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Synthesis and Antifungal Activity of 2,5-Disubstituted-6-arylamino-4,7-benzimidazolediones

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Abstract—2,5-Disubstituted-6-arylamino-4,7-benzimidazolediones were synthesized and tested for in vitro antifungal activity against pathogenic fungi. Among them, 6-arylamino-5-chloro-2-(2-pyridyl)-4,7-benzimidazolediones exhibited potent antifungal activity against *Candida* species and *Aspergillus niger*.

Compounds containing the heterocyclic quinone group represent an important class of biologically active molecules.[1]

The quinones such as 5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole (UHDBT, **1**) and 7-alkyl-6-hydroxy-5,8-quinolinediones blockade a mitochondrial electron transport in *Saccaromyces cerevisiae*.[2] The UHDBT (**1**), one of 4,7-dioxobenzothiazole compounds, has been reported as inhibitors of mitochondrial cytochrome complex in yeast[3,4] and bacteria.[5] In our previous reports,[6,7] 6-arylamino-7-chloro-5,8-quinolinediones **2** and 6-arylamino-4,7-dioxobenzothiazoles **3**, which could be analogues of UHDBT, have demonstrated potent antifungal activity against pathogenic fungi (Fig. 1). The arylamino-substituents of quinones **2** and **3** improve sometimes the activity.[6,7] From this information, 5-substituted- and 2,5-disubstituted-6-arylamino-4,7-benzimidazolediones **4**–**7**, as bioisosteres of quinones **2** and **3**, were synthesized and their antifungal activity was evaluated.

There have been a few reports[8–12] on some 4,7-benzimidazoledione derivatives that exhibited cytotoxic activities[8,9] against cancer cell lines, antiproliferatve activity[10] and inhibitory effect[11] on protozoal purine nucleoside phosphorylase. However, the antifungal activity of 4,7-benzimidazoledione classes against fungi has not been reported. Therefore, we synthesized a series of 4,7-benzimidazolediones **4**–**7** to elucidate their contribution to the antifungal activity.

Chemistry

The method used to synthesize the 2-aryl-6-arylamino-4,7-benzimidazolediones **4**–**7** is shown in Scheme 1. 2,3-Diamino-1,4-dimethoxybenzene (**8**) was prepared according to the known method.[12] Cyclizations of the compound **8** with appropriate arylaldehydes such as 2-, 3- or 4-pyridinecarboxaldehyde gave 2-aryl-4,7-dimethoxybenzimidazoles **9a**–**9c** resulting in 67–75% yields.

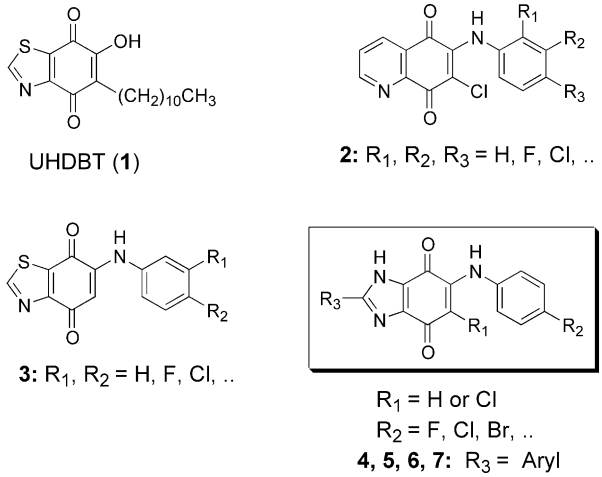

Figure 1. Antifungal quinone derivatives.

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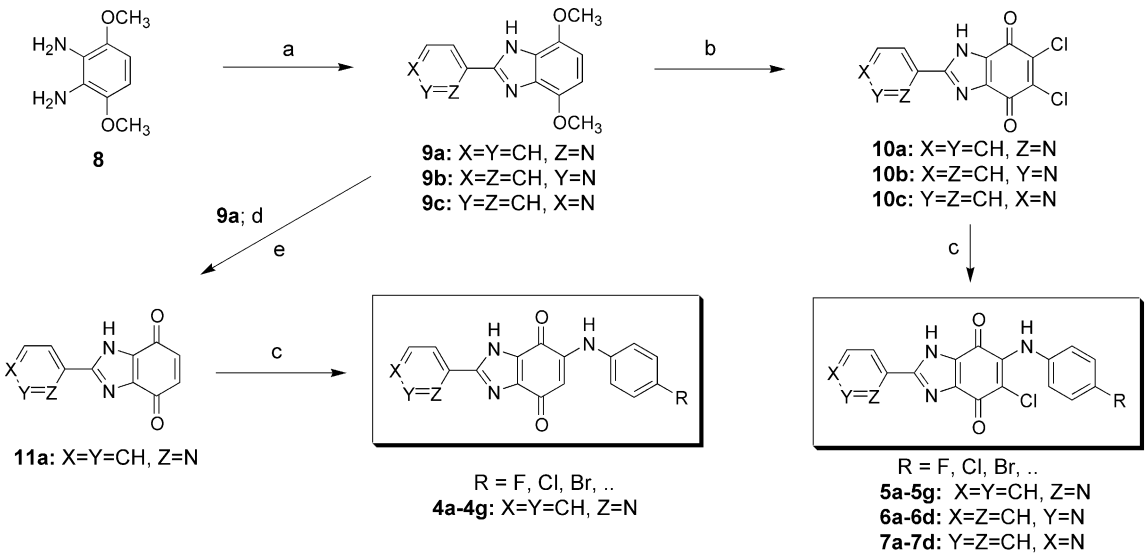

Scheme 1. Synthesis of 2-aryl-6-arylamino-4,7-benzimidazolediones. Reagents and conditions: (a) arylaldehyde (1 equiv)/toulene/reflux/4 h/67–75%; (b) c-HCl/c-HNO_3/reflux/1 h/27–61%; (c) arylamine (1 equiv)/EtOH/reflux/5 h/52–94%; (d) **9a**/c-HBr/H_2O/reflux/6 h/56%; (e) $FeCl_3/H_2O$/reflux/2 h/42%.

2-Aryl-5,6-dichloro-4,7-benzimidazolediones **10a–10c** were synthesized by oxidizing compounds **9a–9c** with HNO_3/HCl variation resulting in 27–61% yields. The 2-aryl-6-arylamino-5-chloro-4,7-benzimidazolediones **5a–5g**, **6a–6d** and **7a–7d** (Tables 1 and 2) were prepared by nucleophilic substitution on compounds **10a–10c** with appropriate arylamines. Most of these substitutions went as expected and had overall high yields of 52–93%. 2-(2-Pyridyl)-4,7-benzimidazoledione (**11a**) was prepared from 2,3-diamino-1,4-dimethoxybenzene[12] (**8**) according to the known procedure.[10] The 2-aryl-6-arylamino-4,7-benzimidazolediones **4a–4g** (Tables 1 and 2) were synthesized by nucleophilic substitution on the compound **11a** with the arylamines in 66–94% yields.

Table 1. Structures and in vitro antifungal activity for 4,7-benzimidazolediones

Compd	X	Y	Z	R	MIC[a] (μg/mL)			
					C. albicans[b]	*C. tropicalis*	*C. krusei*	*A. niger*
4a	CH	CH	N	F	100	1.6	50	100
4b	CH	CH	N	Cl	50	0.8	1.6	3.2
4c	CH	CH	N	Br	50	0.8	1.6	1.6
4d	CH	CH	N	I	50	0.8	1.6	100
4e	CH	CH	N	CH_3	3.2	0.8	0.4	6.3
4f	CH	CH	N	OCH_3	6.3	0.8	1.6	50
4g	CH	CH	N	OCH_2CH_3	50	0.8	1.6	50
5a	CH	CH	N	F	12.5	3.2	6.3	25
5b	CH	CH	N	Cl	6.3	3.2	6.3	6.3
5c	CH	CH	N	Br	3.2	1.6	6.3	6.3
5d	CH	CH	N	I	50	3.2	100	>100
5e	CH	CH	N	CH_3	12.5	1.6	3.2	25
5f	CH	CH	N	OCH_3	12.5	1.6	12.5	25
5g	CH	CH	N	OCH_2CH_3	12.5	3.2	12.5	25
6a	CH	N	CH	F	>100	12.5	>100	100
6b	CH	N	CH	Cl	>100	25	>100	100
6c	CH	N	CH	Br	>100	50	>100	100
6d	CH	N	CH	OCH_3	>100	50	>100	100
7a	N	CH	CH	F	>100	6.3	>100	100
7b	N	CH	CH	Cl	>100	3.2	>100	100
7c	N	CH	CH	Br	>100	12.5	>100	100
7d	N	CH	CH	OCH_3	>100	25	>100	100
10a	CH	CH	N	—	100	25	>100	100
11a	CH	CH	N	—	>100	100	>100	100
Flucytosine					3.2	6.3	6.3	6.3

[a]The MIC value was defined as the lowest concentration of the antifungal agent at which there showed optically clear. MIC values were read after 1 day for C*andida* species and 2 days for *A. niger* in 37 °C. The inoculum sizes contained approximately 1×10^5 CFU/mL. Culture media tested were the modified Sabouraud dextrose broth (Difco Lab.). The final concentration of antifungal agents was between 0.4 and 100 μg/mL.
[b]Fungi tested: *C. albicans* ATCC 10231, *C. tropicalis* ATCC 28775, *C. krusei* ATCC 749 and *A. niger* KCTC 1231.

Table 2. Physical and spectral data of 4,7-benzimidazolediones

Compd	Mp (°C)	Yield (%)	IR (cm^{-1})	^1H NMR (δ ppm)	Formula	HRMS calcd (found)
4a	285–287	75	3250 (m, NH), 3075, 1693 (s, C=O), 1422–1584	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0.5 (m, 2H), 7.4.3 (m, 4H), 5.6 (s, 1H, H5)	$C_{18}H_{11}FN_4O_2$	334.0866 (334.0868)
4b	258–260	82	3252 (m, NH), 3100, 1693 (s, C=O), 1421–1588	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.5 (q, 1H), 7.5 (m, 2H), 7.4 (m, 2H), 5.8 (s, 1H, H5)	$C_{18}H_{11}ClN_4O_2$	350.0571 (350.0572)
4c	273–275	79	3287 (s, NH), 3000, 1692 (s, C=O), 1421–1583	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.6 (d, J=8.4, 2H), 7.5 (q, 1H), 7.4 (d, J=8.4, 2H), 5.8 (s, 1H, H5)	$C_{18}H_{11}Br\ N_4O_2$	394.0066 (394.0068)
4d	268–269	66	3287 (s, NH), 3000, 1692 (s, C=O), 1419–1530	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.8 (d, J=8.6, 2H), 7.5 (q, 1H), 7.2 (d, J=8.6, 2H), 5.8 (s, 1H, H5)	$C_{18}H_{11}IN_4O_2$	441.9927 (441.9929)
4e	239–240	89	3278 (m, NH), 3029, 1693 (s, C=O), 1419–1592	14.2 (s, 1H, NH), 9.1 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.5 (q, 1H), 7.2.3 (m, 4H), 5.7 (s, 1H, H5), 2.3 (s, 3H, CH_3)	$C_{19}H_{14}N_4O_2$	330.1117 (330.1118)
4f	185–188	94	3326 (s, NH), 3078, 1692 (s, C=O), 1418–1599	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (t, 1H), 7.5 (t, 1H), 7.3 (d, J=9.2, 2H), 7.0 (d, J=9.2, 2H), 5.6 (s, 1H, H5), 3.8 (s, 3H, OCH_3)	$C_{19}H_{14}N_4O_3$	346.1066 (346.1067)
4g	197–199	82	3284 (s, NH), 3062, 1690 (s, C=O), 1421–1597	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7.5 (m, 1H), 7.3 (d, J=8.6, 2H), 7.0 (d, J=8.6, 2H), 5.6 (s, 1H, H5), 4.0 (q, J=7.2, 2H, CH_2), 1.3 (t, J=7.2, 3H, CH_3)	$C_{20}H_{16}N_4O_3$	360.1223 (360.1242)
5a	296–298	66	3315 (m, NH), 3239, 1685 (m, C=O), 1420–1588	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.5 (q, 1H), 7.1 (d, 4H)	$C_{18}H_{10}ClFN_4O_2$	368.0476 (368.0478)
5b	283–286	72	3277 (m, NH), 3218, 1697 (s, C=O), 1418–1586	14.3 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0.5 (m, 2H), 7.3 (d, 2H), 7.1 (d, 2H)	$C_{18}H_{10}Cl_2N_4O_2$	384.0181 (384.0181)
5c	290–292	69	3277 (m, NH), 3218), 1698 (s, C=O), 1418–1583	14.3 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0.6 (m, 2H), 7.5 (d, 2H), 7.0 (d, 2H)	$C_{18}H_{10}BrClN_4O_2$	427.9676 (427.9675)
5d	280–281	74	3229 (s, NH), 3210, 1692 (m, C=O), 1421–1584	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.6.5 (m, 3), 6.9 (d, 2H)	$C_{18}H_{10}ClIN_4O_2$	475.9537 (475.9538)
5e	266–268	86	3282 (s, NH), 3228, 1693 (s, C=O), 1420–1585	14.2 (s, 1H, NH), 9.1 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.5 (td, 1H), 7.1 (d, J=8.4, 2H), 7.0 (d, J=8.4, 2H), 2.3 (s, 3H, CH_3)	$C_{19}H_{13}ClN_4O_2$	364.0727 (364.0729)
5f	216–219	89	3368 (w, NH), 3229, 1696 (m, C=O), 1421–1586	14.2 (s, 1H, NH), 9.2 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.5 (td, 1H), 7.1 (d, 2H), 6.9 (d, 2H), 3.8 (s, 3H, OCH_3)	$C_{19}H_{13}ClN_4O_2$	380.0676 (380.0677)
5g	241–244	79	3322 (m, NH), 3200, 1680 (m, C=O), 1422–1589	14.2 (s, 1H, NH), 9.1 (s, 1H, NH), 8.7 (d, 1H), 8.2 (d, 1H), 8.0.5 (m, 2H), 7.1.9 (m, 4H), 4.0 (q, J=7, 2H, CH_2), 1.3 (t, J=7, 3H, CH_3)	$C_{20}H_{15}ClN_4O_3$	394.0833 (394.0832)
6a	281–284	69	3300 (m, NH), 3240, 1680 (m, C=O), 1420–1590	14.2 (s, 1H, NH), 9.3 (s, 1H), 8.6.5 (m, 2H), 7.5 (t, 1H), 7.1 (d, 2H), 7.2 (d, 2H)	$C_{18}H_{10}ClFN_4O_2$	368.0476 (368.0480)
6b	250–252	91	3280 (m, NH), 3220, 1695 (s, C=O), 1420–1590	14.2 (s, 1H, NH), 9.3 (s, 1H), 8.6.7 (d, 1H), 8.4.5 (d, 1H), 7.3 (d, 2H), 7.1 (d, 2H)	$C_{18}H_{10}Cl_2N_4O_2$	384.0181 (384.0183)
6c	287–288	75	3270 (m, NH), 3220), 1680 (s, C=O), 1420–1580	14.1 (s, 1H, NH), 9.3 (s, 1H, NH), 8.7.5(m, 2H), 7.6 (m, 1H), 7.5 (d, 2H), 7.1 (d, 2H)	$C_{18}H_{10}BrClN_4O_2$	427.9676 (427.9678)
6d	215–217	93	3225 (s, NH), 3210, 1690 (m, C=O), 1420–1580	14.2 (s, 1H, NH), 9.3 (s, 1H), 8.6 (d, 1H), 8.5 (d, 1H), 7.5 (t, 1H), 7.0.8 (m, 4H), 3.7 (s, 3H, OCH_3)	$C_{19}H_{14}N_4O_3$	346.1066 (346.1069)
7a	350–353	52	3223 (s, NH), 3100, 1690 (s, C=O), 1450–1513	14.2 (s, 1H, NH), 8.7 (d, J=6, 2H), 8.1 (d, J=6, 2H), 7.2 (d, J=6.8, 2H), 7.1 (d, J=6.8, 2H)	$C_{18}H_{10}ClFN_4O_2$	368.0476 (368.0479)
7b	348–349	64	3227 (w, NH), 3080, 1680 (s, C=O), 1441–1553	14.1 (s, 1H, NH), 8.9 (d, J=6, 2H), 8.1 (d, J=6, 2H), 7.2 (d, 2H), 7.0 (d, 2H)	$C_{18}H_{10}Cl_2N_4O_2$	384.0181 (384.0184)
7c	342–343	59	3225 (w, NH), 3088, 1685 (s, C=O), 1448–1551	14.2 (s, 1H, NH), 8.9 (d, 2H, J=6), 8.1 (d, 2H, J=6), 7.1 (m, 2H), 7.0 (m, 2H)	$C_{18}H_{10}BrClN_4O_2$	427.9676 (427.9676)
7d	337–338	84	3201 (s, NH), 3088, 1681 (s, C=O), 1421–1584	14.4 (s, 1H, NH), 8.8 (d, J=6, 2H), 8.1 (d, J=6, 2H), 7.0 (d, J=9, 2H), 6.9 (d, J=9, 2H), 3.7 (s, 3H, OCH_3)	$C_{19}H_{14}N_4O_3$	346.1066 (346.1067)
9b	214–216	67	3325 (w, NH), 3320, 1425–1590, 1255	14.2 (s, 1H, NH), 9.3 (s, 1H), 8.6 (d, 1H), 8.5 (d, 1H), 7.5 (t, 1H), 6.6 (d, 2H), 3.9 (m, 6H, CH_3)	$C_{14}H_{13}N_3O_2$	255.1008 (255.1010)
9c	230–231	75	3368 (w, NH), 3329, 1421–1585, 1237	14.2 (s, 1H, NH), 8.6 (d, 2H, J=6), 7.1 (d, 2H, J=6), 6.6 (d, 2H), 3.8 (s, 6, OCH_3)	$C_{14}H_{13}N_3O_2$	255.1008 (255.1008)
10a	292–294	61	3280 (s, NH), 3100, 1680 (s, C=O)	14.1 (s, 1H, NH), 8.8 (dd, 1H), 8.2 (d, 1H), 8.0 (td, 1H), 7.6 (m, 1H)	$C_{12}H_5Cl_2N_3O_2$	292.9759 (292.9761)
10b	306–309	27	3295 (s, NH), 3085, 1685 (s, C=O)	14.0 (s, 1H, NH), 9.2.3 (s, 1H), 8.6.7 (d, 1H), 8.4.5 (d, 1H), 7.5.6 (t, 1H)	$C_{12}H_5Cl_2N_3O_2$	292.9759 (292.9762)
10c	318–319	45	3201 (s, NH), 3088, 1681 (s, C=O), 1420–1554	14.2 (s, 1H, NH), 8.9 (d, J=6.4, 2H), 8.4 (d, J=6.4, 2H)	$C_{12}H_5Cl_2N_3O_2$	292.9759 (292.9759)

J values in Hz.

Biological activities

The synthesized 4,7-benzimidazolediones **4**–**7** were tested in vitro for their growth inhibitory activity against pathogenic fungi by the standard method.[13] The MIC (minimum inhibitory concentration) values were determined by comparison to flucytosine[13] as a fungicidal standard agent. As indicated in the Table 1, the most active potential among the 4,7-benzimidazoledione series **4**–**7** was found for 6-arylamino-2-(2-pyridyl)-4,7-benzimidazolediones **4a**–**4g** and **5a**–**5g**, which showed generally good activity against all tested *Candida* species and *A. niger*. In contrast, compounds **6a**–**6d** and **7a**–**7d** did not show significant antifungal activity, although many compounds of them exhibited good activity against *Candida tropicalis*.

Most of the 6-arylamino-2-(2-pyridyl)-4,7-benzimidazolediones **4a–4g** and **5a–5g** showed potent antifungal activity against all tested fungal species, and the activity against *C. tropicalis* was prominent. Most of compounds **4a–4g** and **5a–5g** had more potent antifungal activity against *C. tropicalis* than flucytosine. Actually, the activity of compounds **4f**, **5b** and **5c** was superior or comparable to those of flucytosine against all tested fungi. The 4,7-dioxobenzothiazoles **4f**, **5b** and **5c** completely inhibited the growth of all fungal species tested at the MIC level of 0.4 ~6.3 μg/mL.

The cytotoxic potential of compounds **4a–4g** and **5a–5g** was also determined in human cancer cells according to the NCI protocols.[14] All of the tested compounds did not show significant cytotoxic activities and showed the selectivity, in that they possess the potent antifungal activity without cytotoxicities in mammalian cells.[15]

In terms of structure–activity relationship, the 6-arylamino-2-(2-pyridyl)-4,7-benzimidazolediones **4a–4g** and **5a–5g** showed, in general, more potent antifungal activity than 4,7-benzimidazolediones (**6a–6d** and **7a–7d**) with 2-(3-pyridyl)- or 2-(4-pyridyl)-moieties. The 2-(2-pyridyl)-substituted compounds **4a–4g** and **5a–5g** exhibited the greatest activity, indicating a correlation that may offer insight into the mode of action of these compounds.

In addition, the 4,7-benzimidazolediones **10a** and **11a** without an 6-arylamino group exhibited poor antifungal activity. Thus, 6-arylamino moiety of benzimidazolediones **4a–4g** and **5a–5g** improves the antifungal activity significantly. The 5-chloro moieties of compounds **5a–5g** did not appear to contribute partially toward biological potency. The structure–activity relationship may not exist between properties of substituents (R: F, Cl, Br...) for the 5-arylamino moieties of 4,7-benzimidazolediones **4**.

Experimental

All melting points were measured with Buchi melting point B-545 and were uncorrected. The IR spectra were taken from Perkin–Elmer 1420r IR spectrometer with KBr pellets. ^{1}H NMR spectra were recorded on Brucker DPX 250 MHz spectrometer using DMSO-d_6 with TMS. High-resolution mass spectra (HRMS EI) were taken from Jeol JMS AX505 WA.

General procedure for synthesis of 2-(pyridyl)-4,7-dimethoxybenzimidazoles 9b and 9c

A solution of the compound **8** (6.25 mmol), 3- or 4-pyridynecarboxaldehyde (6.25 mmol) in toluene (20 mL) was heated at reflux for 4 h. The solvent was removed under vacuum, and the residue was triturated with water (20 mL). The precipitate was filtered, and crystallization from MeOH afforded compounds **9b** and **9c**. Their physical and spectral data are given in Table 2.

General procedure for synthesis of 5,6-dichloro-2-(pyridyl)-4,7-benzimidazolediones 10a–10c

5 mL of c-HNO_3 was added over a period of 1 h to a stirred suspension of compounds **9a**,[10] **9b** or **9c** (2.55 g, 10 mmol) in 15 mL of c-HCl at 80–90 °C. The mixture was stirred at rt for 2 h and was extracted twice with ether. The extract was evaporated and crystallization from EtOH afforded compounds **10a–10c** (Table 2).

General procedure for synthesis of 6-arylamino-2-(pyridyl)-4,7-benzimidazolediones 4–7

A solution of compounds **10a–10c** or **11a**[10] (0.34 mmol) in 15 mL of 95% EtOH was added to the solution of the arylamine (0.35 mmol) in 5 mL of 95% EtOH and stirred at rt for 2 h and then refluxed for 5 h. After the mixture was kept overnight in the refrigerator or poured into 20 mL of ice water, the precipitate was collected by filtration and crystallization from aq EtOH afforded the compounds **4–7** (Table 2).

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15. Unpublished data; we also tested cytotoxic activity of compounds **4a–4g** and **5a–5g** against human tumor cell lines such as A 549, HL-60 and HepG2 according to the NCI protocols.[14]