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Microwave-Assisted One-Pot Synthesis of 2-(Substituted phenyl)-1*H*-benzimidazole Derivatives

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Abstract: A series of 2-(substituted phenyl)-1*H*-benzimidazole derivatives with various 5-and 6-position substituents (-H, $-CH_3$, $-CF_3$) were synthesized via microwave irradiation using a short synthetic route and $Na_2S_2O_5$ as oxidant. This simple, fast, and efficient preparation of benzimidazole derivatives has been developed using readily available and inexpensive reagents (aldehydes and 1,2-phenylenediamines) under solvent-free conditions.

Keywords: benzimidazole, microwave-assisted synthesis, solvent-free reaction

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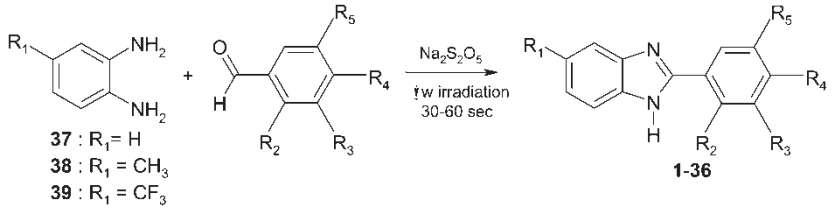
It is well-known that the benzimidazole pharmacophore is an important structural core in medicinal chemistry that shows a broad spectrum of pharmacological activities. Several compounds containing the benzimidazole scaffold have been used as antiparasitic,[1] antimicrobial,[2] antitumor,[3] and antihistaminic agents.[4]

Recently, the microwave as heating source has been used for the rapid synthesis of a variety of heterocyclic compounds both in solution phase as well as under solvent-free conditions.[5] Usually, 2-arylbenzimidazoles have been prepared by classical cyclocondensation of 1,2-phenylenediamines with the corresponding carboxylic acids under harsh dehydrating reaction conditions[6] or aldehydes under oxidative conditions.[7] The condensation of 1,2-phenylenediamines and aldehydes requires an oxidative reagent to generate the benzimidazole core. Various reagents such as nitrobenzene,[8] benzoquinone,[9] sodium metabisulfite,[2,7,10] and air[11] have been employed for this purpose. Because of the availability of commercial aldehydes, this method has been chosen as the most general procedure. However, in most of the cases, the reaction requires at least 4 to 48 h, giving yields between 30 to 75%. Using microwave irradiation as heating source, the rates of reactions involving polar components are usually very fast. Reactions that require hours or even days by conventional heating may often be accomplished in seconds by microwave heating, and that is the reason why this technology is widely applied to drug discovery.

Taking this into consideration, we planned to apply microwave methodology to our research project aimed at the discovery of new vasorelaxant and spasmolytic drugs based on the benzimidazole scaffold.[12–14] The design of these new benzimidazole derivatives explore the change in the electronic density of the pharmacophoric group by introducing nonclassical bioisosteric groups (-CH_3, -CF_3, -H) with different electronic properties in the C-5(6) position of the benzimidazole ring. In addition, substitution of the phenyl ring at positions 2–5 with -OH, -OR, -NO_2, and -NMe_2 radicals is explored.

In this study, 36 benzimidazole derivatives (**1**–**36**) have been synthesized by the reaction of 1,2-phenylenediamines **37**–**39** with aromatic substituted aldehydes (Scheme 1) and sodium metabisulfite under microwave irradiation (Table 1). Solid compounds were purified by recrystallization, and the



Scheme 1.

Table 1. Comparison of yields and reaction times of synthesized 2-(substituted phenyl)benzimidazole derivatives obtained under microwave and thermal conditions

							Reaction time		Yield (%)	
Entry	R_1	R_2	R_3	R_4	R_5	Mp (°C)	Microwave irradiation	Thermal conditions	Microwave irradiation	Thermal conditions
1	H	H	H	H	H	293.0–296.1	46 s	4 h	88	83
2	H	OH	H	H	H	242.1–243.5	36 s	4 h	95	80
3	H	OCH_3	H	H	H	171.7–173.9	48 s	4 h	89	75
4	H	OCH_2CH_3	H	H	H	149.4–150.3	50 s	4 h	89	78
5	H	NO_2	H	H	H	168.0–170	48 s	4 h	88	55
6	H	H	H	OH	H	254.1–256.6	48 s	4 h	92	75
7	H	H	H	OCH_3	H	229.9–231.4	60 s	4 h	96	82
8	H	H	H	$N(CH_3)_2$	H	294.2–296.3	60 s	4 h	88	70
9	H	H	OCH_3	OH	H	224.7–225.4	60 s	4 h	90	76
10	H	H	OCH_3	OCH_3	H	235.5–236.7	60 s	4 h	85	70
11	H	OCH_3	H	OCH_3	OCH_3	258.7 –259.7	40 s	4 h	87	72
12	H	H	OCH_3	OCH_3	OCH_3	259.9 –262.1	50 s	4 h	94	80
13	CH_3	H	H	H	H	216.9–219.7	40 s	3 h	85	72
14	CH_3	OH	H	H	H	240.2–242.1	40 s	3 h	94	78
15	CH_3	OCH_3	H	H	H	200.5–203.7	40 s	3 h	86	75
16	CH_3	OCH_2CH_3	H	H	H	179.2–181.2	50 s	3 h	88	80
17	CH_3	NO_2	H	H	H	212.1–215.0	24 s	3 h	75	58
18	CH_3	H	H	OH	H	300.1–302.6	48 s	3 h	85	73
19	CH_3	H	H	OCH_3	H	ND[a]	48 s	3 h	95	80

(*continued*)

Table 1. Continued

Entry	R_1	R_2	R_3	R_4	R_5	Mp (°C)	Reaction time		Yield (%)	
							Microwave irradiation	Thermal conditions	Microwave irradiation	Thermal conditions
20	CH_3	H	H	$N(CH_3)_2$	H	209.5–211.0	50 s	3 h	85	75
21	CH_3	H	OCH_3	OH	H	225.3–227.1	60 s	3 h	82	70
22	CH_3	H	OCH_3	OCH_3	H	202.9–204.1	60 s	3 h	80	70
23	CH_3	OCH_3	H	OCH_3	OCH_3	224.1–226.3	60 s	3 h	85	75
24	CH_3	H	OCH_3	OCH_3	OCH_3	249.0–251.2	60 s	3 h	80	72
25	CF_3	H	H	H	H	ND	50 s	4.5 h	85	80
26	CF_3	OH	H	H	H	263.6–265.4	50 s	4.5 h	80	64
27	CF_3	OCH_3	H	H	H	204.3–205.5	50 s	4.5 h	82	70
28	CF_3	OCH_2CH_3	H	H	H	121.5–122.9	50 s	4.5 h	80	78
29	CF_3	NO_2	H	H	H	155.8–157.1	30 s	4.5 h	65	60
30	CF_3	H	H	OH	H	300.2–303.3	50 s	4.5 h	80	65
31	CF_3	H	H	OCH_3	H	250.3–253.1	50 s	4.5 h	75	60
32	CF_3	H	H	$N(CH_3)_2$	H	222.1–224.4	50 s	4.5 h	78	75
33	CF_3	H	OCH_3	OH	H	214.4–216.6	60 s	4.5 h	75	56
34	CF_3	H	OCH_3	OCH_3	H	192.5–194.2	60 s	4.5 h	80	68
35	CF_3	OCH_3	H	OCH_3	OCH_3	214.8–217.0	60 s	4.5 h	83	70
36	CF_3	H	OCH_3	OCH_3	OCH_3	238.4–240.2	60 s	4.5 h	89	70

[a]ND: Not determined.

structure of the pure compounds was established by spectroscopic and spectrometric data. All prepared compounds showed blue emissions under UV irradiation in methanol solutions. The reaction between 1,2-phenylenediamines **37**–**39** and the corresponding aromatic aldehyde was carried out in 24–60 s under microwave irradiation and afforded the corresponding products **1**–**36** in good yield (Table 1). After irradiation for 10 s, the reaction mixture was taken out, mixed again, and then heated at the same power level for an additional 10 s. This step was repeated until the starting materials were consumed (TLC). All reactions were performed without solvent in only 60 s as a maximum time, confirming that the focused microwave irradiation is a very effective technique for accelerating thermal organic reactions in solvent-free conditions. Table 2 reports microanalysis data and molecular ions obtained in mass spectra from all compounds.

With extended heating times, a decrease of the yield due to formation of several by-products was observed. For comparison, Benzimidazoles **1**–**36** were also prepared by the classical thermal method (i.e., refluxing the 1,2-phenylendiamine, the aldehyde, and sodium metabisulfite in DMF for 3–4.5 h). Classical heating afforded lower yields for almost all compounds and other by-products, for which separation was difficult. The reaction proceeded smoothly under microwave irradiation within 24–60 s whereas under reflux conditions it needed 3–4.5 h. The most important result of our approach is the optimization of yields and reaction times using microwave irradiation. In conclusion, we have developed a simple, rapid, and efficient method for the preparation of 2-(substituted phenyl)-1*H*-benzimidazole compounds under solvent-free conditions using readily available and inexpensive reagents and a household microwave oven.

EXPERIMENTAL

Melting points were determined on a Büchi B-540 melting-point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on 0.2-mm precoated silica-gel 60 F_{254} plates (E. Merck). ^{1}H NMR and ^{13}C NMR spectra were measured with a Varian EM-390 (300 MHz and 75.5 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (Me_4Si, $\delta = 0$) in $CDCl_3$; J values are given in Hertz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublet; t, triplet; m, multiplet; bs, broad signal. MS were recorded on a Jeol JMS-SX102A spectrometer by electron impact (EI). Elemental analyses were performed by Elementar Vario ELIII Analyzer, and results for C,H,N were within $\pm 0.4\%$ of calculated values. All the chemicals and solvents used in this study were of analytical grade. Reactions under microwave irradiation were performed in a domestic microwave oven, Samsung MW1446WC, 1000 W.

Table 2. Microanalysis data and molecular ion in mass spectra of 2-(substituted phenyl)benzimidazole derivatives

Entry	Formula	Experimental (%)			Calculated (%)			Molecular ion (m/z)
		C	H	N	C	H	N	
1	$C_{13}H_{10}N_2$	80.27	5.22	14.51	80.39	5.19	14.42	194
2	$C_{13}H_{10}N_2O$	73.99	4.66	13.38	74.27	4.79	13.33	210
3	$C_{14}H_{12}N_2O$	74.90	5.36	12.37	74.98	5.39	12.49	224
4	$C_{15}H_{14}N_2O$	75.73	5.99	11.81	75.61	5.92	11.76	238
5	$C_{13}H_9N_3O_2$	65.01	3.82	17.66	65.27	3.79	17.56	239
6	$C_{13}H_{10}N_2O$	74.19	4.79	13.09	74.27	4.79	13.33	210
7	$C_{14}H_{12}N_2O$	74.91	5.39	12.36	74.98	5.39	12.49	224
8	$C_{15}H_{15}N_3$	75.86	6.43	17.71	75.92	6.37	17.71	237
9	$C_{14}H_{12}N_2O_2$	70.06	5.08	11.70	69.99	5.03	11.66	240
10	$C_{15}H_{14}N_2O_2$	70.78	5.55	11.10	70.85	5.55	11.02	254
11	$C_{16}H_{16}N_2O_3$	67.50	5.62	9.91	67.59	5.67	9.85	284
12	$C_{16}H_{16}N_2O_3$	67.43	5.60	9.77	67.59	5.67	9.85	284
13	$C_{14}H_{12}N_2$	80.42	6.15	13.43	80.74	5.81	13.45	208
14	$C_{14}H_{12}N_2O$	ND[a]	ND	ND	74.98	5.39	12.49	224
15	$C_{15}H_{14}N_2O$	74.31	5.92	11.63	75.61	5.92	11.75	238
16	$C_{16}H_{16}N_2O$	ND	ND	ND	76.16	6.39	11.10	252

17	$C_{14}H_{11}N_3O_2$	66.03	4.36	16.39	66.39	4.37	16.59	253
18	$C_{14}H_{12}N_2O$	ND	ND	ND	74.98	5.39	12.49	224
19	$C_{15}H_{14}N_2O$	ND	ND	ND	75.61	5.92	11.76	238
20	$C_{16}H_7N_3$	76.58	6.81	16.61	76.46	6.82	16.72	251
21	$C_{15}H_{14}N_2O_2$	70.72	5.52	11.23	70.85	5.54	11.01	254
22	$C_{16}H_{16}N_2O_2$	71.02	6.01	10.39	71.62	6.01	10.44	268
23	$C_{17}H_{18}N_2O_3$	67.53	5.99	9.38	68.34	6.08	9.39	298
24	$C_{17}H_{18}N_2O_3$	68.29	6.09	9.36	68.34	6.08	9.39	298
25	$C_{14}H_9N_2F_3$	63.87	3.35	21.66	64.12	3.46	21.73	262
26	$C_{14}H_9N_2OF_3$	60.37	3.22	20.39	60.44	3.26	20.48	278
27	$C_{15}H_{11}N_2OF_3$	61.12	3.70	19.43	61.64	3.79	19.50	292
28	$C_{16}H_{13}N_2OF_3$	62.60	4.21	18.52	62.74	4.28	18.61	306
29	$C_{14}H_8N_3O_2F_3$	54.71	2.59	18.62	54.73	2.62	18.55	307
30	$C_{14}H_9N_2OF_3$	60.62	3.29	20.53	60.44	3.26	20.48	278
31	$C_{15}H_{11}N_2OF_3$	61.39	3.68	19.42	61.64	3.79	19.50	292
32	$C_{16}H_{14}N_3F_3$	63.01	4.65	18.80	62.95	4.62	18.67	305
33	$C_{15}H_{11}N_2O_2F_3$	58.36	3.49	18.40	58.45	3.60	18.49	308
34	$C_{16}H_{13}N_2O_2F_3$	59.59	4.05	17.66	59.63	4.07	17.68	322
35	$C_{17}H_{15}N_2O_3F_3$	57.79	4.19	5.99	57.96	4.29	6.18	352
36	$C_{17}H_{15}N_2O_3F_3$	57.89	4.20	6.21	57.96	4.29	6.18	352

[a]ND: not determined.

General Method of Synthesis of 2-(Substituted Phenyl)-1*H*-benzimidazoles 1–36

Microwave Irradiation Conditions

An appropriate 1,2-phenylenediamine (0.0313 mol), 1.01 equivalents of appropriate aldehyde, and 1.01 equivalents of sodium metabisulfite were mixed and introduced in an open Erlenmeyer flask. The mixture was irradiated in a household microwave oven for 24–60 s. After irradiation, the mixture was poured onto cold water. The precipitate was collected by filtration, washed with water, dried, and recrystallized.

Thermal Conditions

A mixture of an appropriate 1,2-phenylenediamine (0.0313 mol), 1.01 equivalents of appropriate aldehyde, and 1.01 equivalents of sodium metabisulfite in 10 mL of DMF was heated to reflux for 3–4.5 h. After cooling, water (20 mL) was added, and the mixture was extracted with AcOEt (3 × 15 mL). The organic layer was dried over magnesium sulfate and removed under vacuum. Purification was done by chromatography on silica gel eluting with chloroform and recrystallization from adequate solvent. The spectral data of some representative benzimidazoles are given here.

Data

2-(1*H*-Benzimidazol-2-yl)phenol (**2**): White solid, mp 243.5–245.3°C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.73 (dd, 1H, H-3′, $J = 7.91$, $J = 1.3$ Hz), 7.11 (td, 1H, H-5′, $J = 7.7$, $J = 7.7$, $J = 1.3$ Hz), 7.18 (td, 1H, H-4′, $J = 7.7$, $J = 7.9$, $J = 1.7$ Hz), 7.21–7.26 (m, 2H, H-5, H-6, $J = 8.5$, $J = 1.3$ Hz), 7.59–7.63 (m, 2H, H-4, H-7, $J = 8.5$, $J = 6.8$, $J = 1.4$ Hz), 7.76 (dd, 1H, H-6′, $J = 7.7$, $J = 1.7$ Hz), 11.76 (bs, 2H, N-H, O-H) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 113.93 (C-1), 116.05 (C-4, C-7), 117.56 (C-3′), 120.65 (C-5′), 123.48 (C-5, C-6), 128.77 (C-6′), 132.72 (C-4′), 141.11 (C-3a, C-7a), 156.39 (C-2), 157.60 (C-2′) ppm; EIMS: m/z (% rel. int.) 210 (M^+, 100), 192 (2), 181 (25); HRMS: calcd. for $C_{13}H_{10}N_2O$: 210.0793, found: 210.0795.

2-(2-Ethoxyphenyl)-1*H*-benzimidazole (**4**): White solid, mp 149.4–150.3°C (ethanol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (t, 3H, CH_3), 4.37 (q, 2H, CH_2-O-), 7.08–7.14 (m, 2H, H-3′, H-5′, $J = 8.2$, $J = 1.1$ Hz), 7.18–7.22 (dd, 1H, H-4′, $J = 7.1$, $J = 2.74$ Hz), 7.41 (dd, 1H, H-2′, $J = 7.1$, $J = 1.6$ Hz), 7.59–7.64 (m, 2H, H-5, H-6, $J = 6.6$, $J = 3.3$, $J = 1.4$ Hz), 8.52–8.55 (dd, 2H, H-4, H-7, $J = 7.96$, $J = 1.9$ Hz), 11.7 (bs, 1H, N-H) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.42 (CH_3), 64.64 (CH_2-O-),

112.97 (C-5′), 121.11 (C-4, C-7), 122.05 (C-1′), 123.06 (C-3′, C-5′), 130.38 (C-5, C-6), 131.19 (C-2′), 131.21 (C-4′), 150.12 (C-3a, C-7a), 156.39 (C-2), 167.76 (C-6′) ppm; EIMS: m/z (% rel. int.) 238 (M^+, 48), 223 (100), 209 (15); 194 (85). HRMS: calcd. for $C_{15}H_{14}N_2O$: 238.1106, found: 238.1119.

2-(4-Methoxyphenyl)-1*H*-benzimidazole (**7**): White solid, mp 228.6–230.5°C (ethanol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H, CH_3-O-), 7.05–7.09 (m, 2H, H-3′, H-5′, $J = 8.5$, $J = 2.2$ Hz), 7.21–7.25 (m, 2H, H-5, H-6, $J = 8.5$, $J = 7.0$, $J = 1.4$ Hz), 7.57–7.61 (m, 2H, H-4, H-7, $J = 8.5$, $J = 1.4$ Hz), 8.03–8.06 (m, 2H, H-2′, H-6′, $J = 8.5$, $J = 1.4$ Hz), 10.88 (bs, 1H, N-H) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 55.43 (CH_3-O-), 114.59 (C-3′, C-5′), 116.08 (C-4, C-7), 123.48 (C-5, C-6), 125.28 (C-2′, C-6′), 125.22 (C-1′), 139.85 (C-3a, C-7a), 152.12 (C-2), 161.06 (C-4′) ppm; EIMS: m/z (% rel. int.) 224 (M^+, 100), 209 (35), 181 (25); HRMS: calcd. for $C_{14}H_{12}N_2O$: 224.0949, found: 224.0952.

2-(3-Hydroxy-4-methoxyphenyl)-1*H*-benzimidazole (**9**): Pale yellow solid, mp 224.7–225.4°C (methanol). ^{1}H NMR (300 MHz, DMSO-d6) δ 3.97 (s, 3H, -OCH_3), 6.91(d, 1H, H-5′, $J = 8.4$ Hz), 7.11–7.16 (m, 2H, H-5, H-6, $J = 9.6$, $J = 3$ Hz), 7.53 (sa, 1H, H-6′, $J = 0.9$ Hz), 7.61 (dd, 2H, H-4, H-7, $J = 8.1$, $J = 1.8$ Hz), 7.74 (d, 1H, H-2, $J = 1.5$ Hz), 9.57 (bs, 2H, N-H, O-H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ55.67 (CH_3), 110.24 (C-2′), 116.07 (C-4, C-7), 117.28 (C-5′), 123.08 (C-1′), 123.48 (C-5, C-6), 124.72 (C-6′), 139.73 (C-3a, C-7a), 146.81 (C-4′), 150.22 (C-3′), 151.67 (C-2) ppm.

2-(5-Methyl-1*H*-benzimidazol-2-yl)phenol (**14**): White solid, mp 240–242°C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.43 (s, 3H, CH_3), 6.62 (dd, 1H, H-3′, $J = 7.8$, $J = 1.2$ Hz), 7.08–7.11 (m, 1H, H-6, $J = 8.6$, $J = 1.8$ Hz), 7.09–7.13 (m, 1H, H-5′, $J = 7.7$, $J = 1.3$ Hz), 7.18 (td, 1H, H-4′, $J = 7.8$, $J = 7.7$, $J = 1.8$ Hz), 7.24–7.25 (m, 1H, H-4, $J = 1.8$ Hz), 7.26–7.28 (m, 1H, H-7, $J = 8.6$ Hz), 7.78 (dd, 1H, H-6′, $J = 7.8$ Hz), 7.78 (dd, 1H, H-6′, $J = 7.8$, $J = 1.8$ Hz), 10.95 (bs, 2H, N-H, O-H) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.86 (CH_3), 112.34 (C-7), 113.94 (C-1′), 117.56 (C-3′), 119.58 (C-4), 119.56 (C-4), 120.65 (C-5′), 124.42 (C-6), 128.77 (C-6′), 132.86 (C-4′), 136.68 (C-3a), 137.43 (C-7a), 140.75 (C-5), 156.39 (C-2), 159.60 (C-2′) ppm; MS: m/z (% rel. int.) 224 (M^+, 100), 209 (2), 195 (25); HRMS: calcd. for $C_{14}H_{12}N_2O$: 224.0949, found: 224.0953.

2-(4-Methoxyphenyl)-5-methyl-1*H*-benzimidazole (**19**): Workup by extraction with EtOAc and concentration under vacuum left an oil, which was purified by column chromatography (4 × 60 cm, 60 g of silica gel, petroleum ether), colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.43 (s, 3H, CH_3-C-5), 3.86 (s, 3H, CH_3-O-), 7.06–7.09 (m, 2H, H-3′, H-5′, $J = 8.4$, $J = 2.4$ Hz), 7.08–7.11 (m, 1H, H-6, $J = 8.6$, $J = 1.7$ Hz), 7.22–7.23 (m, 1H, H-4, $J = 1.7$ Hz), 7.22–7.26 (m, 1H, H-7, $J = 8.6$,

$J = 0.9$ Hz), 8.03–8.06 (m, 2H, H-2′, H-6′, $J = 8.5$, $J = 1.8$ Hz), 11.01 (bs, 1H, N-H) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 20.68 (CH_3-C-5), 55.47 (CH_3-O-), 111.36 (C-7), 114.59 (C-3′, C-5′), 119.60 (C-4), 124.42 (C-6), 125.31 (C-2′, C-6′), 125.20 (C-1′), 136.17 (C-3a), 136.68 (C-5), 139.85 (C-7a), 152.21 (C-2), 161.12 (C-4′) ppm; MS: m/z (% rel. int.) 238 (M^+, 100), 223 (30), 195 (20); HRMS: calcd. for $C_{15}H_{14}N_2O$: 238.1106; found: 238.1110.

2-[(5-Trifluoromethyl)-1*H*-benzimidazol-2-yl]phenol (**26**): White solid, mp 263.6–265.4°C (ethanol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42 (dd, 1H, H-6′, $J = 8.8$, $J = 1.6$ Hz), 7.02 (m, 2H, H-4′, H-5′, $J = 7.69$, $J = 1.09$ Hz), 7.59 (d, 1H, H-3′, $J = 7.7$, $J = 1.1$ Hz), 7.81 (d, 1H, H-7, $J = 8.2$ Hz), 8.0 (dd, 1H, H-6, $J = 7.7$, $J = 1.6$ Hz), 8.0 (dd, 1H, H-4, $J = 1.64$ Hz), ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 113.91 (C-7), 114.13 (C-4), 115.94 (C-1′), 119.66 (C-6), 120.65 (C-5′), 123.85 (q, CF_3, $J = 285.2$ Hz), 125.97 (q, C-5, $J = 285.2$ Hz), 128.77 (C-6′), 132.77 (C-4′), 139.18 (C-3a), 144.30 (C-7a), 156.39 (C-2), 157.66 (C-2′) ppm; MS: m/z (% rel. int.) 278 (M^+, 100), 209 (2), 249 (33); HRMS: calcd. for $C_{14}H_9F_3N_2O$: 278.0667, found: 278.0656.

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REFERENCES

1. Navarrete-Vázquez, G.; Yepez-Mulia, L.; Hernández-Campos, A.; Tapia, A.; Hernández-Luis, F.; Cedillo, R.; González, J.; Martínez-Fernández, M.; Martínez-Grueiro, M.; Castillo, R. Synthesis and antiparasitic activity of albendazole and mebendazole analogues. *Bioorg. Med. Chem.* **2003**, *11*, 4615–4622.
2. Özden, S.; Atabey, D.; Yıldız, S.; Göker, H. Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1H-benzimidazole-5-carboxylates derivatives carrying amide or amidine groups. *Bioorg. Med. Chem.* **2005**, *13*, 1587–1597.
3. Andrzejewska, M.; Yépez-Mulia, L.; Cedillo-Rivera, R.; Tapia, A.; Vilpo, L.; Vilpo, J.; Kazimierczuk, Z. Synthesis, antiprotozoal and anticancer activity of substituted 2-trifluoromethyl- and 2-pentafluoroethylbenzimidazoles. *Eur. J. Med. Chem.* **2002**, *37*, 973–978.
4. Terzioglu, N.; van Rijn, R.; Bakker, R. A.; De Esch, I. J. P.; Leurs, R. Synthesis and structure–activity relationships of indole and benzimidazole piperazines as

histamine H_4 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5251–5256.
5. Mavandadi, F.; Lidström, P. Microwave-assisted chemistry in drug discovery. *Curr. Top. Med. Chem.* **2004**, *4*, 773–792.
6. Navarrete-Vázquez, G.; Cedillo, R.; Hernández-Campos, A.; Yepez-Mulia, L.; Hernández-Luís, F.; Valdez, J.; Morales, R.; Cortes, R.; Hernandez, M.; Castillo, R. Synthesis and antiparasitic activity of 2-(trifluoromethyl)-benzimidazole derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 187–190.
7. Göker, H.; Ku, C.; Boykin, D. W.; Yildiz, S.; Altanar, N. Synthesis of some new 2-substituted-phenyl-1H-benzimidazole-5-carbonitriles and their potent activity against *Candida* species. *Bioorg. Med. Chem.* **2002**, *10*, 2589–2596.
8. Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. Benzimidazoles: Oxydation hétérocyclisante par le nitrobenzène ou le diméthylsulfoxyde sur silice et sous irradiation micro-ondes ou ultra-violet. *Tetrahedron Lett.* **1998**, *39*, 4481–4384.
9. Verner, E.; Katz, B. A.; Spencer, J. R.; Allen, D.; Hataye, J.; Hruzewicz, W.; Hui, H. C.; Kolesnikov, A.; Li, Y.; Luong, C.; Martelli, A.; Radika, K.; Rai, R.; She, M.; Shrader, W.; Sprengeler, P. A.; Trapp, S.; Wang, J.; Young, W. B.; Mackman, R. L. Development of serine protease inhibitors displaying a multicentered short (<2.3 A) hydrogen bond binding mode: Inhibitors of urokinase-type plasminogen activator and factor Xa. *J. Med. Chem.* **2001**, *44*, 2753–2771.
10. Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. Synthesis and DNA interactions of benzimidazole dications which have activity against opportunistic infections. *J. Med. Chem.* **1996**, *39*, 1452–1462.
11. Lin, S.; Yang, L. A simple and efficient procedure for the synthesis of benzimidazoles using air as the oxidant. *Tetrahedron Lett.* **2005**, *46*, 4315–4319.
12. Estrada-Soto, S.; Villalobos-Molina, R.; Aguirre-Crespo, F.; Moreno-Díaz, H.; Torres-Piedra, M.; Navarrete-Vázquez, G. Relaxant activity of 2-(substituted phenyl)-1*H*-benzimidazoles on isolated rat aortic rings: Design and synthesis of 5-nitro derivatives. *Life Sci.* **2006**, *79*, 430–435.
13. Navarrete-Vázquez, G.; Moreno-Díaz, H.; Aguirre-Crespo, F.; León-Rivera, I.; Villalobos-Molina, R.; Muñoz-Muñiz, O.; Estrada-Soto, S. Design, microwave-assisted synthesis, and spasmolytic activity of 2-(alkyloxyaryl)-1*H*-benzimidazole derivatives as constrained stilbene bioisosteres. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4169–4173.
14. Moreno-Díaz, H.; Navarrete-Vázquez, G.; Estrada-Soto, S.; Tlahuext, H. 2-(4-Methoxyphenyl)-1*H*-benzimidazole. *Acta Cryst.* **2006**, *E62*, o2601–o2602.