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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF NEW BENZIMIDAZOLE DERIVATIVES

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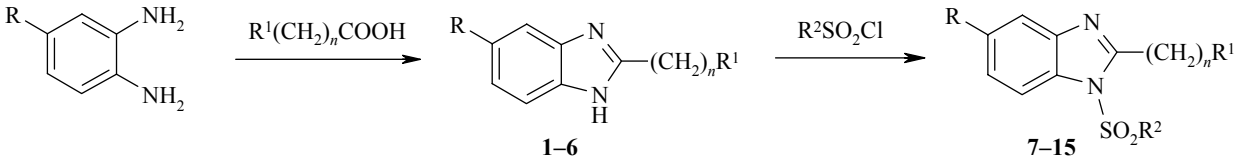
The reactions of o-phenylenediamine and 3,4-diaminotoluene with such acids as 3-cyclohexylpropionic, 4-phenylbutyric, 4-cyclohexylbutyric, 3,3-diphenylpropionic, and 3,4-dimethoxyphenylacetic resulted in the formation of the corresponding 2-substituted benzimidazoles. These compounds were transformed into methane- and benzenesulfonamide derivatives. The benzimidazole derivatives obtained were tested in vitro for their tuberculostatic activity. Compounds with good activity (MIC 6.2-25 μg/ml) have been found.

Keywords: benzimidazoles, methane- and benzenesulfonamides, tuberculostatics.

Among benzimidazole derivatives, the 2-substituted ones that have varied pharmacological activity (e.g. antitumor, antiverminous, antiviral, hypotensive, spasmolytic, immunosuppressive, neuroleptic, analgesic, antihistaminic) are particularly abundant [1]. Recently the antibacterial (including tuberculostatic) activity of benzimidazole derivatives was reported too [2-6].

In the present study the syntheses of benzimidazole derivatives with cyclohexylalkyl and aralkyl substituents in position 2 were accomplished. *o*-Phenylenediamine and 3,4-diaminotoluene as well as 3-cyclohexylpropionic, 4-phenylbutyric, 4-cyclohexylbutyric, 3,3-diphenylpropionic, and 3,4-dimethoxyphenylacetic acids were the substrates used.

The Phillips method, *i.e.*, the heating of substrates in NH_4Cl, was tested first, but much better yields of benzimidazoles **1-6** were obtained by fusion of the starting materials at 160-180°C, the process of which was elaborated earlier by our team [7, 8]. In the next step compounds **1-6** reacted with methane- and benzenesulfonyl chloride in anhydrous dioxane in the presence of triethylamine, giving the corresponding sulfonamide derivatives **7-15** (Tables 1 and 2).



1–6 **7–15**

1-5, 7-13 R = H, **6**, **14**, **15** R = Me, **1**, **3**, **6**, **7**, **10**, **11**, **14**, **15** R^1 = *cyclo*-C_6H_{11}, **2**, **8**, **9** R^1 = Ph, **4**, **12** R^1 = $CHPh_2$, **5**, **13** R^1 = 3,4-$(MeO)_2C_6H_3$, **7**, **8**, **10**, **14** R^2 = Me, **9**, **11-13**, **15** R^2 = Ph; **1**, **7** *n* = 2, **2**, **3**, **6**, **8-11**, **14**, **15** *n* = 3, **4**, **5**, **12**, **13** *n* = 1

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TABLE 1. Characteristics of the Synthesized Compounds **1-15**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C, solvent	Yield, %
		C	H	N		
1	$C_{15}H_{20}N_2$	78.81 / 78.90	8.79 / 8.83	12.11 / 12.27	193-194 MeOH	22
2	$C_{16}H_{16}N_2$	81.09 / 81.32	6.65 / 6.82	11.97 / 11.85	148-149 Benzene	45
3	$C_{16}H_{22}N_2$	79.15 / 79.29	9.32 / 9.15	11.45 / 11.56	151-153 Dioxane	56
4	$C_{21}H_{18}N_2$	84.42 / 84.53	6.15 / 6.08	9.15 / 9.39	198-200 Benzene	41
5	$C_{16}H_{16}N_2O_2$	71.37 / 71.62	5.92 / 6.01	10.27 / 10.44	158-160 Benzene	69
6	$C_{17}H_{24}N_2$	79.38 / 79.64	9.28 / 9.44	10.82 / 10.93	143-145 Cyclohexane	47
7	$C_{16}H_{22}N_2O_2S$	62.64 / 62.72	7.35 / 7.24	9.02 / 9.14	106-107 MeOH	61
8	$C_{17}H_{18}N_2O_2S$	64.75 / 64.94	5.57 / 5.77	8.65 / 8.91	115-118 Cyclohexane	40
9	$C_{22}H_{20}N_2O_2S$	70.22 / 70.19	5.17 / 5.35	7.28 / 7.44	120-124 MeOH	54
10	$C_{17}H_{24}N_2O_2S$	63.57 / 63.72	7.41 / 7.55	8.48 / 8.74	103-107 Dioxane	73
11	$C_{22}H_{26}N_2O_2S$	69.92 / 69.08	6.89 / 6.85	7.11 / 7.32	125-130 MeOH	46
12	$C_{27}H_{22}N_2O_2S$	73.81 / 73.95	4.82 / 5.06	6.14 / 6.39	143-147 EtOH	38
13	$C_{22}H_{20}N_2O_4S$	64.72 / 64.69	5.28 / 4.94	6.62 / 6.86	115-117 EtOH	50
14	$C_{18}H_{26}N_2O_2S$	64.39 / 64.64	7.97 / 7.83	8.17 / 8.38	136-140 MeOH	66
15	$C_{23}H_{28}N_2O_2S$	69.48 / 69.66	7.32 / 7.12	6.89 / 7.06	152-153 MeOH	67

The compounds obtained were tested against the standard *Mycobacterium tuberculosis* $H_{37}Rv$ strain as well as two strains isolated from tuberculosis patients: one resistant to isonicotinic acid (INH), ethambutol (ETB), and rifampicin (RFP), the other fully susceptible to the tuberculostatics administered. Tuberculostatic activity was determined *in vitro* by the classical test tube method with Youman's liquid medium containing 10% of bovine serum.

Based on the minimum inhibiting concentration (MIC) values obtained, one may conclude that some of the compounds tested exhibited a high tuberculostatic activity. The most active were compounds **1, 2**, **4**, **6**, **7**, **10**, **14**, as their MIC values were within the limits of 6.2-25 μg/ml (Table 3). The majority of the active compounds possessed cyclohexylethyl or cyclohexylpropyl substituents in position C(2) of the benzimidazole system. The presence of the sulfomethyl group at the nitrogen atom did not change the activity.

EXPERIMENTAL

Melting points were determined with the Reichert apparatus and are uncorrected. The ^1H NMR spectra were recorded with a Varian Gemini 200 (200 MHz) spectrometer in $CDCl_3$ and given in the δ scale from TMS (recalculated using $CHCl_3$ signal).

TABLE 2. ^{1}H NMR Spectra of Compounds **1-15**

Compound	δ, ppm (*J*, Hz)
1	0.88-1.82 (13H, m, CH_2, C_6H_{11}); 2.96 (2H, t, *J* = 8, CH_2); 7.22-7.52 (4H, m, C_6H_5)
2	2.10-2.26 (2H, m, CH_2); 2.70 (2H, t, *J* = 8, CH_2); 2.91 (2H, t, *J* = 8, CH_2); 7.11-7.57 (4H, m, C_6H_5)
3	0.80-1.93 (15H, m, $(CH_2)_2C_6H_{11}$); 2.94 (2H, t, *J* = 8, CH_2); 7.21-7.57 (4H, m, C_6H_5)
4	3.66 (2H, d, *J* = 8, CH_2); 4.63 (1H, t, *J* = 8, CH); 7.15-7.47 (14H, m, C_6H_5)
5	3.78 (3H, s, CH_3); 3.85 (3H, s, CH_3); 4.21 (2H, s, CH_2); 4.82 (3H, m, C_6H_5); 7.21 (2H, m, C_6H_5); 7.53 (2H, m, C_6H_5)
6	0.75-2.00 (15H, m, $(CH_2)_2C_6H_{11}$); 2.43 (3H, s, CH_3); 2.85 (2H, t, *J* = 7, CH_2); 6.82-7.56 (3H, m, C_6H_5)
7	0.96-1.87 (13H, m, $CH_2C_6H_{11}$); 3.11-3.22 (5H, m, CH_2 and CH_3); 7.26-7.40 (2H, m, C_6H_5); 7.70-7.87 (2H, m, C_6H_5)
8	2.28 (2H, m, CH_2); 2.83 (2H, t, *J* = 7, CH_2); 3.18 (5H, m, CH_2 and CH_3); 7.19-7.88 (9H, m, C_6H_5)
9	2.24 (2H, m, CH_2); 2.80 (2H, t, *J* = 7, CH_2); 3.15 (2H, t, *J* = 7, CH_2); 7.11-8.08 (14H, m, C_6H_5)
10	2.86-2.01 (15H, m, $(CH_2)_2C_6H_{11}$); 3.11 (2H, t, *J* = 8, CH_2); 3.22 (3H, s, CH_3); 7.26-7.88 (4H, m, C_6H_5)
11	0.81-1.98 (11H, m, C_6H_{11}); 2.25 (2H, m, CH_2); 2.80 (2H, t, *J* = 7, CH_2); 3.12 (2H, t, *J* = 7, CH_2); 7.20-8.20 (9H, m, C_6H_5)
12	3.94 (2H, d, *J* = 7, CH_2); 5.08 (1H, t, *J* = 7, CH); 7.12-7.99 (19H, m, C_6H_5)
13	3.73 (6H, s, CH_3); 3.81 (2H, s, CH_2); 6.51 (3H, m, C_6H_5); 7.26-7.93 (9H, m, C_6H_5)
14	0.85-2.00 (15H, m, $(CH_2)_2C_6H_{11}$); 2.46 (3H, s, CH_3); 3.02-3.25 (5H, m, CH_2 and CH_3); 7.06-7.75 (3H, m, C_6H_5)
15	0.72-2.11 (15H, m, $(CH_2)_2C_6H_{11}$); 2.50 (3H, s, CH_3); 3.15 (2H, t, *J* = 7, CH_2); 7.06-7.95 (8H, m, C_6H_5)

TABLE 3. Tuberculostatic Activity of Compounds **1-15**

Compound	MIC μg/ml		
	$H_{37}Rv$	Drug-resistant strain	Drug-susceptible strain
1	3.1	6.2	6.2
2	6.2	25	12.5
3	12.5	6.2	25
4	6.2	25	12.5
5	25	50	25
6	6.2	6.2	6.2
7	25	6.2	25
8	25	50	25
9	12.5	50	12.5
10	6.2	25	12.5
11	12.5	25	12.5
12	100	100	100
13	25	50	25
14	12.5	6.2	6.2
15	25	25	25

Cyclohexylalkyl- and Arylalkylbenzimidazoles 1-6. *o*-Phenylenediamine (10 mmol) or 3,4-diaminotoluene (10 mmol) and the corresponding acid – 3-cyclohexylpropionic, 4-phenylbutyric, 4-cyclohexylbutyric, 3,3-diphenylpropionic, or 3,4-dimethoxyphenylacetic (10 mmol) were heated on Wood's metal bath at 160-180°C for 1 h. On cooling down, 10% NaOH solution (10 ml) was added, and the whole

stirred and allowed to stand for 24 h. Then the precipitated compounds **1-6** were filtered off, washed with water to the neutral reaction, dried, and purified by crystallization.

1-Methane- and 1-Benzenesulfonyl-2-substituted Benzimidazoles 7-15. Compounds **1-6** (5 mmol) were dissolved in anhydrous dioxane (10 ml), treated with triethylamine (2 ml) and then dropwise with methane- and benzenesulfonyl chloride (10 mmol), and the whole stirred while heating at 50°C for 5 h and then at ambient temperature for another 12 h. The solvent was evaporated and some water with ice added. After a few hours the precipitated compounds **7-15** were filtered off, washed with water, and crystallized.

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