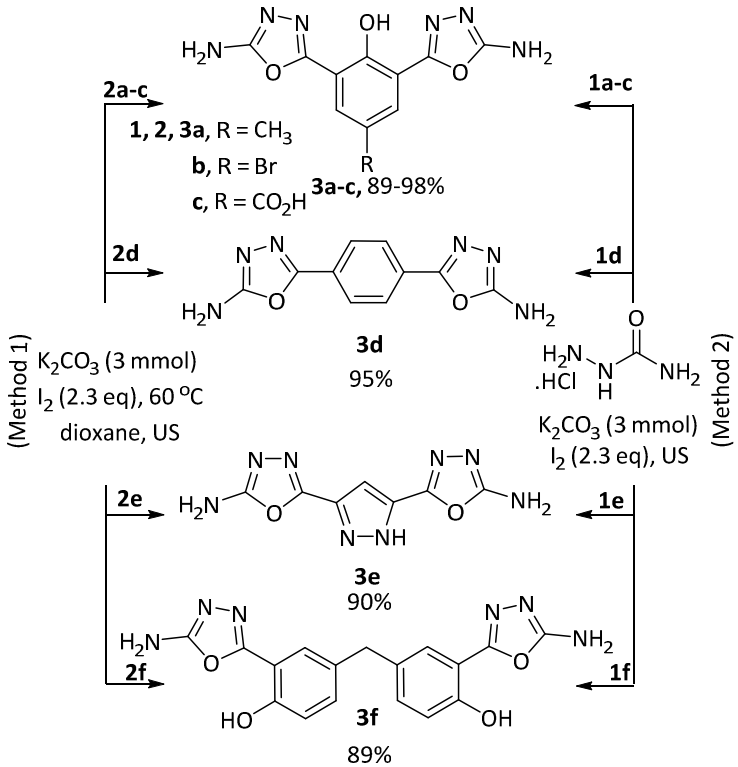
Products **3a-f** can also be obtained in one-pot synthesis without the isolation of intermediates **2a-f**. Thus, upon completion of the condensation of dialdehydes **1a-f** and the semicarbazide hydrochloride under ultrasound irradiation (monitored by TLC), the solvent was evaporated under reduced pressure and then the remaining bis-semicarbazones **2a-f** were redissolved in 1,4-dioxane, followed by the addition of potassium carbonate and iodine and the reaction mixture was subjected to ultrasound irradiation at 60 ^{o}C for an additional 10 min to afford the required products (**3a-f**, Scheme 2, method 2). The structures of synthesized bis-1,3,4-oxadiazole derivatives **3a-f** were elucidated by elemental analysis, IR, ^{1}H and ^{13}C NMR data, and high-resolution mass spectra. The ^{1}H NMR spectrum of derivative **3a** showed a signal at 2.25 ppm corresponding to the CH_3 group. The singlets at δ 7.17 and 7.51 ppm were due to the NH_2 and aromatic protons, respectively. ^{13}C NMR spectra, C-2 and C-5 of the bis-1,3,4-oxadiazole moiety were observed around 164.1 and 157.8 ppm, respectively. The chemical shifts of the other carbons of the final bis-1,3,4-oxadiazoles were as expected. The high-resolution mass spectra (HRMS) of the synthesized derivatives were in conformity with the proposed structures.

Table 1. Optimization of the reaction conditions for the synthesis of bis-2-amino-1,3,4-oxadiazole **3a** under conventional (Conv.) and ultrasound (US) methods



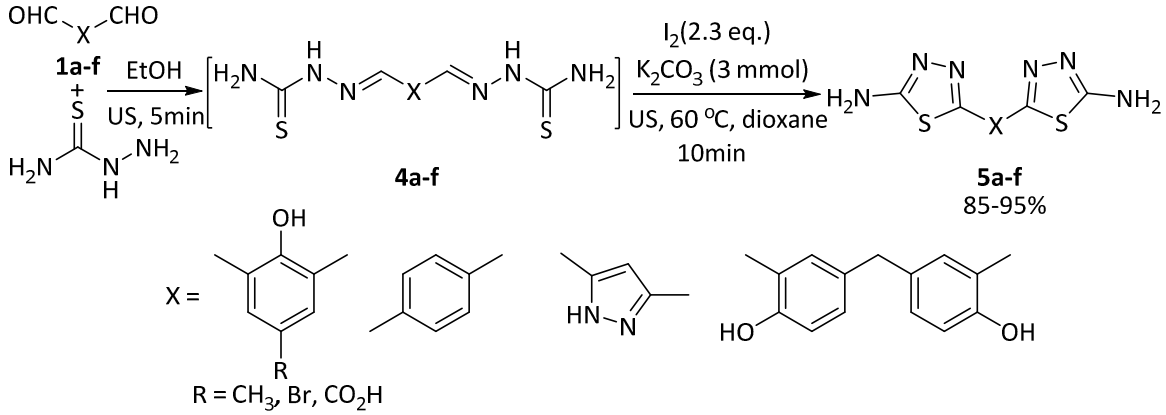
2a **3a**

Entry	Method	I_2 (equiv.)	Time (min)	Temp. (^oC)	Frequency (kHz)	Yield (%)
1	Conv.	2.3	60	rt	-	66
2	Conv.	2.3	120	rt	-	68
3	Conv.	2.3	180	60	-	76
4	US	2.3	5	rt	40	83
5	US	2.3	10	rt	40	88
6	US	2.3	5	50	40	92
7	US	2.3	10	60	40	**96**
8	US	2.3	10	60	20	87
9	US	2.3	10	60	30	95
10	US	2.3	10	60	50	95
11	US	2.3	10	60	60	92
12	US	2.0	10	60	40	90
13	US	2.5	10	60	40	96



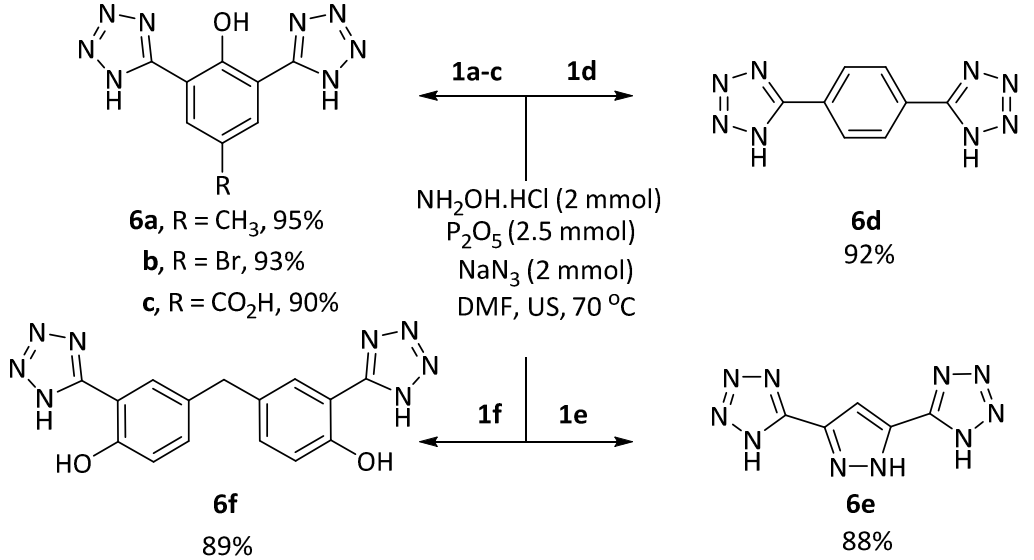
Scheme 2. Synthesis of bis-oxadiazole derivatives (**3a-f**) by different methods.

Encouraged by the success of bis-2-amino-1,3,4-oxadiazoles synthesis, we sought to further extend the scope of this practical approach by replacing semicarbazide hydrochloride with thiosemicarbazide aiming to prepare bis-2-amino-1,3,4-thiadiazoles **5a-f** (Scheme 3). Upon completion (monitored by TLC) of the condensation of thiosemicarbazide and the corresponding dialdehydes **1a-f**, the solvent was evaporated under reduced pressure and the remaining bis-thiosemicarbazones **4a-f** were redissolved in 1,4-dioxane, followed by the treatment with molecular iodine and potassium carbonate. Stirring the resulting mixture at 60 ^{o}C under ultrasound irradiation for 10 min produced the desired bis-2-amino-1,3,4-thiadiazoles **5a-f** in excellent yields (85-95%).



Scheme 3. Synthesis of bis-thiadiazole derivatives **5a-f**.

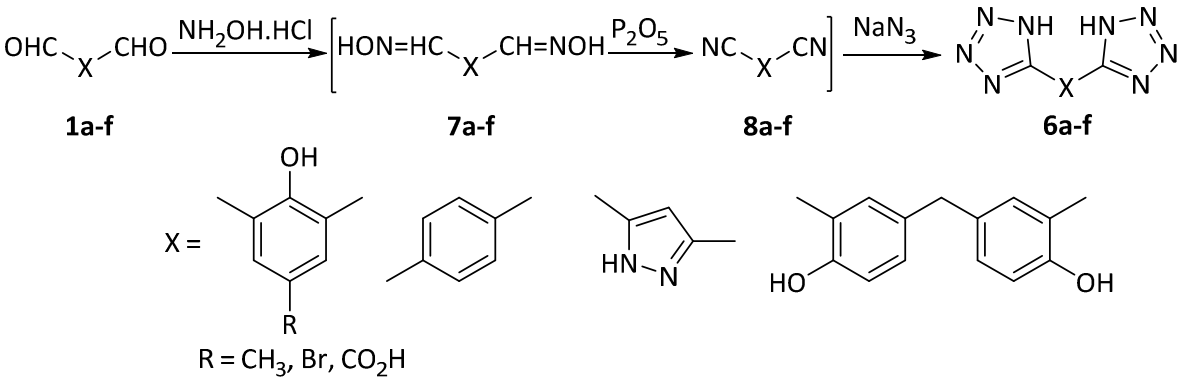
Although the preparation of bis-tetrazoles (**6a-f**) under ultrasonic irradiation, to the best of our knowledge, has not been reported in the existing literatures until date, synthesis of relevant mono-tetrazoles have been achieved by several methods, for example, one-pot reactions for tetrazole synthesis have been carried out by using aldehydes, ammonia and iodine.[39-41] However, the use of ammonia should be avoided in order to prevent the generation of hydrazoic acid and nitrogen triiodide monoamine (explosive) which are formed from the reaction of ammonia with sodium azide and iodine, respectively. In order to prevent the formation of these dangerous and undesirable by-products, Khalid Mohammed Khan *et al*.[42] developed a method that included the replacement of iodine and ammonia with hydroxylamine and phosphorus pentoxide under thermal conditions for nitrile formation followed by addition of sodium azide for the synthesis of a number of tetrazoles, but this method had some shortcomings such as long reaction times and poor yields.



Scheme 4. Synthesis of bis-tetrazole derivatives (**6a-f**).

Our first approach to the synthesis of novel bis-tetrazoles commenced using the conventional method, with the reaction in DMF under reflux of the dialdehydes **1a-f** and hydroxylamine hydrochloride followed by addition of phosphorus pentoxide (Schemes 4, 5).

These reactions yielded the corresponding dinitriles (**8a-f**, not isolated), which on reaction with sodium azide afforded bis-tetrazoles (**6a-f**) but in poor yields (Table 2) and their purification was difficult. Notwithstanding this outcome, we explored other conditions for the above reaction in order to obtain optimum conditions for this protocol. Under ultrasound irradiation, the synthesis of bis-tetrazoles (**6a-f**) was achieved by the addition of hydroxylamine hydrochloride in DMF to dialdehydes (**1a-f**) and heating (70 ^{o}C) under ultrasound irradiation (40 kHz) for 25 min to generate the corresponding oximes (**7a-f**). Phosphorus pentoxide was then added and the resulting mixture was heated under ultrasound irradiation for another 15 min. Finally, sodium azide was added to the formed bis-nitriles (**8a-f**) and the obtained mixture was heated for another 15 min followed by acidic work-up, furnished the required products (**6a-f**, Scheme 4) in excellent overall yields (88-95%, Table 2). This synthetic process comprises a new protocol for the synthesis of this class of bis-tetrazoles (**6a-f**). These derivatives displayed IR, HRMS, NMR spectra and elemental analyses consistent with the assigned structures (partial assignments are given in the Experimental section).



Scheme 5. Proposed intermediates in the synthesis of bis-tetrazoles (**6a-f**).

Table 2. Comparison results with different conditions in the synthesis of bis-tetrazoles (**6a-f**)

Entry	Products	Time (min)		Yield (%)	
	(**6a-f**)	Conv.	US	Conv.	US
1	**6a**	180	55	46	95
2	**6b**	180	55	51	93
3	**6c**	200	55	37	90
4	**6d**	200	75	43(50)[43]	92
5	**6e**	180	75	46	88
6	**6f**	180	55	52	89

Conclusions

A powerful one-pot protocol has been developed to provide a rapid synthesis of bis-2-amino-1,3,4-oxadiazoles, bis-2-amino-1,3,4-thiadiazoles, and bis-tetrazoles from easily available starting materials. The use of

ultrasonic irradiation effectively speeds up the reaction to produce higher yields within shorter reaction times than with conventional heating. These notable features make the present protocol appropriate for automation in a high-throughput synthesis of hybrid compounds which can be of potential use for medicinal chemistry purposes.

Experimental Section

General. Starting materials were commercially available and were used without further purification. Silica gel G [E-Merck] was used for thin layer chromatography (TLC). ^{1}H and ^{13}C NMR spectra were recorded using Bruker UltraShield spectrometer at 400 and 100 MHz, respectively. Splitting patterns are designated as singlet (s), doublet (d), triplet (t), doublet of doublet (dd), doublet of triplet (dt), triplet of triplet (tt) quartet (q), broad (br). Splitting patterns that could not be interpreted or easily visualized are written as multiplet (m). High resolution mass spectra (HRMS) measurements were recorded on a Bruker Daltonics microTOF spectrometer. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer, using samples prepared as KBr discs. Sonication was done in a SY5200DH-T ultrasound cleaner with an output power of 250 W and frequency range of 20-60 kHz. The reaction vial was placed in the maximum energy area in the cleaner.[44] Water was added or removed in order to control the bath temperature.

General procedure for the synthesis of bis-semicarbazones (**2a-f**)

Conventional Method. A 10 mL ethanolic solution of dialdehydes (**1a-f**) (1 mmol) was added dropwise to an aqueous solution of semicarbazide hydrochloride (2 mmol) and sodium acetate (2.5 mmol). The mixture was stirred well at room temperature for 2h (the reaction was monitored by TLC). The obtained solid was filtered, washed with chilled aqueous ethanol (3x5 mL), and dried to afford the desired products (**2a-f**)**.**

Ultrasound Method. A mixture of dialdehydes (**1a-f**) (1 mmol), semicarbazide hydrochloride (2 mmol) and sodium acetate (2.5 mmol) in aqueous ethanol (15 mL) was irradiated in the water bath of the ultrasonic cleaner at room temperature. To optimize time, the tests were implemented with several times (2, 5, 7, 10, and 15 min) and 5 min was selected as optimum time, also with increasing time from 5 to 15 min no changes were observed in the formed products. After completion of the reaction (confirmed TLC), the obtained solid was filtered off, washed with chilled aqueous ethanol (3x5 mL) and dried to afford the desired products (**2a-f**), which in all cases were essentially pure semicarbazones.

2,2′-[(2-Hydroxy-5-methyl-1,3-phenylene)bis(methanylidene)]bis(hydrazine-1-carboxamide) (**2a**)**.**[45] Yield 98%; light yellow solid; mp 197-199 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 10.67 (s, 1H, OH), 10.30 (s, 2H, NH), 8.11 (s, 2H, C*H*=N), 7.48 (s, 2H, ArH), 6.43 (s, 4H, NH_2), 2.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 156.6 (C=O), 152.9 (ArC), 139.0 (*C*H=N), 129.3, 128.6, 121.0 (ArC), 20.4 (*C*H_3). IR (KBr, cm^{-1}): ν_{max} 3264 (br, NH_2, NH& OH), 1676 (C=O) cm^{-1}. HRMS (EI) for (M - H)$^{+}$: calcd. 277.1044; found 277.1061. Anal. Calcd. for $C_{11}H_{14}N_6O_3$: C, 47.48; H, 5.07; N, 30.20. Found: C, 47.51; H, 5.12; N, 30.16%

2,2′-[(5-Bromo-2-hydroxy-1,3-phenylene)bis(methanylidene)]bis(hydrazine-1-carboxamide) (**2b**)**.** Yield 95%; yellow solid; mp 231-233 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 11.10 (s, 1H, OH), 10.43 (s, 2H, NH), 8.10 (s, 2H, C*H*=N), 7.88 (s, 2H, ArH), 6.53 (s, 4H, NH_2). ^{13}C NMR (100 MHz, DMSO): δ 156.8 (C=O), 153.5 (ArC), 139.1 (*C*H=N), 129.2, 128.9, 123.1 (ArC). IR (KBr, cm^{-1}): ν_{max} 3213 (br, NH_2, NH, OH), 1660 (C=O) cm^{-1}. HRMS (EI) for (M - H)$^{+}$: calcd. 341.0070; found 340.9992. Anal. Calcd. for $C_{10}H_{11}BrN_6O_3$: C, 35.00; H, 3.23; N, 24.49. Found: C, 35.11; H, 3.35; N, 24.52%.

3,5-Bis-[(2-carbamoylhydrazono)methyl]-4-hydroxybenzoic acid (**2c**)**.** Yield 95%; light yellow solid; mp 205-207 °C; ^{1}H NMR (400 MHz, DMSO): δ 11.91 (s, 1H, OH), 10.45 (s, 2H, NH), 8.21 (s, 2H, C*H*=N), 8.16 (s, 2H, ArH), 6.46 (s, 4H, NH_2). ^{13}C NMR (100 MHz, DMSO): δ 167.2, 158.4 (2 C=O), 138.7 (*C*H=N), 129.9, 122.7, 121.1 (ArC). IR (KBr, cm^{-1}): ν_{max} 3199 (br, NH_2, NH& OH), 1693, 1672 (C=O) cm^{-1}. HRMS (EI) for (M - H)$^+$: calcd. 307.0769; found 307.0785. Anal. Calcd. for $C_{11}H_{12}N_6O_5$: C, 42.86; H, 3.92; N, 27.26. Found: C, 42.80; H, 4.05; N, 27.33%.

2,2′-[1,4-Phenylenebis(methanylidene)]bis(hydrazine-1-carboxamide) (**2d**)**.** Yield 97%; light yellow solid; mp 221-224 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.33 (s, 2H, NH), 8.18 (s, 2H, C*H*=N), 8.09 (s, 4H, ArH), 6.32 (s, 4H, NH_2). ^{13}C NMR (100 MHz, DMSO): δ 157.5 (C=O), 139.7 (*C*H=N), 136.33, 129.9 (ArC). IR (KBr, cm^{-1}): ν_{max} 3205 (br, NH_2 & NH), 1671 (C=O) cm^{-1}. HRMS (EI) for (M - H)$^+$: calcd. 247.0948; found 247.0945. Anal. Calcd. for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.41; H, 4.80; N, 33.99%.

2,2′-[(1*H*-Pyrazole-3,5-diyl)bis(methanylidene)]bis(hydrazine-1-carboxamide) (**2e**)**.** Yield 92%; white solid; mp 262-264 °C; ^{1}H NMR (400 MHz, DMSO): δ 14.11 (s, 1H, NH), 10.47 (s, 2H, NH), 8.12 (s, 2H, C*H*=N), 7.17 (s, 1H, Pyrazole-C4), 6.44 (s, 4H, NH_2). ^{13}C NMR (100 MHz, DMSO): δ 158.1 (*C*=O), 138.9 (*C*H=N), 135.7, 109.2, (Pyrazole-C3,4). IR (KBr, cm^{-1}): ν_{max} 3159 (br, NH_2 & NH), 1688 (C=O) cm^{-1}. HRMS (EI) for (M - H)$^+$: calcd. 237.0850; found 237.0849. Anal. Calcd. for $C_7H_{10}N_8O_2$: C, 35.30; H, 4.23; N, 47.04. Found: C, 35.25; H, 4.33; N, 47.11 %.

2,2′-[Methylenebis-(6-hydroxy-3,1-phenylene)bis(methanylidene)]bis(hydrazine-1-carboxamide) (**2f**)**.** Yield 96%; white solid; mp 242-244 °C; ^{1}H NMR (400 MHz, DMSO): δ 11.67 (s, 1H, OH), 10.44 (s, 2H, NH), 8.18 (s, 2H, C*H*=N), 7.41 (d, *J* 7.4 Hz, 2H, Ar), 7.32 (s, 2H, Ar), 6.99 (d, *J* 7.4 Hz, 2H, Ar), 6.45 (s, 4H, NH_2), 4.09 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 159.1 (C=O), 152.7 (ArC), 138.8 (*C*H=N), 133.5, 131.4, 120.1, 117.4 (ArC), 40.5 (*C*H_2). IR (KBr, cm^{-1}): ν_{max} 3184 (br, NH_2, NH& OH), 1684 (C=O) cm^{-1}. HRMS (EI) for (M - H)$^+$: calcd. 369.1318; found 369.1320. Anal. Calcd. for $C_{17}H_{18}N_6O_4$: C, 55.13; H, 4.90; N, 22.69. Found: C, 55.09; H, 4.98; N, 22.74%.

Synthesis of derivatives 3a-f and 5a-f

A mixture of dialdehydes **1a-f** (1 mmol), semicarbazide hydrochloride or thiosemicarbazide (2mmol) and sodium acetate (2 mmol, added only in case of semicarbazide hydrochloride) in aqueous ethanol (75%, 10 mL) was sonicated for 5 min. Then the solvent was evaporated under reduced pressure, and the resulting residue was redissolved in 1,4-dioxane (10 mL), followed by addition of potassium carbonate (3 mmol) and iodine (2.3 equiv.) in sequence. The reaction mixture was sonicated again at 60 °C for about 10 min (monitored by TLC). After cooling to ambient temperature, 5% $Na_2S_2O_3$ (30 mL) was added and the mixture was extracted with CH_2Cl_2/MeOH (6:4, 3x15 mL). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated. Upon standing at room temperature, the corresponding bis-1,3,4-oxa(thia)diazoles were precipitated in pure form which is then washed with chilled ethanol, filtered and dried.

2,6-Bis-(5-amino-1,3,4-oxadiazol-2-yl)-4-methylphenol (**3a**)**.** Yield 93%; white solid; mp 221-223 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.64 (s, 1H, OH), 7.51 (s, 2H, ArH), 7.17 (br, s, 4H, NH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 164.1, 157.8, 152.6, 129.1, 128.3, 120.8 (ArC), 20.3 (*C*H_3). IR (KBr, cm^{-1}): ν_{max} 3164 (br, NH_2 & OH). HRMS (EI) for (M - H)$^+$: calcd. 277.1044; found 277.1061. Anal. Calcd. for $C_{11}H_{10}N_6O_3$: C, 47.48; H, 5.07; N, 30.20. Found: C, 47.51; H, 5.12; N, 30.16%.

2,6-Bis-(5-amino-1,3,4-oxadiazol-2-yl)-4-bromophenol (**3b**)**.** Yield 98%; yellow solid; mp 255-257 °C; ^{1}H NMR (400 MHz, DMSO): δ 11.12 (s, 1H, OH), 7.85 (s, 2H, ArH), 7.24 (br, s, 4H, NH_2). ^{13}C NMR (100 MHz, DMSO): δ 164.4, 158.4, 153.1, 129.6, 129.0, 123.6 (ArC). IR (KBr, cm^{-1}): ν_{max} 3199 (br, NH_2 & OH). HRMS (EI) for (M + Na)$^+$: calcd. 360.9665; found 360.9662. Anal. Calcd. for $C_{10}H_7BrN_6O_3$: C, 35.42; H, 2.08; N, 24.78. Found: C, 35.40; H, 2.12; N, 24.83%.

3,5-Bis-(5-amino-1,3,4-oxadiazol-2-yl)-4-hydroxybenzoic acid (**3c**)**.** Yield 89%; yellow solid; mp 267-269 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 12.88 (br, s, 1H, CO_2H), 11.94 (s, 1H, OH), 8.13 (s, 2H, ArH), 7.44 (br, s, 4H, N*H*$_2$). ^{13}C NMR (100 MHz, DMSO): δ 167.6 (*C*O_2H), 164.9, 158.0, 130.3, 123.1, 121.9 (ArC). IR (KBr, cm^{-1}): ν_{max} 3157 (br, NH_2 & OH), 1687 (C=O). HRMS (EI) for $(M + Na)^+$: calcd. 327.0457; found 327.0453. Anal. Calcd. for $C_{11}H_8N_6O_5$: C, 43.43; H, 2.65; N, 27.63. Found: C, 43.40; H, 2.72; N, 27.56%.

5,5′-(1,4-Phenylene)bis-(1,3,4-oxadiazol-2-amine) (**3d**)**.** Yield 95%; yellowish solid; mp 277-280 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 7.93 (s, 4H, ArH), 7.32 (s, 4H, N*H*$_2$). ^{13}C NMR (100 MHz, DMSO): δ 165.6, 159.8, 135.6, 129.4 (ArC). IR (KBr, cm^{-1}): ν_{max} 3184 (br, NH_2 & OH). HRMS (EI) for $(M)^+$: calcd. 244.0711; found 244.0708. Anal. Calcd. for $C_{10}H_8N_6O_2$: C, 49.18; H, 3.30; N, 34.41. Found: C, 49.22; H, 3.24; N, 34.35 %.

5,5′-(1*H*-Pyrazole-3,5-diyl)bis-(1,3,4-oxadiazol-2-amine) (**3e**)**.** Yield 90%; yellow solid; mp 301-304 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 14.24 (s, 1H, NH), 7.21 (s, 4H, N*H*$_2$), 7.18 (s, 1H, Pyrazole-C4). ^{13}C NMR (100 MHz, DMSO): δ 166.4, 161.3, 135.3, 109.8, (Pyrazole-C3,4). IR (KBr, cm^{-1}): ν_{max} 3122 (br, NH_2). HRMS (EI) for $(M + Na)^+$: calcd. 257.0512; found 257.0516. Anal. Calcd. for $C_7H_6N_8O_2$: C, 35.90; H, 2.58; N, 47.85. Found: C, 35.98; H, 2.50; N, 47.92%.

4,4′-Methylenebis-[2-(5-amino-1,3,4-oxadiazol-2-yl)phenol] (**3f**)**.** Yield 89%; yellow solid; mp 296-299 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 11.58 (s, 1H, OH), 7.44 (d, *J* 7.4 Hz, 2H, Ar), 7.33 (m, 6H, Ar + N*H*$_2$), 7.01 (d, *J* 7.4 Hz, 2H, Ar), 4.11 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 164.7, 162.0, 152.6, 134.3, 131.6, 121.4, 119.6 (ArC), 40.4 (*C*H_2). IR (KBr, cm^{-1}): ν_{max} 2199 (br, NH_2 & OH). HRMS (EI) for $(M)^+$: calcd. 366.1079; found 366.1076. Anal. Calcd. for $C_{17}H_{14}N_6O_4$: C, 55.74; H, 3.85; N, 22.94. Found: C, 55.70; H, 3.92; N, 23.05%.

2,6-Bis-(5-amino-1,3,4-thiadiazol-2-yl)-4-methylphenol (**5a**)**.** Yield 95%; yellow solid; mp 311-313 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 10.66 (s, 1H, OH), 7.53 (s, 2H, ArH), 7.60 (br, s, 4H, N*H*$_2$), 2.26 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 175.2, 163.3, 152.6, 129.7, 128.5, 121.2 (ArC), 20.6 (*C*H_3). IR (KBr, cm^{-1}): ν_{max} 3177 (br, NH_2 & OH). HRMS (EI) for $(M - H)^+$: calcd. 305.0281; found 305.0279. Anal. Calcd. for $C_{11}H_{10}N_6OS_2$: C, 43.13; H, 3.29; N, 27.43. Found: C, 43.19; H, 3.20; N, 27.51%.

2,6-Bis-(5-amino-1,3,4-thiadiazol-2-yl)-4-bromophenol (**5b**)**.** Yield 93%; yellow solid; mp 288-290 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 11.20 (s, 1H, OH), 7.83 (s, 2H, ArH), 7.47 (br, s, 4H, N*H*$_2$). ^{13}C NMR (100 MHz, DMSO): δ 171.4, 164.2, 152.3, 129.1, 128.7, 122.7 (ArC). IR (KBr, cm^{-1}): ν_{max} 3214 (br, NH_2 & OH). HRMS (EI) for $(M - H)^+$: calcd. 368.9229; found 368.9225. Anal. Calcd. for $C_{10}H_7BrN_6OS_2$: C, 32.35; H, 1.90; N, 22.64. Found: C, 32.30; H, 1.99; N, 22.57%.

3,5-Bis-(5-amino-1,3,4-thiadiazol-2-yl)-4-hydroxybenzoic acid (**5c**)**.** Yield 91%; yellow solid; mp 323-326 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 12.90 (br, s, 1H, CO_2H), 11.99 (s, 1H, OH), 8.17 (s, 2H, ArH), 7.60 (br, s, 4H, N*H*$_2$). ^{13}C NMR (100 MHz, DMSO): δ 173.5, 167.9 (*C*O_2H), 162.6, 158.8, 132.5, 125.0, 123.2 (ArC). IR (KBr, cm^{-1}): ν_{max} 3186 (br, NH_2 & OH), 1689 (C=O). HRMS (EI) for $(M - H)^+$: calcd. 335.0024; found 335.0020. Anal. Calcd. for $C_{11}H_8N_6O_3S_2$: C, 39.28; H, 2.40; N, 24.99. Found: C, 39.18; H, 2.47; N, 24.83%.

5,5′-(1,4-Phenylene)bis-(1,3,4-thiadiazol-2-amine) (**5d**)**.**[46] Yield 95%; white solid; mp 291-293 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 7.83 (s, 4H, ArH), 7.10 (s, 4H, N*H*$_2$). ^{13}C NMR (100 MHz, DMSO): δ 175.2, 163.2, 135.1, 129.5 (ArC). IR (KBr, cm^{-1}): ν_{max} 3195 (br, NH_2). HRMS (EI) for $(M)^+$: calcd. 276.0255; found 276.0251. Anal. Calcd. for $C_{10}H_8N_6O_2$: C, 43.47; H, 2.92; N, 30.41. Found: C, 43.52; H, 2.86; N, 30.33%.

5,5′-(1*H*-Pyrazole-3,5-diyl)bis-(1,3,4-thiadiazol-2-amine) (**5e**)**.** Yield 88%; light yellow solid; mp 311-314 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 14.33 (s, 1H, NH), 7.40 (s, 4H, N*H*$_2$), 7.21 (s, 1H, Pyrazole-C4). ^{13}C NMR (100 MHz, DMSO): δ 174.0, 161.5, 136.0, 111.2, (Pyrazole-C3,4). IR (KBr, cm^{-1}): ν_{max} 3265 (br, NH_2). HRMS (EI) for $(M + Na)^+$: calcd. 289.0059; found 289.0056. Anal. Calcd. for $C_7H_6N_8S_2$: C, 31.57; H, 2.27; N, 42.08. Found: C, 31.50; H, 2.32; N, 42.13%.

4,4′-Methylenebis-[2-(5-amino-1,3,4-thiadiazol-2-yl)phenol] (**5f**)**.** Yield 85%; light yellow solid; mp 195-198 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 11.66 (s, 1H, OH), 7.47 (d, *J* 7.4 Hz, 2H, Ar), 7.43 (s, 4H, N*H*$_2$), 7.38 (s, 2H, Ar), 7.11 (d, *J* 7.4 Hz, 2H, Ar), 4.13 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 173.9, 161.5, 151.8, 135.4, 132.3, 121.2, 120.2 (ArC), 40.8 (*C*H_2). IR (KBr, cm^{-1}): ν_{max} 3223 (br, NH_2 & OH). HRMS (EI) for $(M)^+$: calcd. 398.0624; found 398.0629. Anal. Calcd. for $C_{17}H_{14}N_6O_2S_2$: C, 51.24; H, 3.54; N, 21.09. Found: C, 51.20; H, 3.45; N, 21.16%.

Synthesis of derivatives 6a-f

Dialdehydes (**1a-f**, 1 mmol) and hydroxylamine hydrochloride (2 mmol) were dissolved in dry DMF (10 ml). The reaction mixture was sonicated at 70 ^{o}C for 25 min under nitrogen. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature and 2.5 mmol of phosphorus pentoxide was added. The sonication was continued at 70 ^{o}C for another 15 min (till the disappearance of oximes). Sodium azide (2 mmol) was added to the resulting mixture and then sonicated at 70 ^{o}C for 15 min. After cooling to ambient temperature, 20 g of ice-water mixture was added and the pH of the medium was adjusted to be around 3 by addition of HCl (3 N). The mixture was extracted with CH_2Cl_2/MeOH (7:3, 3 x 15 mL). The organic layers were collected, washed with brine solution (3x10 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford a pure white solid of the desired products **6a-f**.

4-Methyl-2,6-di-(1*H*-tetrazol-5-yl)phenol (**6a**)**.** Yield 95%; white solid; mp 316-319 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 10.78 (s, 1H, OH), 7.59 (s, 2H, ArH), 2.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 155.7, 152.1, 129.9, 129.3, 121.7 (ArC), 20.9 (*C*H_3). IR (KBr, cm^{-1}): ν_{max} 3173 (br, NH & OH). HRMS (EI) for $(M)^+$: calcd. 244.0824; found 244.0820. Anal. Calcd. for $C_9H_8N_8O$: C, 44.26; H, 3.30; N, 45.88. Found: C, 44.20; H, 3.39; N, 45.96%.

4-Bromo-2,6-di-(1*H*-tetrazol-5-yl)phenol (**6b**)**.** Yield 93%; white solid; mp 192-193 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 11.31 (s, 1H, OH), 7.85 (s, 2H, ArH). ^{13}C NMR (100 MHz, DMSO): δ 154.6, 152.0, 129.5, 128.3, 121.5 (ArC). IR (KBr, cm^{-1}): ν_{max} 3244 (br, NH & OH). HRMS (EI) for $(M)^+$: calcd. 307.9774; found 307.9771. Anal. Calcd. for $C_8H_5BrN_8O$: C, 31.09; H, 1.63; N, 36.25. Found: C, 31.13; H, 1.69; N, 36.33%.

4-Hydroxy-3,5-di-(1*H*-tetrazol-5-yl)benzoic acid (**6c**)**.** Yield 90%; white solid; mp 302-303 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 12.97 (br, s, 1H, CO_2H), 11.86 (s, 1H, OH), 8.22 (s, 2H, ArH). ^{13}C NMR (100 MHz, DMSO): δ 167.9 (*C*O_2H), 158.0, 156.7, 132.0, 126.4, 122.5 (ArC). IR (KBr, cm^{-1}): ν_{max} 3286 (br, NH & OH), 1678 (C=O). HRMS (EI) for $(M)^+$: calcd. 274.0566; found 274.0564. Anal. Calcd. for $C_9H_6N_8O_3$: C, 39.42; H, 2.21; N, 40.87. Found: C, 39.34; H, 2.27; N, 40.94%.

1,4-Di-(1*H*-tetrazol-5-yl)benzene (**6d**)**.**[43] Yield 92%; white solid; mp 300-302 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 8.24 (s, 4H, ArH). ^{13}C NMR (100 MHz, DMSO): δ 154.5, 128.0, 127.7 (ArC). IR (KBr, cm^{-1}): ν_{max} 3208 (NH). HRMS (EI) for $(M)^+$: calcd. 214.0718; found 214.0714. Anal. Calcd. for $C_8H_6N_8$: C, 44.86; H, 2.82; N, 52.32. Found: C, 44.93; H, 2.77; N, 52.40%.

5,5′-(1*H*-Pyrazole-3,5-diyl)bis-(1*H*-tetrazole) (**6e**)**.** Yield 88%; white solid; mp 199-202 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 14.27 (s, 1H, NH), 7.26 (s, 1H, Pyrazole-C4). ^{13}C NMR (100 MHz, DMSO): δ 158.4, 136.7, 113.7, (Pyrazole-C3,4). IR (KBr, cm^{-1}): ν_{max} 3244 (NH). HRMS (EI) for $(M)^+$: calcd. 204.0623; found 204.0619. Anal. Calcd. for $C_5H_4N_{10}$: C, 29.42; H, 1.97; N, 68.61. Found: C, 29.47; H, 1.90; N, 68.55%.

4,4′-Methylenebis-[2-(1*H*-tetrazol-5-yl)phenol] (**6f**)**.** Yield 89%; white solid; mp 187-189 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 11.29 (s, 1H, OH), 7.45 (d, *J* 7.4 Hz, 2H, Ar), 7.42 (s, 2H, Ar), 7.07 (d, *J* 7.4 Hz, 2H, Ar), 4.17 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 154.2, 151.4, 135.1, 133.2, 122.5, 120.9 (ArC), 41.2 (*C*H_2). IR (KBr, cm^{-1}): ν_{max} 3273 (br, NH & OH). HRMS (EI) for $(M)^+$: calcd. 336.1081; found 336.1084. Anal. Calcd. for $C_{15}H_{12}N_8O_2$: C, 53.57; H, 3.60; N, 33.32. Found: C, 53.65; H, 3.54; N, 33.27%.

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