Synthesis and Antifungal Evaluation of Hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones and Their Thioanalogs

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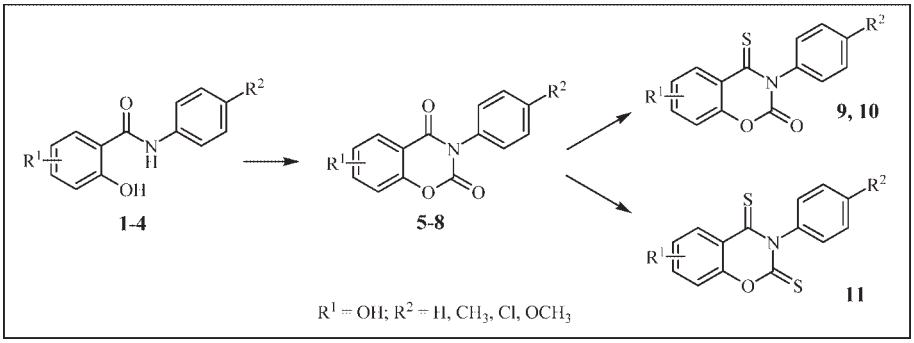

A series of substituted 5-, 6-, 7-, and 8-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (**5–8**) was synthesized by cyclization of corresponding dihydroxy-*N*-phenylbenzamides (**1–4**) with methyl chloroformate. The starting compounds **1–4** were prepared by the reaction of the respective dihydroxybenzoic acid, aniline and phosphorus trichloride *via* microwave irradiation. Thionation of compounds **8a–d** employing Lawesson's reagent was used to prepare 5-hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones (**10a–d**) and 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (**11a–d**). The position of sulfur in monothionated derivatives **9c** and **10a–d** was confirmed by 2D NMR methods. Attempts to prepare dithionated derivatives from the isomeric 6-, 7- or 8-hydroxy compounds **5–7** failed. All compounds were tested for their *in vitro* antifungal activity against eight test strains. Compounds **1–4** showed moderate activity and the cyclization to corresponding hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (**5–8**) resulted in a decrease in antifungal activity. No antifungal activity was observed in thionated compounds **9c** and **10–11**.

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INTRODUCTION

Salicylanilides and their derivatives [1] are paid great attention to, particularly from the viewpoint of their antibacterial, antifungal, and other activities [2]. The most important analogs include benzoxazinediones [3] and thiosalicylanilides [4].

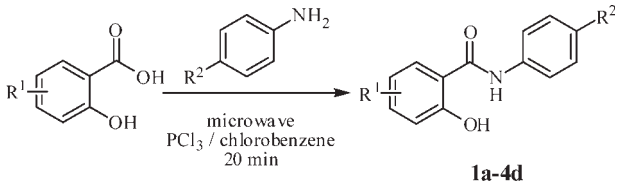
This article focuses on the synthesis of novel salicylanilide derivatives, dihydroxy-*N*-phenylbenzamides, which include two hydroxyl groups in the acyl moiety of the molecule, and their cyclic analogs hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones. Until now, the synthesized substances included mainly dihydroxy-*N*-phenylbenzamides with hydroxyl groups in positions 2 and 6, which were tested as anthelmintics and plant-protecting agents [5]. Resorantel, *N*-(4-bromophenyl)-2,6-dihydroxybenzamide, was introduced into practice as a veterinary anthelmintic agent [6]. As to the cyclic analogs, 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones were patented as fungicidally active agents against rice blast pathogen *Pyricularia oryzae* (*Magnaporthe grisea*) [7].

In the obtained derivatives an attempt was made to prepare the corresponding mono- and dithionated analogs.

RESULTS AND DISCUSSION

Chemistry. The starting dihydroxy-*N*-phenylbenzamides **1a–4d** were synthesized by the microwave-assisted reaction of dihydroxybenzoic acid, appropriate aniline

Scheme 1



1a-4d

R^1 = OH; R^2 = H, CH_3, Cl, OCH_3

and PCl_3 at 135°C for 20 min (Scheme 1). The crude reaction mixtures were purified by column chromatography on silica gel using acetone-hexane (1:5). The products were recrystallized from ethanol-water mixture. For the details of compounds **1a–4d** see Table 1.

For the sake of comparison, when the reaction was carried out using conventional oil bath heating, the reaction was completed in 3 h [2a,f]. The use of a microwave oven resulted in shortening of reaction times, as described by other authors [2d,13], but not in an increase of yields. The use of column chromatography before crystallization has a significant influence on practical yields.

The synthesis of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5a–8d** was based on literature reports describing cyclization reactions of salicylanilides with methyl chloroformate [3a], ethyl chloroformate [3e], or triphosgene [14]. In our experiments, the cyclization reagent was methyl chloroformate in pyridine (Scheme 2). After 2–h refluxing followed by 10–h stirring at room temperature, the reaction mixture was acidified to pH $\approx$ 6 with 5% HCl. The resulting white heterogeneous mixture was cooled to obtain crystalline compounds. Recrystallization from ethanol gave products **5a–8d** in the yields of 77–94% (Table 1).

Further experiments concerned thionation of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5a–8d**. The published methods include thionation using P_2S_5, either in solution [15] or in melt [3f], and Lawesson's reagent [16]. For the synthesis of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones, we made use melting of compounds **5a–8d** with Lawesson's reagent at 190–200°C for 4 min. Starting from 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **8a–d**, this treatment afforded 5-hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones **10a–d** and 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones **11a–d**, which were separated by column chromatography on silica gel (Scheme 3).

Monothionated analogs **10a–d** and dithionated analogs **11a–d** were prepared in the yields of 31–42% and 24–33%, respectively. The yields were essentially the same as in the case of thionation with P_2S_5 [3d]. In the case of compounds **5–7** with hydroxyl group in position 8, 7 or 6, we did not succeed to isolate any desired product; except for compound **6c**, which gave only monothionation product **9c** in a 5% yield. Attempts to prepare desired thioxo derivatives using P_2S_5 instead of Lawesson's reagent also failed.

For monothionated compounds **9c** and **10a–d**, the presence of sulfur in position four was unequivocally corroborated by 2D NMR (gHMQC and gHSCQ experiments). All gHSQC correlations are shown in Figure 1.

***In vitro* antifungal activity.** All compounds were tested for their *in vitro* antifungal activity [17] against eight test strains. All experiments were performed in comparison with fluconazole, a known antifungal agent. Some compounds were not sufficiently soluble in the testing medium RPMI 1640 and precipitated during the testing period, therefore their minimum inhibitory concentrations MICs could not be determined accurately. The activities of the substances are shown in Table 2. Only compounds with MICs $\leq$ 125 μmol/L for at least one tested strain were included.

All compounds presented in Table 2 exhibited activities against *Aspergillus fumigatus* and *Absidia corymbifera* higher than or comparable with that of fluconazole. Generally, 2,3-dihydroxy derivatives **1** and 2,6-dihydroxy derivatives **4** were the most active compounds. As for the effect of the substituent in the aniline moiety, chloro substitution increased antifungal activity. Only compound **4c** was more active than fluconazole against *Trichophyton mentagrophytes* (MIC = 1.95 μmol/L after 120 h).

The cyclization of compounds **1–4** to corresponding 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5–8** results in a decrease of antifungal activity. Only compound **5c** retained activity against at least one strain, *Candida glabrata*. No antifungal activity was observed in thionated compounds **9c** and **10a–11d** (Table 2).

CONCLUSIONS

We have described a convenient microwave-assisted method for the synthesis of dihydroxy-*N*-phenylbenzamides **1–4**, which were transformed into hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5–8** by a reaction with methyl chloroformate. We have been successful in thionation of benzoxazines with a free hydroxyl group in position five only, *i.e.* derivatives **8a–d**. In the case of derivatives **5–7**, attempts to prepare dithioxo-analogs failed, both with the use of P_2S_5 and Lawesson's reagent. The prepared compounds showed only moderate antifungal activity in comparison with the standard fluconazole. Cyclization of dihydroxy-*N*-phenylbenzamides **1–4** to produce benzoxazines **5–8** markedly decreased the activity and transformation to mono- and dithionated analogs destroyed the activity.

Table 1

Physical and analytical data of compounds **1a–11d**.

Compound	R^1	R^2	Mp (°C)	Yield (%)	Molecular formula	Analysis % Calcd./Found			
						C	H	N	S
1a	3-OH	4-H	113–114	75	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.23	4.96	6.22	–
1b	3-OH	4-CH_3	161–163	81	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						69.31	5.52	5.88	–
1c	3-OH	4-Cl	137–139	69	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.41	3.96	5.36	–
1d	3-OH	4-OCH_3	129–130	77	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						64.98	5.20	5.44	–
2a	4-OH	4-H	132–134 [8,9]	66	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.26	5.02	6.19	–
2b	4-OH	4-CH_3	164–166 [9]	71	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						69.36	5.49	5.82	–
2c	4-OH	4-Cl	166–168	55	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.38	4.05	5.39	–
2d	4-OH	4-OCH_3	191–193 [9]	62	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						65.03	5.14	5.43	–
3a	5-OH	4-H	176–178 [10,11]	58	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.23	4.91	6.20	–
3b	5-OH	4-CH_3	208–210	71	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						69.01	5.66	5.87	–
3c	5-OH	4-Cl	204–207	59	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.15	3.94	5.38	–
3d	5-OH	4-OCH_3	113–114 [10]	63	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						64.95	5.18	5.38	–
4a	6-OH	4-H	195–197 [5b,12]	72	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.22	4.96	6.16	–
4b	6-OH	4-CH_3	201–203 [12]	76	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						68.88	5.51	5.81	–
4c	6-OH	4-Cl	225–228 [5a]	63	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.40	3.89	5.41	–
4d	6-OH	4-OCH_3	213–215 [12]	55	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						64.96	5.26	5.50	–
5a	8-OH	4-H	276–278.5	88	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.96	3.77	5.58	–
5b	8-OH	4-CH_3	243–245	91	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						67.09	4.22	5.22	–
5c	8-OH	4-Cl	255–257	90	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						57.87	2.91	4.84	–
5d	8-OH	4-OCH_3	245–247	89	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						63.29	4.11	4.88	–
6a	7-OH	4-H	283–286	81	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.59	3.62	5.49	–
6b	7-OH	4-CH_3	282–285	86	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						66.98	4.29	5.23	–
6c	7-OH	4-Cl	250–252	77	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						58.31	2.86	4.76	–
6d	7-OH	4-OCH_3	262–265	84	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						63.21	3.97	5.06	–
7a	6-OH	4-H	266–269	89	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.71	3.82	5.53	–
7b	6-OH	4-CH_3	269–272	87	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						66.59	4.24	5.23	–
7c	6-OH	4-Cl	233–235	83	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						57.81	2.75	4.84	–
7d	6-OH	4-OCH_3	275–278	90	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						62.91	3.98	4.84	–
8a	5-OH	4-H	172–173 [6]	87	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.95	3.76	5.63	–
8b	5-OH	4-CH_3	179–181 [6]	89	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						66.68	4.29	5.26	–

Table 1
(*Continued*)

Compound	R^1	R^2	Mp (°C)	Yield (%)	Molecular formula	Analysis % Calcd./Found C	H	N	S
8c	5-OH	4-Cl	232–234 [6]	93	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						57.89	3.09	4.86	–
8d	5-OH	4-OCH_3	212–214	85	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						63.20	4.04	5.07	–
9c	7-OH	4-Cl	258–261	5	$C_{14}H_8ClNO_3S$	55.00	2.64	4.58	10.49
						55.22	2.74	4.60	10.40
10a	5-OH	4-H	178–179	42	$C_{14}H_9NO_3S$	61.98	3.34	5.16	11.82
						62.02	3.46	5.09	12.20
10b	5-OH	4-CH_3	206–209	37	$C_{15}H_{11}NO_3S$	63.14	3.89	4.91	11.24
						63.05	4.09	4.65	11.51
10c	5-OH	4-Cl	218–220	39	$C_{14}H_8ClNO_3S$	55.00	2.64	4.58	10.49
						54.89	2.74	4.52	10.68
10d	5-OH	4-OCH_3	185–187	31	$C_{15}H_{11}NO_4S$	63.77	5.02	4.65	10.64
						63.81	5.12	4.53	10.89
11a	5-OH	4-H	192–193	32	$C_{14}H_9NO_2S_2$	58.52	3.16	4.87	22.32
						58.66	3.25	4.65	22.46
11b	5-OH	4-CH_3	179–180	24	$C_{15}H_{11}NO_2S_2$	59.78	3.68	4.65	21.28
						59.81	3.78	4.55	21.24
11c	5-OH	4-Cl	166–167	27	$C_{14}H_8ClNO_2S_2$	52.25	2.51	4.35	19.93
						52.16	2.55	4.35	20.21
11d	5-OH	4-OCH_3	150–152	33	$C_{15}H_{11}NO_3S_2$	56.77	3.49	4.41	20.20
						56.88	3.57	4.42	20.51

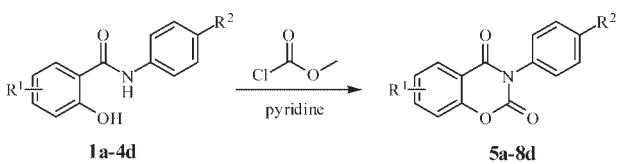
EXPERIMENTAL

The starting compounds were purchased from Sigma-Aldrich Company. Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. IR spectra were taken on a Nicolet Impact 400 spectrometer in KBr pellets. The NMR spectra was recorded on a Varian Mercury-Vx BB 300 (300 MHz) and Bruker AC 250 (250 MHz). The samples were dissolved in hexadeuteriodimethyl sulfoxide (DMSO-d_6) or deuteriochloroform ($CDCl_3$). Chemical shifts were recorded as δ values, and were indirectly referenced to tetramethylsilane *via* the solvent signal. The elemental analyses were performed with a Perkin-Elmer 2400 CHNS/O analyzer. Microwave experiment was performed on a Millestone-MicroSYNTH (MLS ETHOS 1600 URM) instrument at 600 W output power. Column chromatography was carried out on silica gel 60 from E. Merck and purifications were monitored by TLC (UV detection) on aluminum sheets coated with silica gel 60 F_{254} (Merck).

General method for preparation of dihydroxy-*N*-phenylbenzamides (1a–4d) *via* microwave irradiation. A mixture of dihydroxybenzoic acid (3.08 g, 20 mmol) and respective aniline (30 mmol) in chlorobenzene (120 mL) was stirred. PCl_3 (0.87 mL, 10 mmol) was added, and the mixture was stirred and irradiated in a microwave reactor at 600 W for 20 min. The mixture was than cooled to room temperature and evaporated at reduced pressure. The crude product was purified by chromatography on a silica-gel column using acetone-hexane (1:5). The product was recrystallized from an ethanol/water mixture. For details see Table 1.

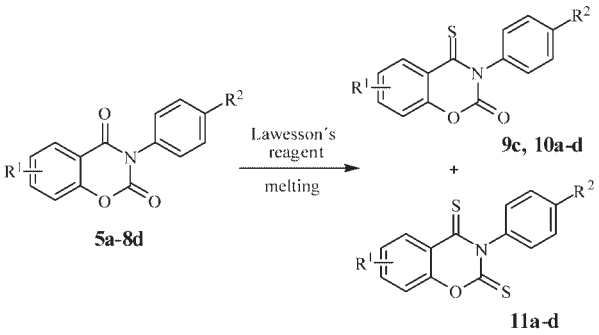
General method for preparation of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (5a–8d). Methyl chloroformate (0.5 mL, 6 mmol) was added dropwise to a stirred solution of dihydroxy-*N*-phenylbenzamide 1a–4d (5 mmol) in dry pyridine (40 mL) at 0°C. The mixture was heated on an oil bath for 2 h. After 10–h stirring at room temperature, the pH of the reaction mixture was adjusted to pH ≈ 6 (HCl aq., 5%). The resulting white heterogeneous mixture was cooled to obtain crystalline compound. The product was filtered off and recrystallized from ethanol. For details see Table 1.

Scheme 2



R^1 = OH; R^2 = H, CH_3, Cl, OCH_3

Scheme 3



R^1 = OH; R^2 = H, CH_3, Cl, OCH_3

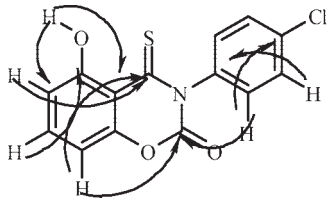


Figure 1. gHSCQ correlations present in **10c**.

Preparation of hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones (9c, 10a–d) and hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (11a–d). 5-Hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dione **5a–8d** (4 mmol) was melted with Lawesson's reagent (4 mmol) for 4 min at 190–200°C. After cooling to room temperature, the melt was dissolved in chloroform, washed with aq. $NaHCO_3$ (5%, 1 × 100 mL), water (1 × 100 mL) and the solvent was evaporated under reduced pressure. Column chromatography on silica gel using toluene-hexane (1:1) was performed to obtain 3-(4-chlorophenyl)-7-hydroxy-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (**9c**), 5-hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones **10a–d** (lower R_f) and 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones **11a–d** (higher R_f) as orange-yellow solids. For details see Table 1.

***In vitro* antifungal susceptibility testing.** The broth microdilution test M27-A [17] was used for the assessment of *in vitro* antifungal activity of the synthesized compounds against *Candida albicans* ATCC 44859 (CA), *Candida tropicalis* 156 (CT), *Candida krusei* E28 (CK), *Candida glabrata* 20/I (CG), *Trichosporon asahii* 1188 (TA), *Trichophyton mentagrophytes* 445 (TM), *Aspergillus fumigatus* 231 (AF), and *Absidia corymbifera* 272 (AC). Fluconazole was used as the reference drug. The procedure was performed with two-fold dilution of the compounds in RPMI 1640 medium (Sevapharma, Prague, Czech Republic) buffered to pH 7.0 with 0.165 *M* of 3-morpholinopropane-1-sulfonic acid. Drug-free controls were included. The minimum inhibitory concentrations (MICs) were defined as 80% (IC_{80}) and higher reduction of growth in comparison with control. The values of MICs were determined after 24 h and 48 h of static incubation at 35°C. For *T. mentagrophytes*, the final MICs were determined after 72 h and 120 h of incubation. The results for selected substances are summarized in Table 2.

2,3-Dihydroxy*-N-*phenylbenzamide (1a). IR (KBr): CO 1642 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.78 (t, J = 7.8 Hz, 1 H, *H-5*), 6.99 (dd, J = 1.5 Hz, J = 7.8 Hz, 1 H, *H-4*), 7.12–7.18 (m, 1 H, *H-4′*), 7.34–7.40 (m, 2 H, *H-3′*, *H-5′*), 7.45 (dd, J = 1.5 Hz, J = 7.8 Hz, 1 H, *H-6*), 7.67–7.72 (m, 2 H, *H-2′*, *H-6′*), 9.43 (bs, 1 H, *OH*), 10.36 (bs, 1 H, *NH*), 11.69 (bs, 1 H, O*H*); ^{13}C (75 MHz, DMSO): δ 117.2, 118.6, 118.7, 119.2, 121.5, 124.6, 128.9, 138.2, 146.4, 148.6, 168.0.

2,3-Dihydroxy*-N-*(4-methylphenyl)benzamide (1b). IR (KBr): CO 1653 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 2.26 (s, 3 H, *CH_3*), 6.40 (t, J = 2.1 Hz, 1 H, *H-5*), 6.76 (d, J = 2.1 Hz, 2 H, *H-4*, *H-6*), 7.08–7.15 (m, 2 H, *H-3′*, *H-5′*), 7.59–7.66 (m, 2 H, *H-2′*, *H-6′*), 9.56 (bs, 2 H, *OH*), 10.00 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 117.1, 118.3, 119.1, 119.5, 120.9, 124.7, 128.3, 138.7, 146.6, 148.9, 168.5.

N-(4-Chlorophenyl)-2,3-dihydroxybenzamide (1c). IR (KBr): CO 1647 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.78 (t, J = 7.8 Hz, 1 H, *H-5*), 6.98 (dd, J = 1.5 Hz, J = 7.8 Hz, 1 H, *H-4*), 7.39 (d, J = 1.5 Hz, 1 H, *H-6*), 7.40–7.46 (m, 2 H, *H-3′*, *H-5′*), 7.70–7.77 (m, 2 H, *H-2′*, *H-6′*), 9.46 (bs, 1 H, *OH*), 10.43 (bs, 1 H, *NH*), 11.46 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 117.5, 118.6, 118.7, 119.2, 122.9, 128.1, 128.8, 137.3, 146.4, 148.3, 167.9.

2,3-Dihydroxy*-N-*(4-methoxyphenyl)benzamide (1d). IR (KBr): CO 1640 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.75 (s, 3 H, *OCH_3*), 6.76 (t, J = 8.1 Hz, 1 H, *H-5*), 6.91–6.98 (m, 2 H, *H-3′*, *H-5′*), 6.98 (d, J = 1.5 Hz, 1 H, *H-4*), 7.45 (dd, J = 1.5 Hz, J = 8.1 Hz, 1 H, *H-6*), 7.54–7.61 (m, 2 H, *H-2′*, *H-6′*), 9.35 (bs, 1 H, *OH*), 10.25 (bs, 1 H, *NH*), 11.93 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 114.0, 116.6, 118.2, 118.5, 119.2, 123.4, 131.0, 146.4, 149.1, 156.3, 168.0.

Table 2

In vitro antifungal activity (MIC, μmol/L) of the selected compounds compared with standard fluconazole.

Comp.	CA 24 h/48 h	CT 24 h/48 h	CK 24 h/48 h	CG 24 h/48 h	TA 24 h/48 h	AF 24 h/48 h	AC 24 h/48 h	TM 72 h/120 h
1a	15.63/62.5	7.81/15.63	62.5/62.5	7.81/15.63	62.5/125	62.5/250	125/125	31.25/31.25
1b	31.25/62.5	7.81/15.62	31.25/62.5	7.8/15.62	62.5/125	125/125	62.5/62.5	31.25/31.25
1c	7.81/31.25	3.91/7.81	15.63/31.25	3.91/7.81	31.25/62.5	31.25/62.5	62.5/31.25	7.81/15.63
1d	31.25/62.5	62.5/62.5	31.25/62.5	62.5/62.5	31.25/62.5	62.5/250	15.62/15.62	31.25/31.25
2c	62.5/125	250/250	250/250	250/250	250/250	125/250	250/250	31.25/62.5
3c	31.25/62.5	125/125	125/250	125/250	250/250	125/250	125/250	31.25/31.25
4a	250/250	250/250	125/250	125/250	62.5/250	62.5/250	125/250	31.25/31.25
4b	15.63/31.25	62.5/62.5	31.25/31.25	62.5/62.5	31.25/62.5	31.25/62.5	62.5/62.5	7.81/15.63
4c	3.91/7.81	15.63/31.25	7.81/7.81	15.63/31.25	7.81/15.63	15.63/31.25	31.25/62.5	1.95/1.95
5b	125/125	125/250	125/125	15.62/31.25	62.5/125	125/250	125/125	31.25/31.25
5c	15.62/31.25	31.25/62.5	31.25/31.25	3.91/3.91	31.25/62.5	62.5/125	15.62/31.25	62.5/62.5
8b	125/125	125/125	125/125	250/250	62.5/125	62.5/125	125/125	31.25/31.25
8c	125/>125	>125/>125	>125/>125	>125/>125	7.81/15.63	>125/>125	>125/>125	7.81/7.81
11c	>125/>125	>125/>125	>125/>125	>125/>125	>125/>125	>125/>125	>125/>125	15.62/31.25
FLU	0.06/0.12	0.12/>125	3.91/15.62	0.98/3.91	0.24/0.48	>125/>125	>125/>125	1.95/3.91

CA, *Candida albicans* ATCC 44859; CT, *Candida tropicalis* 156; CK, *Candida krusei* E28; CG, *Candida glabrata* 20/I; TA, *Trichosporon asahii* 1188; AF, *Aspergillus fumigatus* 231; AC, *Absidia corymbifera* 272; TM, *Trichophyton mentagrophytes* 445.

2,4-Dihydroxy*-N-*phenylbenzamide (2a). IR (KBr): CO 1635 cm^{-1}; ^1H NMR (75 MHz, DMSO): δ 6.34 (d, J = 2.4 Hz, 1 H, *H-3*), 6.39 (dd, J = 2.4 Hz, J = 8.7 Hz, 1 H, *H-5*), 7.08–7.15 (m, 1 H, *H-4′*), 7.31–7.39 (m, 2 H, *H-3′*, *H-5′*), 7.64–7.70 (m, 2 H, *H-2′*, *H-6′*), 7.90 (d, J = 8.7 Hz, 1 H, *H-6*), 10.15 (bs, 1 H, *OH*), 10.20 (bs, 1 H, *OH*), 12.28 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 103.1, 107.7, 108.0, 121.4, 124.2, 128.9, 130.6, 138.4, 161.9, 162.8, 167.5.

2,4-dihydroxy*-N-*(4-methylphenyl)benzamide (2b). IR (KBr): CO 1636 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 2.27 (s, 3 H, CH_3), 6.31 (d, J = 2.1 Hz, 1 H, *H-3*), 6.36 (dd, J = 2.1 Hz, J = 8.7 Hz, 1 H, *H-5*), 7.12–7.20 (m, 2 H, *H-3′ H-5′*) 7.51–7.57 (m, 2 H, *H-2′*, *H-6′*), 7.88 (d, J = 8.7 Hz, 1 H, *H-6*), 10.01 (bs, 1 H, *NH*), 10.17 (bs, 1 H, *OH*), 12.36 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 103.1, 107.6, 107.8, 121.5, 129.3, 130.4, 133.3, 135.8, 162.0, 162.7, 167.5.

N-*(4-Chlorophenyl)-2,4-dihydroxybenzamide (2c).* IR (KBr): CO 1647 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.33 (d, J = 2.1 Hz, 1 H, *H-3*), 6.38 (dd, J = 2.1 Hz, J = 8.8 Hz, 1 H, *H-5*), 7.36–7.43 (m, 2 H, *H-3′ H-5′*), 7.69–7.75 (m, 2 H, *H-2′*, *H-6′*), 7.87 (d, J = 8.8 Hz, 1 H, *H-6*), 10.23 (bs, 2 H, *OH*), 12.14 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 103.0, 107.8, 108.0, 122.8, 127.8, 128.8, 130.7, 137.5, 161.7, 162.8, 167.5.

2,4-Dihydroxy*-N-*(4-methoxyphenyl)benzamide (2d). IR (KBr): CO 1640 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.74 (s, 3 H, OCH_3), 6.31 (d, J = 2.4 Hz, 1 H, *H-3*), 6.37 (dd, J = 2.4 Hz, J = 8.7 Hz, 1 H, *H-5*), 6.90–6.96 (m, 2 H, *H-3′*, *H-5′*), 7.52–7.58 (m, 2 H, *H-2′*, *H-6′*), 7.89 (d, J = 8.7 Hz, 1 H, *H-6*), 10.04 (bs, 1 H, *OH*), 10.17 (bs, 1 H, *OH*), 12.47 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 103.1, 107.5, 107.6, 114.0, 123.1, 130.1, 13102, 156.1, 162.3, 162.7, 167.6.

2,5-Dihydroxy*-N-*phenylbenzamide (3a). IR (KBr): CO 1635 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 7.02 (d, J = 8.7 Hz, 1 H, *H-3*), 7.10–7.17 (m, 1 H, *H-4′*), 7.22 (dd,1 H, J = 2.7 Hz, J = 8.7 Hz, *H-4*), 7.34-7.41 (m, 2 H, *H-3′*, *H-5′*), 7.67–7.74 (m, 3 H, *H-6*, *H-2′*, *H-6′*), 9.78 (bs, 1 H, *OH*), 10.40 (bs, 1 H, *NH*), 11.79 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 118.1, 118.3, 121.0, 122.0, 124.5, 127.4, 129.0, 138.3, 142.6, 155.6, 169.7.

2,5-Dihydroxy*-N-*(4-methylphenyl)benzamide (3b). IR (KBr): CO 1636 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 2.27 (s, 3 H, CH_3), 6.80 (d, J = 8.7 Hz, 1 H, *H-3*), 6.87 (dd, J = 3.0 Hz, J = 8.7 Hz, 1 H, *H-4*), 7.12–7.17 (m, 2 H, *H-3′*, *H-5′*), 7.36 (d, J = 3.0 Hz, 1 H, *H-6*), 7.54–7.59 (m, 2 H, *H-2′*, *H-6′*), 9.10 (bs, 1 H, *OH*), 10.32 (bs, 1 H, *NH*), 11.10 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 114.7, 118.0, 118.1, 120.9, 121.3, 129.4, 133.3, 136.0, 149.9, 150.9, 166.0.

N-*(4-Chlorophenyl)-2,5-dihydroxybenzamide (3c).* IR (KBr): CO 1635 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.82 (d, J = 8.7 Hz, 1 H, *H-3*), 6.88 (dd, J = 2.7 Hz, J = 9.0 Hz, 1 H, *H-4*), 7.33 (d, J = 2.7 Hz, 1 H, *H-6*), 7.36–7.44 (m, 2 H, *H-3′*, *H-5′*), 7.71–7.78 (m, 2 H, *H-2′ H-6′*), 9.14 (bs, 1 H, *OH*), 10.48 (bs, 1 H, *NH*), 10.95 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 114.8, 118.1, 118.3, 121.4, 122.3, 127.8, 128.9, 137.6, 149.9, 150.6, 166.1.

2,5-Dihydroxy*-N-*(4-methoxyphenyl)benzamide (3d). IR (KBr): CO 1637 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.75 (s, 3 H, OCH_3), 6.81 (d, J = 8.7 Hz, 1 H, *H-3*), 6.89 (dd, J = 2.7 Hz, J = 8.7 Hz, 1 H, *H-4*), 6.91–6.96 (m, 2 H, *H-3′ H-5′*), 7.38 (d, J = 2.7 Hz, 1 H, *H-6*),7.56–7.62 (m, 2 H, *H-2′*, *H-6′*), 9.09 (bs, 1 H, *OH*), 10.28 (bs, 1 H, *NH*), 11.19 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 114.1, 114.5, 117.7, 118.0, 121.3, 122.7, 131.5, 149.8, 151.2, 156.1, 166.1.

2,6-Dihydroxy*-N-*phenylbenzamide (4a). IR (KBr): CO 1654 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.41 (d, J = 8.4 Hz, 2 H, *H-3*, *H-5*), 7.10–7.15 (m, 1 H, *H-4′* 7.19 (t, J = 8.4 Hz, 1 H, *H-4*), 7.32–7.38 (m, 2 H, *H-3′*, *H-5′*), 7.61–7.65 (m, 2 H, *H-2′*, *H-6′*), 10.73 (bs, 1 H, *NH*), 12.24 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 104.3, 107.6, 121.2, 124.7, 129.2, 133.8, 13.7, 159.8, 168.3.

2,6-Dihydroxy*-N-*(4-methylphenyl)benzamide (4b). IR (KBr): CO 1651 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 2.28 (s, 3 H, CH_3), 6.43 (d, J = 8.4 Hz, 2 H, *H-3*, *H-5*), 7.16–7.22 (m, 3 H, *H-4*, *H-3′*, *H-5′*), 7.50–7.56 (m, 2 H, *H-2′*, *H-6′*), 10.69 (bs, 1 H, *NH*), 12.34 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 104.1, 107.6, 121.2, 129.5, 133.8, 133.9, 135.1, 159.9, 168.3.

N-*(4-Chlorophenyl)-2,6-dihydroxybenzamide (4c).* IR (KBr): CO 1648 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.42 (d, J = 8.1 Hz, 2 H, *H-3*, *H-5*), 7.19 (t, J = 8.1 Hz, 1 H, *H-4*), 7.39–7.45 (m, 2 H, *H-3′*, *H-5′*), 7.66–7.72 (m, 2 H, *H-2′ H-6′*), 10.74 (bs, 1 H, *NH*), 11.97 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 105.1, 107.5, 122.6, 128.2, 129.0, 133.7, 136.8, 159.5, 168.1.

2,6-Dihydroxy*-N-*(4-methoxyphenyl)benzamide (4d). IR (KBr): CO 1652 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.75 (s, 3 H, OCH_3), 6.42 (d, J = 8.1 Hz, 2 H, *H-3*, *H-5*), 6.90–6.97 (m, 2 H, *H-3′*, *H-5′*), 7.20 (t, J = 8.1 Hz, 1 H, *H-4*), 7.52–7.58 (m, 2 H, *H-2′*, *H-6′*), 10.63 (bs, 1 H, *NH*), 12.40 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 103.8, 107.6, 114.2, 122.9, 130,5, 133.8, 156.4, 160.0, 168.1.

8-Hydroxy-3-phenyl-2*H-*1,3-benzoxazine-2,4(3*H*)-dione (5a). IR (KBr): CO 1785, 1676 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 7.24 (t, J = 7.8 Hz, 1 H, *H-6*), 7.31 (dd, J = 1.8 Hz, J = 7.8 Hz, 1 H, *H-7*), 7.40 (dd, J = 1.8 Hz, J = 7.8 Hz, 1 H, *H-5*), 7.42–7.54 (m, 5 H, *H-2′*, *H-3′*, *H-4′*, *H-5′*, *H-6′*), 10.54 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 116.1, 116.9, 122.2, 125.4, 128.8, 129.2, 135.6, 141.7, 145.2, 147.7, 161.1.

8-Hydroxy-3-(4-methylphenyl)-2*H-*1,3-benzoxazine-2,4(3*H*)-dione (5b). IR (KBr): CO 1753, 1701 cm^{-1}; ^1H NMR (250 MHz, DMSO): δ 2.37 (s, 3 H, CH_3), 7.23 (t, J = 7.5 Hz, 1 H, *H-6*), 7.25–7.34 (m, 5 H, *H-7*, *H-2′*, *H-3′*, *H-5′*, *H-6′*), 7.39 (dd, J = 1.8 Hz, J = 7.5 Hz, 1 H, *H-5*), 10.49 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, DMSO): δ 20.5, 115.5, 116.5, 121.8, 124.9, 128.0, 129.2, 132.4, 137.9, 141.2, 144.7, 147.3, 160.7.

3-(4-Chlorophenyl)-8-hydroxy-2*H-*1,3-benzoxazine-2,4(3*H*)-dione (5c). IR (KBr): CO 1742, 1699 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 7.24 (t, J = 7.8 Hz, 1 H, *H-6*), 7.30 (dd, J = 1.8 Hz, J = 7.8 Hz, 1 H, *H-7*), 7.39 (dd, J = 1.8 Hz, J = 7.8 Hz, 1 H, *H-5*), 7.44–7.50 (m, 2 H, *H-3′*, *H-5′*), 7.54–7.61 (m, 2 H, *H-2′*, *H-6′*), 10.55 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 116.0, 116.9, 122.3, 125.4, 129.3, 130.8, 133.5, 134.5, 141.6, 145.2, 147.6, 161.1.

8-Hydroxy-3-(4-methoxyphenyl)-2*H-*1,3-benzoxazine-2,4(3*H*)-dione (5d). IR (KBr): CO 1766, 1704 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.81 (s, 3 H, OCH_3), 7.00–7.07 (m, 2 H, *H-3′*, *H-5′*), 7.23 (t, J = 7.8 Hz, 1 H, *H-6*), 7.27–7.36 (m, 3 H, *H-7*, *H-2′*, *H-6′*), 7.39 (dd, J = 1.8 Hz, J = 7.8 Hz, 1 H, *H-5*), 10.48 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.6, 114.4, 116.1, 116.9, 122.1, 125.3, 128.0, 129.9, 141.6, 145.2, 147.9, 159.4, 161.3.

7-Hydroxy-3-phenyl-2*H-*1,3-benzoxazine-2,4(3*H*)-dione (6a). IR (KBr): CO 1770, 1699 cm^{-1}; ^1H NMR (300 MHz, DMSO):

δ 6.74 (d, J = 2.1 Hz, 1 H, *H-8*), 6.86 (dd, J = 2.1 Hz, J = 8.7 Hz, 1 H, *H-6*), 7.38-7.52 (m, 5 H, *H-2′*, *H-3′*, *H-4′*, *H-5′*, *H-6′*), 7.82 (d, J = 8.7 Hz, 1 H, *H-5*), 11.08 (bs, H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 101.9, 106.3, 114.1, 129.2, 129.5, 130.9, 133.4, 134.4, 148.0, 154.6, 160.3, 164.9.

7-Hydroxy-3-(4-methylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (6b). IR (KBr): CO 1771, 1698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 2.37 (s, 3 H, CH_3), 6.73 (d, J = 2.1 Hz, 1 H, *H-8*), 6.85 (dd, J = 2.1 Hz, J = 8.7 Hz, 1 H, *H-6*), 7.23–7.31 (m, 4 H, *H-2′*, *H-3′*, *H-5′*, *H-6′*), 7.81 (d, J = 8.7 Hz, 1 H, *H-5*), 11.07 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 21.0, 101.8, 106.4, 114.0, 128.6, 129.5, 129.6, 132.8, 138.2, 148.3, 154.5, 160.4, 164.8.

3-(4-Chlorophenyl)-7-hydroxy-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (6c). IR (KBr): CO 1766, 1703 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 6.74 (d, J = 2.1 Hz, 1 H, *H-8*), 6.86 (dd, J = 2.1 Hz, J = 8.5 Hz, 1 H, *H-6*), 7.41–7.47 (m, 2 H, *H-3′*, *H-5′*), 7.53–7.59 (m, 2 H, *H-2′ H-6′*), 7.81 (d, J = 8.5 Hz, 1 H, *H-5*), 11.10 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 101.9, 106.3, 114.1, 129.2, 129.5, 130.9, 133.4, 134.4, 148.0, 154.6, 160.3, 164.9.

7-Hydroxy-3-(4-methoxyphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (6d). IR (KBr): CO 1766, 1704 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.80 (s, 3 H, OCH_3), 6.73 (d, J = 2.1 Hz, 1 H, *H-8*), 6.85 (dd, J = 2.1 Hz, J = 8.7 Hz, 1 H, *H-6*), 6.99–7.05 (m, 2 H, *H-3′*, *H-5′*), 7.27-7.32 (m, 2 H, *H-2′*, *H-6′* 7.81 (d, J = 8.7 Hz, 1 H, *H-5*), 11.05 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 56.0, 102.3, 106.9, 114.5, 114.8, 128.5, 130.0, 130.4, 148.8, 155.0, 159.8, 161.0, 165.3.

6-Hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (7a). IR (KBr): CO 1735, 1680 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.24 (dd, J = 2.4 Hz, J = 8.7 Hz, 1 H, *H-7*), 7.28 (d, J = 2.4 Hz, 1 H, *H-5*), 7.35 (d, J = 8.7 Hz, 1 H, *H-8*), 7.38–7.54 (m, 5 H, *H-2′*, *H-3′*, *H-4′*, *H-5′*, *H-6′*), 11.05 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 111.3, 115.4, 117.8, 124.2, 128.8, 129.2, 135.6, 145.8, 148.0, 154.7, 160.9.

6-Hydroxy-3-(4-methylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (7b). IR (KBr): CO 1749, 1683 cm^{-1}; ^{1}H NMR (DMSO): δ 2.37 (s, 3 H, CH_3), 7.23 (dd, J = 3.0 Hz, J = 8.7 Hz, 1 H, *H-7*), 7.26–7.35 (m, 6 H, *H-5*, *H-8*, *H-2′*, *H-3′*, *H5′*, *H6′*), 10.04 (bs, 1 H, *OH*); ^{13}C NMR (DMSO): δ 21.0, 111.3, 115.4, 117.8, 124.2, 128.5, 129.7, 132.9, 138.3, 145.8, 148.0, 154.7, 160.9.

3-(4-Chlorophenyl)-6-hydroxy-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (7c). IR (KBr): CO 1749, 1685 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.20–7.24 (m, 2 H, *H-5*, *H-7*), 7.34 (d, J = 8.3 Hz, 1 H, *H-8*), 7.42–7.47 (m, 2 H, *H-3′*, *H-5′*), 7.54–7.59 (m, 2 H, *H-2′*, *H-6′*), 10.15 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 110.8, 114.8, 117.4, 123.9, 128.8, 130.3, 133.1, 133.9, 145.3, 147.3, 154.2, 160.3.

6-Hydroxy-3-(4-methoxyphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (7d). IR (KBr): CO 1751, 1704 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.81 (s, 3 H, OCH_3), 7.00–7.06 (m, 2 H, *H-3′*, *H-5′*), 7.23 (dd, J = 2.7 Hz, J = 8.7 Hz,1 H, *H-7*), 7.27 (d, J = 2.7 Hz, 1 H, *H-5*), 7.28–7.35 (m, 3 H, *H-8*, *H-2′*, *H-6′*), 10.04 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.6, 111.3, 114.4, 115.4, 117.8, 124.2, 128.0, 129.8, 145.8, 148.2, 154.7, 159.4, 161.0.

5-Hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (8a). IR (KBr): CO 1761, 1662 cm^{-1}; ^{1}H NMR (250 MHz, DMSO): δ 6.88 (d, J = 8.3 Hz, 1 H, *H-6*), 6.92 (d, J = 8.3 Hz, 1 H, *H-8*), 7.44–7.57 (m, 5 H, *H-2′*, *H-3′, H-4′, H-5′*, *H-6′),* 7.69 (t, J = 8.3 Hz, 1 H, *H-7*), 10.78 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, DMSO): δ 100.9, 105.9, 112.0, 128.2, 128.7, 128.8, 133.9, 136.9, 146.7, 152.3, 159.1, 164.3.

5-Hydroxy-3-(4-methylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (8b). IR (KBr): CO 1752, 1667 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 2.38 (s, 3 H, CH_3), 6.88 (dd, J = 0.9 Hz, J = 8.3 Hz, 1 H, *H-6*), 6.93 (dd, J = 0.9 Hz, J = 8.3 Hz, 1 H, *H-8*), 7.29–7.35 (m, 4 H, *H-2′*, *H-3′, H-5′*, *H-6′),* 7.69 (t, J = 8.3 Hz, 1 H, *H-7*), 10.79 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 21.0, 101.5, 106.4, 112.5, 128.5, 129.8, 31.8, 137.4, 138.7, 147.3, 152.8, 159.7, 165.0.

3-(4-Chlorophenyl)-5-hydroxy-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (8c). IR (KBr): CO 1757, 1666 cm^{-1}; ^{1}H NMR (250 MHz, DMSO): δ 6.84–6.95 (m, 2 H, *H-6*, *H-8*), 7.44–7.52 (m, 2 H, *H-3′ H-5′*), 7.54–7.62 (m, 2 H, *H-2′*, *H-6′*), 7.68 (t, J = 8.3 Hz, 1 H, *H-7*), 10.68 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, DMSO): δ 101.7, 106.7, 112.9, 129.6, 131.0, 133.5, 134.2, 137.7, 147.3, 153.0, 159.9, 164.9.

5-Hydroxy-3-(4-methoxyphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (8d). IR (KBr): CO 1765, 1679 cm^{-1}; ^{1}H NMR (DMSO): δ 3.81 (s, 3 H, OCH_3), 6.87 (dd, J = 0.9 Hz, J = 8.2 Hz, 1 H, *H-6*), 6.92 (dd, J = 0.9 Hz, J = 8.2 Hz, 1 H, *H-8*), 7.02–7.08 (m, 2 H, *H-3′*, *H-5′*), 7.33–7.39 (m, 2 H, *H-2′*, *H-6′*), 7.69 (t, J = 8.2 Hz, 1 H, *H-7*), 10.81 (bs, 1 H, *OH*); ^{13}C NMR (DMSO): δ 55.6, 101.5, 106.4, 112.4, 114.5, 126.8, 129.8, 137.4, 147.4, 152.8, 159.6, 159.7, 165.2.

3-(4-Chlorophenyl)-7-hydroxy-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (9c). IR (KBr): CO 1733 cm^{-1}; ^{1}H NMR (300 MHz, Me_2CO-d_6): δ 6.72 (d, J = 2.1 Hz, 1 H, *H-8*), 6.93 (dd, J = 2.1 Hz, J = 9.0 Hz, 1 H, *H-6*), 7.43–7.47 (m, 2 H, *H-3′*, *H-5′*), 7.53–7.57 (m, 2 H, *H-2′*, *H-6′*), 8.27(d, J = 9.0 Hz, 1 H, *H-5*), 10.10 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, Me_2CO-d_6): δ 102.0, 115.4, 129.8, 130.1, 130.3, 131.4, 134.6, 139.8, 145.6, 152.6, 165.7, 192.6.

5-Hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (10a). IR (KBr): CO 1759 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.79 (dd, J = 1.0 Hz, J = 8.5 Hz, 1 H, *H-6*), 6.95 (dd, J = 1.0 Hz, J = 8.5 Hz, 1 H, *H-8*), 7.23–7.28 (m, 2 H, *H-2′* H-6′), 7.52–7.63 (m, 4 H, *H-3′*, *H-4′*, *H-5′*, *H-7*), 12.86 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 106.1, 107.8, 115.2, 128.1, 129.7, 130.1, 137.0, 137.4, 144.5, 149.6, 161.8, 192.5.

5-Hydroxy-3-(4-methylphenyl)-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (10b). IR (KBr): CO 1751 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.46 (s, 3 H, CH_3), 6.78 (dd, J = 1.0 Hz, J = 8.4 Hz, 1 H, *H-6*), 6.94 (dd, J = 1.0 Hz, J = 8.4 Hz, 1 H, *H-8*), 7.08–7.17 (m, 2 H, *H-3′*, *H-5′*), 7.34–7.42 (m, 2 H, *H-2′*, *H-6′*), 7.55 (t, J = 8.4 Hz, 1 H, *H-7*), 12.89 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.4, 106.1, 107.8, 115.2, 127.7, 130.8, 134.8, 136.9, 139.9, 144.5, 149.6, 161.8, 192.6.

3-(4-Chlorophenyl)-5-hydroxy-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (10c). IR (KBr): CO 1752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79 (dd, J = 1.2 Hz, J = 8.5 Hz, 1 H, *H-6*), 6.95 (dd, J = 1.2 Hz, J = 8.5 Hz, 1 H, *H-8*), 7.16–7.21 (m, 2 H, *H-2′ H-6′*), 7.51–7.60 (m, 3 H, *H-7*, *H-3′*, *H-5′*), 12.76 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.1, 107.7, 115.3, 129.6, 130.4, 135.7, 135.8, 137.2, 144.3, 149.5, 161.8, 192.2.

5-Hydroxy-3-(4-methoxyphenyl)-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (10d). IR (KBr): CO 1766 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 3.87 (s, 3 H, *OCH_3*), 6.78 (dd, $J = 1.2$ Hz, $J = 8.5$ Hz, 1 H, *H-6*), 6.94 (dd, $J = 1.2$ Hz, $J = 8.5$ Hz, 1 H, *H-8*), 7.02–7.09 (m, 2 H, *H-3′*, *H-5′*), 7.12–7.19 (m, 2 H, *H-2′*, *H-6′*), 7.55 (t, $J = 8.5$ Hz, 1 H, *H-7*), 12.90 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 106.0, 107.8, 115.1, 115.3, 129.1, 129.8, 136.9, 144.7, 149.5, 160.2, 161.7, 192.8.

5-Hydroxy-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dithione (11a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (dd, $J = 1.2$ Hz, $J = 8.4$ Hz, 1 H, *H-6*), 6.94 (dd, $J = 1.2$ Hz, $J = 8.4$ Hz, 1 H, *H-8*), 7.19–7.23 (m, 2 H, *H-2′*, *H-6′*), 7.49–7.62 (m, 4 H, *H-7*, *H-3′ H-4′*, *H-5′*), 12.74 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.7, 109.2, 115.4, 128.1, 129.4, 130.2, 137.5, 141.5, 149.9, 161.6, 177.0, 187.9.

5-Hydroxy-3-(4-methylphenyl)-2H-1,3-benzoxazine-2,4(3H)-dithione (11b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3 H, *CH_3*), 6.84 (dd, $J = 0.9$ Hz, $J = 8.1$ Hz, 1 H, *H-6*), 6.95 (dd, $J = 0.9$ Hz, $J = 8.1$ Hz, 1 H, *H-8*), 7.06–7.11 (m, 2 H, *H-3′*, *H-5′*), 7.35–7.40 (m, 2 H, *H-2′*, *H-6′*), 7.58 (t, $J = 8.1$ Hz, 1 H, *H-7*), 12.76 (s, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 105.7, 109.2, 115.4, 127.7, 130.9, 137.4, 139.0, 139.7, 149.9, 161.6, 177.2, 188.0.

3-(4-Chlorophenyl)-5-hydroxy-2H-1,3-benzoxazine-2,4(3H)-dithione (11c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (dd, $J = 1.0$ Hz, $J = 8.3$ Hz, 1 H, *H-6*), 6.95 (dd, $J = 1.0$ Hz, $J = 8.3$ Hz, 1 H, *H-8*), 7.11–7.20 (m, 2 H, *H-2′*, *H-6′*), 7.48–7.57 (m, 2 H, *H-3′*, *H-5′*), 7.59 (t, $J = 8.3$ Hz, 1 H, *H-7*), 16.64 (s, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.8, 109.2, 115.6, 129.7, 130.6, 135.5, 137.6, 139.9, 149.9, 161.7, 176.8, 188.8.

5-Hydroxy-3-(4-methoxyphenyl)-2H-1,3-benzoxazine-2,4(3H)-dithione (11d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3 H, *OCH_3*), 6.83 (dd, $J = 1.2$ Hz, $J = 8.3$ Hz, 1 H, *H-6*), 6.94 (dd, $J = 1.2$ Hz, $J = 8.3$ Hz, 1 H, *H-8*), 7.03–7.14 (m, 4 H, *H-2′, H-3′*, *H-5′*, *H-6′*), 7.58 (t, $J = 8.3$ Hz, 1 H, *H-7*), 12.78 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 105.7, 109.2, 115.3, 115.4, 129.1, 134.2, 137.4, 149.9, 160.0, 161.5, 177.4, 188.2.

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