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Application of Sulfinyl bis(2,4-dihydroxythiobenzoyl) in the Synthesis of N-Substituted 2-Amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles

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Abstract: One-stage synthesis of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles is described. The compounds were prepared by the reaction of the sulfinyl bis(2,4-dihydroxythiobenzoyl) (STB) with 4-substituted 3-thiosemicarbazides. STB was obtained from 2,4-dihydroxybenzenecarbodithioic acid and thionyl dichloride. The structure of compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and EI-MS data.

Keywords: 2-Amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles, Cyclization, Sulfinyl-bis(2,4-dihydroxythiobenzoyl), Thiosemicarbazides

Among 2,5-disubstituted 1,3,4-thiadiazoles there are derivatives that possess valuable biological properties, such as antitumor,[1,2] anticonvulsant,[3] antibacterial,[3] antifungal,[4] anti-inflammatory,[5] antihypertensive,[6] anesthetic,[7] and cardiotonic.[8] 2-Aminoderivatives are a very important group of these substitution patterns.[1–3] Some of them were entered in phase II clinical trials in patients with different tumors.[2]

There is a large number of methods for 2-amino-5-substituted 1,3,4-thiadiazoles synthesis with variations among them. The most universal is a two-stage method consisting of acylation of thiosemicarbazide using carboxylic acid chlorides and subsequent cyclization of the intermediate acylthiosemicarbazides. Various dehydrating agents are used in commonly

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applied methods: sulfuric acid, phosphorus oxychloride, benzoyl chloride, and acetyl chloride. Not all of these substances are readily available and convenient to use; moreover, they often take part in side reactions that significantly lower the yield of the products and complicate their separation.[3,4,9–15] Acylthiosemicarbazides can be also obtained in the reaction of acenylhydrazine from isothiocyanates. Ring closure to thiadiazole occurs by heating with sulfuric or methanesulfonic acid.[16,17] Specific substitutions were obtained from 5-nitro-2-furfurilidene diacetate and thiosemicarbazides.[18]

2-Amino-5-substituted 1,3,4-thiadiazoles were prepared in a one-step reaction of thiosemicarbazides with arylthio- and arylsulfonylacetic (-propionic) acids or their nitriles in the polyphosphoric acid medium,[19] or with benzonitrile in trifluoroacetic acid.[20] Recently, based on the typical reagents for preparation of 1,3,4-thiadiazoles, new techniques have been developed: cyclization of linear structures under microwave irradiation in the presence of glacial acetic acid[21,22] and solid-phase synthesis.[23]

The conversion of 4-amino-Δ^2-1,2,4-oxadiazolines into 2-arylamino-1,3,4-thiadiazoles was described by Hussein and coworkers.[24] Oxidative cyclization of 1-thioaroylsemicarbazides by bromine (hydrogen peroxide)[25] or thiosemicarbazones and A-CH═N-NR-CX-B system by iron(III) chloride gave also the described compounds.[26,27]

For the synthesis of 1,3,4-thiadiazole ring substituted in another way than by the amine group, there are commonly applied thiohydrazides[28] and thioacylamidrazones.[29] Sulfur-containing reagents are used for analogues cyclization of amidrazones.[30] 1,4-Dicarbonyl compounds are converted to the described heterocyclic nucleus under the microwave irradiation conditions in the presence of Lawesson's reagent.[31]

The electrophilic reagent sulfinyl bis(2,4-dihydroxythiobenzoyl) (STB) prepared in our laboratory gives thiobenzanilides[32] or thiobenzamides[33] in the reactions with primary or secondary aryl- and heterocyclic amines. In the reaction of STB with N^3-substituted amidrazones, the linear products, N^1-thioacyl derivatives, and the cyclic products, 2,5-disubstituted 1,3,4-thiadiazoles, with a considerably higher fungistatic activity, were obtained.[34] These investigations show that this compound can also act as an endogenous cyclizing reagent. Endocyclizing properties were next confirmed in the case of some transition products of S_E reaction using STB and compounds with amine nitrogen atoms of different electron density.[35]

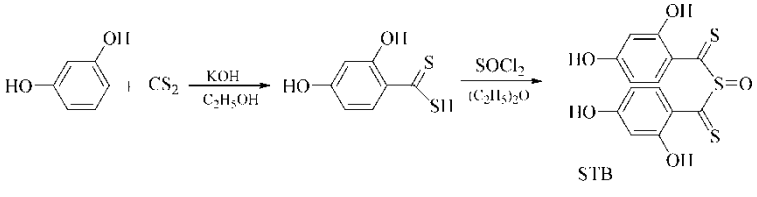
In this work we report the preparation of a new series of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles as continuation of the studies connected with searching for biologically active derivatives. The compounds were prepared in one-stage synthesis from sulfinyl bis(2,4-dihydroxythiobenzoyl) (STB) and commercially available 3-thiosemicarbazides.

STB was synthesized from 2,4-dihydroxybenzenecarbodithioic acid and thionyl dichloride.[36] 2,4-Dihydroxybenzenecarbodithioic acid was prepared from 1,3-dihydroxybenzene in the electrophilic substitution reaction of CS_2 in ethanol (alkaline medium) according to the modified Kolbe–Schmidt

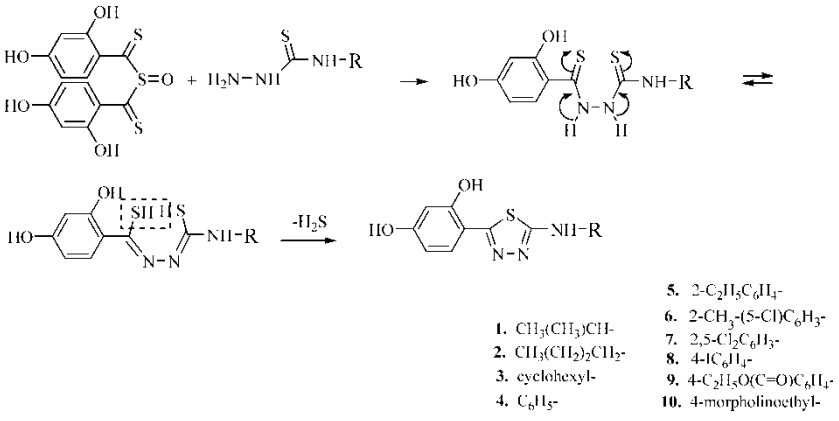
reaction.[36] The process of 2,4-dihydroxybenzenecarbodithioic acid with $SOCl_2$ in diethyl ether gave sulfinyl bis(2,4-dihydroxythiobenzoyl) (STB) (Scheme 1). The strongly reducing character of acid and tendency toward desulfhydrylation (EI-MS, $[M\text{-}SH^{\circ}]^{+} \rightarrow (HO)_2C_6H_3C^{+}{=}S$, 153 m/z, B = 100) allow us to explain the course of the $SOCl_2$ reduction forming a specific reagent of electrophilic properties. In the reaction of acid with $SOCl_2$, -SH groups split off from the acid reduce chlorine from thionyl dichloride to HCl, forming elementary sulfur and $[(HO)_2C_6H_3C{=}S)]_2SO$ (STB). Properties of 2,4-dihydroxybenzenecarbodithioic acid that allow STB to be obtained are also due to the stability of -OH groups bonded with ring and resistance to oxidation processes of *meta*- substituted dihydroxyphenol system. Anhydrousethyl ether used as solvent is capable of stabilizing of $(HO)_2C_6H_3C^{+}{=}S$ cations released in the desulfhydrylation reaction and other transient forms.

STB as an electrophilic reagent makes the course of the reaction with various 4-substituted 3-thiosemicarbazides as organic bases and selective endocyclization of thioacylderivatives possible. After the S_E reaction of STB and thiosemicarbazide, the process is due to stabilization of the linear structure by the thiol form and then oxidative bonding of H_2S by the excess of electrophylic reagent takes place (Scheme 2). The proposed mechanism is considerably different from that described for acylthiosemicarbazides (cyclization and elimination of H_2O).[19] It promotes a tendency of compounds with thioamide moiety for transition into the imidothiol forms compared with the analogous ones with oxygen.[37]

The compounds were obtained with high efficiency and chromatographic purity: RP-HPLC and RP-OPLC; methanol–water mobile phases. Their characterization is based on the IR (KBr), ^{1}H NMR, ^{13}H NMR, EI-MS spectra, and elemental analyses. The molecular peak was found to be present in all the derivatives, although their relative intensity is differentiated. The ^{1}H NMR spectral data show bands in the range 9.9–7.9 ppm characteristic of NH proton and in about 11.1–10.8 and 10.6–9.8 ppm of 2C-OH and 4C-OH protons in the resorcinol moiety respectively. There are characteristic signals at 165–163 and 155–156 ppm for C-2 and C-5 respectively of 2-aminothiadiazole ring in ^{13}C NMR spectra. The IR spectra exhibit characteristic strong absorption at 1650–1610 cm^{-1} for C=N and weak band at 1050–1010 cm^{-1} for N=C-S-C=N.



Scheme 1.



Scheme 2.

In conclusion, the simple synthesis method of 1,3,4-thiadiazoles has been presented. The methodology described herein is expected to be quite general for the synthesis of N-differently substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles. The synthesis methods reported in literature do not describe preparation of hydroxyl derivatives. The studies of various groups of compounds with 2,4-dihydroxyphenyl moiety indicate favorable influence of this fragment on biological effect with simultaneous relatively low level of toxicity. Therefore, work will be undertaken to prepare a large number of derivatives as compounds with diverse biological activity.

EXPERIMENTAL

The melting point (mp) was determined on a Buchi B-540 (Switzerland) melting-point apparatus. The elemental analysis was performed in order to determine C, H, and N contents (Perkin-Elmer 2400). Analyses of C, N, and H were within $\pm 0.4\%$ of the theoretical values. The vibrational spectra were recorded with a Perkin-Elmer FT-IR 1725X spectrophotometer using KBr pellets in the range of $600-4000\,cm^{-1}$. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Varian Mercury 400 or Bruker DRX 500 instrument. Chemical shifts (δ, ppm) were given in with tetramethylsilane (TMS). The spectra MS (EI, 70 eV) were run on a AMD-604 apparatus.

Preparation of Compounds

2,4-Dihydroxybenzenecarbodithioic Acid

Resorcinol (0.1 mol) was dissolved in solution of KOH (2 M, 50 ml). Ethanol (50 ml) was added, CS_2 (0.1 mol) was dropped in, and the mixture was heated

(3 h). After cooling, the solution was acidified with small portions of HCl (2 M). The evolved product was doubly crystallized from ethanol. Yield: 82%, mp: 132–133°C. EI-MS (m/z, rel. intens.): 186 (M^+, 36), 153 (100), 141 (12), 124 (9), 97 (12), 69 (5), 65 (14). Anal. Calcd. for $C_7H_6O_2S_2$ (186.25): C, 45.14; H, 3.25; N, 17.18. Found: C, 45.10; H, 3.23; N, 17.21.

Sulfinyl bis(2,4-dihydroxythiobenzoyl) (STB)

2,4-Dihydroxybenzenecarbodithioic acid (0.35 mol) was dissolved in anhydrous diethyl ether (250 mL). At 20°C the solution was saturated with dry CO_2; $SOCl_2$ (0.7 mol) was slowly dropped in and then heated over the water bath (4 h). A red product was removed from the solution. The solvent and $SOCl_2$ remains were separated by distillation under reduced pressure. The obtained compound was washed with DMSO. Amorphous red powder, mp 259–260°C. ^{1}H NMR (DMSO-d_6): δ 8.19–7.54 (m, 2H, 6,6′-CH), 6.92–6.27 (m, 4H, 3,5,3′,5′-CH), (in the range of absorption of -OH protons there are blurred, not distinct bands). IR (KBr, cm^{-1}): 3392 (OH), 2960, 1614 (C═C), 1542, 1507, 1457 (C═C), 1396, 1372, 1237 (C-OH), 1135, 1048 (S═O), 1019 (C═S), 976, 948, 902, 876, 845. EI-MS (m/z, rel. intens.): 200 (15), 184 (94), 154 (42), 153 (60) 137 (15), 136 (16), 124 (32), 110 (11), 108 (11), 97 (10), 96 (25), 69 (20), 64 (89), 33 (100). Anal. calcd. for $C_{14}H_{10}O_5S_3$ (354.42): C, 47.44; H, 2.84; S, 27.14. Found: C, 47.57; H, 2.83; S, 27.24.

Compounds 1–10

STB (0.0075 mol) and corresponding commercially available 4-substituted 3-thiosemicarbazide (0.01 mol) were put into methanol (50 ml) and heated to boiling (3 h). During the synthesis the compounds was (**9**, **5**) removed; the mixture was hot filtered and the filtrate was concentrated to 20 ml (**1**). The filtrate was concentrated to dry (**2**, **4**, **6**, **7**); water (50 ml) was added to the filtrate (**3**, **8**, **10**). The removed compound was filtrated, washed with water, and crystallized from methanol (30 ml) (**1**, **3**, **4**, **5**, **9**) or from methanol-water solutions (50 ml) (**2**, **6**, **7**, **8**, **10**).

2-Isopropylamino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (1). Yield: 63%, mp: 124–126°C. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 11.11 (s, 1H, 2-COH), 9.93 (s, 1H, 4-COH), 7.95 (m, 1H, NH), 3.80 (m, 1H, CH), 1.23–1.12 (m, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 165.97 (C_{thia}-2), 160.99 (C-2), 156.36 (C-4), 153.00 (C_{thia}-5), 128.20 (C-6), 108.40 (C-1), 107.30 (C-5), 102.42 (C-3), 47.57 (CH), 21.93 (CH_3). IR (KBr, cm^{-1}): 3417 (OH, NH), 1613 (C═N, C═C), 1534, 1213 (C-OH), 1119, 807, 675 (C-S-C). EI-MS (m/z, rel. intens.): 251 (M^+, 100), 236 (39), 209 (40), 207 (7), 192 (10), 163 (13), 161 (35), 153 (25), 150 (9), 149 (10), 145 (8), 137 (23), 136 (45), 135 (29), 121 (9), 120 (19), 117 (26), 64 (65), 58

(28), 44 (61), 40 (89). Anal. calcd. for $C_{11}H_{13}N_3O_2S$ (251.30): C, 52.57; H, 5.21; N, 16.72. Found: C, 52.74; H, 5.19; N, 16.78.

2-Butylamino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (2). Yield: 62%, mp: 135–136°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 11.05 (broad band, 1H, 2-COH), 9.93 (s, 1H, 4-COH), 8.35 (s, 1H, NH), 1.61–1.24 (m, 6H, CH_2), 0.93-0.87 (m, 3H, CH_3). IR (KBr, cm^{-1}): 3438 (OH, NH), 2923 (CH_2), 1617 (C═N, C═C), 1532, 1218 (C-OH), 1121, 838. EI-MS (m/z, rel. intens.): 265 (M^+, 75), 256 (40), 222 (28), 209 (40), 192 (20), 170 (32), 160 (24), 135 (41), 111 (15), 91 (39), 69 (19), 64 (100), 40 (73). Anal. calcd. for $C_{12}H_{15}N_3O_2S$ (265.33): C, 54.32; H, 5.70; N, 15.84. Found: C, 54.52; H, 5.72; N, 15.89.

2-Cyclohexylamino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (3). Yield: 80%, mp: 107–108°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 11.03 (s, 1H, 2-COH), 9.90 (s, 1H, 4-COH), 2.65–2.51 (m, 1H, CH), 1.99–1.57 (m, 4H, CH_2), 1.36–1.15 (m, 6H, CH_2). IR (KBr, cm^{-1}): 3431 (OH, NH), 2924, 2854 (CH_2), 1616 (C═N, C═C), 1535, 1420, 1320, 1263 (C-OH), 1114, 1046 (N═C-S-C═N), 809, 670 (C-S-C). EI-MS (m/z, rel. intens.): 291 (M^+, 48), 256 (9), 248 (5), 210 (12), 209 (100), 192 (4), 168 (3), 167 (6), 160 (7), 157 (10), 156 (17), 153 (9), 150 (10), 137 (6), 136 (32), 123 (5), 113 (8), 94 (6), 83 (5), 74 (11), 64 (17), 55 (19). Anal. calcd. for $C_{14}H_{17}N_3O_2S$ (291.37): C, 57.71; H, 5.88; N, 14.42. Found: C, 57.29; H, 5.86; N, 14.48.

2-Phenylamino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (4). Yield: 81%, mp: 238–240°C. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 10.91 (s, 1H, 2-COH), 10.39 (s, 1H, 4-COH), 9.94 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 163.51 (C_{thia}-2), 160.25 (C-2), 155.71 (C-4), 154.79 (C_{thia}-5), 140.89 (C-1′), 129.03 (C-3′,5′), 128.57 (C-6), 121.48 (C-4′), 117.22 (C-2′,6′), 108.50 (C-1), 108.09 (C-5), 102.44 (C-3). IR (KBr, cm^{-1}): 3367, 3251, 3198 (OH, NH), 1623 (C═N), 1601 (C═C), 1576, 1531, 1501, 1456, 1434, 1410, 1325, 1240, 1218 (C-OH), 1184, 1111, 1032 (N═C-S-C═N), 986, 968, 875, 841, 803, 672 (C-S-C). EI-MS (m/z, rel. intens.): 285 (M^+, 100), 256 (2), 150 (63), 118 (17), 91, 77 (18), 40 (12). Anal. calcd. for $C_{14}H_{11}N_3O_2S$ (285.32): C, 58.93; H, 3.89; N, 14.73. Found: C, 59.15; H, 3.72; N, 14.90.

2-(2-Ethylphenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (5). Yield: 65%, mp: 253–254°C. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm) 10.85 (broad band, 1H, 2-COH), 9.87 (s, 1H, 4-COH), 9.43 (s, 1H, NH), 2.70–2.66 (q, 2H, CH_2), 1.16–1.13 (t, 3H, CH_3). IR (KBr, cm^{-1}): 3437 (OH, NH), 2920 (CH_2), 1626 (C═N, C═C), 1532, 1454, 1211 (C-OH), 1021 (N═C-S-C═N), 845. EI-MS (m/z, rel. intens.): 313 (M^+, 78), 284 (19), 280 (11), 195 (6), 178 (34), 177 (4), 163 (25), 153 (19), 151 (18), 146

(10), 145 (100), 144 (47), 136 (10), 135 (8), 131 (20), 119 (17), 106 (17), 94 (10), 91 (11), 77 (26), 39 (12). Anal. calcd. for $C_{16}H_{15}N_3O_2S$ (313.33): C, 61.32; H, 4.82; N, 13.41. Found: C, 60.20; H, 4.80; N, 13.46.

2-(5-Chloro-2-methylphenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (6). Yield: 65%, mp: 257–258°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 10.88 (broad band, 1H, 2-COH), 9.88 (s, 1H, 4-COH), 9.58 (s, 1H, NH), 2.27 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 164.23 (C_{thia}-2), 160.45 (C-2), 155.79 (C-4), 155.63 (C_{thia}-5), 140.25 (C-1′), 131.83 (C-5′), 130.60 (C-2′), 128.43 (C-6), 125.90 (C-3′), 122.01 (C-4′), 118.86 (C-6′), 108.42 (C-1), 108.18 (C-5), 102.44 (C-3), 17.65 (CH_3). IR (KBr, cm^{-1}): 3267, 3089 (OH, NH), 2965 (CH_3), 1634 (C═N), 1597 (C═C), 1537, 1402, 1320, 1224 (C-OH), 1234, 1211, 1169, 1140, 1110, 1105 (C-Cl), 1052 (N = C-S-C═N), 987, 971, 849, 672 (C-S-C). EI-MS (m/z, rel. intens.): 333 (M^+, 100), 318 (13), 302 (6), 299 (22), 284 (4), 200 (18), 199 (8), 198 (50), 184 (5), 183 (7), 171 (12), 167 (24), 153 (35), 149 (10), 136 (21), 135 (17), 131 (19), 121 (12), 94 (22), 77 (18), 39 (20). Anal. calcd. for $C_{15}H_{12}ClN_3O_2S$ (333.79): C, 53.97; H, 3.62; N, 12.59. Found C, 53.81; H, 3.61; N, 12.53.

2-(2,5-Dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (7). Yield: 82%, mp: 255–256°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 10.88 (s, 1H, 2-COH), 9.91 (s, 1H, 4-COH), 9.84 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 163.38 (C_{thia}-2), 160.52 (C-2), 156.57 (C-4), 155.77 (C_{thia}-5), 138.45 (C-1′), 132.11 (C-5′), 130.80 (C-2′), 128.43 (C-6), 122.41 (C-3′), 119.94 (C-4′), 119.50 (C-6′), 108.55 (C-1), 108.21 (C-5), 102.44 (C-3). IR (KBr, cm^{-1}): 3287 (OH, NH), 1632 (C═N), 1588 (C═C), 1537, 1402, 1320, 1265 (C-OH), 1234, 1212, 1169, 1134, 1110, 1099 (C-Cl), 1046 (N = C-S-C═N), 987, 967, 848, 670 (C-S-C). EI-MS (m/z, rel. intens.): 354 (M^+, 18), 353 (94), 321 (96), 320 (38), 319 (18), 318 (100), 220 (7), 218 (10), 186 (5), 185 (9), 183 (22), 153 (4), 136 (3), 135 (4), 94 (3), 69 (3), 66 (3), 39 (5). Anal. calcd. for $C_{14}H_9Cl_2N_3O_2S$ (354.21): C, 47.47; H, 2.56; N, 11.86. Found: C, 47.28; H, 2.57; N, 11.81.

2-(4-Iodophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (8). Yield: 61%, m. p.: 206-208°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 10.80 (broad band, 1H, 2-COH), 10.39 (s, 1H, 4-COH), 9.90 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 163.14 (C_{thia}-2), 160.40 (C-2), 155.71 (C-4), 154.96 (C_{thia}-5), 140.62 (C-1), 137.51 (C-2′,6′), 128.51 (C-6), 119.56 (C-3′,5′), 108.39 (C-1), 108.15 (C-5), 102.42 (C-3), 84.47 (C-4′). IR (KBr, cm^{-1}): 3176 (OH, NH), 1620 (C═N), 1560 (C═C), 1526, 1486, 1435, 1397, 1318, 1211 (C-OH), 1181, 1119, 1063, 1005, 986, 968, 807, 669 (C-S-C). EI-MS (m/z, rel. intens.): 411 (M^+, 100), 285 (6), 276 (23), 244 (6), 153 (9), 150 (9), 149 (19), 142 (4), 136 (4), 135 (9), 128 (6), 122 (9),

94 (10), 90 (8), 76 (10), 66 (6), 63 (7). Anal. calcd. for $C_{14}H_{10}IN_3O_2S$ (411.22): C, 40.89; H, 2.45; N, 10.22. Found: C, 40.61; H, 2.46; N, 10.20.

2-(4-Ethoxycarbonylphenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (9). Yield: 69%, m. p.: 246–247°C. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 10.86 (s, 1H, 2-COH), 10.57 (s, 1H, 4-COH), 4.31-4.27 (q, 2H, CH_2), 1.34–1.31 (t, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 165.42 (C═O), 162.79 (C_{thia}-2), 160.90 (C-2), 156.02 (C-4), 155.80 (C_{thia}-5), 144.84 (C-1′), 130.65 (C-3′,5′), 128.50 (C-6), 122.33 (C-4′), 116.62 (C-2′,6′), 108.33 (C-1), 107.99 (C-5), 102.46 (C-3), 60.30 (CH_2), 14.29 (CH_3). IR (KBr, cm^{-1}): 3313, 3186 (OH, NH), 2985 (CH_3), 1686 (C═O), 1608 (C═N, C═C), 1553, 1471, 1415, 1370, 1286, 1180 (C-OH), 1112, 1019 (N═C-S-C═N), 887, 966, 850, 811, 670 (C-S-C). EI-MS (m/z, rel. intens.): 357 (M^+, 100), 312 (8), 222 (9), 194 (10), 178 (3), 177 (17), 162 (3), 156 (8), 153 (5), 150 (9), 145 (5), 121 (3), 94 (6), 66 (3), 65 (3). Anal. calcd. for $C_{17}H_{15}N_3O_4S$ (357.38): C, 57.13; H, 4.23; N, 11.76. Found: C, 57.43; H, 4.21; N, 11.81.

2-(4-Morpholinoethylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (10). Yield: 60%, mp: 301–303°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.89 (s, 1H, 2-COH), 9.99 (s, 1H, 4-COH), 9.84 (s, 1H, NH), 3.59 (t, 4H, OCH_2), 3.45–3.41 (m, 2H, $C\underline{H}_2NH$, m), 3.34 (s, 6H, NCH_2). IR (KBr, cm^{-1}): 3268 (OH, NH), 2942, 2874 (CH_2), 1602 (C═N), 1529 (C═C), 1474, 1419, 1332, 1252, 1192 (C-OH), 1131, 1110, 1068, 1019 (N═C-S-C═N), 1003, 985, 960, 911, 851, 803, 675 (C-S-C). EI-MS (m/z, rel. intens.) 322 (M^+, 1.4), 302 (38), 222 (3), 209 (9), 167 (12), 153 (5), 135 (8), 113 (47), 100 (100), 56 (6). Anal. calcd. for $C_{14}H_{18}N_4O_3S$ (322.38): C, 52.16; H, 5.63; N, 17.38. Found: C, 52.49; H, 5.48; N, 17.52.

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