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Note

Microwave assisted synthesis and antimicrobial activity of some 2-(benzofuran-2-yl) -7-(substituted)imidazo[2,1-*b*]benzothiazoles

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2-(Benzofuran-2-yl)-7-(substituted)imidazo[2,1-*b*]benzothiazoles have been prepared by condensation of 2-(2-bromoacetyl)-benzofurans and various 2-amino-7-(substituted) benzothiazoles under normal thermal condition as well as microwave irradiations. The latter condition for the reaction has been found to be much more efficient in terms of time and yield. The structures of the compounds have been established on the basis of their elemental analysis, IR and ^{1}H NMR spectral data. The antibacterial and antifungal properties of these compounds are described.

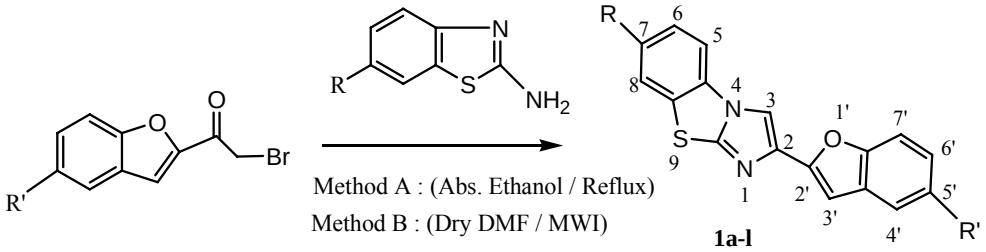
Keywords: 2-Aminobenzothiazoles, 2-acetylbenzofurans, 2-(2-bromoacetyl)benzofurans, imidazo[2,1-*b*]benzothiazoles, microwave irradiation

2-Aminobenzothiazoles and its derivatives have found an important place in bioorganic and medicinal chemistry with applications in development of new drugs for the treatment of diabetes[1], epilepsy[2], inflammation[3], analgesia[4], tumors[5], tuberculosis[6] and viral infections[7]. Benzofuran derivatives, a class of naturally occurring compounds[8] and their synthetic analogues exhibit physiological, pharmacological and toxic properties and find application as sedatives[9], hypotonic[9], agrochemicals[10], pharmaceuticals[11-15], cosmetics[16] and as the building blocks of optical brighteners[17]. Further imidazo[2,1-*b*] benzothiazoles also display pharmacological activities[18-20]. Keeping this in view, synthesis of benzofuran substituted imidazo[2,1-*b*]benzothiazoles was taken up and this forms the subject matter of present work. The starting compounds 2-amino-7-(substituted)benzothiazoles were synthesized according to the reported procedure[21] by addition of bromine to a mixture of potassium thiocyanate and substituted aniline at 5°C. 2-(2-Bromoacetyl)benzofurans were obtained by bromination of 2-acetylbenzofurans[22]. 2-Aminobenzothiazole was condensed with 2-(2-bromoacetyl)benzofuran in absolute ethanol under reflux. The reaction was found to be complete in 5 hr (TLC). The compound obtained (61%) after work-up was identified to be 2-(benzofuran-2-yl) imidazo[2,1-*b*]-benzothiadiazole **1a** based on its IR, ^{1}H NMR and elemental analysis. In IR the compound exhibited a band at 1660 cm^{-1} which was attributed to >C=N– stretching, 1552 cm^{-1} due to >C=C< stretching, 1500 cm^{-1} and 1161 cm^{-1} corresponding to >C–N= stretching. In the ^{1}H NMR spectra the compound exhibited a singlet at δ 7.10 due to the $C_{3'}$-H proton, a multiplet for eight protons at δ 7.21-7.71 due to aromatic protons and a singlet at δ 8.09 due to the C_3-H of the imidazole ring confirming the cyclisation. As a large number of organic reactions are known to get improved in terms of time and yield when carried out under microwave conditions[23], the above reaction was repeated using dry DMF as solvent under microwave irradiation, when the reaction was found to be complete in 3.0 min (12 × 15 sec) and product was obtained in 68% yield. The compound was found to be identical to the compound prepared above under thermal conditions (Co-IR and Co-TLC). Using the above conditions, various 2-(benzofuran-2-yl) -7-(substituted)imidazo[2,1-*b*]benzothiazoles were prepared **1a-l** (**Scheme I**). The results of both the methods have been compared in **Table I**. It can be stated that the desired compounds were obtained in much shorter time with higher yield when the reaction was carried out using microwave irradiation. Molecular formulae and elemental analyses of the synthesized compounds are given in **Table II**.

Biological activities

The antibacterial activities of compounds **1a-l** were determined *in vitro* with paper disc method[24] against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* at concentration of 1000 ppm, 500 ppm and 100 ppm in the nutrient agar media.

The test compounds were dissolved in N,N-dimethylformamide (DMF) to obtain solutions of 1000 ppm, 500 ppm and 100 ppm concentration. The inhibition zones of microbial growth produced by different compounds were measured in millimeters at the end of an incubation period of 24 hr at 37°C.



Scheme I

Table I — Comparison of reaction time and yield of compounds **1a-l**

Compd	R	R′	m.p. °C	Method A %Yield / Time (hr)	Method B % Yield / Time (min)
1a	H	H	175-76	61/5.0	68/3.0
1b	Cl	H	209-10	59/7.0	65/2.5
1c	CH_3	H	224-25	59/6.0	65/3.0
1d	OCH_3	H	234-35	59/6.0	66/2.5
1e	H	Cl	210-11	58/7.0	64/3.0
1f	Cl	Cl	249-50	56/7.0	61/3.0
1g	CH_3	Cl	234-35	61/6.0	66/2.5
1h	OCH_3	Cl	200-01	61/5.0	67/3.0
1i	H	CH_3	215-16	60/6.0	66/2.5
1j	Cl	CH_3	243-45	60/6.0	66/2.5
1k	CH_3	CH_3	240-41	59/6.0	65/3.0
1l	OCH_3	CH_3	200-01	61/5.0	67/3.0

DMF alone showed no inhibition zone. Ciprofloxacin was employed as the reference standard to evaluate the potency of the tested compounds. The result are illustrated in **Table III**. The compounds **1a-h** were found to possess mild to moderate activity. The same set of imidazo[2,1-*b*]benzothiazole derivatives were also screened for their antifungal activity against *Candida albicans* using paper-disc method[24]. The test compounds were dissolved in DMF to get solutions of 1000 ppm, 500 ppm and 100 ppm concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 24 hr at 37°C. Fluconazole was used as a reference standard and the result are shown in **Table III**. The compounds **1e-h** were found to possess strong activity while other compounds were found to possess moderate antifungal activity.

Experimental Section

Melting points were determined in open capillary tubes using liquid paraffin bath and are uncorrected. IR spectra (KBr) were recorded in Perkin-Elmer Spectrum BX series FT-IR spectrophotometer, ^{1}H NMR on Bruker Avance II 400 MHz Spectrometer using TMS as an internal standard and elemental analysis on Perkin-Elmer 2400 CHN elemental analyser.

Synthesis of 2-(benzofuran-2-yl)imidazo[2,1-*b*]benzothiazole, 1a

Method A (Thermal method)

An equimolar mixture of 2-aminobenzothiazole (3.0 mmole) and 2-(2-bromoacetyl)benzofuran (3.0 mmole) in anhydrous ethanol (25 mL) was heated under reflux for 5 hr. The completion of reaction was checked on TLC. The reaction mixture was cooled and the solid that separated out was filtered under vacuum, washed with cold ethanol and the solid on purification by recrystallisation from methanol gave 2-(benzofuran-2-yl)imidazo[2,1-*b*]benzothiazole **1a**.

Method B (MWI Method)

An equimolar mixture of 2-aminobenzothiazole (3.0 mmole) and 2-(2-bromoacetyl)benzofuran (3.0

mmole) in dimethylformamide (5 mL) in a loosely stoppered 20 mL round bottom flask was irradiated in a microwave oven at 400 W for 3.0 min (12 × 15 sec). After completion of the reaction (TLC), the reaction mixture was diluted with ice cold water (20 mL), the solid that separated out was filtered, washed with water and purified by recrystallization from methanol to give 2-(benzofuran-2-yl) imidazo[2,1-*b*]benzothiazole.

1a: IR (KBr): 1660 (C=N), 1552 (C=C), 1500, 1161 cm^{-1} (C-N); ^{1}H NMR ($CDCl_3$): δ 7.10(s, 1H, $C_{3'}$-H), 7.21-7.71(m, 8H, Ar-H), 8.09(s, 1H, C_3-H).

1b: IR (KBr): 1670 (C=N), 1595 (C=C), 1490, 1138 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.46(s, 3H, CH_3 at C_7), 7.05(s, 1H, $C_{3'}$-H), 7.23-8.10(m, 7H, Ar-H), 8.12(s, 1H, C_3-H).

1c: IR (KBr): 1670 (C=N), 1595 (C=C), 1490, 1138 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.46(s, 3H, CH_3 at C_7), 7.05(s, 1H, $C_{3'}$-H), 7.23-8.10(m, 7H, Ar-H), 8.12(s, 1H, C_3-H).

1d: IR (KBr): 1670 (C=N), 1549 (C=C), 1439, 1156 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 3.96(s, 3H, OCH_3 at C_7), 7.10(s, 1H, $C_{3'}$-H), 7.20-7.89(m, 7H, Ar-H), 8.37(s, 1H, C_3-H).

1e: IR (KBr): 1635 (C=N), 1576 (C=C), 1490, 1154 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 7.05(s, 1H, $C_{3'}$-H), 7.22-7.86(m, 7H, Ar-H), 8.40(s, 1H, C_3-H).

1f: IR (KBr): 1650 (C=N), 1582 (C=C), 1452, 1156 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 7.13(s, 1H, $C_{3'}$-H), 7.28-7.86(m, 6H, Ar-H), 8.34(s, 1H, C_3-H).

1g: IR (KBr): 1636 (C=N), 1580 (C=C), 1438, 1156 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.49(s, 3H, CH_3 at C_7), 7.04(s, 1H, $C_{3'}$-H), 7.20-7.68(m, 6H, Ar-H), 8.32(s, 1H, C_3-H).

1h: IR (KBr): 1630 (C=N), 1585 (C=C), 1490,

Table II — Elemental analyses of compounds **1a-l**

Compd	Mol. formula	Found (Calcd) (%)		
		C	H	N
1a	$C_{17}H_{10}N_2OS$	70.60 (70.34	3.14 3.44	9.54 9.65)
1b	$C_{17}H_9N_2OSCl$	62.59 (62.86	2.69 2.77	8.83 8.62)
1c	$C_{18}H_{12}N_2OS$	71.27 (71.05	3.79 3.94	9.10 9.21)
1d	$C_{18}H_{12}N_2O_2S$	67.35 (67.50	3.69 3.75	8.69 8.75)
1e	$C_{17}H_9N_2OSCl$	62.70 (62.86	2.40 2.77	8.81 8.62)
1f	$C_{17}H_8N_2OSCl_2$	56.64 (56.82	2.10 2.22	7.54 7.79)
1g	$C_{18}H_{11}N_2OSCl$	63.59 (63.81	3.10 3.24	8.07 8.27)
1h	$C_{18}H_{11}N_2O_2SCl$	60.74 (60.93	3.25 3.10	7.69 7.89)
1i	$C_{18}H_{12}N_2OS$	71.25 (71.05	3.80 3.94	9.05 9.21)
1j	$C_{18}H_{11}N_2OSCl$	63.51 (63.81	3.16 3.24	8.54 8.27)
1k	$C_{19}H_{14}N_2OS$	71.56 (71.69	4.21 4.40	8.93 8.80)
1l	$C_{19}H_{14}N_2O_2S$	68.09 (68.26	4.12 4.19	8.15 8.38)

Table III — Antimicrobial activity data of compounds **1a-l** at different concentration (Diameter of zone of inhibition in mm)

Compd	*E. coli*			*S. aureus*			*P. aeruginosa*			*C. albicans*		
	1000 ppm	500 ppm	100 ppm	1000 ppm	500 ppm	100 ppm	1000 ppm	500 ppm	100 ppm	1000 ppm	500 ppm	100 ppm
1a	8	7	-	13	11	-	8	-	-	13	11	8
1b	7	-	-	13	12	-	8	-	-	12	9	8
1c	8	-	-	14	10	-	9	7	-	11	9	8
1d	8	-	-	13	11	-	8	-	-	11	10	9
1e	9	7	-	18	15	11	10	8	-	15	12	10
1f	9	7	-	18	15	11	9	-	-	16	13	10
1g	8	-	-	17	14	10	10	8	-	17	13	9
1h	8	-	-	17	15	12	10	8	-	17	12	9
1i	-	-	-	-	-	-	-	-	-	12	10	8
1j	-	-	-	-	-	-	-	-	-	12	10	8
1k	-	-	-	-	-	-	-	-	-	10	8	-
1l	-	-	-	-	-	-	-	-	-	11	10	-
Std(cip)	21	20	18	29	20	17	29	28	20	-	-	-
Std(flu)	-	-	-	-	-	-	-	-	-	19	18	10

Disc size: 6 mm Standard: Ciprofloxacin (cip) and Fluconazole (flu) (-) = non-active (inhibition zone 6 mm) control: DMF

1140 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 3.89(s, 3H, OCH_3 at C_7), 7.02(s, 1H, $C_{3'}$-H), 7.42-7.79(m, 6H, Ar-H), 8.03(s, 1H, C_3-H).

1i: IR (KBr): 1650 (C=N), 1580 (C=C), 1492, 1134 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.16(s, 3H, CH_3 at $C_{5'}$), 7.02(s, 1H, $C_{3'}$-H), 7.09-7.76(m, 7H, Ar-H), 8.20(s, 1H, C_3-H).

1j: IR (KBr): 1624 (C=N), 1580 (C=C), 1450, 1158 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.15(s, 3H, CH_3 at $C_{5'}$), 7.12(s, 1H, $C_{3'}$-H), 7.26-7.82(m, 6H, Ar-H), 8.32(s, 1H, C_3-H).

1k: IR (KBr): 1627 (C=N), 1588 (C=C), 1448, 1140 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.44(s, 3H, CH_3 at $C_{5'}$), 2.49(s, 3H, CH_3 at C_7), 7.05(s, 1H, $C_{3'}$-H), 7.07-7.75(m, 6H, Ar-H), 8.32(s, 1H, C_3-H).

1l: IR (KBr): 1623 (C=N), 1580 (C=C), 1498, 1134 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.43(s, 3H, CH_3 at $C_{5'}$), 3.86(s, 3H, OCH_3 at C_7), 7.00(s, 1H, $C_{3'}$-H), 7.10-7.74(m, 6H, Ar-H), 8.25(s, 1H, C_3-H).

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References

1 Suter H & Zutter H, *Helv Chim Acta*, 50, **1967**, 1084.
2 Hays S J, Rice M J, Ortwine D F, Johnson G, Schwartz R D, Boyd D K, Copeland L F, Vartanian M G & Boxer P A, *J Pharm Sci*, 83, **1994**, 1425.
3 Sawhney S N, Arora S K, Singh J V, Bansal O P & Singh S P, *Indian J Chem*, 16B, **1978**, 605.
4 Foscolos G, Tsatsas G, Champagnac A & Pommier M, *Ann Pharm Fr*, 35, **1977,** 295.
5 Caleta I, Grdisa M, Mrvos S D, Cetina M, Tralic K V K, Pavelic G & Zamola K, *Il Farmaco*, 59, **2004**, 297.
6 Shirke V G, Bobade V D, Bhamaria R P, Khadse B G & Sengupta S R, *Indian Drugs*, 27, **1990**, 350.
7 Paget C J, Kisner K, Stone R L & Delong D C, *J Med Chem,* 12, **1969**, 1016.
8 Gommers F J, *Photochemistry*, 10, **1971**, 1945.
9 Nasef M, El-Naem S J A & El-Shbrawy O A, *Egypt J Pharm Sci*, 33, **1992**, 463.
10 Keay B A & Dibble P W, in *Comprehensive Heterocyclic Chemistry II* – A review of the literature 1982-1995 (Pergamon, New York), 2, **1996**, 413.
11 Powers L J, *J Med Chem*, 19, **1976**, 57.
12 Nagahara T, Yokoyama Y, Inamura K, Katakura S, Komoriya S, Yamaguchi H, Hara T & Iwamoto M, *J Med Chem*, 37, **1994**, 1200.
13 Kumar D B A, Prakash G K, Nandeshwarappa B P, Kiran B M, Sherigara B S & Mahadevan K M, *Indian J Pharm Sci*, 68, **2006**, 809.
14 Kumar D B A, Prakash G K, Nandeshwarappa B P, Sherigara B S & Mahadevan K M, *Indian J Chem*, 45B, **2006**, 1699.
15 Basawaraj R, Naubade K & Sangapura S S, *Indian J Heterocycl Chem*, 17, **2008**, 217.
16 Leung A Y & Foster S, *Encyclopedia of Common Natural Ingredients used in Food, Drugs and Cosmetics* (Wiley, New York), **1996**.
17 Schmidt E, *Ullmann's Encyclopedia 6th edn, Optical Brighteners (Electronic Release)*, **1999**.
18 Amit B N, Kamath R V & Khadse G B, *Indian J Heterocycl Chem*, 9, **2000**, 309.
19 Tanabe Y, Kawai A, Yoshida Y, Ogura M & Okumura H, *Heterocycles*, 45**, 1997,** 1579.
20 Trapani G, Franco M, Lofta A, Reho A & Liso G, *Eur J Pharm Sci*, 14, **2001,** 209.
21 Gurupadaiah B M, Jayachandran E, Kumar B S, Nagappa A N & Nargund L V G, *Indian J Heterocycl Chem*, 7, **1998**, 213.
22 Elliot E D, *J Amer Chem Soc*, 73, **1951**, 754.
23 El Ashry E S H, Ramdan E, Kassem A A & Hagar M, *Adv Heterocycl Chem*, 88, **2005**, 1.
24 Czerkinsby G, Diding N & Ouchterleng P, *Scand J Clin Lab Invest,* 7, **1955**, 259.